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

PRINCIPAL INVESTIGATOR: Steven L. Batki, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
San Francisco, CA 94121-1545

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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.					
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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.

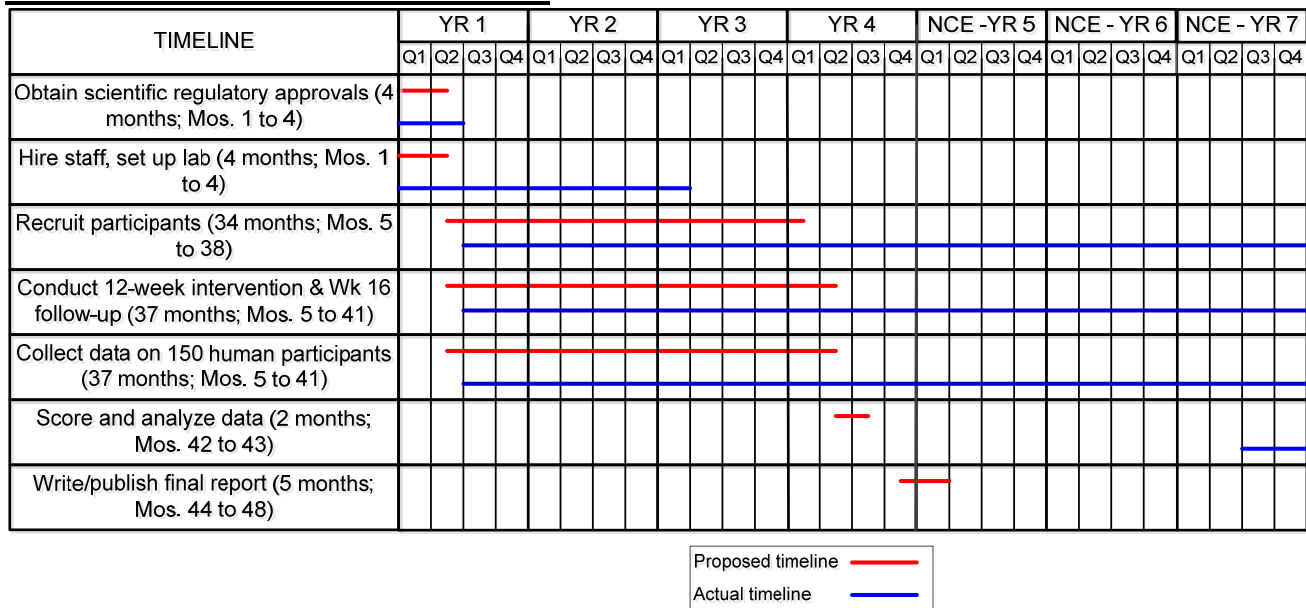
3.2 is tested by estimating subject-specific slopes from random coefficients mixed models predicting changes in alcohol use, impulsivity, and risk-taking, and calculating the Pearson correlation coefficients between slopes of change in alcohol use and changes in impulsivity and risk-taking.

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 7 of this project covers the time period September 30, 2018 through September 29, 2019. Our final study visit was completed on August 29, 2019, completing the data collection of 150 participants. All tasks for Year 7 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



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 7. A Human Research Protection Program Regulatory audit by the San Francisco VA Medical Center's Research Compliance Office was conducted on 5 June 2019 and found our study to be in compliance.

Core lab personnel remained the same during Year 7 with a few changes in the Research Practicum Trainees and volunteer Research Assistants. For the majority of the year the lab personnel included: 1 Lab Manager, 2 Study Coordinators, 1 Research Psychologist, 1 Research Statistician, 1 Research Physician and 1 Database Developer/Manager. Additional staff that either work at a less percent effort or as volunteers include: 4 PhD students/Research Practicum Trainees and volunteer Research Assistants who helped with recruitment, pre-screening, brief weekly alcohol counseling, neurocognitive testing, and structured psychological interviews.

All study staff were trained on the study protocol and standard operating procedures were revised as necessary to maintain clarification and standardization of processes and purposes. Both the Access interface/database and the Qualtrics methods of online data collection are complete. All measures and procedures were in active use, and drinking and medical data were monitored in real time for safety purposes.

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

Participant recruitment began on 2/27/13 and the first informed consent was signed on 3/20/13. The final participant was randomized to treatment on 4 April 2019 and the final study visit was completed on 29 July 2019. There were 5,535 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, which means someone on the study team reviewed their medical record to determine initial eligibility. In total, 265 participants signed informed consent form and 158 were randomly assigned to treatment with topiramate (top) or placebo (PLA). Based on our current review of the data, only 150 of the 158 participants provided data that can be used in the final analysis. The cohort is mostly male (131/150 = 87%), non-Hispanic (113/150 = 75%) and predominantly Caucasian (62/150 = 41%).

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. A randomization number was assigned to 158 participants, with the intent to treat with either topiramate or placebo. Eight of the 158 will be excluded from the final analysis because they were either lost to follow-up or dropped out immediately following randomization and therefore, no data was collected during the treatment phase of the study. Of the 150 who were assigned to treatment and will be included in the final analysis, 100 (67%) completed the study, 21 (14%) dropped out, 11 (7%) were lost to follow-up and 18 (12%) were withdrawn by the PI. The average last visit attended was study visit 8.

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

Data collection is complete and we are currently in the process of cleaning the data.

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***

Data collection is complete. We are currently in the process of cleaning the data.

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*

Data collection is complete. We are currently in the process of cleaning the data.

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

1. Created a modified version of the NIAAA Medical Management Treatment Manual, 2010 edition. This adaptation takes into consideration the study population, the nature of the medication, the context of a clinical trial, and the varying levels of medical training among study clinicians. 4/23/13
2. Developed a glaucoma screen to detect subjects that may be at a higher risk of developing narrow angle glaucoma, a contraindicated condition to topiramate. 5/30/13
3. Modified the Clinician Administered PTSD Scale (CAPS) to incorporate questions from the original CAPS and the new version, CAPS5. By administering the revised version, we will be able to characterize the study population's PTSD diagnosis as defined by DSM-IV and DSM5. 4/1/13-6/30/13
4. Modified the PTSD Checklist (PCL) to incorporate questions from the original PCL-S and the new version, PCL5. By administering the revised version, we will be able to characterize the study population's PTSD diagnosis as defined by DSM-IV and DSM5. 4/1/13-6/30/13
5. Added additional question to the Structured Clinical Interview for DSM-IV, Substance Used Disorder section (SCID, SUD) so that we may describe the study population's alcohol use disorders in terms of DSM-IV and addictive disorders, as defined by DSM5. 4/1/13-6/30/13
6. 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.
7. Created 2 databases/interfaces for data collection in real-time. Tasks included the design, development, testing, and validation of activities.
8. Qualtrics, an online user interface was designed to directly collect and store information at the time of study visit. All self-report measures are collected in this format.
9. Data gleaned from measures and procedures that are more structured or involved are collected via an Access database/interface. Measures such as psychological assessments or procedures such as blood collection are entered in this system.
10. All data are stored on a SQL server which resides behind the San Francisco VA Medical Center firewall. 12/1/12 – 9/29/13
11. Completed the recruitment, enrollment and data collection of 150 participants for the investigation of topiramate as an intervention for Veterans with alcohol use disorder and PTSD. This represents the largest randomized controlled clinical trial of pharmacotherapy in Veterans with PTSD and alcohol use disorder.
12. Produced 6 peer-review publications, 1 letter to the editor and 7 published abstracts, from data directly or indirectly related the study, and produced during the preparation for, and conduct of, the clinical trial.
13. Completed data cleaning of final study data.
14. Conducted preliminary analyses of the data for the completed trial.
15. Submitted the results of the preliminary analysis to the Research Society on Alcoholism for the 2020 Annual Scientific Meeting, to be held in New Orleans in June, 2020. These results are presented in abstract form, below:

The abstract reporting the results of the preliminary analysis is as follows:

Submitted to the 2020 Annual Scientific Meeting of the Research Society on Alcoholism

TOPIRAMATE TREATMENT OF ALCOHOL USE DISORDER IN VETERANS WITH PTSD: PRELIMINARY ANALYSIS OF A CONTROLLED TRIAL

S.L. Batki, D.L. Pennington, B.A. Lasher, E. Herbst, T.C. Neylan, N. Bautista.

UCSF Department of Psychiatry and San Francisco VA Health Care System, San Francisco, CA 94121

Background:

Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) frequently co-occur among Veterans, yet effective pharmacotherapy for these comorbid conditions is still elusive.

Methods:

A single-site prospective 12-week, randomized, double-blind, placebo-controlled trial of flexible-dose topiramate or placebo, up to 300 mg/day in 150 Veterans with PTSD and AUD. All participants received weekly Medical Management counseling.

Primary outcome was between-group reduction in drinking days per week. Secondary outcomes included other measures of alcohol use, alcohol craving (Obsessive-Compulsive Drinking Scale [OCDS], PTSD symptoms, and safety outcomes.

Results:

All participants were military Veterans. 87% were male. Mean ($\pm$ SD) age was 51.3 ($\pm$ 13.4). 40% were exposed to combat.

PTSD symptom severity at entry was high. Mean baseline CAPS/PCL score was 74.1/54.8 ($\pm$ 16.5/13.4).

At entry, mean baseline drinking days per week was 5.1 ($\pm$ 1.8), mean heavy drinking days per week was 3.8 ($\pm$ 2.3), mean drinks per week was 48.8 ($\pm$ 33.5) and mean drinks/drinking day was 9.9 ($\pm$ 6.6). Mean baseline OCDS was 17.1 ($\pm$ 7.4). There were no differences between groups in reported drinking data in the 90 days prior to study entry.

Both the topiramate and the placebo groups significantly reduced alcohol use and PTSD symptom severity over the 12-weeks of treatment. A linear mixed model found that topiramate significantly reduced alcohol craving on OCDS compared to placebo (treatment-by-time interaction, $p < 0.01$). However, there were no other statistically significant treatment condition differences or treatment-by-time interactions observed for other alcohol use measures and for PTSD symptom severity. Retention measured by the total number of study visits attended also did not differ between the two groups.

Adverse effects differed between the two groups: those receiving topiramate had significantly more participants reporting treatment-emergent numbness (topiramate [TOP]=21 vs placebo [PLA]=12; $p=.04$), loss of appetite (TOP=37 vs PLA = 24; $p<0.01$), and confusion (TOP=24 vs PLA=11; $p<0.01$). There were no medication-related serious adverse effects.

Conclusions:

In this preliminary analysis, topiramate treatment reduced alcohol craving but did not appear to reduce alcohol use or PTSD symptom severity as compared to placebo in Veterans with co-occurring AUD and PTSD.

Source of Funding: Department of Defense Grant No: W81XWH -11-PHTBI-BAPHA

ClinicalTrials.gov identifier (NCT number): NCT01749215

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

PEER REVIEWED PUBLICATIONS:

1. Kalapatapu RK, Delucchi KL, Lasher BA, Vinogradov S, Batki SL. (2014) Alcohol Use Biomarkers Predicting Cognitive Performance: A Secondary Analysis in Veterans with Alcohol Dependence and Posttraumatic Stress Disorder. *Military Medicine*, 178(9), 974-980.
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3. 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*, 224(3):281-7, PMID: 25444536.
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6. Abram, S.V., Batki, S.L., Bielenberg, J. Pennington, D.L. (Under Review) Working Memory Moderates the Relations Between Alcohol Demand Characteristics and PTSD Symptoms. *Journal of Studies on Alcohol and Drugs*

PUBLISHED ABSTRACTS:

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CONCLUSIONS:

Our preliminary analysis of the results of the completed clinical trial lead us to the following conclusions, *which, at the time of this final report, must still be viewed as preliminary*, in that we are currently engaged the process of reviewing, and if needed, revising preparing for the June 2020 presentation of our findings at the Research Society on Alcoholism meeting.

Preliminary conclusions:

1. It was feasible to conduct a large controlled clinical trial of topiramate treatment for alcohol use disorder (AUD) in Veterans with posttraumatic stress disorder (PTSD) who were recruited from the patient population at a large VA medical center and its outlying community-based outpatient clinics.
2. The Veterans who were participants in the study appeared to be well-representative a group of patients with high levels of severity in both their AUD and PTSD:
 - a. 13% of the cohort were women
 - b. Mean ($\pm$ SD) age was 51.3 ($\pm$ 13.4).
 - c. 40% were exposed to combat.
 - d. At entry, PTSD symptom severity at entry was high: mean baseline CAPS/PCL score was 74.1/54.8 ($\pm$ 16.5/13.4).
 - e. At entry, alcohol use was heavy: mean baseline drinking days per week was 5.1 ($\pm$ 1.8), mean heavy drinking days per week was 3.8 ($\pm$ 2.3), mean drinks per week was 48.8 ($\pm$ 33.5) and mean drinks/drinking day was 9.9 ($\pm$ 6.6). Mean baseline alcohol craving, as measured by the Obsessive-Compulsive Drinking Scale (OCDS) was 17.1 ($\pm$ 7.4).
 - f. There were no differences between groups in reported drinking data in the 90 days prior to study entry.
3. Topiramate was generally safe and was generally well-tolerated in the flexible dose procedure that was employed in the trial.
4. Study-medication adverse effects, however, differed between the two groups, with participants who received topiramate reporting more adverse effects:
 - a. those receiving topiramate had significantly more participants reporting treatment-emergent numbness (topiramate [TOP]=21 vs placebo [PLA]=12; $p=.04$),
 - b. those receiving topiramate had significantly more participants reporting treatment-emergent loss of appetite (TOP=37 vs PLA = 24; $p<0.01$),
 - c. and those receiving topiramate had significantly more participants reporting treatment-emergent confusion (TOP=24 vs PLA=11; $p<0.01$).
5. There were no medication-related serious adverse effects.
6. Study participation over the 12-week course of treatment was associated with significant reductions in the behaviors and symptoms associated with the targeted conditions of

AUD and PTSD, but for the primary outcomes, there were no significant differences between the participant group assigned to topiramate and the group assigned to placebo:

- a. Both the topiramate and placebo groups significantly reduced alcohol use over the 12-week treatment as measured by heavy drinking days, drinking days, drinks per drinking day, and drinks per week, but there were no between-group differences.
 - i. The only alcohol-related measure for which there was a clear benefit for topiramate in this preliminary analysis was alcohol craving. A linear mixed model found that topiramate significantly reduced alcohol craving on OCDS compared to placebo (treatment-by-time interaction, $p < 0.01$).
 - b. Both the topiramate and placebo groups significantly reduced PTSD symptom severity over the 12-week treatment as measured by the PTSD Checklist (PLC), but there were no between-group differences.
7. Retention, measured by the total number of study visits attended also did not differ between the topiramate and placebo groups.
 8. These findings suggest that study participation, with its combination of study medication (topiramate or placebo), weekly study visits with weekly NIAAA Medication Management counseling, multiple measures and forms of monitoring, and the psychosocial support and structure that the study provided, had a net effect of producing clinical improvements in PTSD symptom severity and reduction in alcohol use.
 9. Study procedures may have produced a powerful enough therapeutic effect to possibly “wash out” or overwhelm whatever specific therapeutic effects may have been produced by topiramate, as compared to placebo (e.g. the reduced alcohol craving found in the topiramate group).
 10. On the basis of this preliminary analysis, there does not appear to be sufficient evidence to support the conduct of a larger multi-site randomized controlled trial (RCT) to further test topiramate’s efficacy in treating co-occurring AUD and PTSD in Veterans.
 11. On the basis of this preliminary analysis, there does not appear to be sufficient evidence to recommend the routine use of topiramate to treat co-occurring AUD and PTSD in Veterans – particularly as topiramate is associated with a clinically significant adverse effect potential.
 12. Our continuing work in finalizing our analyses and conducting secondary analyses as well as assessing our exploratory outcomes may lead to revisions in these preliminary conclusions. For example, it may be possible that certain subgroups within the study cohort had better outcomes with topiramate than with placebo, and that predictors for improved outcomes may be identified.

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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.

*separate PDF

Alcohol Use Biomarkers Predicting Cognitive Performance: A Secondary Analysis in Veterans With Alcohol Dependence and Posttraumatic Stress Disorder

Raj K. Kalapatapu, MD*†; Kevin L. Delucchi, PhD*; Brooke A. Lasher, BA†‡; Sophia Vinogradov, MD*†‡; Steven L. Batki, MD*†‡

ABSTRACT Objective: We conducted a secondary analysis of baseline data from a recently completed pharmacological pilot clinical trial among 30 veterans with alcohol dependence and posttraumatic stress disorder (PTSD). This trial included baseline measures of alcohol use biomarkers, both indirect (carbohydrate-deficient transferrin, GGT [γ -glutamyltransferase], mean corpuscular volume, AST [aspartate aminotransferase], alanine aminotransferase) and direct (ethyl glucuronide, ethyl sulfate), as well as neurocognitive measures (Trail Making Test parts A and B, Hopkins Verbal Learning Test—Revised, Balloon Analogue Risk Task, Delay Discounting Task). Methods: Two regression models were estimated and tested for each neurocognitive measure (dependent measure). The first model included the alcohol use biomarker alone as the predictor. The second model included the alcohol use biomarker along with the following 3 additional predictors: Beck Depression Inventory, Clinician-Administered PTSD Scale, and receiving medications. Results: In both models, the indirect biomarkers, such as GGT and AST, significantly predicted performance on the Hopkins Verbal Learning Test—Revised %Retention. GGT alone significantly predicted performance on the Trail Making Test part A. Conclusions: Indirect alcohol use biomarkers may have a specific role in identifying those veterans with alcohol dependence and PTSD who have impaired cognitive performance. However, direct alcohol use biomarkers may not share such a role.

INTRODUCTION

Alcohol use disorders are a major public health problem¹ and constitute the most prevalent forms of addiction in veterans.² Cognition is a key area of research in the field of alcohol use disorders.^{3,4} Cognitive impairment is well-documented in individuals with alcohol use disorders,⁵ and alcohol-related clinical outcomes (e.g., abstinence, relapse, treatment completion) are moderated by a range of cognitive impairments.^{6–11} Cognition plays an important role in clinical outcomes, yet recognizing and screening for cognitive impairment in addiction populations remains uncertain and difficult.^{12–16} A comprehensive neurocognitive evaluation may not be routinely feasible in addiction settings, as these evaluations are often time intensive and resource consuming.^{16–18} When managing veterans with alcohol use disorders, quicker

adjunctive tools that clinicians could use to screen for those individuals at higher risk of cognitive impairment are needed.

One potential tool that may fulfill this role is the alcohol use biomarker. Alcohol use biomarkers are broadly divided into indirect and direct biomarkers.^{19,20} The indirect biomarkers include aspartate aminotransferase (AST), alanine aminotransferase (ALT), mean corpuscular volume (MCV), γ -glutamyltransferase (GGT), and carbohydrate-deficient transferrin (CDT). The direct biomarkers include ethyl glucuronide (EtG), ethyl sulfate (EtS), and phosphatidylethanol. Past research has shown that several indirect alcohol use biomarkers are correlated with cognitive performance in individuals with alcohol use disorders: AST,²¹ ALT,²² MCV,²³ and GGT.^{24–29} Thus, alcohol use biomarkers may not only be used to screen for alcohol problems or abstinence,¹⁹ but also have a specific role in screening for cognitive impairment in individuals with alcohol use disorders. These biomarkers may offer more than simply getting a history of the amount and frequency of recent alcohol use.

Though several indirect biomarkers have been explored with respect to cognitive performance, the newer direct biomarkers, such as EtG and EtS, have not received any attention in the literature. Although the direct biomarkers are minor metabolites of alcohol,³⁰ these biomarkers, such as EtG, can also be found in the brain.³¹ Whether any of the direct biomarkers are associated with cognitive performance in individuals with alcohol use disorders remains an open question.

In an effort to add to this scarce literature on the association of alcohol use biomarkers and cognitive performance, we conducted a secondary analysis of baseline data from

*Department of Psychiatry, University of California, 401 Parnassus Avenue, San Francisco, CA 94143.

†San Francisco Veterans Affairs Medical Center, 4150 Clement Street, Building 8 (Mental Health), San Francisco, CA 94121.

‡Northern California Institute for Research and Education (NCIRE), 4150 Clement Street, 151NC, San Francisco, CA 94121.

Dr. Kalapatapu completed the background literature search and completed the statistical analyses (with guidance from Dr. Delucchi). Dr. Kalapatapu wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

The authors report no conflicts of interest. The authors alone are responsible for the content, the study design, protocol implementation, statistical analysis, interpretation of results, manuscript preparation, and decision to submit the manuscript for publication. The views expressed in this article are those of the authors and do not necessarily represent the official views of the NIH.

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a recently completed pharmacological pilot clinical trial among veterans with alcohol dependence and posttraumatic stress disorder (PTSD). This study included the measures, at baseline, of indirect (CDT, GGT, MCV, AST, ALT) and direct (EtG, EtS) alcohol use biomarkers and neurocognitive measures, which allowed us to explore the relationship between biomarkers and cognitive performance.

Because this study was conducted in alcohol-dependent veterans with comorbid PTSD, we were also able to explore the unique relationship between alcohol use biomarkers and cognitive performance in a group having particularly poor clinical outcomes.^{32–35} To the best of our knowledge, the relationship between alcohol use biomarkers and cognitive performance specifically in veterans with alcohol dependence and PTSD has not been previously explored.

In this sample of veterans with alcohol dependence and PTSD, we hypothesized that the indirect biomarkers would predict baseline cognitive performance. On the basis of the evidence that they can be found in the brain, we also hypothesized that the direct biomarkers would predict baseline cognitive performance.

METHODS

Study Setting

Full details of the study used for this analysis can be found on Clinicaltrials.gov (identifier no. NCT01087736), titled “Topiramate Treatment of Alcohol Use Disorders in Veterans With Post Traumatic Stress Disorder (PTSD): A Pilot Controlled Trial of Augmentation Therapy”. Briefly, this two-armed double-blind randomized controlled pilot study enrolled 30 veteran participants with alcohol dependence and PTSD. Participants met *Diagnostic and Statistical Manual of Mental Disorders*, 4th Ed, Text Revision (DSM-IV-TR) criteria for current alcohol dependence and for “heavy drinking” in the past 30 days before screening. For men, “heavy drinking” was defined as, on average, drinking more than 15 standard drinks per week. For women, “heavy drinking” was defined as, on average, drinking more than 8 standard drinks per week.³⁶ The 12-week double-blind treatment phase consisted of randomly assigning participants to either topiramate or placebo. Participants also received weekly manualized alcohol counseling³⁷ and standard PTSD treatment.

All research activities were conducted at the San Francisco Veterans Affairs Medical Center (SFVAMC). All participants provided informed consent. The study was approved by the Committee on Human Research at the University of California, San Francisco; the Research and Development Committee at the SFVAMC; and the U.S. Army Medical Research and Materiel Command Human Research Protection Office.

Measures

Demographic data, such as age, sex, race, ethnicity, years of education, marital status, and occupational status, were

collected. Psychiatric diagnoses and concurrent medication use were captured by a review of each participant's electronic medical record at the SFVAMC. Substance use disorder diagnoses were assessed using the Substance Use Disorders module of the Structured Clinical Interview for DSM-IV-TR, Research Version, Patient Edition (SCID-I/P).³⁸ The level of substance use for the past 90 days was assessed using the Timeline Followback Method.³⁹ PTSD was diagnosed by the Clinician-Administered PTSD Scale.⁴⁰ The level of depression was assessed using the 21-item self-report Beck Depression Inventory.⁴¹

Blood samples were obtained for CDT (specifically serum %disialo-CDT), GGT, MCV, AST, and ALT levels. Urine samples were obtained for EtG and EtS levels. Standard operating procedures were followed by the Clinical and Translational Science Institute at the SFVAMC to obtain these samples. Levels of GGT, MCV, AST, and ALT were analyzed locally at the SFVAMC Department of Laboratory Medicine. CDT sample was shipped and analyzed at the Clinical Neurobiology Laboratory in the Institute of Psychiatry at the Medical University of South Carolina. EtG and EtS samples were shipped and analyzed at the Department of Laboratory Medicine at the Yale University School of Medicine.

