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

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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 problem[1] and constitute the most prevalent forms of addiction in veterans.[2] Cognition is a key area of research in the field of alcohol

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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 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 counseling[37] 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 taking[44]; we used the primary score of "adjusted average number of pumps on unexploded balloons." The Delay Discounting (DD) Task was used to assess impulsivity[45]; 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 medications[48] 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 parameters[49] 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.

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 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 decline[50] 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 decline[