The Trail Making Test (TMT) part A was used to assess psychomotor speed and simple visual attention and part B was used to assess task switching and cognitive flexibility; the raw scores were converted to *T* scores.⁴² The Hopkins Verbal Learning Test—Revised (HVLT-R) was used to assess verbal memory.⁴³ We used the %retention score for this analysis, where the raw score was converted to a *T* score; the assessment of retention is relatively free of effortful memory search and retrieval.⁴³ The Balloon Analogue Risk Task (BART) was used to assess risk taking⁴⁴; we used the primary score of “adjusted average number of pumps on unexploded balloons.” The Delay Discounting (DD) Task was used to assess impulsivity⁴⁵; we used the *Kln* score, defined as the log-transformed DD after applying the hyperbolic function.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics, version 20 (Armonk, New York). All continuous variables were checked for normality (Kolmogorov–Smirnov and Shapiro–Wilk tests), and nonparametric tests were used when appropriate. All continuous variables were also checked for extreme values; values with a *z*-score > 3.29 or < -3.29 were adjusted to the next highest value. Where adjusted results differed from the original data, the adjusted results are presented. Because most values were undetectable at <100 ng/mL, EtG was dichotomized into <100 ng/mL vs. >100 ng/mL. Because most values were undetectable at <50 ng/mL, EtS was dichotomized into <50 vs. >50 ng/mL.

Two multiple regression models were estimated and tested for each neurocognitive measure (dependent measure). The

first model included the alcohol use biomarker alone as the predictor. The second model included the alcohol use biomarker along with the following 3 additional predictors: Beck Depression Inventory (Total score), Clinician-Administered PTSD Scale (Severity score), and receiving medications (PTSD, substance use disorder, or other psychiatric medications). As mood symptoms,⁴⁶ PTSD symptoms,⁴⁷ and medications⁴⁸ can affect cognitive performance, we included these 3 additional predictors in the second model to determine if they would make a significant contribution.

Because this was an exploratory secondary analysis, we did not control for type I error; *p*-values < 0.05 were considered statistically significant. Assumptions in each regression model were checked by assessing several parameters⁴⁹ such as Durbin-Watson statistic (close to 2 and not <1 or >3), collinearity (Tolerance and Variance Inflation Factor close to 1), standardized residuals (not >3), Cook's distance (not >1), linearity/homoscedasticity (plots of *ZRESID against *ZPRED randomly and evenly dispersed), and normality of residuals (normal histograms and normal probability plots with data points near the line). All of these assumptions in each multiple regression model for each neurocognitive measure were met.

TABLE I. Baseline Demographic and Clinical Data

	Mean (SD) ^a , Median (Range, IQR) ^b , or %
Age	55 (25–65, 20)
Male	93.30%
Caucasian	53.30%
African American	26.70%
Hispanic	10.00%
Years of Education	14 (7–18, 2)
Married	26.70%
Unemployed	36.70%
Major Depressive Disorder	13.30%
Any Type of Bipolar Disorder	3.30%
Generalized Anxiety Disorder	3.30%
Panic Disorder	3.30%
Obsessive-Compulsive Disorder	3.30%
Cannabis Abuse or Dependence	6.70%
Cocaine Abuse or Dependence	16.70%
Sedative Abuse or Dependence	6.70%
Opiate Abuse or Dependence	3.30%
Receiving Medications for PTSD	46.70%
Receiving Medications for a Substance Use Disorder	6.70%
Receiving Other Psychiatric Medications	60.00%
Beck Depression Inventory: Total Score ^c	24.9 (11.9)
Clinician-Administered PTSD Scale: Intensity Score	39.4 (8.3)
Clinician-Administered PTSD Scale: Frequency Score	38.9 (9.3)
Clinician-Administered PTSD Scale: Severity Score	78.3 (16.6)

n = 30 except where noted. ^aSD = standard deviation. ^bIQR = interquartile range. ^c*n* = 29 because of 1 missing data point.

TABLE II. Baseline Substance Use, Alcohol Use Biomarker, and Neurocognitive Data

	Mean (SD), Median (Range, IQR), or %
Baseline Drinking Severity	
No. of Drinks in the Past 30 Days	183 (68–637, 158)
No. of Drinking Days in the Past 30 Days	22.5 (5–30, 19)
No. of Drinks Per Drinking Day in the Past 30 Days	9.5 (3.6–27.2, 7.4)
No. of Heavy Drinking Days in the Past 30 Days	14.5 (0–30, 19)
No. of Days of Cannabis Use in the Past 90 Days [<i>n</i> = 9]	45 (9–90, 78)
No. of Days of Cocaine Use in the Past 90 Days [<i>n</i> = 3]	37.0 (45.9)
No. of Days of Opiate Use in the Past 90 Days [<i>n</i> = 1]	1
No. of Cigarettes Used in the Past 90 Days [<i>n</i> = 13]	1,075.5 (648.9)
EtG ^{a,b} (>100 ng/mL)	30%
EtS ^{a,c} (>50 ng/mL)	37%
CDT ^d	1.7% (0.9–5.0, 1.05)
GGT	47.5 (16–722, 52)
MCV	96.2 (69.9–103.6, 8.5)
AST	35.5 (17–174, 32.8)
ALT	38 (18–106, 49)
HVLT-R	
%Retention <i>T</i> Score	55 (25–80, 11)
BART	
Adjusted Average Number of Pumps on Unexploded Balloons ^e	35.9 (15.4)
DD	
Kln ^{e,f}	–5.4 (2.0)
TMT-A	
<i>T</i> Score	44.9 (11.6)
TMT-B	
<i>T</i> Score	45.6 (11.0)

n = 30 except where noted. ^a*n* = 27 because of 3 missing data points. ^bBecause most values were undetectable at <100 ng/mL, EtG was dichotomized into <100 vs. >100 ng/mL. ^cBecause most values were undetectable at <50 ng/mL, EtS was dichotomized into <50 vs. >50 ng/mL. ^d*n* = 29 because of 1 missing data point. Values represent serum %disialo-CDT. ^e*n* = 28 because of 2 missing data points. ^fKln = log-transformed delay discounting after applying the hyperbolic function.

Finally, previous evidence shows that alcohol intake itself can affect cognitive performance.⁵ We explored whether the number of drinks significantly correlated (Pearson's correlation) with any of the neurocognitive measures.

RESULTS

Table I presents baseline demographic and clinical data. Table II presents baseline substance use, alcohol use biomarker, and neurocognitive data. Tables III and IV present the multiple regression analyses between alcohol use biomarker data and neurocognitive data. Table III presents the results with the first model that included the alcohol use biomarker alone as the predictor; Table IV presents the

TABLE III. Multiple Regression Analyses Between Alcohol Use Biomarker Data and Neurocognitive Data (Dependent Measure)

	HVLT-R: %Retention <i>T</i> Score	BART: Adjusted Average Number of Pumps on Unexploded Balloons	DD: Kln	TMT-A: <i>T</i> Score	TMT-B: <i>T</i> Score
EtG	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
EtS	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
CDT	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
GGT	$F(1,27) = 7.27, p = 0.01,$ $R^2 = 0.21, \beta = 0.46^a$	$p > 0.10$	$p > 0.10$	$F(1,27) = 5.12, p = 0.032,$ $R^2 = 0.16, \beta = -0.40^b$	$p > 0.10$
MCV	$p > 0.10$	$F(1,25) = 3.01,$ $p = 0.095, R^2 = 0.11, \beta = 0.33$	$p > 0.10$	$p > 0.10$	$p > 0.10$
AST	$F(1,27) = 6.53, p = 0.017,$ $R^2 = 0.20, \beta = 0.44^b$	$p > 0.10$	$p > 0.10$	$F(1,27) = 3.50, p = 0.072,$ $R^2 = 0.12, \beta = -0.34^b$	$p > 0.10$
ALT	$p > 0.10$	$p > 0.10$	$p > 0.10$	$F(1,27) = 4.12, p = 0.052,$ $R^2 = 0.13, \beta = -0.36$	$p > 0.10$

Alcohol use biomarker alone as the predictor. ^aCorrection for extreme values did not change results, so original results are presented. ^bCorrection for extreme values changed results, so corrected results are presented.

TABLE IV. Multiple Regression Analyses Between Alcohol Use Biomarker Data and Neurocognitive Data (Dependent Measure)

	HVLT-R: %Retention <i>T</i> Score	BART: Adjusted Average Number of Pumps on Unexploded Balloons	DD: Kln	TMT-A: <i>T</i> Score	TMT-B: <i>T</i> Score
EtG	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
EtS	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
CDT	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
GGT	$F(4,24) = 4.70, p = 0.006, R^2 = 0.44$ GGT $\beta = 0.64^a, p = 0.001$ [1] $\beta = -0.36, p = 0.045$ [2] $\beta = 0.47, p = 0.01$ [3] $\beta = 0.29, p = 0.095$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
MCV	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
AST	$F(4,24) = 2.94, p = 0.041, R^2 = 0.33$ AST $\beta = 0.49^b, p = 0.01$ [1] $\beta = -0.27, p = 0.16$ [2] $\beta = 0.36, p = 0.06$ [3] $\beta = 0.17, p = 0.33$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$
ALT	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$	$p > 0.10$

Alcohol use biomarker plus 3 predictors: (1) Beck Depression Inventory (Total score), (2) Clinician-Administered PTSD Scale (Severity score), and (3) receiving medications (PTSD, substance use disorder, or other psychiatric medications). Significant and approaching significance results are reported. ^aCorrection for extreme values did not change results, so original results are presented. ^bCorrection for extreme values changed results, so corrected results are presented.

results with the second model that included the alcohol use biomarker along with the 3 additional predictors (Beck Depression Inventory [Total score], Clinician-Administered PTSD Scale [Severity score], receiving medications [PTSD, substance use disorder, or other psychiatric medications]).

CDT did not significantly predict performance on any neurocognitive measure. In both models, GGT significantly predicted performance on the HVLT-R %Retention; the Beck Depression Inventory (Total score) and the Clinician-Administered PTSD Scale (Severity score) also significantly contributed to the second model along with GGT. In only the first model, GGT significantly predicted performance on the TMT-A. GGT did not significantly predict performance on the BART, DD, TMT-B, and in the second model on the TMT-A.

In only the first model, MCV predicting performance on the BART approached significance. It did not significantly predict performance on any other neurocognitive measure.

In both models, AST significantly predicted performance on the HVLT-R %Retention. In only the first model, AST predicting performance on the TMT-A approached significance. AST did not significantly predict performance on the BART, DD, TMT-B, and in the second model on the TMT-A.

In the first model, ALT predicting performance on the TMT-A approached significance. It did not significantly predict performance on any other neurocognitive measure. EtG and EtS did not significantly predict performance on any neurocognitive measure.

The number of drinks did not significantly correlate with any of the neurocognitive measures (all p 's > 0.05). These

results were nonsignificant for the number of drinks in the past 4 to 90 days. Also, because GGT and AST were the only two measures to predict performance on the HVLT-R %Retention, we assessed whether these were correlated; GGT and AST were correlated in this analysis ($r = 0.74$, $p < 0.001$).

DISCUSSION

Baseline alcohol use biomarker and neurocognitive data from a pilot clinical trial among veterans with alcohol dependence and PTSD were analyzed in this secondary analysis. GGT and AST significantly predicted performance on the HVLT-R %Retention; the Beck Depression Inventory (Total score) and the Clinician-Administered PTSD Scale (Severity score) also significantly contributed to predicting performance on the HVLT-R %Retention along with GGT. GGT alone, without any other predictors, significantly predicted performance on TMT-A. Without any other predictors, AST and ALT alone predicting performance on the TMT-A approached significance. Without any other predictors, MCV alone predicting performance on the BART approached significance. Thus, the initial hypotheses were partially supported.

The indirect biomarkers may predict neurocognitive performance for several reasons such as (1) by serving as a surrogate marker for heavy alcohol use, thereby representing alcohol's potential for direct neurotoxicity; (2) by serving as a marker of hepatic dysfunction for transaminases, thereby representing hepatic effects on brain function; and (3) by having a direct neurotoxic effect of their own. The finding that GGT and AST predicted performance on some neurocognitive measures is consistent with that of previous research.^{21,24-29} For example, increases in GGT may increase the transport of amino acids into the brain across the blood-brain barrier, which may alter cognitive performance.²⁴ GGT has also been associated with gray matter decline⁵⁰ and brain shrinkage,⁵¹ which may affect cognitive performance. GGT is known to be a marker of oxidative stress and has been found to be elevated in patients with Alzheimer's disease,⁵² which highlights a potential association of GGT with cognitive performance. Cognitive changes because of poor liver function may be due to the liver failing to catabolize circulating neurotoxins,⁵³ and GGT and AST may help identify patients who show a change in visual attention and verbal memory performance.

ALT significantly predicted performance on the TMT-A, but the limitations of the sample might have contributed to ALT not fully achieving significance. Approaching significance, the MCV predicting BART performance is interesting. Though MCV may appear to be unrelated to cognition, some studies have shown that erythrocyte volume may influence cognition,⁵⁴ and that MCV can predict delirium after surgery.²³ MCV has also been associated with gray matter decline⁵⁰ and ventricular enlargement.⁵⁵ One pos-

sibility is that the increased erythrocyte volume, which is found in alcohol dependence¹⁹ and during times of stress,^{56,57} may lead to erythrocytes having difficulty passing through narrow brain capillaries and subsequently affecting cognitive performance.⁵⁴

CDT not predicting performance on any neurocognitive measure is consistent with previous reports.²⁵ It is important to note that other studies in individuals with alcohol use disorders have similarly shown no association of indirect biomarkers with any neurocognitive measure.^{58,59} One plausible explanation for this is that because the direct biomarkers are minor metabolites of alcohol,³⁰ the concentrations of these biomarkers in the brain may not have been sufficient to affect the neural pathways underlying cognitive performance. Another plausible explanation may be that the direct biomarkers represent alcohol use for a much briefer time than the indirect markers, which represents anywhere from several weeks (GGT, AST, ALT) to several months (MCV)¹⁹; therefore, the indirect biomarkers represent more chronic measures of heavy drinking and more likely represent the direct toxic effects of alcohol on brain function.

This analysis suggests that in addiction settings, some of the indirect alcohol use biomarkers serve as an indicator of a subset of patients who are at high risk for cognitive impairment. Alcohol use biomarkers cannot replace a comprehensive neurocognitive evaluation for assessing cognitive impairment. Rather, in settings where a comprehensive neurocognitive evaluation is not feasible, alcohol use biomarkers might be the next best tool that clinicians could potentially use to identify veterans with alcohol dependence and PTSD who are likely to show cognitive impairment. Cost and practicality of ordering alcohol use biomarkers would be some hurdles for a clinician to implement these biomarkers in routine clinical practice. For example, in our own San Francisco Veterans Affairs clinical setting, the two indirect biomarkers (GGT, AST) in this analysis that predicted cognitive performance can more easily be ordered through our computerized medical record system, compared to the direct biomarkers that require special ordering and processing. Thus, in addition to the scientific relationship between alcohol use biomarkers and cognitive performance, clinicians must consider cost and practicality of ordering alcohol use biomarkers when implementing these biomarkers in routine clinical practice.

This analysis has several strengths. First, seven alcohol use biomarkers were analyzed. Second, three additional predictors were integrated into the second regression model and yet still found significance with a few biomarkers. Third, a naturalistic sample of veterans was analyzed, which can help generalize these findings to veterans with alcohol dependence and comorbid PTSD. Finally, this is the first known analysis to explore the relationship between alcohol use biomarkers and cognitive performance in veterans with both alcohol dependence and PTSD.

Inevitably, this analysis also has limitations. First, the study was not specifically designed to assess the aims of this post hoc analysis. As a result, the number of exploratory analyses conducted (Tables III and IV) likely produced some type I errors. Second, because the sample size was small, this may have been the reason for only obtaining approaching significance level findings for some biomarkers. A larger sample size can help clarify the results. Third, because the sample was naturalistic and included veterans with other comorbid non-PTSD and non-alcohol use disorders and concurrent medication use (Table I), such broad inclusion/exclusion criteria may have contributed to some of the nonsignificant findings given in Tables III and IV. A future study with more stringent delineation of primary psychiatric disorder, substance use disorder, and medication use criteria may help clarify the relationship between alcohol use biomarkers and cognitive performance in veterans specifically with alcohol dependence and PTSD.

Fourth, because most EtG and EtS values were undetectable, dichotomizing the continuous variables of EtG and EtS most likely resulted in a loss of statistical power.^{60–62} As a result, the nonsignificant results for EtG and EtS (Tables III and IV) may have been due to a “floor effect.” A future study with more accurate EtG and EtS detection at levels below the current threshold can help maintain these variables as continuous when conducting data analyses. Finally, a more comprehensive neurocognitive battery evaluating other cognitive domains (e.g., visuospatial memory, attentional bias, and executive function) may add further information on the relationship between alcohol use biomarkers and other cognitive domains.

CONCLUSIONS

This analysis of alcohol use biomarkers and cognitive performance in a pilot clinical trial among veterans with alcohol dependence and PTSD found that indirect biomarkers, such as GGT and AST, may have a specific role in identifying those veterans who show a change in visual attention and verbal memory performance. However, direct biomarkers may not have a similar role. Future directions to confirm or refute these findings include the use of a larger sample size, a more comprehensive neurocognitive battery, and recruiting a sample with more stringent inclusion/exclusion criteria.

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

Steven L. Batki, David L. Pennington, Brooke Lasher, Thomas C. Neylan, Thomas Metzler, Angela Waldrop, Kevin Delucchi, and Ellen Herbst

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

From the San Francisco, California; San Francisco Veterans Affairs Medical Center (SLB, DLP, BL, TCN, TM, AW, EH), San Francisco, California; Addiction Research Program (SLB, DLP, BL, TCN, TM, AW, EH), Northern California Institute for Research and Education (NCIRE), San Francisco, California; and Department of Psychiatry (SLB, TCN, TM, AW, KD, EH), University of California, San Francisco, California.

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Reprint requests: Steven L. Batki, MD, UCSF Department of Psychiatry, Substance Abuse Programs and Addiction Research Program, San Francisco VA Medical Center (116-E), 4150 Clement St, San Francisco, CA 94121; Tel.: 415-221-4810, ext:3671; Fax: 415-750-2187; E-mail: steven.batki@ucsf.edu

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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

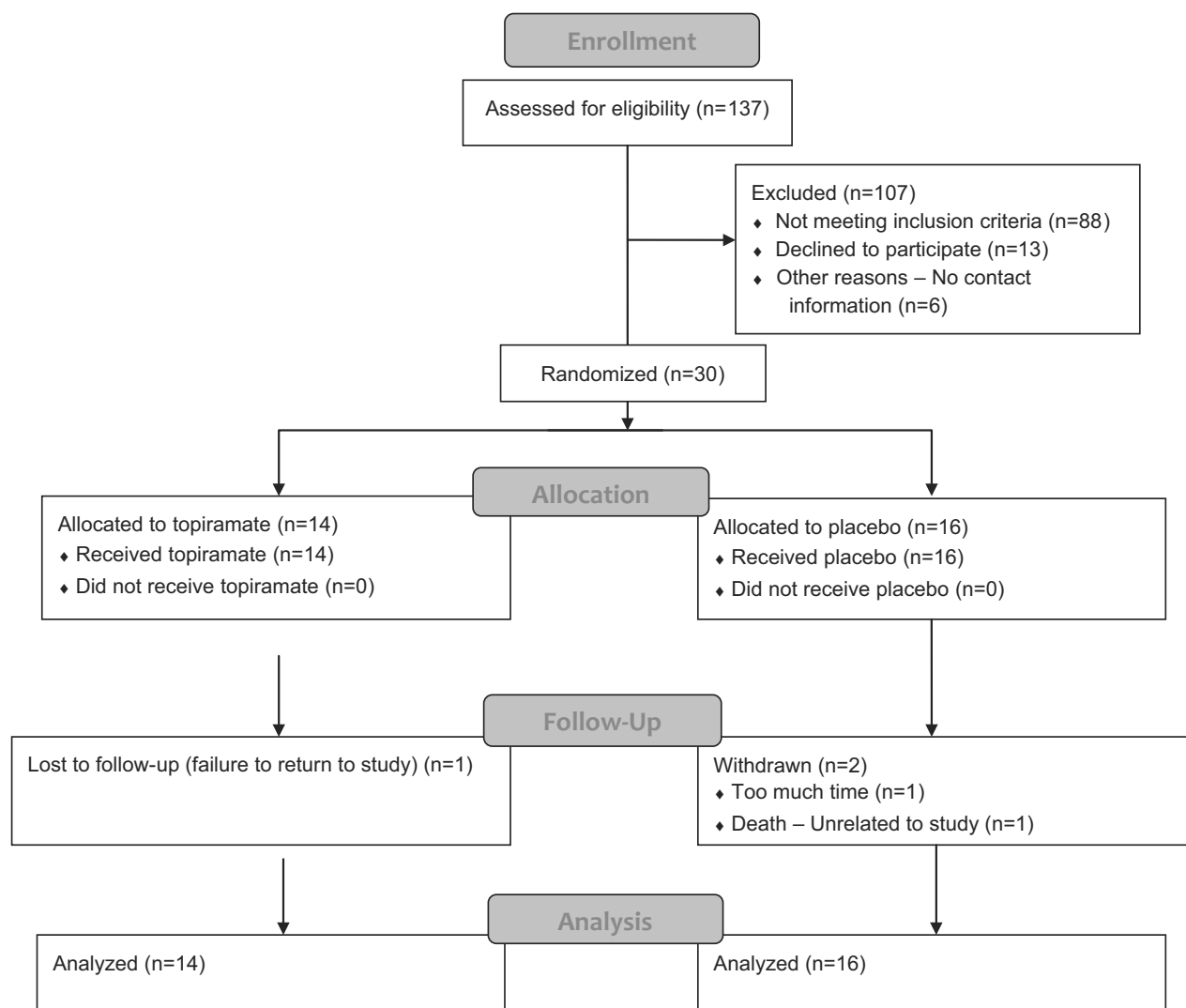


Fig. 1. CONSORT flow diagram.

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.

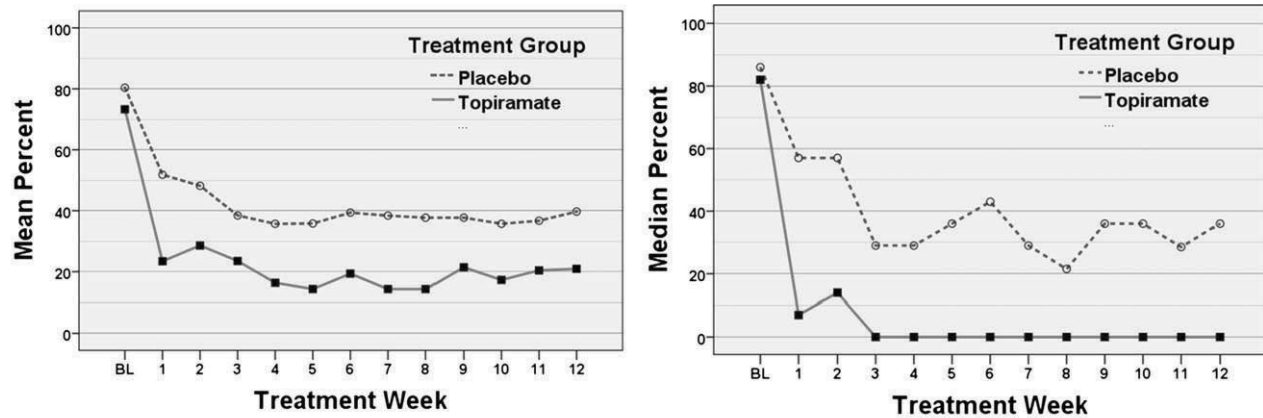
PTSD Symptom Outcome. Univariate analysis revealed a significant reduction within TOP in PTSD symptom severity as measured by the PCL total score and all 3 subscale scores from baseline through week 12 (Table 2). When compared to PLA, there were trends for main effects of treatment on PCL-total, $F(1, 48) = 2.81$, $p = 0.100$, 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		IRR (β)	95% CI	% Δ	TOP		PLA	%Diff.
		Mean $\pm$ SD	Weeks 1 to 12 Avg.				Weeks 1 to 12 Avg.	Mean $\pm$ SD		
Alcohol consumption										
%DD	73.3 $\pm$ 30.3	19.5 $\pm$ 34.2	19.5 $\pm$ 34.2	0.019	0.82 to 0.98	-74	19.5 $\pm$ 34.2	39.7 $\pm$ 36.5	0.38 ^a	0.15 to 0.94
%HDD	58.5 $\pm$ 33.7	11.1 $\pm$ 27.1	11.1 $\pm$ 27.1	0.035	0.76 to 0.99	-81	11.1 $\pm$ 27.1	16.8 $\pm$ 26.3	0.56	0.17 to 1.87
Std. drinks per week	52.4 $\pm$ 34.2	8.7 $\pm$ 19.0	8.7 $\pm$ 19.0	0.028	0.75 to 0.98	-83	8.7 $\pm$ 19.0	19.3 $\pm$ 30.5	0.43	0.16 to 1.17
Drinks per DD	11.1 $\pm$ 6.1	1.9 $\pm$ 3.3	1.9 $\pm$ 3.3	0.008	0.74 to 0.96	-83	1.9 $\pm$ 3.3	4.8 $\pm$ 6.5	0.45	0.20 to 1.02
PTSD symptoms										
PCL total score	57.1 $\pm$ 13.4	42.3 $\pm$ 16.4	42.3 $\pm$ 16.4	0.001	-1.84 to -0.62	-26	42.3 $\pm$ 16.0	49.0 $\pm$ 16.5	(-9.01)	-19.8 to 1.80
PCL B-reexperiencing	15.9 $\pm$ 5.2	12.3 $\pm$ 5.5	12.3 $\pm$ 5.5	0.026	-0.53 to -0.04	-23	12.3 $\pm$ 5.4	14.3 $\pm$ 5.5	(-2.75)	-6.57 to 1.08
PCL C-avoidance	23.9 $\pm$ 5.7	17.6 $\pm$ 7.4	17.6 $\pm$ 7.4	0.002	-0.73 to -0.20	-26	17.6 $\pm$ 7.2	19.9 $\pm$ 6.9	(-3.07)	-8.61 to 2.48
PCL D-Arousal	17.3 $\pm$ 4.8	12.4 $\pm$ 4.9	12.4 $\pm$ 4.9	0.000	-0.71 to -0.25	-28	12.4 $\pm$ 4.9	14.9 $\pm$ 5.0	(-3.23)	-6.74 to 0.29
Alcohol craving										
OCDS total	16.93 $\pm$ 8.70	5.53 $\pm$ 6.55	5.53 $\pm$ 6.55	0.002	-1.48 to -0.43	-67	5.53 $\pm$ 6.55	11.08 $\pm$ 8.12	(-7.02)	-13.1 to -0.91

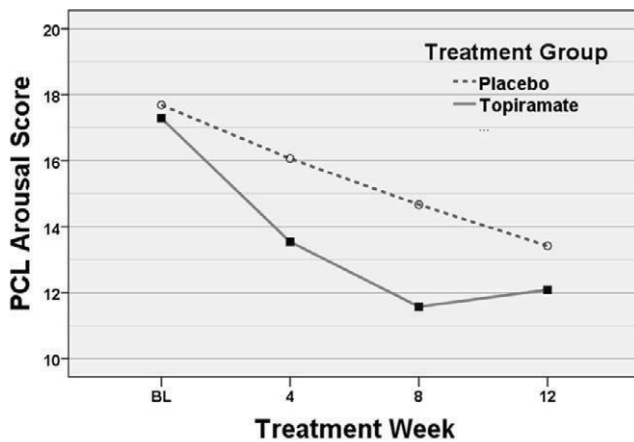
%DD, percent drinking days; %HDD, percent heavy drinking days (>4 standard alcoholic drinks for men, >3 standard alcoholic drinks for women; standard alcoholic drink is defined as containing 13.6 g of pure alcohol); CI, confidence interval; IRR, incidence rate ratio (average relative change in outcome 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.

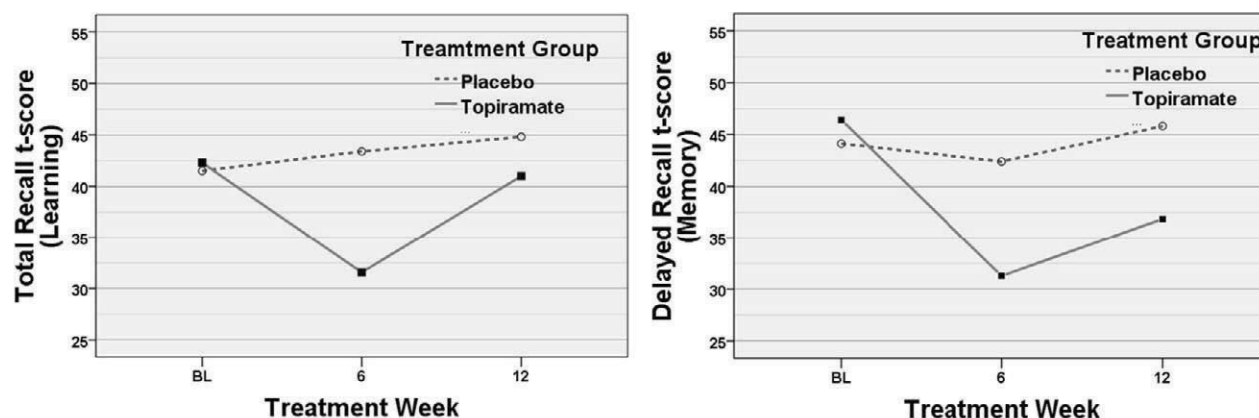
HVLT-R Total (Learning). There was a significant treatment by week interaction for HVLT-R total recall, $F(1, 21) = 6.63, p = 0.018$ (Fig. 4). Follow-up univariate analyses indicated that TOP decreased in performance between baseline and week 6, $F(1, 13) = 15.04, p = 0.002$, and then significantly regained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

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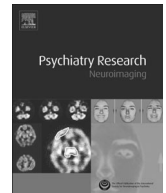
DISCLOSURE

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

David Louis Pennington^{a,f,*}, Christoph Abé^c, Steven Laszlo Batki^{a,d,f},
Dieter Johannes Meyerhoff^{b,e,f}

^a Addiction Research Program, Veterans Affairs Medical Center, San Francisco, CA, USA

^b Center for Imaging of Neurodegenerative Diseases, Veterans Affairs Medical Center, San Francisco, CA, USA

^c Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

^d Department of Psychiatry, University of California, San Francisco, CA, USA

^e Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

^f Northern California Institute for Research and Education, San Francisco, CA, USA

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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 (mI) 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 mI 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 (mI), creatine- (Cr), and choline-containing compounds (Cho) serve as intracellular

* Corresponding author at: Addiction Research Program, Veterans Administration Medical Center, 4150 Clement Street, 116P, San Francisco, CA 94121, USA.
Tel.: +1 415 221 4810x4504; fax: +1 415 750 2187.

E-mail address: david.pennington2@va.gov (D.L. Pennington).

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.

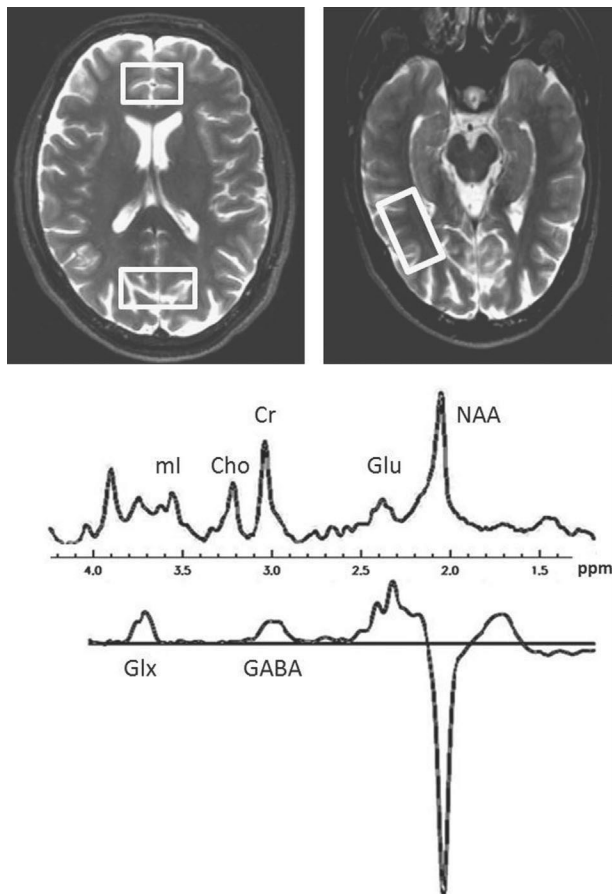


Fig. 1. Locations of volumes of interest on T2-weighted magnetic resonance Images (left: ACC and POC; right: TEMP). Examples of analyzed stimulated echo acquisition mode spectrum (top) and J-edited spectrum (bottom) from the POC. Spectra shown on different vertical scales for clarity. Major metabolite 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 1Patient characteristics (mean $\pm$ 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 $\pm$ 13.9	35.4 $\pm$ 10.5	36.3 $\pm$ 12.4	< 0.001	0.001	NS
Education [years]	14.6 $\pm$ 2.1	15.1 $\pm$ 2.4	15.8 $\pm$ 2.2	NS	NS	NS
Smoker <i>n</i> (%)	5 (50)	8 (29)	5 (25)	–	–	–
Insomnia Severity Index	16.7 $\pm$ 7.3	14.8 $\pm$ 6.4	2.5 $\pm$ 2.6	NS	< 0.001	< 0.001
Beck depression Inventory	23.7 $\pm$ 10.5	14.4 $\pm$ 10.1	1.1 $\pm$ 2.0	0.009	< 0.001	< 0.001
Beck Anxiety Inventory	21.3 $\pm$ 12.9	12.8 $\pm$ 13.3	1.1 $\pm$ 2.9	0.057	< 0.001	0.003
AUDIT Score	25.1 $\pm$ 9.3	4.6 $\pm$ 6.2	0.9 $\pm$ 1.3	< 0.001	< 0.001	NS
Total# of alcoholic drinks ^a						
last week	39 $\pm$ 34	4 $\pm$ 8	2 $\pm$ 4	< 0.001	< 0.001	NS
last 30 days	169 $\pm$ 81	17 $\pm$ 34	10 $\pm$ 16	< 0.001	< 0.001	NS
last 90 days	588 $\pm$ 291	50 $\pm$ 101	29 $\pm$ 47	< 0.001	< 0.001	NS
CAPS Total	78.6 $\pm$ 17.9	55.2 $\pm$ 18.3	2.7 $\pm$ 4.5	0.000	< 0.001	< 0.001
Intrusion	19.5 $\pm$ 7.4	14.8 $\pm$ 6.6	0.5 $\pm$ 1.6	0.036	< 0.001	< 0.001
Avoidance	34.0 $\pm$ 6.2	19.3 $\pm$ 9.2	1.1 $\pm$ 2.8	< 0.001	< 0.001	< 0.001
Arousal	25.1 $\pm$ 6.6	21.0 $\pm$ 7.8	1.1 $\pm$ 2.1	NS	< 0.001	< 0.001
ACC GM-tissue (% of VOI) ^b	49 $\pm$ 3	45 $\pm$ 4	48 $\pm$ 3	0.009	NS	0.013
POC GM-tissue (% of VOI) ^b	64 $\pm$ 3	62 $\pm$ 3	63 $\pm$ 4	NS	NS	NS
TEM GM-tissue (% of VOI) ^b	52 $\pm$ 7	44 $\pm$ 6	45 $\pm$ 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 $\pm$ 0.89 (10)	5.39 $\pm$ 0.83 (23)	5.92 $\pm$ 0.81 (14)	NS (0.36)	0.024 ^a (0.99)	0.059 ^a (0.64)
	Cr	3.72 $\pm$ 0.80 (8)	4.08 $\pm$ 0.80 (24)	4.44 $\pm$ 0.80 (14)	NS (0.45)	0.049 ^a (0.90)	NS (0.45)
	Cho	1.03 $\pm$ 0.25 (9)	1.32 $\pm$ 0.25 (24)	1.34 $\pm$ 0.25 (14)	0.004 (1.16)	0.005 (1.25)	NS (0.08)
	ml	2.68 $\pm$ 0.66 (9)	4.08 $\pm$ 0.66 (24)	3.93 $\pm$ 0.66 (14)	< 0.001 (2.13)	< 0.001 (1.90)	NS (0.23)
	Glu	3.06 $\pm$ 0.78 (9)	4.13 $\pm$ 0.78 (24)	4.38 $\pm$ 0.78 (14)	0.001 (1.38)	< 0.001 (1.70)	NS (0.32)
	GABA	1.43 $\pm$ 0.32 (9)	1.14 $\pm$ 0.31 (22)	1.10 $\pm$ 0.32 (12)	0.027 ^a (0.92)	0.023 ^a (1.05)	NS (0.13)
POC	NAA	5.50 $\pm$ 0.59 (10)	5.67 $\pm$ 0.59 (24)	5.64 $\pm$ 0.59 (16)	NS (0.29)	NS (0.24)	NS (0.05)
	Cr	4.46 $\pm$ 0.60 (10)	4.38 $\pm$ 0.56 (24)	4.28 $\pm$ 0.54 (16)	NS (0.14)	NS (0.32)	NS (0.18)
	Cho	0.82 $\pm$ 0.11 (10)	0.78 $\pm$ 0.11 (24)	0.75 $\pm$ 0.11 (16)	NS (0.38)	NS (0.65)	NS (0.27)
	ml	3.00 $\pm$ 0.58 (10)	3.34 $\pm$ 0.57 (24)	3.18 $\pm$ 0.58 (16)	NS (0.59)	NS (0.31)	NS (0.28)
	Glu	3.92 $\pm$ 0.50 (10)	4.17 $\pm$ 0.50 (24)	4.17 $\pm$ 0.50 (16)	NS (0.50)	NS (0.50)	NS (0.00)
	GABA	1.88 $\pm$ 0.31 (10)	1.67 $\pm$ 0.31 (23)	1.90 $\pm$ 0.31 (16)	NS (0.68)	NS (0.06)	0.026 ^a (0.75)
TEMP	NAA	4.58 $\pm$ 0.66 (10)	5.65 $\pm$ 0.66 (23)	5.52 $\pm$ 0.66 (14)	< 0.001 (1.62)	0.001 (1.42)	NS (0.20)
	Cr	3.53 $\pm$ 0.71 (10)	3.86 $\pm$ 0.70 (23)	3.71 $\pm$ 0.71 (14)	NS (0.47)	NS (0.25)	NS (0.21)
	Cho	0.81 $\pm$ 0.15 (10)	0.96 $\pm$ 0.15 (23)	0.94 $\pm$ 0.15 (14)	0.014 ^a (0.97)	0.058 ^a (0.84)	NS (0.13)
	ml	2.69 $\pm$ 0.59 (10)	3.09 $\pm$ 0.59 (23)	3.12 $\pm$ 0.59 (14)	0.082 ^a (0.68)	0.092 ^a (0.73)	NS (0.05)
	Glu	2.56 $\pm$ 0.83 (10)	3.43 $\pm$ 0.77 (23)	2.73 $\pm$ 0.76 (14)	0.009 (1.08)	NS (0.21)	0.009 (0.91)
	GABA	1.23 $\pm$ 0.23 (6)	1.10 $\pm$ 0.22 (22)	1.22 $\pm$ 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 3Significant ($p < 0.04$) 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

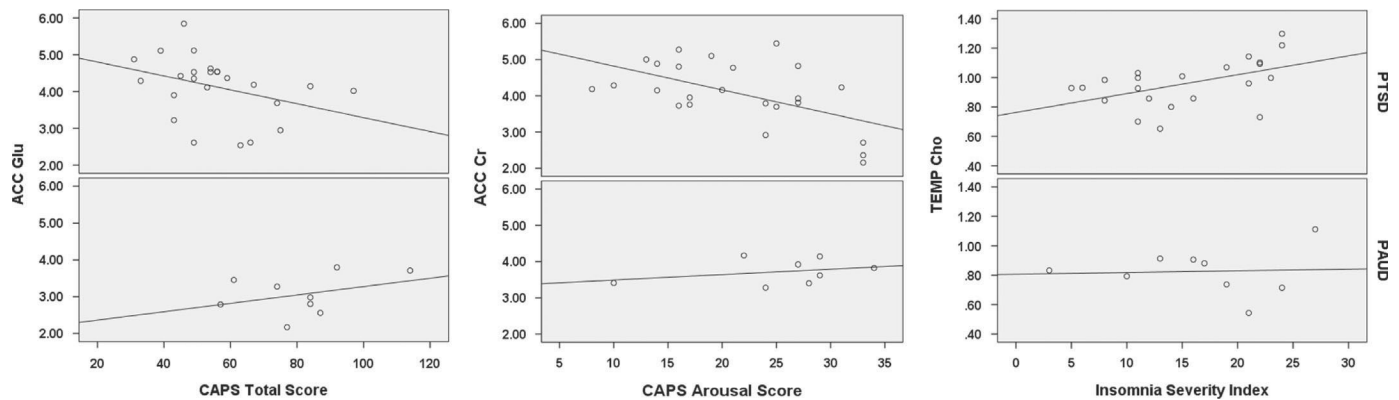


Fig. 2. Examples of different relationships between metabolite concentrations, PTSD symptomology and sleep problems by PTSD group.

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.

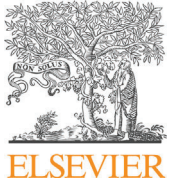
Acknowledgments

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Comparative utilization of pharmacotherapy for alcohol use disorder and other psychiatric disorders among U.S. Veterans Health Administration patients with dual diagnoses



Anna D. Rubinsky^{a, b, *}, Cheng Chen^b, Steven L. Batki^{c, d}, Emily C. Williams^{e, f}, Alex H.S. Harris^{a, b}

^a Veterans Affairs (VA) Substance Use Disorder Quality Enhancement Research Initiative (SUD QUERI), VA Palo Alto Health Care System, 795 Willow Road (MPD 152), Menlo Park, CA 94025, USA

^b Center for Innovation to Implementation (Ci2i), Health Services Research and Development, VA Palo Alto Health Care System, 795 Willow Road (MPD 152), Menlo Park, CA 94025, USA

^c Addiction Psychiatry Research Program, San Francisco VA Medical Center, 4150 Clement Street, San Francisco, CA 94121, USA

^d Department of Psychiatry, University of California, San Francisco, 401 Parnassus Ave., San Francisco, CA 94143, USA

^e Seattle Center of Innovation for Veteran-Centered and Value-Driven Care, Health Services Research and Development (S-152), VA Puget Sound Health Care System, 1660 S. Columbian Way, Seattle, WA 98108, USA

^f Department of Health Services, University of Washington, Box 357660, Seattle, WA 98195, USA

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ABSTRACT

Patients with alcohol use disorder (AUD) and another co-occurring psychiatric disorder are a vulnerable population with high symptom severity. Such patients may benefit from a full arsenal of treatment options including pharmacotherapy. Receipt of AUD pharmacotherapy is generally very low despite recommendations that it be made available to every patient with AUD, including those with co-occurring disorders. Little is known about pharmacotherapy rates for AUD compared to other psychiatric disorders among patients with dual diagnoses. This study compared rates of pharmacotherapy for AUD to those for non-substance use psychiatric disorders and tobacco use disorder among patients with dual diagnoses in the U.S. Veterans Affairs (VA) healthcare system. VA data were used to identify patients with AUD and another psychiatric disorder in fiscal year 2012, and to estimate the proportion receiving pharmacotherapy for AUD and for each comorbid condition. Among subsets of patients with AUD and co-occurring schizophrenic, bipolar, posttraumatic stress or major depressive disorder, receipt of medications for AUD ranged from 7% to 11%, whereas receipt of medications for the comorbid disorder ranged from 69% to 82%. Among patients with AUD and co-occurring tobacco use disorder, 6% received medication for their AUD and 34% for their tobacco use disorder. Among patients with dual diagnoses, rates of pharmacotherapy for AUD were far lower than those for the comorbid disorders and contrary to evidence that medications for AUD are effective. Additional system-wide implementation efforts to identify and address patient- and provider-level barriers are needed to increase AUD pharmacotherapy in this high-need population.

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Alcohol use disorder (AUD) affects approximately 8.5% of U.S. adults (Grant et al., 2004a) and is associated with substantial societal and personal costs (Schuckit, 2009; Rehm et al., 2014). Excessive alcohol consumption accounts for 10% of deaths among

working-age adults in the U.S. (Stahre et al., 2014) and is estimated to have annual economic costs of more than \$300 billion, primarily due to losses in productivity (Bouchery et al., 2011). Further, AUD exacerbates a wide range of medical and other psychiatric conditions (Schuckit, 2009; Falk et al., 2006; Kelly and Daley, 2013).

Individuals with AUD are twice as likely to have a non-substance use psychiatric disorder, three times as likely to have tobacco use disorder and over 10 times as likely to have a drug use disorder than individuals with no AUD (Falk et al., 2006; Grant et al., 2004b;

* Corresponding author. Veterans Affairs (VA) Substance Use Disorder Quality Enhancement Research Initiative (SUD QUERI), VA Palo Alto Health Care System, 795 Willow Road (MPD 152), Menlo Park, CA 94025, USA.

E-mail address: Anna.Rubinsky@va.gov (A.D. Rubinsky).

Stinson et al., 2005). Such comorbidity can add to symptom severity and result in poorer prognosis and treatment outcomes (Kelly and Daley, 2013; Baca and Yahne, 2009). Patients with AUD and another co-occurring psychiatric disorder may require more intensive, multi-faceted treatment combining pharmacotherapy, psychotherapy and/or behavioral interventions (Kelly and Daley, 2013; Baca and Yahne, 2009; Kessler et al., 2005; Petrakis et al., 2002).

Effective medications are available for AUD (American Society of Addiction Medicine, 2012) and many other psychiatric disorders. Further, although studies of pharmacotherapy among patients with AUD and another co-occurring psychiatric disorder are limited, evidence suggests that efficacious medications for AUD and other psychiatric conditions are effective for dually diagnosed patients (Baca and Yahne, 2009; Tiet and Mautsach, 2007; Yuodelis-Flores et al., 2010). Therefore, AUD and co-occurring psychiatric disorders should be treated concurrently, ideally in the same integrated treatment program (Kelly and Daley, 2013; Baca and Yahne, 2009; National Institute on Alcohol Abuse and Alcoholism, 2007 (October 2008 medications update); O'Brien et al., 2004).

Although pharmacotherapy is widely recognized as a critical component of evidence-based care for AUD based on its effectiveness for reducing drinking and associated decreases in health care utilization and costs (Baser et al., 2011; Mark et al., 2010), only 3–10% of individuals with AUD receive medication treatment, depending on the healthcare system (Mark et al., 2009; Thomas et al., 2013). The largest integrated healthcare system in the U.S., the Veterans Affairs healthcare system (VA), has implemented nationwide clinical practice guidelines that specify that pharmacotherapy options should be discussed with all patients with AUD and offered if not contraindicated (Department of Veterans Affairs (VA) and Department of Defense (DoD), 2009b). These guidelines explicitly state that for patients with AUD and another co-occurring psychiatric disorder, AUD medications should be offered in addition to indicated medications for the co-occurring disorder(s). Further, the VA Handbook stipulates that other psychiatric disorders “must never be a barrier to treating patients with substance use disorders” (Department of Veterans Affairs, 2008).

While rates of guideline-congruent pharmacotherapy for AUD among patients with other co-occurring psychiatric disorders are unknown, as of 2009, only 3.4% of all VA patients with documented AUD received a medication approved by the U.S. Food and Drug Administration (FDA) for treatment of AUD (Harris et al., 2012) and 1.0% received topiramate, which has recently been shown to be effective for reducing drinking (Arbaizar et al., 2010; Blodgett et al., 2014) and is being used increasingly to treat AUD (Del Re et al., 2013). In contrast, the vast majority of VA patients with schizophrenia (82%), bipolar disorder (75%), posttraumatic stress disorder (PTSD; 60%), and major depressive disorder (95%) receive related medications (U.S. Government Accountability Office, 2014; Kilbourne et al., 2005; Bernardy et al., 2012; Leslie and Rosenheck, 2003). Possible reasons for this discrepancy are provider perceptions that AUD medications are ineffective or that patients want treatment only for their non-substance use psychiatric disorders (Carey et al., 2000; Harris et al., 2013; Abraham et al., 2009; Thomas and Miller, 2007). However, receipt of medications for tobacco use disorder is relatively high (~40% among smokers) (Gifford et al., 2013), despite inferior efficacy (Jonas et al., 2014; Stead et al., 2012) and some of the same initial implementation barriers to prescribing as for medications for AUD (e.g., medication restrictions, lack of provider training/knowledge) (Harris et al., 2013; Smith et al., 2010).

Little is known about the comparative utilization of pharmacotherapy for AUD and non-substance use psychiatric disorders or tobacco use disorder among patients with dual diagnoses. Patients with AUD and another co-occurring psychiatric disorder may tend

to have the greatest complexity of symptoms, be least likely to engage in psychosocial interventions and benefit most from a full arsenal of treatment options including pharmacotherapy (Kelly and Daley, 2013; Baca and Yahne, 2009; Kessler et al., 2005; Merikangas and Kalaydjian, 2007; Kelly et al., 2012). This study aimed to describe rates of receipt of guideline-congruent medication for AUD compared to non-substance use psychiatric disorders and tobacco use disorder among VA patients with dual diagnoses.

1. Methods

1.1. Sample and data sources

This cross-sectional study included VA patients who had an AUD and a comorbid non-substance use psychiatric disorder or tobacco use disorder documented in their electronic health record (EHR) in fiscal year 2012 (FY12). Diagnoses were identified based on primary or secondary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from the VA's National Patient Care Database (NPCD) inpatient and outpatient files. Socio-demographic characteristics of the study sample were also determined from the NPCD. Any utilization of medications for each condition of interest in FY12 was determined based on inpatient and outpatient pharmacy benefits data from the VA Decision Support System (DSS).

2. Measures

2.1. Clinical diagnoses of interest

AUD was identified using ICD-9-CM codes 291.XX, 303.XX, 305.0–305.03, 535.3 or 571.1 (National Committee for Quality Assurance, 2013). Although alcohol pharmacotherapy is approved by the FDA to treat alcohol dependence, patients with any AUD—including abuse or dependence—were considered the target population for alcohol pharmacotherapy in this study for several reasons. First, alcohol abuse and dependence no longer exist as separate disorders in standard classification of mental health disorders in the U.S. (Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013)). Second, clinical distinction between alcohol abuse and dependence may not be reliable, given that patients often have alternating or concurrent diagnoses of abuse and dependence documented in the EHR (Fernandes-Taylor and Harris, 2012). Finally, the target population of patients with any AUD is consistent with quality measures for alcohol pharmacotherapy being used in the VA Mental Health Information System as well as with previous studies of alcohol pharmacotherapy in VA (Harris et al., 2012; Fernandes-Taylor and Harris, 2012; Iheanacho et al., 2013). Codes for diagnoses of alcohol abuse or dependence “in remission” were included because patients in treatment are sometimes coded this way even though complete, sustained remission has not been achieved.

Co-occurring other psychiatric disorders included: *schizophrenia* (ICD-9-CM 295.XX), *bipolar disorder* (ICD-9-CM 296.0–296.19, 296.4–296.89), *posttraumatic stress disorder* (PTSD; ICD-9-CM 309.81), *major depressive disorder* (ICD-9-CM 296.20–296.25, 296.30–296.35, 298.0, 311) and *tobacco use disorder* (ICD-9-CM 305.1).

2.2. Medication receipt

A dichotomous indicator of any medication receipt for each condition of interest was constructed based on the patient had at least one prescription filled (regardless of quantity, days' supply, or dosage) in FY12. Medications for each condition of interest (Table 1)

Table 1

Included medications for alcohol use disorder (AUD) and other psychiatric conditions.

AUD	Schizophrenia	Bipolar disorder	Posttraumatic stress disorder	Major depressive disorder	Tobacco use disorder
Disulfiram	Clozapine ^a	Lithium	Fluoxetine	Citalopram	Nicotine
Naltrexone (oral)	Risperidone	Valproate	Paroxetine	Escitalopram	Gum
Extended-release Naltrexone (injection)	Olanzapine	Carbamazepine	Sertraline	Fluoxetine	Inhaler
Acamprosate	Quetiapine	Aripiprazole	Fluvoxamine ^a	Paroxetine	Lozenge
Topiramate ^b	Ziprasidone	Olanzapine	Citalopram ^a	Sertraline	Nasal spray
	Aripiprazole	Quetiapine	Escitalopram ^a	Duloxetine	Patch Bupropion
	Paliperidone ^c	Risperidone	Venlafaxine	Venlafaxine	Varenicline
		Ziprasidone		Bupropion	
		Clozapine ^a		Mirtazapine	
		Haloperidol			
		Oxcarbazepine ^a			
		Lamotrigine			
		Olanzapine/Fluoxetine			

^a Although these medications are recommended for consideration in first-line treatment in some cases, the overall strength of recommendation is less strong; thus, these medications were excluded in sensitivity analyses.

^b Although topiramate was not explicitly recommended in the most recent VA/DoD Clinical Guideline for the Management for substance use disorders (Department of Veterans Affairs (VA) and Department of Defense (DoD), 2009a), it was said to show promise for the treatment of AUD, and evidence of effectiveness (Blodgett et al., 2014; Arbaizar et al., 2010) and utilization in VA (Del Re et al., 2013) has since increased markedly.

^c Paliperidone was approved by the FDA for treatment of schizophrenia subsequent to the VA's most recent guideline for schizophrenia (Veterans Health Administration (VHA), 2001).

were consistent with published VA/DoD Clinical Practice Guidelines (Department of Veterans Affairs (VA) and Department of Defense (DoD), 2009a; Department of Veterans Affairs (VA) and Department of Defense (DoD), 2009b; Department of Veterans Affairs (VA) and Department of Defense (DoD), 2010a; Department of Veterans Affairs (VA) and Department of Defense (DoD), 2010b; Tobacco Use and Dependence Guideline Panel, 2008; Veterans Health Administration (VHA), 2001) except for additional medications included because evidence of effectiveness and adoption followed publication of VA/DoD Guidelines. Medications for non-substance use psychiatric disorders and tobacco use disorder were limited to first-line agents, whereas all possible medications for AUD were included. As a final step, medication lists were reviewed by coauthor SLB to ensure they reflected current prescribing practices for each condition.

2.3. Analyses

Descriptive analyses were used to characterize the overall study sample and subsets of patients with AUD and each of the five co-occurring conditions of interest in terms of socio-demographics. For each subset, we then estimated the proportion of patients who received medications for their AUD and the proportion who received medications for their comorbid disorder. Because prescription fills are not linked to a specific health care visit and therefore are not necessarily preceded by a diagnosis within a specific timeframe, both the diagnoses used to identify candidates for pharmacotherapy and the medication fills data were obtained from a single year. This approach estimates the proportion of patients with a documented diagnosis in the measurement year who received pharmacotherapy for the condition and is commonly used for calculating quality measures for pharmacotherapy utilization (Thomas et al., 2013).

Because some medications recommended for consideration in first-line treatment in the VA/DoD clinical practice guidelines have greater strength of evidence than others, we conducted sensitivity analyses limiting medications for schizophrenia, bipolar disorder and PTSD to those with the strongest overall support (Table 1).

All analyses were conducted using Stata 13 software (StataCorp, 2013). The study received approval and waivers of informed consent and HIPAA authorization from the Stanford University institutional review board and VA Palo Alto Health Care System research

committee.

3. Results

Among 5.78 million VA patients who utilized care in FY12, 393,134 (6.8%) had an AUD documented in their electronic health record in FY12. Of these, 306,315 (78%) also had documentation of a co-occurring non-substance use psychiatric disorder or tobacco use disorder in FY12 and were included in the present study. Included patients were largely male (95%), non-Hispanic white (61%), and over 50 years old (71%) (Table 2). More than a quarter had full coverage of VA services including prescriptions (Table 2). Patient characteristics were generally similar across subsets of patients with each co-occurring condition of interest, though those with co-occurring schizophrenia were less likely to be married and those with comorbid schizophrenia or PTSD were more likely to have full coverage of VA services (Table 2).

Among subsets of patients with AUD and co-occurring schizophrenia, bipolar disorder, PTSD or major depressive disorder, receipt of medications for AUD ranged from 6.8% to 11.1%, whereas receipt of medications for the comorbid psychiatric disorder ranged from 68.5% to 82.3% (Table 3). The greatest discrepancy was found among patients with AUD and co-occurring schizophrenia and least discrepancy among those with AUD and bipolar disorder. Medication fill rates were slightly higher for bipolar disorder (82.3%) than schizophrenia (77.8%) but receipt of medications for co-occurring AUD was considerably less common among those with schizophrenia than those with bipolar disorder (6.8% vs. 11.1%). Among the subset of patients with AUD and co-occurring tobacco use disorder, 6.0% received medications for AUD and 33.9% received medications for tobacco use disorder.

In sensitivity analyses limited to the subset of first-line medications for schizophrenia, bipolar disorder, and PTSD with the strongest support, receipt of pharmacotherapy for these conditions was 5–10 times higher than for AUD: 71.8% vs. 6.5%, 78.1% vs. 11.1%, and 43.9% vs. 8.1%, respectively.

4. Discussion

Among VA patients with AUD and co-occurring schizophrenia, bipolar disorder, PTSD or major depressive disorder documented in the EHR, a large majority (69–82%) received medication for their

Table 2

Characteristics of the study sample by comorbid condition.

	Alcohol use disorder (AUD) and Co-Occurring:					Total sample ^a (N = 306,315)
	Tobacco use disorder (N = 176,287)	Schizophrenia (N = 19,163)	Bipolar disorder (N = 34,430)	Posttraumatic stress disorder (N = 121,630)	Major depressive disorder (N = 172,18)	
Female	7452 (4)	833 (4)	No. (Column %) 3487 (10)	7445 (6)	10,856 (6)	15,221 (5)
Age						
<50	43,682 (25)	4449 (23)	12,737 (37)	47,137 (39)	54,765 (32)	88,329 (29)
50–64	101,958 (58)	12,552 (66)	18,135 (53)	53,034 (44)	90,074 (52)	162,149 (53)
65+	30,647 (17)	2162 (11)	3558 (10)	21,459 (18)	27,341 (16)	55,837 (18)
Race/Ethnicity						
Non-hispanic white ^b	110,153 (62)	8970 (47)	24,038 (70)	72,513 (60)	103,358 (60)	185,844 (61)
Non-hispanic black ^c	42,843 (24)	7986 (42)	6267 (18)	27,252 (22)	41,868 (24)	72,707 (24)
Hispanic	7665 (4)	1203 (6)	1775 (5)	9417 (8)	11,219 (7)	18,293 (6)
Other	3335 (2)	370 (2)	683 (2)	3524 (3)	3898 (2)	6691 (2)
Unknown/Missing	12,291 (7)	634 (3)	1667 (5)	8924 (7)	11,837 (7)	22,780 (7)
Marital Status						
Never married	47,365 (27)	8574 (45)	10,251 (30)	29,619 (24)	45,335 (26)	81,005 (26)
Previously married	75,927 (43)	7328 (38)	15,225 (44)	40,118 (33)	67,049 (39)	120,670 (39)
Married	52,209 (30)	3191 (17)	8848 (26)	51,160 (42)	58,979 (34)	103,028 (34)
Unknown/Missing	786 (<0.5)	70 (<0.5)	106 (<0.5)	733 (1)	817 (<0.5)	1612 (0.5)
VA service coverage						
Full VA coverage	38,207 (22)	7572 (40)	9543 (28)	56,867 (47)	47,031 (27)	82,978 (27)
Service-connected<50%	36,201 (21)	2897 (15)	7019 (20)	26,873 (22)	38,768 (23)	65,379 (21)
Non service-connected	101,874 (58)	8690 (45)	17,867 (52)	37,882 (31)	86,374 (50)	157,944 (52)
Unknown/Missing	5 (<0.5)	4 (<0.5)	1 (<0.5)	8 (<0.5)	7 (<0.5)	14 (<0.5)

^a Total number of patients with AUD and one or more co-occurring disorder of interest.^b Includes patients with documentation of white race only.^c Includes patients with any documentation of Black race.

non-substance use psychiatric disorder, regardless of the condition, whereas only a small minority (7–11%) received medication for their AUD. Depending on the condition, receipt of evidence-based pharmacotherapy was 7–11 times more common for the non-substance use psychiatric disorder than the AUD. Those with comorbid bipolar disorder were most likely to receive medications for their AUD, possibly due to relatively high prevalence of severe AUD among patients with bipolar disorder compared to other non-substance use psychiatric disorders (Grant et al., 2004b; Kessler et al., 2005, 1996). It is also possible that topiramate, which was counted as a medication for AUD but shows some promise as a mood stabilizer, especially for treatment of bipolar depression (Vasudev et al., 2006; Arnone, 2005), was prescribed for bipolar disorder rather than AUD in some cases. Patients with comorbid schizophrenia, which is highly disabling and accounts for a disproportionate share of mental health services (Mueser and McGurk, 2004), were least likely to receive medications for their AUD. Among patients with AUD and co-occurring tobacco use disorder, receipt of pharmacotherapy for AUD was even less common (6%) and receipt of pharmacotherapy for tobacco use disorder was 6 times more likely (40%).

This was the first study to compare medication rates for AUD to medication rates for non-substance use psychiatric and tobacco use disorders among patients with dual diagnoses. Previous studies have found that receipt of medications for AUD is more likely

among patients with a co-occurring non-substance use psychiatric disorder than those without (Harris et al., 2012) but this study demonstrates that, even among such patients, rates are exceedingly low and much lower than medication rates for the comorbid disorders. Results align with findings in the general population that treatment of any type is less likely for AUD than other psychiatric disorders (Kohn et al., 2004; Edlund et al., 2012) and that medications for AUD tend to be underutilized (Mark et al., 2009; Harris et al., 2013; Knudsen et al., 2010; Roman et al., 2011). Findings are similar to those from a post-hoc comparison of receipt of FDA-approved medications for AUD versus receipt of selective serotonin reuptake inhibitors (SSRIs) among VA patients with both AUD and a psychiatric diagnosis for which an SSRI might be indicated (Harris et al., 2010). That study, published in 2010 and based on VA data from 2006 to 2007, found 12-fold higher rates of receipt of SSRIs than AUD medications. Given that the present, more rigorous evaluation shows that a discrepancy in the use of evidence-based pharmacotherapy persists five years later and across several co-occurring psychiatric disorders, further attention and action is warranted to improve prescribing practices for AUD.

Medications for AUD may not be clinically appropriate for all patients and the optimal percentage of patients with AUD who should be using medications has not been established. Nonetheless, the consistently very low rates of receipt of medications for AUD among patients with AUD and co-occurring non-substance use

Table 3

Patients with AUD and another co-occurring psychiatric disorder who received appropriate medications for each condition.

Comorbid condition:	Total N ^a	Medication for AUD	Medication for comorbid condition
Schizophrenia	19,163	6.8%	77.8%
Bipolar disorder	34,430	11.1%	82.3%
Posttraumatic stress disorder	121,630	8.1%	68.5%
Major depressive disorder	172,180	8.2%	76.1%
Tobacco use disorder	176,287	6.0%	33.9%

^a Number of unique VA patients with both AUD and the noted comorbid condition documented in their electronic health record in FY12.

psychiatric disorders or tobacco use disorder suggest that medications for AUD may be severely underutilized even among those who may benefit most. Pharmacotherapy may be an especially crucial treatment option for patients with AUD and another co-occurring psychiatric disorder as such patients tend to have the most severe symptoms and be least likely to engage in psychosocial treatment (Kelly and Daley, 2013; Baca and Yahne, 2009; Kessler et al., 2005; Petrakis et al., 2002). Such patients may have difficulty using traditional alcohol treatment groups and self-help groups in which many patients do not share their experience with co-occurring disorders (Petrakis et al., 2002). Further, given that most patients with AUD and a co-occurring psychiatric disorder already use medications for their comorbid condition, one could reasonably speculate that such patients may tend to be open to pharmacological treatment for their AUD.

Low rates of receipt of medications for AUD persisted despite high rates of receipt of medications for all other, co-morbid, psychiatric conditions. One common perception is that patients with AUD are not interested in medication due to a total abstinence-based orientation taught by many mutual-help and specialty addictions treatment programs (e.g., 12 step recovery principles). However, medications for AUD do not cause intoxication or physiological dependence, and research suggests that most 12-step participants are in favor of both psychotropic and anti-relapse/anti-craving medication use (Saxon and McCarty, 2005). Further, rates of receipt of medications for tobacco use disorder and all non-substance use psychiatric conditions were similarly high compared to those within VA patients overall (U.S. Government Accountability Office, 2014; Kilbourne et al., 2005; Bernardy et al., 2012; Leslie and Rosenheck, 2003; Gifford et al., 2013), suggesting that patients with co-occurring AUD do not tend to be more averse to psychiatric medications in general. Another perception is that patients are interested in treatment only for their non-substance use psychiatric disorders. However, patients with AUD and co-occurring tobacco use disorder were nearly 6 times more likely to receive medication for their tobacco use disorder than their AUD, suggesting that the exceedingly low rate of pharmacotherapy for AUD is not common to all substance use disorders but may be unique to AUD. Further, a previous study found that nearly 30% of VA patients with a documented opioid use disorder receive opioid agonist therapy (Oliva et al., 2013).

The large discrepancies in receipt of medications for AUD compared to other comorbid psychiatric disorders cannot be explained by differences in the effectiveness or side effects of available medications. Based on recent meta-analyses of the efficacy of medications for AUD, the number needed to treat (NNT) to prevent return to any drinking ranged from 2 to 20 depending on the particular drug (Blodgett et al., 2014; Jonas et al., 2014; Skinner et al., 2014). The efficacy of medications for non-substance use psychiatric conditions compared to placebo is similar, with NNTs generally ranging from 4 to 20 (Leucht et al., 2013; Selle et al., 2014; Stein et al., 2006; Williams et al., 2000; Hansen et al., 2008). Medications for tobacco use disorder have lower efficacy than those for AUD: an NNT of 33–50 would be needed to produce one successful abstainer at 1 year (Stead et al., 2012). Medications for AUD, as with other classes of psychiatric medications, have particular contraindications and side effects depending on the specific drug. However, given the variety of efficacious medications for AUD, it is likely that at least one would be well tolerated by most patients.

Findings from the present study suggest that despite recent efforts in VA to promote coordinated care for substance use disorders, including updated clinical guidelines recommending encouragement of pharmacotherapy for AUD when not contraindicated (Department of Veterans Affairs (VA) and Department of Defense (DoD), 2009b) and metrics for monitoring access to

pharmacotherapy (Trafton et al., 2013), rates of prescribing remain very low, even among patients with other co-occurring psychiatric disorders who may benefit most. A previous study of barriers to use of pharmacotherapy for AUD in VA identified perceived low patient demand, pharmacy procedures or formulary restrictions, and lack of provider knowledge regarding medication availability, efficacy and safety as top barriers (Harris et al., 2013). Restricted provider access to two AUD medications, acamprosate and extended-release naltrexone, may have served as an important intentional barrier to prescribing in the present study. The addition of these medications to the VA formulary in FY14 may promote provider utilization of pharmacological treatment for AUD; however, preliminary data suggest that fill rates for these medications remain very low. From FY12 to FY14, rates of acamprosate and extended-release naltrexone among all VA patients with diagnosed AUD increased from 0.4% to 0.6% and from 0.2% to 0.4%, respectively.

Additional efforts are likely needed to educate providers about the efficacy of pharmacotherapy for AUD and encourage a disease model of addiction whereby alcohol dependence is seen as a chronic illness that requires treatment, including consideration of pharmacotherapy, even in the absence of patient request or interest (Harris et al., 2013; Oliva et al., 2011; McLellan et al., 2000). Based on the high rates of pharmacotherapy for non-substance use psychiatric disorders, it is unlikely that providers consider medications for these disorders optional or encourage them only when prompted by patient interest. Rates of receipt of medications for AUD have been shown to vary widely (0–12%) across VA facilities (Harris et al., 2012), suggesting that action strategies to facilitate prescribing may be effective and system-wide implementation is crucial. Given the 6-fold higher rates of receipt of medications for tobacco use disorder than AUD and 60% increase in prescription fills for medications for tobacco use disorder in four years (Smith et al., 2010), there may be lessons to be learned from VA initiatives that have been implemented to encourage tobacco pharmacotherapy. Such initiatives have included system-level policies that support nicotine replacement therapy (e.g., clinical decision support and performance measures requiring each smoker be offered medications), integration of treatment for tobacco use disorder into routine care for psychiatric patients as a high prevalence population, and provider education and mentoring around prescribing practices (Hamlett-Berry et al., 2009). Many of the system- and provider-level barriers to treatment of tobacco use disorder that these efforts have addressed (e.g., restrictions on prescribing, lack of provider accountability and training) are common to pharmacological treatment of AUD (Harris et al., 2013; Oliva et al., 2011).

This study is purely descriptive and subject to several limitations. Data on prescription fills do not necessarily reflect use and impart no knowledge of persistence or adherence, which could vary by condition. Records of all medications dispensed by VA pharmacies were included but some VA patients may have obtained medications elsewhere. Treatment outside the VA, including utilization of non-VA pharmacies, may have differed by clinical condition and patient characteristics such as insurance coverage (Stroupe et al., 2013; Voils et al., 2014). While many VA patients engage in addictions treatment in VA, it is possible that some VA patients with AUD may not be comfortable receiving treatment in VA and thus may seek treatment elsewhere. Because both diagnoses and prescription fills are from a single year, this study would not capture prescriptions that were triggered by a diagnosis in FY12 but were not filled until FY13. Patients' preferences and medical contraindications regarding particular medications could not be determined. However, because there are several medications available for each condition, at least one was likely to be appropriate for each condition for most patients. It could also not be determined whether patients with no prescription fill were offered

medications but declined or were not offered medications. However, the consistently low rates of prescription fills for efficacious medications for AUD indicates need for quality improvement irrespective of how often patients were offered such medications given that high rates of disinterest would suggest a role for the provider to better educate patients about pharmacological treatment options. Generalizability of results may be limited outside the VA as diagnostic and prescribing patterns may differ in other health care systems. Although alcohol abuse and dependence no longer exist as separate diagnoses in DSM-5 and clinical distinction has not been reliable historically, it is important to note that rates of prescription fills for alcohol pharmacotherapy would be higher if calculated among patients with alcohol dependence rather than any AUD. A prior study of VA patients found 40% higher rates of prescription fills for alcohol pharmacotherapy among those with documented dependence versus any AUD (4.7% vs. 3.4%) (Harris et al., 2012). However, it is expected that the overall conclusions in this study would be unchanged if only patients with documented alcohol dependence were included. If rates of alcohol pharmacotherapy were 50% higher (or even twice as high) among patients with alcohol dependence, they still be nowhere near as high as medication rates for the co-occurring conditions. On the other hand, this study included all possible medications for AUD but limited medications for all other psychiatric disorders to first-line agents, so that differences in prescription rates would be more pronounced if second-line medications were included across the board. Topiramate, which has some limited evidence of efficacy for use in treating non-substance use psychiatric conditions (Arnone, 2005), may have been prescribed for the comorbid condition in some cases, without knowledge of its effectiveness for treating AUD.

Despite these limitations, this study of all VA patients with clinically recognized AUD and another co-occurring psychiatric disorder in FY12 found that the majority (69–82%) received appropriate medications for their non-substance use psychiatric disorder, whereas only 7–11% received medications for their AUD. Further, medication use for tobacco use disorder was nearly 6 times higher than for AUD among patients with both disorders, despite initially similar barriers to prescribing. The limited use of medications for AUD among VA patients with AUD and another co-occurring psychiatric disorder is inconsistent with these patients' use of psychiatric medications in general and contrary to evidence that medications for AUD are both safe and effective. Because patients with dual diagnoses often have more severe and persistent symptoms, pharmacotherapy may be an especially valuable tool for effective treatment. Findings suggest that multifaceted system-wide efforts to identify and address patient and provider barriers to the use of pharmacotherapy for AUD are needed to increase utilization and improve outcomes in this complex, vulnerable population.

Conflicts of interest

None; none of the authors has any conflict of interest related to this work.

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Contributors

Dr. Rubinsky made substantial contributions to the design of this study, interpretation of the data, and preparation of the manuscript.

Ms. Chen made substantial contributions to the acquisition of and analysis of the data.

Dr. Batki made substantial contributions to the conception and design of this study, and to the revision of the manuscript for important intellectual content.

Dr. Williams made substantial contributions to the interpretation of the data and the revision of the manuscript for important intellectual content.

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

Adrienne J. Heinz, PhD*; David L. Pennington, PhD†‡§; Nicole Cohen, BA*; Brandi Schmeling, MA||; Brooke A. Lasher, BA†‡; Emily Schrodek, BA†‡; Steven L. Batki, MD†‡

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}

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 functioning²⁰ 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

*National Center for Post-Traumatic Stress Disorder, Center for Innovation to Implementation, Palo Alto Veterans Affairs Health Care System, 795 Willow Road, Menlo Park, CA 94025.

†San Francisco Veteran Affairs Medical Center 4150 Clement Street, San Francisco, CA 94121.

‡Department of Psychiatry, University of California San Francisco, 500 Parnassus Avenue, San Francisco, CA 94143.

§Northern California Institute for Research and Education, 4150 Clement Street No. 151NC, San Francisco, CA 94121.

||Palo Alto University, 1791 Arastradero Road, Palo Alto, CA 94304.
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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 sub-optimal 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) criteria⁵⁹ 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-IV⁵⁹ 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 as 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 Battery⁷⁶ 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)	

^aStandardized 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				
Step 1			0.12	
Step 2	PCL—PTSD Symptom Severity	0.35**	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	
Step 2	PCL—PTSD Symptom Severity	0.25*	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				
Step 1			0.17	
Step 2	PCL—PTSD Symptom Severity	0.41**	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				
Step 1			0.22	
Step 2	Average Drinks per Week	0.24*	0.27	0.05
	Alcohol Craving—OCDS	0.34**		
	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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Working Memory Moderates Relations Between Alcohol Demand Characteristics and PTSD Symptoms

Samantha V. Abram, PhD^{1,2,3}

Steven L. Batki, MD^{1,2},

Jennifer Bielenberg, PhD^{1,2},

David L. Pennington, PhD^{1,2,*}

¹San Francisco Veterans Affairs Health Care System (SFVAHCS), San Francisco, California

²Department of Psychiatry, University of California, San Francisco, San Francisco, California

³Sierra Pacific Mental Illness Research Education and Clinical Centers

***Corresponding Author:** David Pennington, David.Pennington2@va.gov, SFVAHCS, 4150

Clement St, San Francisco, California 94121

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Abstract

Objective: Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are highly comorbid with complex and often unclear associations. Working memory deficits may represent a shared mechanism implicated in emotion regulation and control over impulsive alcohol use. Here we test whether working memory abilities and performance on a behavioral economic task influence relations between PTSD symptoms and real-world alcohol consumption. **Methods:** 96 veterans (mean age 50 years; 92% male) completed an Alcohol Purchase Task (APT) and were assessed for PTSD, alcohol use, and working memory at the San Francisco Veterans Affairs Health Care System. We conducted two moderated-mediation models (Hayes PROCESS Model 58) to examine the effects of PTSD symptoms on alcohol use. APT *intensity* (consumption at \$0) and *elasticity* (sensitivity to price change) were entered as mediators and working memory as the moderator in each model. **Results:** Arousal symptoms were directly related to average drinks per week. While APT intensity did not mediate the relationship between PTSD arousal and alcohol use, working memory significantly moderated relations between PTSD arousal and APT intensity and produced a signal for moderation between APT intensity and average drinks per week. Arousal symptoms were also directly related to APT price sensitivity. **Conclusions:** Working memory influenced the extent to which PTSD symptoms impacted over-valuing of alcohol in a laboratory setting and the extent to which alcohol demand characteristics influenced real-world alcohol use. This work highlights working memory as a potential target for interventions geared towards reducing alcohol use in veterans with co-occurring PTSD and AUD.

Keywords: alcohol, PTSD, working memory, alcohol purchase task, behavioral economics

1. Introduction

The field of behavioral economics has become increasingly valuable for understanding the nature of human decision-making, and how decisions can lead to heavy alcohol use and alcohol related problems (MacKillop et al., 2010). Problematic alcohol use does not always occur in isolation --- alcohol disorders are highly comorbid with posttraumatic stress disorder (PTSD; Helzer et al., 1987; Kessler et al., 1995; Kulka et al., 1990), with PTSD symptoms often predicting greater alcohol use (Possemato et al., 2015; Simpson et al., 2014). One theory suggests this comorbidity is driven by the use of substances for self-medication of PTSD symptoms (Leeies et al., 2010; Simpson et al., 2014). Patients with co-occurring PTSD and substance use disorders often have more severe clinical profiles and poorer treatment response (Jacobsen et al., 2001; Schäfer & Najavits, 2007), spawning intervention development targeting this complex population (Sofuoglu et al., 2014). Working memory, an underlying component of future planning and cognitive flexibility (Baddeley, 2003), may represent a common mechanism across these disorders that may inform intervention development. This follows from findings that decision-making among individuals with lower working memory capacity may be more susceptible to acute stress effects (Otto et al., 2013) whereas individuals with high working memory may engage in more future-oriented thinking which aids in the prediction and planning of personal goals (Baird et al., 2011). The aim of the current study is to investigate dynamics between alcohol use, PTSD symptoms, and working memory using a behavioral-economic framework.

Behavioral economics entails the application of economic principles to human decision making (Camerer, 1999). Using this lens, the extreme consumption behaviors observed in substance use disorders can be framed in terms of *reinforcer pathology*, which encompasses two features: (1) the continually high valuation of a reinforcer (i.e., tangible commodity or

experience), and/or (2) heightened preference for immediate consumption of a commodity despite long-term consequences (Bickel et al., 2014). Hypothetical purchase tasks are feasible for assessing persistently high reward valuations, i.e., feature (1) of reinforcer pathology described above (Jacobs & Bickel, 1999; Murphy & MacKillop, 2006), which we focus on in the current study. The Alcohol Purchase Task (APT), in particular, is a self-report measure of estimated alcohol consumption at a fixed set of increasing prices. APT-derived demand characteristics quantify the amount of resources allocated for obtaining alcohol and price change sensitivity (*demand elasticity*; Hursh, 1980). These demand characteristics have been linked with individual differences in weekly consumption, frequency of heavy drinking, alcohol-related problems (MacKillop et al., 2010, 2009; Murphy & MacKillop, 2006), and may predict treatment response to brief alcohol intervention (MacKillop & Murphy, 2007). Alternatively, feature (2) of reinforcer pathology is often studied using delay-discounting paradigms that measure how reward value decreases as a function of delay until reward receipt (Bickel et al., 2011a), and excessive discounting of future rewards is well-documented in addiction (Bickel et al., 2012).

Working memory is integral to future-oriented decision-making and may underlie the heightened discounting observed in addiction. More specifically, working memory allows for the temporary storage and manipulation of information (Baddeley, 2003). The central executive system of working memory is responsible for controlling what information is actively maintained within that limited storage space, keeping relevant information active and inhibiting irrelevant information and/or automatic actions (Miyake et al., 2000). If compromised, one may have reduced attention to more distal possibilities and thus poorer inhibition of prepotent responses, which in turn may increase preference for immediate options (Finn et al., 2014; Hinson et al., 2003; Radu et al., 2011). Computerized working memory training for individuals with addiction

may help to increase preference for delayed rewards (Bickel et al., 2011b) and improve self-regulation (Brooks et al., 2017), suggesting a possible avenue for rehabilitation. We might expect similar relations between working memory and demand elasticity, in cases where reward preference remains high despite increasing costs (reflecting *less* demand elasticity): that is, individuals who are less price sensitive may struggle to simultaneously attend to additional needs (or problematic consequences) as a result of *reduced* working memory capacity.

Working memory deficits have also been documented in PTSD, particularly in the auditory (as opposed to visual) domain (for review, see: Aupperle et al., 2012). Such deficits may be related to prolonged exposure to glucocorticoids following from chronic stress (over periods of weeks to years), which can yield hippocampal atrophy and long-term memory impairments (Gagnon & Wagner, 2016), as well as short-term memory deficits via influence on the prefrontal cortex (Elzinga & Bremner, 2002; Roozendaal, 2002). Further, higher working memory capacity may serve as a protective mechanism against the detrimental effects of stress (Otto et al., 2013). Taken together, the combination of chronic stress and poor working memory may render an individual especially vulnerable during decision-making.

For the current study, we investigated the extent to which working memory affected relations between PTSD symptoms and both alcohol demand and real-world alcohol use, respectively measured by the APT and the Timeline Followback Method (Sobell & Sobell, 1992). We anticipated that APT-derived demand characteristics would mediate the effect of PTSD symptoms on real-world drinking behaviors, following from evidence that demand characteristics mediated relations between posttraumatic stress symptoms and alcohol-related consequences in undergraduates (Soltis et al., 2017; Tripp et al., 2015); specifically, we hypothesized that demand characteristics would be a more proximal predictor of real-world

alcohol use. We also predicted that poorer working memory would moderate the relationship between (1) PTSD symptoms and lab-based alcohol demand, and (2) lab-based alcohol demand and real-world drinking, such that poorer working memory would have a positive relationship with alcohol demand versus a negative relationship between alcohol demand and real-world drinking; our moderation hypotheses stem from notions of working memory/executive functions as protective against automatic cognitive processes (Grenard et al., 2008). This would suggest that working memory is important to both our anticipated behavior and relations between anticipated and actual behavior.

2. Methods

2.1 Participants

Sample demographics are provided in Table 1. Study participants included 96 U.S. military veterans who met DSM-IV symptom criterion for PTSD (Blake et al., 1995) and who were enrolled in one of two randomized clinical trials of topiramate treatment for AUD and PTSD (ClinicalTrials.gov Identifier: NCT01749215, n = 78) or AUD and mild traumatic brain injury (TBI, ClinicalTrials.gov Identifier: NCT01750268, n = 18) at the San Francisco Veterans Affairs Health Care System (SFVAHCS). Of note, assessments for the current study took place before any intervention was received and all participants had to meet DSM-IV symptom criteria for PTSD (Blake et al., 1995). Not all participants from the AUD and PTSD study were evaluated for TBI, thus we were unable to verify TBI status in that population. However, PTSD and TBI frequently co-occur and are representative of the population of veterans seeking treatment for AUD and PTSD at the SFVAHCS and VA at large (Iverson et al., 2012; Reisman, 2016). All participants also met DSM-IV-TR (American Psychiatric Association [APA], 2000) criteria for

current alcohol use disorder and met “heavy” drinking criteria in accordance with NIH/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; National Institute on Alcohol Abuse and Alcoholism, 2007). All participants expressed a desire to reduce alcohol consumption with the possible long-term goal of abstinence. 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, were in acute alcohol withdrawal, or had a legal mandate to participate in alcohol use disorder treatment. Racial distribution among the sample was: 49% Caucasian, 26% black or African American, 16% mixed race, 3% Asian, 1% American Indian/Alaska Native, 5% unknown/not reported. Ethnicity was 20% Hispanic/Latino. The institutional review boards at the University of California, San Francisco, the SFVAHCS, and the Department of Defense approved the study procedures. All participants provided written informed consent and study procedures were carried out at the SFVAHCS in San Francisco, CA.

2.2 Measures

2.2.1 Demographics and Psychiatric Characteristics. We used the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) to diagnose PTSD (for review of the CAPS diagnostic utility, see: Weathers et al., 2001). The CAPS is a structured clinical interview that is divided into symptom clusters that correspond with DSM-IV-TR diagnostic criteria for PTSD, including Criterion B: intrusion (e.g., recurring memories of trauma), Criterion C, avoidance (e.g., avoidance of thoughts, feelings, or places related to the trauma), Criterion D, arousal (e.g., sleeping problems, irritability, anger, anxiety, high startle response). All subjects endorsed a

frequency of at least 1 and severity of at least 2 for each DSM-IV symptom criterion (Blake et al., 1995). Participants were also assessed for PTSD symptom severity with the PTSD Checklist for DSM-IV (PCL; Blanchard et al., 1996), a self-report questionnaire which includes the same subscales capturing arousal, intrusions, and avoidance¹; we used self-reported PCL symptom severity scores for all moderated-mediation analyses given that our other measures (APT and TLFB) were also self-report. Lastly, we estimated socioeconomic status (SES) using the two-factor Hollingshead Scale (Hollingshead, 1957). See Table 1 for CAPS, PCL, and SES distribution details.

2.2.2 Real-world Alcohol Consumption. We evaluated alcohol consumption frequency and amount using the Timeline Followback Method (TLFB; Sobell & Sobell, 1992), a self-report measure that has been found to map onto biological measures of alcohol and illicit substance use (Hjorthøj et al., 2012). Specifically, we measured *average drinks per week* over the past 90 days as our outcome variable (see Table 1); scores were log-transformed to improve normality for all further statistical analyses.

2.2.3 Lab-based Alcohol Demand Characteristics. Demand for alcohol was assessed using the Alcohol Purchase Task (APT; Murphy & MacKillop, 2006), in which participants are presented with a hypothetical situation and asked how many drinks they would purchase and consume at 27 prices (ranging from free to \$20). APT data can be expressed as a demand curve that illustrates consumption as a function of price. Overall consumption and expenditure patterns

(across all subjects) are presented in Figure 1, and are similar to those reported by Amlung et al. (2012).

{Insert Figure 1}

2.2.4 Working Memory. We assessed working memory using the core Working Memory Index subtests from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, 2008), Digit Span and Arithmetic. Scaled scores for the two subscales were averaged to create a composite working memory metric for each subject (see Table 1).

2.3 Data Analysis

2.3.1 Demand for Alcohol. Demand curves were fit to alcohol consumption responses for each participant, using an exponentiated equation described by Koffarnus et al. (2015):

$$Q = Q_0 * 10^{k(e^{-\alpha 10^0 P} - 1)} \quad (1)$$

where Q is consumption of alcohol at price P , Q_0 is derived consumption as alcohol price approaches zero, k reflects the range of consumption in $\log_{10}$ units, and α is demand elasticity. The k parameter was determined using the full sample and held constant across participants; it was calculated as the $\log_{10}$ -transformed average consumption at the lowest price minus $\log_{10}$ -transformed average consumption at the highest price ($k = 2.18$).

This equation was developed as an alternative to the exponential equation proposed by Hursh and Silberberg (2008), as it can accommodate consumption values of zero without having

to omit and replace such values. Importantly, the equation derives independent metrics of *demand intensity* (i.e., consumption at \$0) and *demand elasticity* (i.e., sensitivity to price increases).

After obtaining the demand intensity and elasticity metrics, we used two criterion outlined by Stein et al. (2015) to identify nonsystematic demand functions in specific subjects: (1) the *trend* criterion assumes a non-negligible decrease in consumption from the lowest to highest price, computed as the log-unit reduction in consumption from the first to last price:

$$\Delta Q = \frac{\log Q_1 - \log Q_n}{\log P_n - \log P_1} \quad (2)$$

where ΔQ is the relative change in consumption, Q_1 and Q_n are consumption values for the first and last prices, respectively, and P_1 and P_n are the first and last prices, respectively. We compared computed ΔQ values to a criterion detection limit of 0.025 (as recommended by Stein et al.), with values below 0.025 considered nonsystematic. (2) The *bounce* criterion assesses for frequent trial-to-trial consumption increases, even when the subject has an overall reduction in consumption, i.e., local versus global price effects. The algorithm computes the number of price-to-price consumption increases (or “jumps”) that exceed 25% of initial consumption at the lowest price. The total number of jumps is divided by the number of price increments, and this value is compared to a criterion detection limit of 0.10, which says that nonsystematic data entails jumps at more than 10% of the price increments (also recommended by Stein et al., 2015).

We removed 20 subjects based on the above criteria. The remaining data were log-transformed to improve normality, after which, we removed two subjects with intensity or

elasticity values more than 3.2 standard deviations above or below the mean, and two subjects with intensity values at 2 (reflecting extremely low consumption; total removed subjects = 24, yielding a final N of 96; see Table 1 for APT metric distribution details). We observed good fits for the remaining individual participant data (mean $R^2 = 0.85$; range $R^2 = 0.55$ to 0.99). Examples of subject-specific data fits are presented in Figure 2.

{Insert Figure 2}

2.3.2 Statistical Models. Moderated-mediation analyses were performed using the PROCESS procedure in IBM SPSS Statistics for Windows, Version 24.0 (Hayes, 2012, 2013). As shown in Figure 3, this model tests for direct relations between X and Y (c'), whether M_i mediates relations between X and Y (indirect effects are tested using 5000 bootstrap samples to obtain 95% confidence intervals), and whether variable W moderates relations between X and M_i (a_{li}), and/or relations between M_i and Y (b_{li}).

{Insert Figure 3}

Our models tested whether: (1) log-transformed APT-derived metrics (i.e., intensity and elasticity) mediated relations between PTSD symptoms (i.e., arousal, intrusions, avoidance) and average drinks per week, and if (2) working memory scores moderated relations first between PTSD symptoms and APT-derived metrics, and then between APT-derived metrics and average drinks per week.

Prior to running the moderated-mediation procedure, and in order to isolate potential independent relationships, we conducted a series of pairwise correlations between primary metrics of interest (Table 2). Here we applied a Bonferroni correction to account for the three correlations, i.e., the three PCL subscales ($p = 0.05/3 = 0.02$). Once independent relationships were identified, (only arousal scores were significantly correlated with average drinks per week in the last 90 days, $r(94) = 0.30, p = 0.003$) we constructed two separate moderated-mediation models that included the arousal scale (X), each APT metric ($M_i(a_{li})$), working memory (W), and average drinks per week ($Y(b_{li})$). We initially covaried for age, gender, years of education and SES, given their association to cognitive status and because these variables are frequent predictors of substance use (De Graaf et al., 2002; Eaton et al., 2012; Kessler, 1994; Nolen-Hoeksema, 2004). Gender and SES were not significant predictors in any of the models and were subsequently removed. Lastly, we defined trend-level effects as $p \leq .10$.

3. Results

3.1 Working Memory Moderates Relations between PTSD Symptoms and APT Intensity

We observed a direct relationship between PTSD arousal symptoms and average drinks per week ($\beta(89) = .30, p = .003$; Table 3). We also found that working memory moderated the association between PTSD arousal symptoms and APT intensity (i.e., consumption at \$0), and the association between APT intensity and average drinks per week over the past 90 days at a trend level (Figure 4A, Table 3). However, APT intensity did not mediate relations between arousal and average drinks per week (indirect effects through low, average, and high working memory reported in Table 3). More specifically, Figure 4B shows that lower working memory and higher PTSD arousal symptoms were positively associated with lab-based estimates of consumption at

\$0. Somewhat of a reverse pattern was observed for relations between APT Intensity and average drinks per week, where higher working memory and higher APT Intensity corresponded with greater average drinks per week, although only at a trend level and not significant.

{Insert Figure 4}

3.2 Less Price Sensitivity Predicts More Intense Arousal Symptoms

Compared to the intensity moderated-mediation model, we did not detect significant moderation or mediation effects for the elasticity metric (see Table 4). However, as shown in Figure 5, we found a direct effect between arousal symptoms and elasticity ($\beta(90) = -.17, p = 0.03$), where more negative elasticity values were associated with more intense arousal symptoms.

{Insert Figure 5}

4. Discussion

To our knowledge, this is the first study to test relations between working memory, alcohol demand characteristics, PTSD symptoms, and real-world drinking among veterans. Using two moderated-mediation models, we found that working memory moderated the association between PTSD arousal symptoms and lab-based estimates of alcohol consumption, and working memory moderated the relationship between lab-based estimates and real-world drinking (at a trend level), but lab-based estimates did not mediate relations between arousal symptoms and average drinks per week. Additionally, arousal symptoms directly predicted price sensitivity, irrespective of working memory.

Our primary findings indicate that working memory plays a role in how PTSD symptoms predict lab-based drinking estimates. That is, low working-memory and more intense PTSD symptoms were related to more anticipated alcohol consumption (when cost was not a factor), while high working memory and more intense arousal symptoms were associated with less anticipated alcohol use. These findings suggest that working memory is integral to anticipated top-down control. It is possible that high working memory, i.e., intact executive control, helps integrate information that drinking more when PTSD symptoms are more intense is risky and could lead to more negative outcomes. In comparison, those with poorer executive control may succumb to self-medication tendencies, following from failures to mentally represent and/or incorporate the future negative outcomes associated with drinking more. This follows from theories that working memory supports the mental representation of one's self-regulatory goals, whereby a lack of goal-oriented representations could render self-regulation directionless and more likely to fail (Hofmann et al., 2012).

A pattern (indicated by a trend-level interaction) was also detected for moderation effects on alcohol demand characteristics and real-world drinking, whereby better working memory was associated with better agreement between anticipated and actual drinking. These findings could suggest that working memory is integral to accurate predictions of anticipated top-down control. More specifically, the ability to imagine future experiences may depend on maintaining and utilizing abstract representations of those experiences (Klapproth, 2008), which in turn depend on working memory abilities (Addis et al., 2007). It follows that individuals who can better imagine and maintain representations of the future may have a better sense of how they will behave in real-world situations.

Surprisingly, we did not detect different relations between PTSD symptoms and demand elasticity (i.e., price sensitivity) as a function of working memory ability. While both demand intensity and elasticity involve mentally simulating one's expected consumption of reward, elasticity also involves simultaneously weighing the *cost* of the reward. We might then expect working memory to have a similar if not more substantial relationship with elasticity, if elasticity requires one to monitor and resolve conflicting goals (Barrett et al., 2004). However, while working memory is a foundational domain for executive control, other higher order domains like planning or problem solving may be more sensitive to elasticity, warranting further work in this area. We also note that the current sample is predominantly low SES, and this may have impacted the variability of observed price sensitivities (e.g., income predicts variation in temporal discounting; Anokhin et al., 2011; Green et al., 1996).

Also contrary to expectation, we did not detect a mediation effect for alcohol demand. We anticipated alcohol demand characteristics, i.e., lab-based behavioral indices of drinking, to be more proximal to real-world drinking than PTSD symptoms. These null mediation results diverge from prior reports noting mediation effects for demand intensity (Soltis et al., 2017; Tripp et al., 2015) and elasticity (Tripp et al., 2015) in undergraduate students. Instead, we found evidence for a multiplicative model whereby PTSD symptoms and WM also help explain variation in real-world drinking. One possibility for these null results is that our current model is not comprehensive enough to fully capture the pathways between alcohol demand, PTSD, and real-world drinking. It is likely that other factors, e.g., other executive functioning processes or individual differences in alcohol craving, are critical to the picture. For instance, Tripp et al. (2015) found that craving was a more proximal indicator than demand characteristics when relating post-traumatic stress and alcohol-related consequences. Given the limitations of our

sample size, an important area for future research is to expand our model to account for these additional variables with larger samples.

An important aspect of our results is that real-world drinking and alcohol demand characteristics were correlated with arousal symptoms, but not intrusions or avoidance symptoms. Arousal symptoms reflect difficulties with sleep, irritability or anger, trouble concentrating, hypervigilance, and/or high startle response. A review by Jacobsen et al. (2001) describes how PTSD arousal symptoms show strong overlap with the symptoms of central nervous system (CNS) withdrawal, e.g. alcohol withdrawal, including psychomotor agitation, anxiety, autonomic hyperactivity, and insomnia. They further speculate that PTSD and CNS-withdrawal arousal have additive effects, whereby CNS-withdrawal may exacerbate PTSD symptoms (or make them intolerable); a consequence of compounded anxiety-like symptoms from PTSD and CNS-withdrawal may further encourage self-medication using substances, given that alcohol use can temporarily alleviate anxiety (Kushner et al., 2000). In the current study, more hyperaroused individuals may be especially driven to use alcohol for self-medication (as indicated by a direct association with real-world consumption), and poor working memory may exaggerate their predicted usage (e.g., poor regulatory-goal representation coupled with more internal discomfort leads to more expected drinking).

4.1 Limitations

First, our sample was predominantly male thus limiting our ability to test for gender differences in the mechanisms of interest. Second, given our sample size of $n < 100$, we had limited statistical power to detect mediation and moderation effects. Our mediation analyses may have also been impacted by the cross-sectional nature of the study design (e.g., cross-sectional

mediation analyses may yield biased estimates; Maxwell & Cole, 2007); thus longitudinal assessment is an important area of further inquiry. Lastly, although we focused on AUD and PTSD, veterans with these disorders often present with additional co-morbid disorders (e.g., TBI, chronic pain); because we did not assess for these additional diagnoses in all subjects our analyses were limited to PTSD and AUD symptoms. Future studies may expand on this work by evaluating additionally relevant co-morbid diagnoses.

4.2 Conclusions

In the current study we find that reduced working memory and more intense PTSD arousal symptoms are associated with increases in lab-based estimates of consumption of alcohol (specifically, demand intensity). Further development of valid and generalizable working memory retraining tasks may be especially useful for this population of veterans with co-morbid AUD and PTSD; for instance, prior studies have shown that training for episodic future thinking, i.e., exercises requiring one to vividly imagine future events (Snider et al., 2016), can lead to decreased demand consumption. This represents an important future direction for studies targeting the intersection of PTSD and alcohol use disorders.

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Table 1. Demographic Information

	Mean (SD)
Demographics	
Age, years	50.41 (12.71)
Gender (% male)	92%
Years of education	13.72 (1.83)
Socioeconomic Status	7.85 (2.20)
PTSD Diagnostics	
CAPS criteria B	19.47 (6.03)
CAPS criteria C	31.78 (9.18)
CAPS criteria D	25.44 (5.66)
PTSD Symptom Severity	
PCL Arousal	16.99 (4.18)
PCL Intrusions	15.24 (4.33)
PCL Avoidance	22.12 (5.90)
Real-world Drinking	
Average drinks per week	53.99 (35.42)
APT Demand Characteristics	
Intensity (log)	13.14 (9.37)
Elasticity (log)	0.01 (.82)
Working Memory	
WAIS-IV	9.36 (2.22)

Table 2. Correlation Matrix

	Drinks	Inten	Elast	Arous	Intrus	Avoid	WM	Age	Gend	Edu	SES
Drinks	1										
Inten	.26*	1									
Elast	-.01	-.41***	1								
Arous	.30**	.25*	-.24*	1							
Intrus	.10	.05	-.06	.63***	1						
Avoid	.17 [†]	.08	-.05	.65***	.61***	1					
WM	-.12	-.18 [†]	-.02	-.14	.02	-.08	1				
Age	-.05	-.31**	.40***	-.16	-.04	.03	.02	1			
Gend	.28**	.30**	-.09	.27**	.02	.05	.02	.02	1		
Edu	-.25*	-.34**	.00	.06	.19 [†]	.08	.30**	-.05	-.21*	1	
SES	.20*	.15	.21*	.02	-.19 [†]	.03	-.43***	.05	.17 [†]	-.47***	1

[†] $p \leq 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Abbreviations: *Drink* = average of drinks per week; *Inten* = intensity; *Elast* = elasticity; *Arous* = arousal; *Intrus* = intrusions; *Avoid* = avoidance; *WM* = working memory; *Gend* = gender; *Edu* = years of education, *SES* = socioeconomic status.

Table 3. Hayes PROCESS Model 58: APT Intensity with PCL Arousal

	B (SE)	t-stat	p-value	ΔR^2
Model 1: Predicting <i>APT Intensity</i>				
Arousal Sx	.22 (.08)	2.79	.006	
Working Memory	-.03 (.09)	-.37	.71	
Age	-.27 (.07)	-3.60	.001	
Years of Education	-.32 (.08)	-4.23	<.001	
Arousal Sx x Working Memory	-.23 (.09)	-2.52	.01	.05
Model 2: Predicting <i>Avg Drinks/wk</i>				
Arousal	.30 (.10)	3.01	.003	
APT Intensity	.13 (.12)	1.01	.32	
Working Memory	-.01 (.10)	-.10	.92	
Age	.04 (.10)	.44	.66	
Years of Education	-.19 (.10)	-1.91	.06	
APT Intensity x Working Memory	.22 (.13)	1.67	.10	.03
	Effect (SE)	Lower CI	Upper CI	
Conditional Indirect Effects of <i>APT Intensity</i>				
Low Working Memory	-.03 (.09)	-.19	.16	
Moderate Working Memory	.03 (.03)	-.03	.10	
High Working Memory	-.01 (.05)	-.13	.08	

Model 1: $F_{5,90} = 8.66, p < .001, R^2 = .32$

Model 2: $F_{6,89} = 3.59, p = .003, R^2 = .44$

Note: High, moderate, and low working memory group divisions are for illustration purposes only.

Table 4. Hayes PROCESS Model 58: APT Elasticity with PCL Arousal

	B (SE)	t-stat	p-value	ΔR^2
Model 1: Predicting <i>APT Elasticity</i>				
Arousal Sx	-.17 (.08)	-2.15	.03	
Working Memory	-.06 (.09)	-.68	.50	
Age	.30 (.08)	4.02	<.001	
Years of Education	.05 (.08)	.62	.54	
Arousal Sx x Working Memory	.08 (.09)	.88	.38	.01
Model 2: Predicting <i>Avg Drinks/wk</i>				
Arousal	.32 (.10)	3.22	.002	
APT Elasticity	.11 (.13)	.86	.39	
Working Memory	.01 (.11)	.09	.93	
Age	-.05 (.10)	-.52	.60	
Years of Education	-.25 (.10)	-2.63	.01	
APT Elasticity x Working Memory	.02 (.12)	.21	.83	.00
	Effect (SE)	Lower CI	Upper CI	
Conditional Indirect Effects of <i>APT Elasticity</i>				
Low Working Memory	-.02 (.04)	-.12	.06	
Moderate Working Memory	-.02 (.02)	-.07	.02	
High Working Memory	-.01 (.02)	-.07	.02	

Model 1: $F_{5,90} = 4.70$, $p = .001$, $R^2 = .21$

Model 2: $F_{6,89} = 2.95$, $p = .01$, $R^2 = .17$

Note: High, moderate, and low working memory group divisions are for illustration purposes only.

Figure Captions

Figure 1: Means and standard errors (represented by error bars) for number of consumed drinks (A) and corresponding expenditures (B) at 27 price levels on the APT.

Figure 2: Examples of subject response patterns on the APT. Subject A shows a steeper decline in self-reported consumption as the price increases, suggestive of more price sensitivity; comparatively, subject B shows a shallower consumption pattern with increasing price that indicates less price sensitivity.

Figure 3: Conceptual and statistical diagrams of the moderated-mediation model (Hayes PROCESS Model 58). Figure adapted from Hayes (2013), *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-based Approach*.

Figure 4: (A) Results of moderated-mediation model for APT intensity (i.e., number of self-reported drinks consumed at a price of \$0), arousal symptoms, and average drinks per week. (B) Breakdown of significant and trend-level moderation effects. Individuals with low working memory showed a positive association between arousal symptoms and consumption (*top*), whereas individuals with higher working memory showed a stronger positive association between lab-based and real-world drinking (*bottom*); high and low working memory group divisions are for illustration purposes only.

Figure 5: More intense PTSD arousal symptoms predicted less sensitivity to increasing price (as indicated by more negative APT elasticity values); this result was irrespective of working memory status.

Figure 1. Overall Consumption and Expenditure Patterns on the APT

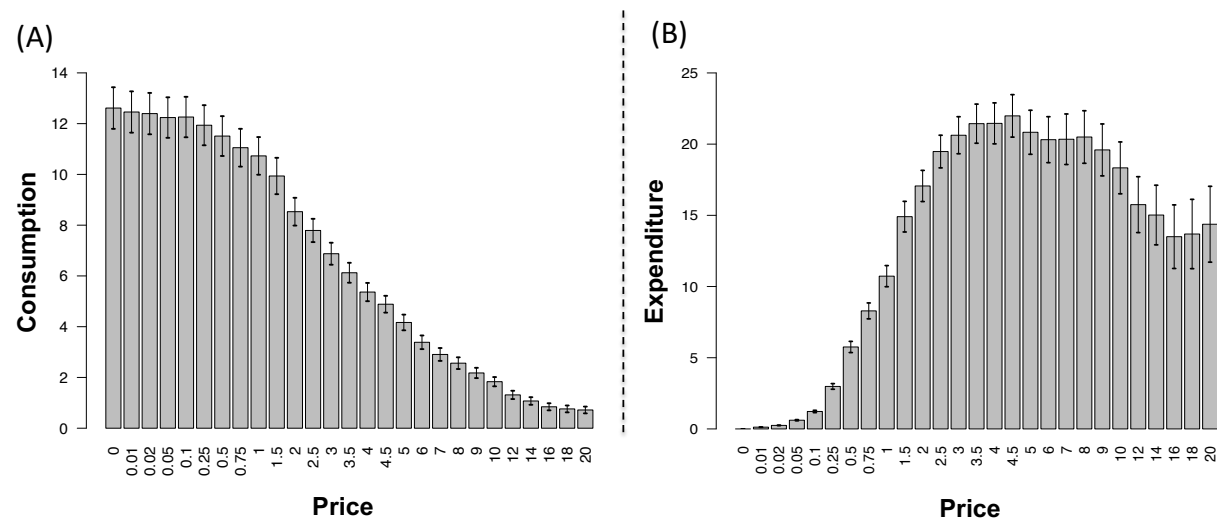


Figure 2. Examples of Price Elasticity

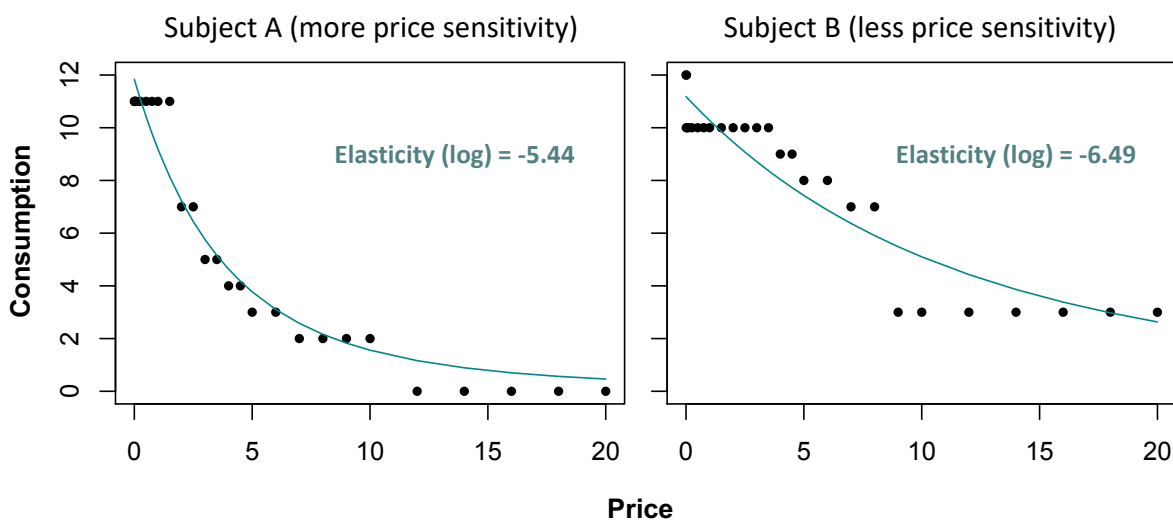
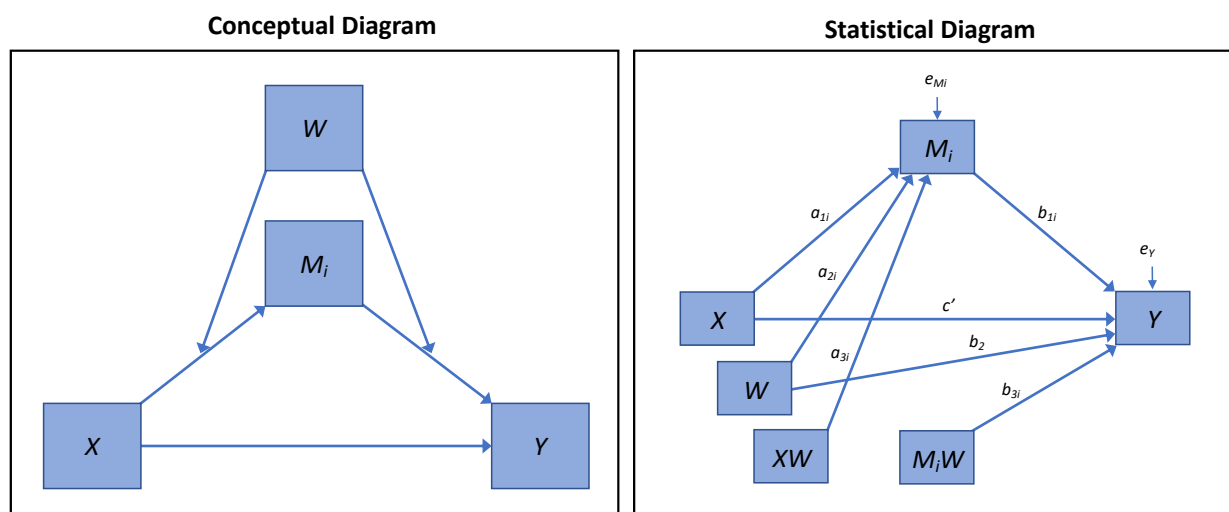


Figure 3. Hayes Process Model 58



Condition indirect effect of X on Y through $M_i = (a_{1i} + a_{3i}W)(b_{1i} + b_{3i}W)$
 Direct effect of X on $Y = c'$

Figure 4. Working Memory Moderates Relations Between Alcohol Demand, Arousal Symptoms, and Alcohol Use

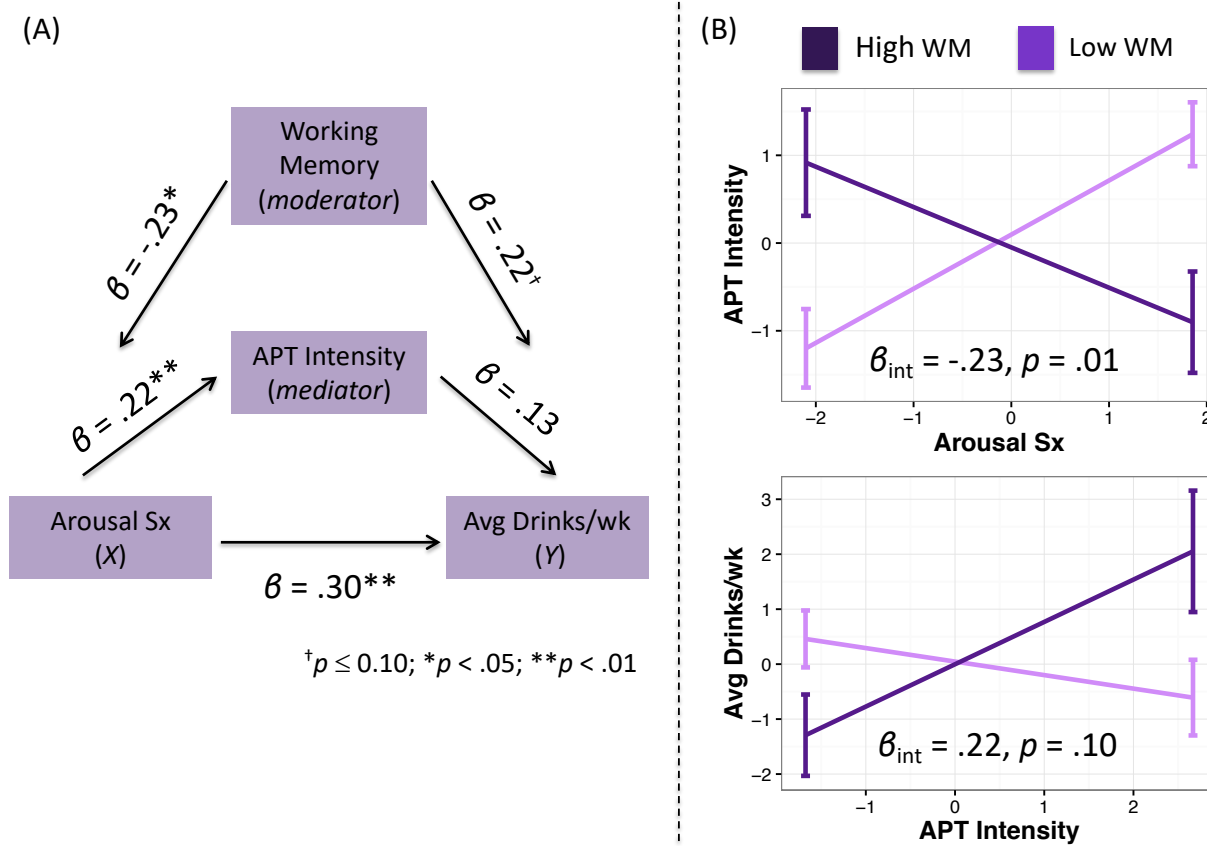
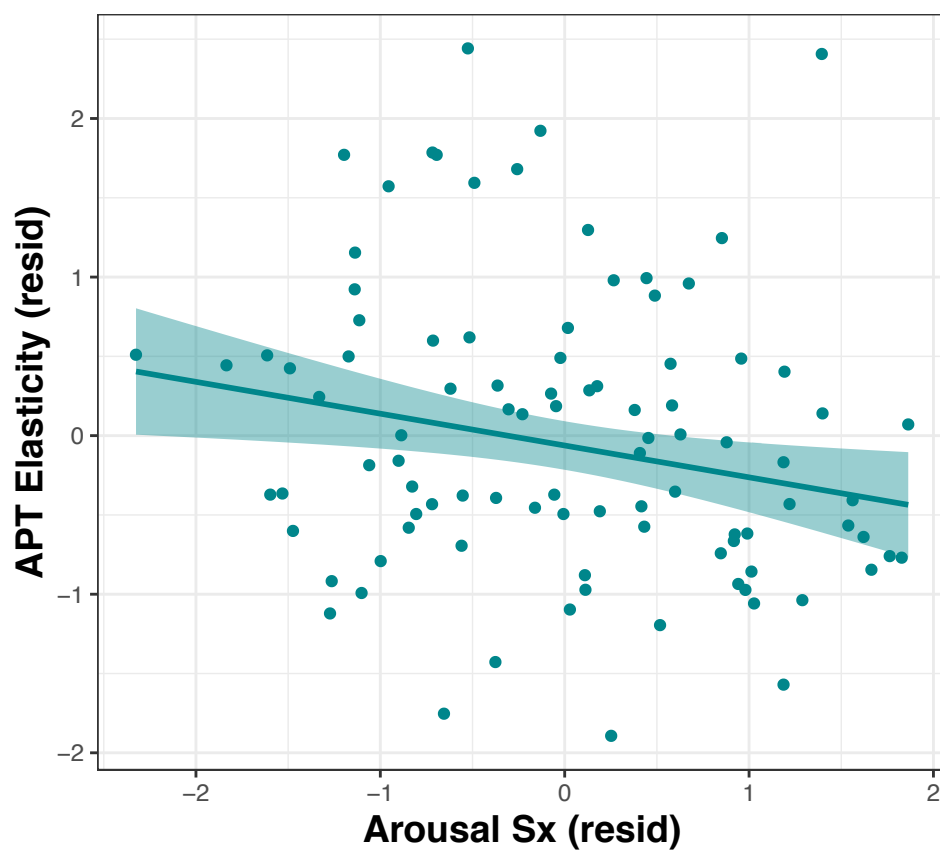


Figure 5. Price Elasticity Predicts Arousal Symptoms

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.

TOPIRAMATE EFFECTS ON SLEEP IN VETERANS WITH PTSD AND ALCOHOL DEPENDENCE: A PILOT CONTROLLED TRIAL

Steven L. Batki, M.D.^{1,2}; David L. Pennington, Ph.D.³; Brooke A. Lasher³; Ellen Herbst^{1,2}, M.D.; Thomas Metzler³; Kevin Delucchi, Ph.D.¹; Anne Richards, M.D.^{1,2}; Adrienne Heinz, Ph.D.⁴; Thomas C. Neylan, M.D.^{1,2}

¹UCSF Department of Psychiatry, San Francisco, CA; ²San Francisco VA Medical Center, ³Northern California Institute for Research and Education, San Francisco, CA, and ⁴Palo Alto VA Health Care System, Menlo Park, CA

Background: Poor sleep quality is associated with heightened PTSD symptom severity and poor treatment outcomes for problematic alcohol use. However, little is known about the effects of topiramate pharmacotherapy on sleep for comorbid PTSD and alcohol dependence (AD). The current investigation sought to examine differences in sleep quality across a 12-week RCT of topiramate vs. placebo.

Methods: We conducted secondary analyses of topiramate vs. placebo in 30 veterans with PTSD/AD. The Pittsburgh Sleep Quality Inventory (PSQI) and the Insomnia Severity Index (ISI) were administered at baseline and throughout the trial to assess sleep quality. Mean/median baseline PSQI and ISI scores were 13.2/14.0 and 17.9/17.0 respectively indicating severely disrupted sleep. We used linear mixed modeling to assess longitudinal change and group differences, covarying for respective baseline scores. Effect sizes (ES) were calculated using average Cohen's d of all cross-sectional post-baseline assessments for each measure.

Results: There were no group-by-time interactions seen on either measure. However, there was a significant main effect for time ($p=.020$) showing a decrease on PSQI scores and a trend ($p=.085$) for decrease on ISI scores over the 12-week trial. There were no significant main effects for group on either measure although the topiramate group had numerically lower scores at each post-baseline assessment with moderate effect sizes (PSQI: $ES=.44$; ISI: $ES=.46$).

We also conducted exploratory analysis examining specific items from the PSQI and PTSD Symptom Checklist (PCL) related to PTSD sleep symptoms. There were no group-by-time interactions or main effects for time. However, the topiramate group had significantly less trouble sleeping due to bad dreams (PSQI-Item 5h) with a strong effect when compared to the placebo group at post-baseline assessments ($p=.017$, $ES=.91$). PCL-Item 2 (disturbing dreams) and 13 (insomnia) were not significant ($p>.162$) but showed moderate group effects ($ES=.45$ and $.39$ respectively).

Conclusions: Involvement in a 12-week RCT of topiramate vs. placebo treatment resulted in decreases in poor sleep quality in those with comorbid PTSD/AD. Topiramate treatment is associated with less trouble sleeping due to bad dreams and may result in better sleep quality overall in this treatment-seeking population. However, due to limited power, a larger trial is warranted to determine clinical significance of topiramate on sleep symptoms in patients with PTSD and AD.

Source of Funding: Department of Defense Grant No: W81XWH-05-2-0094

illicit substance use and violence are associated with a higher rate of risk behaviors, beyond either problem separately. Within a syndemic framework, interventions targeting substance use and trauma should be prioritized to more effectively reduce HIV-related sexual risk behaviors among underserved urban women with and at-risk for HIV.

Financial support: R01DA13564 & T32AT00399.

<http://dx.doi.org/10.1016/j.drugalcdep.2015.07.963>

Smoking and non-alcohol substance use in veterans with PTSD and alcohol use disorder



Steven L. Batki^{1,2,*}, David Pennington², Brooke Lasher², Ellen Herbst², Emily Schrodek², Seghel Yohannes², Jordan McDonald², Brandi Schmeling², Tiffany Wong²

¹ UCSF, San Francisco, CA, United States

² SFVAMC, San Francisco, CA, United States

Aims: To describe co-occurring non-alcohol substance use in veterans with PTSD and alcohol use disorder (AUD) entering controlled trials of topiramate.

Methods: Baseline psychological, alcohol and non-alcohol substance use (NASU) measures are reported for 77 veterans with comorbid AUD and PTSD entering trials of topiramate treatment. PTSD, anxiety, and depression, as well as smoking, non-alcohol substance use (NASU) and NASU disorder diagnoses (NASUDs) were calculated. Subjects with and without smoking or NASU were compared on alcohol use, PTSD, depression, and anxiety severity.

Results: Mean age was 50.4 ± 12.6 , 93.5% were male. 41.6% were Vietnam era and 23.4% were Iraq/Afghanistan veterans. All met criteria for DSM-IV alcohol dependence and PTSD. 58.4% had combat-related PTSD. Mean Clinician Administered PTSD Scale (CAPS) score was 77.9 ± 17.2 ; mean Beck Depression and Anxiety scores were 22.2 ± 12.3 and 24.4 ± 11.5 respectively. During the past 90 days prior to screening, participants had on average 5.4 drinking days per week, 4.5 heavy drinking days per week and consumed 63.7 drinks per week and 12.9 drinks per drinking day. 57.1% were smokers and 41.6% reported NASU in the past 30 days: 36.4% cannabis, 16.9% cocaine, 5.2% amphetamines, and 3.9% opioids. Urine drug screens were positive for cannabis in 23.4%, cocaine in 6.5%, amphetamines in 3.9%, and opiates in 7.6%. 28.6% met SCID NASUD criteria. Compared to nonsmokers, smokers had more drinks per week (72.7 vs. 51.4 , $p = .048$) and more drinks per drinking day (15.7 vs. 9.4 , $p = .011$) in the past 90 days. Smokers did not have higher mean CAPS, BDI, or BAI scores than nonsmokers. Patients with NASU also had more drinks per week (74.1 vs. 53.5 , $p = .05$); but not higher CAPS, BDI or BAI scores than those negative for NASU.

Conclusions: Smoking and other non-alcohol substance use were related with higher amounts of alcohol use but not greater PTSD, depression and anxiety severity in veterans with PTSD and AUD entering pharmacotherapy clinical trials.

Financial support: W81XWH-05-2-0094, W81XWH-11-2-0245, and W81XWH-12-2-0137.

<http://dx.doi.org/10.1016/j.drugalcdep.2015.07.964>

Neuropharmacology of replacement analogs of the designer drug 3,4-methylenedioxymethcathinone



Michael H. Baumann^{*}, Ora Dillon-Carter, Mohammad O. Bukhari, Richard B. Rothman, John S. Partilla

IRP, NIDA, NIH, Baltimore, MD, United States

Aims: The abuse of synthetic cathinones, known as “bath salts” or “research chemicals”, is a public health concern. 3,4-Methylenedioxymethcathinone (methyline) is a popular drug that is now illegal, but new analogs are being marketed as replacements. The purpose of the present investigation was to examine the interaction of methyline analogs with transporters for dopamine (DAT) and 5-HT (SERT).

Methods: β -Keto-*N*-methylbenzodioxolylbutanamine (butylone) and β -keto-*N*-methylbenzodioxolylpentanamine (pentylone) were the analogs studied. In vitro assays were carried out in rat brain synaptosomes to assess drug-induced effects on transporter-mediated uptake and release. In vivo microdialysis was carried out in rat n. accumbens to assess drug-induced changes in extracellular dopamine and 5-HT.

Results: Methyline, butylone and pentylone were fully efficacious uptake blockers at DAT and SERT, but pentylone was more DAT-selective than the other drugs. Methyline was a substrate-type releaser at both transporters, while butylone evoked release at SERT but not at DAT. Pentylone failed to evoke release at either transporter. Intravenous administration of butylone (1–3 mg/kg) increased extracellular 5-HT more than extracellular dopamine in the n. accumbens, while pentylone (1–3 mg/kg) increased both transmitters to the same extent.

Conclusions: Each of the compounds examined displays a unique profile of in vitro transporter activity. Butylone has “hybrid” transporter effects, acting as a substrate at SERT but a blocker at DAT. Pentylone is a DAT-preferring uptake blocker which lacks substrate activity. Overall, the data show that increasing the carbon chain length of methyline creates compounds with reduced releasing activity, converting them to DAT blockers. All of the compounds elevate extracellular dopamine in brain reward circuits, suggesting the drugs possess a significant risk for abuse.

Financial support: This research was generously supported by the Intramural Research Program of NIDA, NIH, DHHS.

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Social processing in aging cocaine smokers



Gillinder Bedi^{1,*}, Ziva D. Cooper¹, Nicholas Van Dam², Margaret Haney¹

¹ Psychiatry, Columbia University and NY State Psychiatric Institute, New York, NY, United States

² Nathan Kline Institute, Orangeburg, NY, United States

Aims: Deficits in social processing, the neurobiological and psychological processes underlying social behavior, are documented in several psychiatric disorders. Although drug abusers often have social problems, little is known about their social processing capacities. We aimed to characterize dimensions of social processing in a growing group of drug users about whom little is known – aging, long-term cocaine smokers – relative to controls. Domains assessed included facial affect recognition and social threat/reward processing. Self and peer reports of daily social function were also collected. We expected social processing to be reduced in cocaine smokers relative to controls.

AN EXAMINATION OF RELATIONS BETWEEN COGNITIVE FUNCTIONING AND ALCOHOL USE AND CRAVING AMONG VETERANS WITH ALCOHOL USE DISORDER AND TRAUMA EXPOSURE

B. Schmeling, A. J. Heinz, D. L. Pennington, N. Cohen, B.A. Lasher, E. Schrodek, S. Yohannes, J. McDonald, and S. L. Batki.

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

Purpose: Cognitive dysfunction is commonly observed among individuals with Alcohol Use Disorder (AUD) and Posttraumatic Stress Disorder (PTSD) and is, in turn, associated with worse treatment outcomes. Accordingly, disruptions in cognitive functioning may be conceptualized as a trans-disease phenomenon representing a potential high-yield target for intervention. The purpose of this study was to examine relations between different cognitive functions and alcohol use and craving among U.S. military Veterans with AUD and trauma exposure.

Methods: Participants were 68 male and female Veterans with AUD (SCID DSM-IV) and trauma exposure (Life Events Checklist) entering treatment to reduce alcohol use. Participants completed measures assessing alcohol use (Timeline Follow Back) and craving (Obsessive Compulsive Drinking Scale), PTSD symptom severity (PCL), and cognitive functioning (executive functioning [Trail Making Test B], risk-taking/impulsivity [Balloon Analogue Risk Task], and verbal learning and memory [Hopkins Verbal Learning Test-Revised]). Three step-wise regressions were performed to assess variance explained by PTSD symptoms and cognitive functions in quantity and frequency of alcohol use and alcohol craving.

Results: Alcohol craving and quantity of alcohol consumption, but not frequency, were positively correlated with PTSD symptom severity and symptom clusters. In addition, higher risk-taking/impulsivity was associated with greater PTSD symptom severity and cluster C symptoms (avoidance and numbing). After controlling for PTSD symptom severity, poorer learning and memory was associated with higher quantity and frequency alcohol consumption in the 90 days prior to treatment and risk-taking/impulsivity was positively associated with alcohol craving.

Conclusions: Findings suggest that interventions to strengthen cognitive functioning might be used as a preparatory step to augment empirically supported treatments for AUD. Clinicians are also encouraged to consider a standard assessment of cognitive functioning, in addition to PTSD severity, in treatment planning and delivery for this vulnerable and high-risk population.

Acknowledgments: This project was supported by Department of Defense W81XWH-05-2-0094, W81XWH-12-2-0137, and W81XWH-11-2-0245 (SLB), administered by the Northern California Institute for Research and Education. Support was also provided by a VA Rehabilitation Research and Development (RR&D) Career Development Award – 2 (1K2RX001492-01A1) granted to Dr. Heinz.

an opportunity to maximize chances of treatment completion.

Source of funding: None

Poster A.21: Perceptions of HCV Treatment and Correlates to Initiation Willingness in HCV+ Methadone Clients

Amy Jessop, PhD, MPH, Associate Professor; Sarah Bass, PhD, MPH, Associate Professor, Social and Behavioral Sciences; Muhamed Gashat, MD, Research Assistant; and Mercedes Gutierrez, MD, Research Assistant

Background: WHO and CDC goals to eliminate hepatitis C (HCV) will be reached only if we achieve sizable increases in treatment initiation among underserved groups such as MMT clients who in the U.S. demonstrate 67–96% HCV seropositivity, but low rates of treatment initiation (<11%). Without treatment they risk end-stage liver disease and serve as a reservoir for infection in communities. To facilitate treatment of this group, clinicians must better understand MMT clients' perceptions of medical care and HCV treatment to effectively communicate. Results of this study can inform clinicians on strategies to enhance communication with MMT clients.

Methods: We administered surveys to 100 self-reported HCV+ MMT clients from four Philadelphia, PA MMT programs. In addition to socio-demographic data and HCV factors, we collected scaled attitude scores about experiences with the healthcare system and care providers, knowledge about HCV and its treatment, psycho-social barriers to initiating treatment, other factors which impact care decisions, and level of interest in initiating HCV care if it were offered. We used bivariate methods (χ^2 , r and ANOVA) and then ordinal regression analysis to examine factors and perceptions associated with interest in treatment initiation.

Results: On bivariate analysis, socio-demographic and HCV factors of education level and discussion about HCV treatment with care providers were significantly associated ($p < 0.05$) with interest in treatment initiation, but age, race, gender, insurance type, difficulty paying for healthcare, and time since screening were not. A range of perceptions were significantly associated ($p < 0.05$) to interest in treatment initiation, including treatment barriers and benefits. Perceptions independently associated with increased interest in treatment by ordinal regression include: lower agreement with statements that there is too much paperwork (OR = .719; 95% CI = .564–.914), another treatment will be available soon (OR = .832, CI .725–.955) don't have a support system (OR = .820; CI = .701–.960), trouble taking medications (OR = .753 CI .603–.940) and being afraid of treatment side effects (OR = .865; CI = .751–.995) and higher agreement with statements about trouble making medical appointments (OR = 1.48; CI 1.14–1.92), had positive interactions with healthcare providers (OR = 1.30; CI = 1.03–1.57), feel they have had enough HCV education (OR = 1.30, CI 1.08–1.57) and believe HCV treatment is easy to take and cures quickly (OR = 1.54, CI: 1.21–1.96).

Conclusions: Results indicate that interventions must address positive attitudes about getting treatment and counter negative perceptions based on previous treatment protocols to move HCV+ MMT clients towards initiating care. These results have implications for clinical practice in how best to communicate with HCV+ MMT clients, as well as inform strategies for intervention in increasing willingness to initiate treatment.

Summary: We describe analysis of survey data with 100 self-report HCV+ Methadone Maintenance Therapy (MMT) clients to assess perceptions of and barriers to treatment initiation. Using multi-variate analysis, we assess correlates to treatment initiation willingness and found that perceptions of treatment, including barriers and benefits, were most associated with treatment willingness and that interventions aimed at these perceptions, rather than socio-demographic variables, would be most important to move HCV+ MMT clients toward treatment. This has specific implications for clinicians working with MMT clients and counseling on HCV treatment.

Source of funding: Independent research grant from Gilead Sciences

Poster A.22: PTSD, Sleep Disturbance, and Alcohol Use in Veterans with Co-Occurring PTSD and AUD

David Pennington, PhD, San Francisco VA Health Care System (SFVA); John Gibbons, BA, University of California, San Francisco (USCF); Erika Tomlinson, MS, SFVA; Brooke Lasher, BA, UCSF; Jennifer Bielenberg, MS, SFVA; Jennifer Dack, MS, SFVA; Alexander Kinzler, BA, SFVA; Ellen Herbst, MD, UCSF; Tauheed Zaman, MD, UCSF; Michael Hoefer, MD, UCSF; and Steven Batki, MD, UCSF

Background: Sleep disturbances are common among individuals with PTSD, and alcohol use is often cited by patients as a way to relieve insomnia. The current investigation sought to examine the associations of sleep disturbances and PTSD severity with alcohol use amount and frequency in patients with co-occurring PTSD and alcohol use disorder (AUD).

Methods: 61 veterans with PTSD and AUD were assessed for PTSD severity (PTSD Checklist; PCL), sleep disturbance (Insomnia Severity Index; ISI), average standard drinks consumed per week, average standard drinks consumed per drinking day, frequency of drinking days, and frequency of heavy drinking days in the week prior to screening (Timeline Followback Method) in two randomized controlled trials of topiramate treatment. We used random-intercept linear mixed models to assess the effects of PTSD severity, sleep disturbance, and the interaction between the two on average number of drinks per week and average drinks per drinking day. The same approach was applied, except using negative binomial models to examine the effects of PTSD severity and sleep disturbance on the frequency of drinking and heavy drinking days. Depression severity (Beck Depression Inventory; BDI-II) was entered as a covariate in each model.

Results: There was a significant PCL-by-ISI interaction for heavy drinking days [$\chi^2(1) = 4.74$, $p = 0.029$]. Main effects for ISI ($p = .032$), but not PCL ($p = .064$) were also observed for heavy drinking days. Results showed trends for a PCL-by-ISI interactions on both drinking days per week [$\chi^2(1) = 3.65$, $p = 0.056$] and drinks per week [$F(1, 62) = 3.39$, $p = 0.070$]. A main effect for ISI ($p = .051$), but not PTSD ($p = .083$) was also observed for drinking days per week. Depression was not a significant predictor in any of the models and was therefore trimmed.

Conclusions: Sleep disturbances and PTSD synergistically combine to increase the frequency and amount of heavy drinking in Veterans with comorbid PTSD and AUD. PTSD alone did not predict drinking amount or frequency.

Summary: These results suggest that sleep disturbances should be assessed and targeted in treatment during the early phases of PTSD and AUD treatment. Further investigations should examine if improvements in sleep disturbances moderate alcohol treatment response in veterans with AUD.

Source of funding: Department of Defense/CDMRP PH TBI, W81XWH-12-2-0137 (Batki); Department of Defense/Gallo Clinic & Research Center at UCSF W81XWH-11-2-0145 (Batki).

Poster A.23: GRIK1 SNP rs2832407, Trauma Burden, and Risk for Alcohol Dependence: Results from the National Health and Resilience in Veterans Study

Albert Arias, MD, Yale University School of Medicine; Shizhong Han, PhD, University of Iowa; Steven Southwick, MD, Yale University School of Medicine; John Krystal, MD, Yale University School of Medicine; Robert Pietrzak, PhD, Yale University School of Medicine

Background: We sought to replicate previous findings that a single nucleotide polymorphism (SNP) in the GRIK1 gene, which encodes the GluK1 subunit of the kainate receptor, is associated with alcohol dependence (AD; Kranzler, Gelernter, Anton, et al., 2009) in a nationally representative sample of European-American (EA) U.S. military veterans. SNP rs2832407 has previously been found to be associated with increased risk for AD (C-allele for risk), as well as preferential treatment response to topiramate in individuals with AD (CC genotype). Preclinical studies have implicated changes in kainate receptor expression and the involvement of glutamatergic changes in the response to stress and trauma, suggesting a potential for moderating influences of these variables on the relation between GRIK1 variants and AD risk.

Methods: Data were analyzed from a nationally representative sample of 1,666 European American (EA) U.S. military veterans. A total of 220 (13.2%) veterans were diagnosed with AD using the Mini Neuropsychiatric Interview. Veterans were genotyped using the Infinium PsychArray chip; GRIK1 rs2832407 genotype data were imputed and genotype frequencies did not differ from Hardy-Weinberg expectations ($p = 0.55$). Multivariable binary logistic regression was used

to examine the relation between GRIK1 genotype, lifetime trauma load, and the interaction of GRIK1 genotype x trauma load on AD risk; age, sex, lifetime history of major depressive disorder (MDD) or posttraumatic stress disorder (PTSD), and ancestral proportion scores were entered as covariates.

Results: After adjustment for age, sex, lifetime history of MDD and/or PTSD, and ancestry, there was a significant additive main effect of the C allele on AD diagnosis (Wald chi-square = 4.95, $p = 0.026$; OR = 1.49, 95%CI = -1.05–2.12), as well as a significant interaction of number of GRIK1 rs2832407C alleles with trauma load (Wald chi-square = 24.76, $p < 0.001$), with C allele carriers with higher trauma load having the highest risk of AD relative to C allele carriers with lower trauma load.

Conclusions: We replicated the association of GRIK1 rs2832407*C to AD in a nationally representative sample of predominantly male EA U.S. military veterans. We also found that the effect of this polymorphism on AD risk was moderated by trauma load, such that higher trauma load in C allele carriers was associated with highest risk of AD. These results suggest that a polymorphism in the GRIK1 rs2832407 genotype, directly and interactively with trauma load, contributes to AD risk in the general population of U.S. military veterans.

Summary: A variant in the gene encoding a glutamatergic kainate receptor subunit protein appears to influence the risk for developing alcoholism and this effect is magnified by trauma exposure. More research into the nature of this phenomenon may help with developing new treatments and preventive efforts.

Source of funding: Research was supported by The U.S. Department of Veterans Affairs National Center for PTSD and a private donation.

Poster A.26: Ether as a Drug of Abuse in the United States

Robert Rymowicz, DO, Rutgers, New Jersey Medical School; Daniel Hamm, DO, Clarion Hospital; Pallavi Joshi, DO, Nothwell SIUH

Background: Diethyl ether, commonly known as “ether,” is a volatile solvent long known to medicine for its anesthetic properties. Ether may be taken as an inhalant or as a drink, and its effects are said to be similar to but more acute than those of alcohol. As an NMDA antagonist, delusions, auditory hallucinations, and euphoria have also been attributed to the effects of ether intoxication. Once widely abused in Europe, especially in Ireland and Poland, the use of ether largely fell out of favor in Western countries prior to the Second World War. A search for published case reports detailing hospitalizations for ether abuse yielded no results, but discussions on internet forums suggest that individuals in the United States regularly attempt ether ingestion for recreational purposes.

Methods: Reviews of ether trips written in English and posted online were studied with a particular interest in the source of the ether used, the user’s subjective emotional or psychological

Summary: Combining medication-assisted treatment, such as buprenorphine or methadone, with A-CRA may reduce the risk of opioid overdose and lower the occurrence of further conditions associated with injection drug use in young adults. While promising, this work should lead to controlled trials of A-CRA and medication-assisted treatment to better assess its effectiveness for opioid use disorders in transitional age youth.

Source of Funding: HHSS270201200001C, No. 270-12-0397 and R01 AA021118.

Poster 14: Buprenorphine Retention in Outpatient Mental Health: Comparing Primary Care and Mental Health Outcomes in a Large Urban Safety Net Hospital

Brad Stankiewicz, MD, Boston Medical Center; Cristina Montalvo, MD, Boston Medical Center

Background: Opioid use disorder is a chronic illness that affects millions of individuals worldwide and continues to be a growing epidemic in the United States. According to the Centers for Disease Control and Prevention, the rate of opioid overdose deaths in the U.S. has increased 2.8 from 2002 to 2015, from just under 12,000 (11,917) in 2002 to over 33,000 (33,091) in 2015. Opioid substitution treatment including buprenorphine and methadone has been shown to be effective in reducing illicit opioid use, improving physical and mental well-being, and decreasing all-cause and overdose mortality (Sordo 2017). Buprenorphine has the advantage of being available in the outpatient setting, often prescribed by primary care physicians or psychiatrists. However, despite the high rates of comorbidity between substance use disorders and other mental health diagnoses, there is a paucity of literature on buprenorphine treatment outcomes in the outpatient mental health setting. Two studies conducted at Boston Medical Center, a large urban safety net hospital in Boston, demonstrate that one-year retention in outpatient buprenorphine treatment in the primary care setting is roughly 50% (Alford 2011, Weinstein 2017). This study set out to investigate the buprenorphine treatment retention rates in the Behavioral Health Clinic of Boston Medical Center with the aim of identifying predictors of treatment success.

Methods: The investigators conducted a retrospective chart review of patients prescribed buprenorphine through the Behavioral Health Clinic at Boston Medical Center from January 2010 through February 2016. IRB approval was granted through the Boston Medical Center Institutional Review Board. Inclusion criteria included age 18–65, diagnosis of opioid use disorder, and history of at least one prescription for buprenorphine prescribed through the Behavioral Health Clinic. Clinical and demographic data were collected through the Clinical Data Warehouse and included gender, age, race/ethnicity, marital status, level of education, employment status, insurance coverage, comorbid diagnoses, addiction history, family psychiatric history, buprenorphine use and dose, urine toxicology results, and co-prescribed medications. Our primary outcome was defined as retention in

treatment at one year, as defined by continuous prescriptions for buprenorphine with no gaps greater than 60 days. We hope to identify demographic and clinical factors that predict successful retention in treatment. We also hope to compare retention rates within Behavioral Health to those already published for the large primary care clinic within Boston Medical Center.

Results: There were 328 patients included in our study, over half of which (50.6%) were retained in treatment for at least one year. Of those retained in treatment, buprenorphine compliance (as measured by urine toxicology screen positive for buprenorphine on at least 80% of occurrences) was high (95%). Significant differences between the retained and non-retained groups included age, race/ethnicity, and comorbid diagnoses. Those patients retained in treatment were more likely to be older (39 vs 37 years of age). Black/African American patients were more likely to be retained in treatment, while Hispanic patients were found less likely to be retained. Those patients with a diagnosis of depressive disorder, other mood disorder, nicotine use disorder, or other substance use disorder were also found more likely to be retained in treatment.

Conclusions: Our findings indicate that just over 50% of patients presenting to the Boston Medical Center Behavioral Health Clinic for outpatient buprenorphine treatment were successfully retained in treatment for at least one year. This retention rate is comparable to that found in Boston Medical Center's large primary care clinic, suggesting that outcomes can be similar in two different treatment settings. Additional work needs to be done to identify reasons for differential retention regarding age, race/ethnicity, and diagnosis.

Summary: Our study offers the opportunity to compare buprenorphine retention rates between a behavioral health clinic and a primary care clinic in a large urban safety net hospital. Our findings indicate that treatment can have similar outcomes in two very different clinical settings. Further research on predictors of treatment outcomes may eventually help develop a triaging protocol based on a patient's baseline characteristics.

Source of Funding: APA SAMHSA Minority Fellowship Grant AU 6003708.

Poster 15: Cardiovascular Disease as a Predictor of Psychological and Medical Problems in Veterans

Alexandria Cantarero, BS, San Francisco VA Medical Center; Steven Batki, MD, UCSF School of Medicine, San Francisco VA Medical Center

Background: Cardiovascular disease (CVD) may exacerbate the severity of psychological and medical problems in Veterans with alcohol use disorder (AUD) and posttraumatic stress disorder (PTSD). We sought to examine the relationship between CVD and the prevalence and severity of common psychiatric and medical co-morbidities in Veterans entering one of two randomized clinical trials (RCT) of topiramate treatment.

Methods: One hundred four (9 female) Veterans with AUD and PTSD completed a medical and psychiatric evaluation upon entering one of two randomized clinical trials of topiramate treatment. Using one-way analysis of variance for continuous variables and the chi-square test (or Fisher's exact test when cell sizes were small) for categorical variables, we compared 40 Veterans with CVD to 64 Veterans without CVD on measures of PTSD symptoms (Clinician Administered PTSD Scale for DSM-IV), alcohol and cigarette use in the 90 days prior to screening (Timeline Follow Back method), substance use (urine toxicology), hypertension, depression (Beck Depression Inventory-II), sleep problems (Insomnia Severity Index), and impulsivity (Barratt Impulsivity Scale-11). Correlations were examined among these baseline characteristics.

Results: Veterans with CVD had significantly higher systolic blood pressures ($p=.01$) and significantly lower total CAPS scores ($p=.01$) than Veterans without CVD. In Veterans with CVD, higher total CAPS scores were associated with higher systolic blood pressures ($r^2=.35$, $p=.04$) and more average drinks consumed per week ($r^2=.34$, $p=.03$). In Veterans without a history of CVD, greater total CAPS scores were associated with higher serum levels of AST ($r^2=.30$, $p=.03$) and ALT ($r^2=.41$, $p < .01$), more sleep problems ($r^2=.31$, $p=.02$), and higher levels of depression ($r^2=.56$, $p < .01$) and impulsivity ($r^2=.48$, $p < .01$); while higher systolic blood pressures ($r^2=.29$, $p=.04$) were associated with more average heavy drinking days per week.

Conclusions: Veterans with AUD, PTSD, and comorbid CVD have higher systolic blood pressures compared to Veterans with AUD, PTSD but without CVD. Surprisingly, Veterans with CVD had lower PTSD symptom severity ratings than those without CVD. Although Veterans with CVD had lower PTSD symptom severity, increases in PTSD severity were associated with increases in both systolic blood pressure and average drinks consumed per week; relationships not evident in Veterans without CVD. On the contrary, Veterans without CVD exhibited associations between PTSD symptomology and systolic blood pressures with amount of heavy drinking days per week, biological measures of alcohol use and other psychiatric comorbidities.

Summary: Our findings suggest that Veterans with AUD and PTSD who have CVD have unique associations between biological markers of health, PTSD symptoms, alcohol use, and other psychiatric symptoms compared to Veterans without CVD. Further investigations should examine the potential mediating impact of CVD on alcohol and PTSD treatment response in Veterans with these comorbid disorders.

Source of Funding: None

Poster 16: Benzodiazepine Usage in an Outpatient Methadone Clinic Setting

Bellelizabeth Foster, MD, University of New Mexico; **Terry Stanton, MD**, University of New Mexico; **Snehal Bhatt, MD**, University of New Mexico

Background: Many patients, who seek treatment for opiate addiction, also experience addiction with other substances

including benzodiazepines, or have been on regimens of benzodiazepines for existing psychiatric conditions. Many agencies have begun to address co-prescribing of opioid medication in context of benzodiazepine usage, including CDC guidelines directed toward primary care physicians and the Baltimore Substance Abuse Systems geared toward opioid replacement therapy programs. Studies overall have shown decreased death rates in MMT programs for patients with opiate use disorder, with decreasing mortality rates over time with ongoing retention in the program. Baltimore guidelines specifically state that patients with benzodiazepine use should still be considered for opioid replacement therapies due to higher mortality rates if patients are turned away, but also warn that doses of opioid replacements should be lower overall and have smaller increases. Our goal of this study was to look at overall rates of patients in ORT that are testing positive for benzodiazepines, and to assess current doses of methadone or Suboxone and compare these to clinic averages and national reported averages.

Methods: Retrospective data was collected from urine drug screens, which are taken regularly from all patients receiving treatment in any form in a MAT clinic. The results of these screens were aggregated into totals to eliminate any PHI. This was compared with patients taking Suboxone and methadone and averages of dosing's were calculated and compared with the averages of daily dosing's in the clinic for all patients.

Results: The overall average prescribed doses for all clinic patients was a methadone daily dose of 101.32 mg, and Suboxone daily dose of 16.1 mg. The total number of patients in the clinic at the time of the study was 446 patients, of which 58 patients tested positive for benzodiazepines during the study interval. Fifty of these patients were prescribed methadone with an average daily dose of 108.7 mg. Four out of the 58 patients were prescribed Suboxone with an average daily dose of 17 mg. Four out of 58 patients, were not prescribed methadone or Suboxone, but had tested positive for benzodiazepines.

Conclusions: Overall there were similar dosing's between the groups of patients, with only slightly higher methadone doses in the benzodiazepine group 108.7 versus 101.32 mg per day. The total percentage of patients with benzodiazepine use was lower than expected given data on national trends. This shows that further research is required to evaluate current guidelines for benzodiazepine prescribing and dressing outcomes.

Summary: We plan to follow up on this study with looking at prescribing practices, how confirmation studies will correlate to compliance with therapy, and if outcomes are significantly different for these patients with co-current benzodiazepine usage in this setting. This will allow for evidence based medicine information to guide prescribing practices of benzodiazepines in a MAT setting.

Source of Funding: None

Poster 17: The Effects of Repeated Delta-9-Tetrahydrocannabinol Administration to Adolescent Rhesus Monkeys on Working Memory

David Mathai, MD, Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine; **Christopher D.**

DETERMINING DRINKING CRITERIA FOR TRANSGENDER VETERANS ENTERING RANDOMIZED CONTROLLED TRIALS OF TOPIRAMATE TREATMENT

Harris E, Herbst E, Pennington D.L., Vitualano-Sztec G, Rife T, Fong F, Lasher B, Kinzler A, Bielenberg J, Muquit L, O'Donnell M, Batki S.

Background: The prevalence of risky alcohol use in transgender (TG) individuals substantially exceeds that seen in the general population. However, National Institute on Alcohol Abuse and Alcoholism's (NIAAA) clinical guidelines for risky drinking levels have not been clearly defined for male-to-female (M → F) and female-to-male (F → M) hormonal transitions or gender identities. Because changes in gonadotropic hormone levels due to hormone replacement therapy (HRT) may affect pharmacodynamics and pharmacokinetics of alcohol metabolism, it is unclear whether biological sex or self-identified sex should be used for low risk alcohol cutoffs and thus may lead to misclassification of TG individuals. To elucidate this issue, we present a description of practices concerning 3 M → F TG Veterans recruited in the context of two randomized controlled trials (RCT) of topiramate treatment.

Methods: Participants were recruited for two RCTs examining topiramate treatment for heavy drinking Veterans with mild traumatic brain injuries or post-traumatic stress disorder. Alcohol use eligibility criteria for both studies were Veterans who reported drinking above NIAAA limits: ≥ 14 standard drinks (SD) per week for males, ≥ 7 SD/week for females. Because no NIAAA cutoffs have been established for TG patients, we describe randomization prevalence of TG participants and our methods for determining eligibility in this understudied sample of TG Veterans entering topiramate treatment trials.

Results: Of the 126 Veterans randomized, 3 M → F TG Veterans enrolled. Two were receiving HRT consisting of Spironolactone and Estradiol, and the final biologically male Veteran identified as female but had never received HRT. We used self-reported gender rather than birth sex to determine NIAAA SD limits. At baseline screening, Veteran 1 reported drinking 48.8 SD/week, Veteran 2 reported drinking 73.2 SD/week, and Veteran 3 reported drinking 22.6 SD/week. All three met NIAAA hazardous drinking criteria for either gender.

Conclusion: No clear clinical guidelines exist for low-risk limits of alcohol use for individuals with alternative gender identities or who receive hormonal therapies. Though NIAAA drinking guidelines differentiate hazardous alcohol use by sex based on epidemiological data, cutoffs may be established considering the use of hormone therapy for TG individuals. Prescribing practices established by endocrinology at San Francisco VA hospital consider the potential for any HRT to effect pharmacodynamics and pharmacokinetics of alcohol metabolism shortly after initiation. While consideration of HRT would not have effected TG study eligibility for the Veterans enrolled in the current RCTs, future studies may want to consider using a more restrictive drinking cutoff of ≥ 7 SD/week used for M → F TG participants due to the potential interaction effects of estrogen and progesterone on alcohol metabolism. Biological females have less gastric first-pass metabolism of ethanol and heavy alcohol use is associated with a

further decrease in gastric alcohol dehydrogenase activity, and lower drinking criteria of ≥ 7 SD/week may also apply to F M TG individuals. Further, the literature supports sociodemographic differences in alcohol risk, as well as neurobiological differences between sexes and sexual orientations, all factors that potentially make heavy alcohol use more harmful to various populations rather than sexes alone.

Summary More research is needed regarding the increased incidence of alcohol risk related to hormonal and non-hormonal factors, as well as for individuals with dynamic rather than categorical gender and sexual characteristics to accurately establish cutoffs for hazardous drinking in such instances.

WORKING MEMORY MODERATES RELATIONS BETWEEN ALCOHOL DEMAND CHARACTERISTICS, PTSD AROUSAL SYMPTOMS AND ALCOHOL USE

Abram, S.V., Pennington, D. L., Bielenberg, J., Muquit, L., Cano, M., Fong, F., Bautista, N., Lasher, B., Batki, S.L.

S.V. Abram, D.L. Pennington, J. Bielenberg, L. Muquit, M. Cano, F. Fong, N. Bautista, B. Lasher, S.L. Batki

San Francisco Veteran Affairs Health Care System and Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA

Background: Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are highly comorbid with complex and often unclear associations. Working memory (WM) dysfunction may represent a shared mechanism implicated in emotion regulation and control over impulsive alcohol use. Here, we investigate the extent to which WM and a laboratory-based behavioral economic task influence effects of PTSD symptoms on real-world alcohol consumption.

Methods: 88 Veterans completed an Alcohol Purchase Task (APT) and were assessed for PTSD (PCL-IV), alcohol use (Timeline Followback; average drinks per week in past 90 days), and WM (WAIS-III). We conducted a series of moderated mediation models (Hayes Process Model 58) to examine the effects of each PTSD symptom cluster on alcohol use, controlling for premorbid verbal IQ (Wechsler Test of Adult Reading) and age. APT “Pmax” (i.e., price at which demand becomes elastic) was entered as the mediator and WM as the moderator in each model.

Results: The direct effect of PCL arousal on alcohol use was significant ($B=0.04$, $p=0.04$). While Pmax did not mediate the relationship between arousal and alcohol use, WM moderated relations between arousal and Pmax ($WM \times \text{arousal}$: $B=-0.02$, $p=0.02$) and between Pmax and real-world alcohol use ($WM \times Pmax$: $B=-0.07$, $p=0.05$).

Conclusions: We find that poor WM influences the extent to which PTSD symptoms influence over-valuing of alcohol in a laboratory setting and high WM influences how alcohol demand characteristics relate to real-world alcohol use. This work highlights WM as a potential target for interventions geared towards reducing alcohol use in Veterans with co-occurring PTSD/AUD.

CORRESPONDENCE

Patients Managing Medications and Reading Their Visit Notes

TO THE EDITOR: I read DesRoches and colleagues' (1) brief research report with interest. Almost 7 years ago to the day, I commented (2) on Walker and associates' article (3) on inviting patients to read their doctors' notes. My comment discussed the benefits of open sharing of patients' medical records and stated, "Through this approach, the patient [becomes] an integral part of the equation for optimal outcomes. Such simple issues as patients listing all medications and supplements with their dosages [enhances] medical care" (2). However, as both a hematologist-oncologist and a patient recently diagnosed with a serious illness, I have realized that patients cannot easily access their medical records. The current patient portals of most medical centers and private practices do not give patients access to information on consultations or office visits. Medications copied and pasted from prior visits are often inaccurate, and a detailed list of supplements and their dosages is rarely included.

I believe that 1 basic issue that underlies DesRoches and colleagues' observations is access to the patient's medical record itself. The many patient portals that I have visited to retrieve medical records are poorly organized, and the presentation of information is often complicated with superfluous data. I suspect that such portals often exist to placate patients with pages of information that are not easy for them to understand and that much of the data presented are frequently unhelpful. There is a need to ensure relevance and quality in what patients are accessing.

Another issue is not only what patients might learn from reading doctors' notes or what is in their patient portal but also the lack of bilateral communication between patients and physicians. From my experience with portals, I find it exasperating that I as a patient cannot provide input to correct errors

in medications, dosages, or other relevant content. We are in the information age; however, insofar as realizing the potential of computer technology, we remain at a beginner's phase of what could and should be done with it. One intervention that could reduce mortality and morbidity would be to embed software that generates a drug and supplement interaction report for each patient in order to prevent the horrendous consequences of such interactions (4).

Stephen B. Strum, MD
Nevada City, California

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IN RESPONSE: We agree that although reading notes can provide patients with information, more can and should be done to invite patients to use and contribute to their electronic health data. We have made progress over the past 7 years toward the goal of providing patients with full electronic access to their medical records (1), but Dr. Strum's frustration with the lack of viable options for correcting data and providing relevant information is all too common. Electronic health data and patient portals offer enormous potential for patients not only to access their health information—including visit notes—but also review their data for errors (2), contribute information (3), and communicate with clinicians. To date, that potential has not been realized. More active engagement of patients and families requires innovative thinking and workflow design, thoughtful attention to underserved populations, and strong commitment to transparency among leadership, at a time when clinician burnout is at an all-time high and resources are limited.

Too often, patient portals are clumsily designed and offer little in the way of innovation, perhaps because electronic health record vendors do not see patients as customers and few health care organizations have demanded better. As we move into the new era of transparency and patient access to data, we must ensure that patients and their care partners are included in robust discussion. How can electronic health records improve their access to data, including clinicians' notes? Perhaps more important, how can such systems help patients contribute in a meaningful way to their electronic records?

Above all, long-standing habits and assumptions among both clinicians and patients may be the primary barrier to the opportunities that Dr. Strum would like to see realized. Exciting technologies appear almost daily, but both the culture of medical practice and the behaviors of patients are slow to change.

Catherine M. DesRoches, DrPH
Tom Delbanco, MD
Sigall K. Bell, MD
Harvard Medical School and Beth Israel Deaconess
Medical Center
Boston, Massachusetts

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Care of the Transgender Patient

TO THE EDITOR: As a provider of care to transgender patients, I read Safer and Tangpricha's (1) article with appreciation and interest. I have provided menopausal hormones for many years before becoming a provider to transgender patients and have been a member of the North American Menopause Society since its inception. As such, I have always followed this organization's evidence-based position statements and treatment guidelines through the years. To my knowledge, the North American Menopause Society has never endorsed injectable estradiol because of the lack of safety data and variable pharmacokinetics, including unequable bioavailability and a notable peak and trough effect.

Safer and Tangpricha's article reflects the commonly accepted recommendation that oral, transdermal, and injectable estradiol valerate are all reasonable options. However, I can find no evidence that supports the use of injectable estradiol. If we are to support evidence-based practice, using a different safety standard for transwomen than for their cisgender counterparts raises concern. Incurring the risk of putting more needles and syringes into the general population also seems objectionable; it creates more plastic and sharps waste and poses avoidable potential health hazards, especially when other options are effective and available. Although exceptions sometimes need to be made, data support the use of transdermal and oral estradiol. Is there a rationale for promoting the injectable formulation?

Wendy Klein, MD
Health Brigade
Richmond, Virginia

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Reference

1. Safer JD, Tangpricha V. Care of the transgender patient. *Ann Intern Med*. 2019;171:ITC1-16. [PMID: 31261405] doi:10.7326/AITC201907020

TO THE EDITOR: Safer and Tangpricha (1) provide a comprehensive summary of the unique clinical considerations relevant to the care of transgender and gender-nonconforming persons. Those who are gender minorities are at higher risk for hazardous substance use and substance use disorders because of stress related to their minority status, stigma, discrimination, trauma, and isolation (2). Screening, brief intervention, and referral to culturally competent treatment for hazardous substance use (including psychiatric treatment, if indicated) are essential in this population.

Of note, current screening methods for hazardous drinking may be insufficient for transgender patient populations. Current U.S. alcohol use guidelines define hazardous use as consumption of greater than 4 standard drinks per day or greater than 14 drinks per week for men younger than 65 years and greater than 3 standard drinks per day or greater than 7 standard drinks per week for women of any age and men older than 65 years, with 1 standard drink equaling 14 g of pure alcohol. These guidelines are based on epidemiologic data for cisgender men and women (3). However, no hazardous alcohol use cutoffs have been established for transgender persons, who may be vulnerable to the adverse effects of alcohol at lower levels than established U.S. cutoffs. Heavy alcohol use is associated with interpersonal violence, sexual and physical assault, depression, sexually transmitted infections, and suicide, and these risks may be increased in transgender patients relative to their cisgender counterparts (2). Whether osteoporosis, cancer, and other adverse health outcomes associated with alcohol use may occur at lower drinking levels among transgender and gender-nonconforming patients who are receiving hormonal therapies because of hypogonadism and hormonal shifts is also unknown. Using the lower screening cutoffs for hazardous drinking that have been established for cisgender women and persons older than 65 years may therefore be prudent in transgender patients until more data are available.

Tobacco use should also be proactively screened for and treated in transgender populations. Some studies report that use of tobacco products is higher in transgender youth than cisgender youth (4), although recent data suggest that the prevalence of tobacco use in adult transgender and cisgender populations is similar (5). The high risk for thromboembolic events with concurrent cigarette use and long-term estrogen administration warrants a proactive approach to screening and treatment.

In summary, screening and referral to trauma-informed substance use and psychiatric treatment, surveillance for haz-

ardous substance use at low levels, and awareness of potential medical complications associated with hormonal therapies in the setting of problematic substance use are best practices in the care of transgender patients.

Ellen D. Herbst, MD
Edith Harris, MA
David L. Pennington, PhD
Steven L. Batki, MD
San Francisco VA Health Care System
and University of California, San Francisco
San Francisco, California

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IN RESPONSE: Dr. Klein raises important concerns about the relative safety among routes of estrogen administration and makes a logical argument that there may be greater risk for harm with injectable estradiol. Absent data, a rationale for promoting injectable estradiol over other products is lacking; however, data to definitively proscribe its use are also lacking.

Dr. Herbst and colleagues present a thoughtful, conservative approach to screening transgender persons for substance use, mental health morbidity, and medical concerns. Future research will be needed to learn the usefulness of specific elements of their proposal.

Joshua D. Safer, MD
Mount Sinai Health System and Icahn School of Medicine at Mount Sinai
New York, New York

Vin Tangpricha, MD, PhD
Emory University School of Medicine and
Atlanta VA Medical Center
Atlanta, Georgia

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Household Firearm Ownership and Storage, Suicide Risk Factors, and Memory Loss Among Older Adults

TO THE EDITOR: I read Morgan and colleagues' brief research report (1) with interest. Approximately 1% of persons in the United States will die by suicide (2). Older men and women have the highest suicide rate in almost all countries—including those with limited access to firearms, such as Japan and China, where the rate of suicide in elderly persons is nearly 3 times that in the United States (2, 3).

Morgan and colleagues cite a review by Anglemyer and associates (4) that concludes that access to firearms is associated with risk for suicide and being the victim of homicide. However, this review was not specific to elderly persons, which makes extrapolating these findings to that population difficult. Morgan and colleagues conclude that "limiting access to lethal weapons for the older adult population represents an important avenue for suicide prevention." On the basis of their study, it is impossible for Morgan and colleagues to draw this conclusion. There is no evidence that limiting access to firearms would change the overall rate of suicide among elderly persons in the United States. Limited access to firearms may reduce the risk for suicide by firearms, but evidence to support that the overall suicide rate would decrease is lacking. This fact is corroborated by the previously mentioned higher rates of suicide among elderly persons in countries with exceptionally limited access to firearms. According to Morgan and colleagues' logic, we should also limit access to acetaminophen, ropes, automobiles, stairs, knives, bathtubs, and a host of other potential suicide risks.

Alan R. Ertle, MD, MPH, MBA
Emeritus Enterprises
Bend, Oregon

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IN RESPONSE: Dr. Ertle discusses the implications of safe storage specific to older adults and the substitution of other methods of suicide if firearms are not available. Studies show that associations between firearm ownership and risk for suicide in persons aged 50 years or older are similar to those among other age groups (1). Risk for suicide is higher in older adults worldwide, but this fact is not solely explained by the availability of firearms. Of note, the case fatality of firearm suicide attempts is far higher than that of suicide attempts by other means (2). Although those who make serious attempts to die by suicide may use other means, these means are less likely to be fatal.

Some countries with a lower prevalence of firearm ownership may have higher rates of suicide among older adults; however, variation in firearm ownership is not the only difference between the United States and Japan or China. Complex cultural differences in such factors as health care, socialization, beliefs held by older adults, stigma surrounding mental health, and honor may also partially explain higher rates of suicide despite limited firearm access (3).

We recognize that limiting access alone is not sufficient to prevent all suicides; however, it does represent 1 potential opportunity for prevention.

Erin R. Morgan, MS
University of Washington
Seattle, Washington

Anthony Gomez, BS
Public Health—Seattle & King County
and University of Washington
Seattle, Washington

Frederick P. Rivara, MD, MPH
Ali Rowhani-Rahbar, MD, PhD
University of Washington
Seattle, Washington

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

TOPIRAMATE TREATMENT OF ALCOHOL USE DISORDER IN VETERANS WITH PTSD: PRELIMINARY ANALYSIS OF A CONTROLLED TRIAL

S.L. Batki, D.L. Pennington, B.A. Lasher, E. Herbst, T.C. Neylan, N. Bautista.

UCSF Department of Psychiatry and San Francisco VA Health Care System, San Francisco, CA 94121

Background:

Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) frequently co-occur among Veterans, yet effective pharmacotherapy for these comorbid conditions is still elusive.

Methods:

A single-site prospective 12-week, randomized, double-blind, placebo-controlled trial of flexible-dose topiramate or placebo, up to 300 mg/day in 151 Veterans with PTSD and AUD. All participants received weekly Medical Management counseling.

Primary outcome was between-group reduction in drinking days per week. Secondary outcomes included other measures of alcohol use, alcohol craving (Obsessive-Compulsive Drinking Scale [OCDS], PTSD symptoms, and safety outcomes.

All participants were military Veterans. 87% were male. Mean ($\pm$ SD) age was 51.3 ($\pm$ 13.4). 40% were exposed to combat.

PTSD symptom severity at entry was high. Mean baseline CAPS/PCL score was 74.1/54.8 ($\pm$ 16.5/13.4).

At entry, mean baseline drinking days per week was 5.1 ($\pm$ 1.8), mean heavy drinking days per week was 3.8 ($\pm$ 2.3), mean drinks per week was 48.8 ($\pm$ 33.5) and mean drinks/drinking day was 9.9 ($\pm$ 6.6). Mean baseline OCDS was 17.1 ($\pm$ 7.4). There were no differences between groups in reported drinking data in the 90 days prior to study entry.

Results:

Both the topiramate and the placebo groups significantly reduced alcohol use and PTSD symptom severity over the 12-weeks of treatment. A linear mixed model found that topiramate significantly reduced alcohol craving on OCDS compared to placebo (treatment-by-time interaction, $p < 0.01$). However, there were no other statistically significant treatment condition differences or treatment-by-time interactions observed for other alcohol use measures and for PTSD symptom severity. Retention, measured by the total number of study visits attended also did not differ between the two groups.

Adverse effects differed between the two groups: those receiving topiramate had significantly more participants reporting treatment-emergent numbness (topiramate [TOP]=21 vs placebo [PLA]=12;

p=.04), loss of appetite (TOP=37 vs PLA = 24; p<0.01), and confusion (TOP=24 vs PLA=11; p<0.01). There were no medication-related serious adverse effects.

Conclusions:

In this preliminary analysis, topiramate treatment reduced alcohol craving but did not appear to reduce alcohol use or PTSD symptom severity as compared to placebo in Veterans with co-occurring AUD and PTSD.

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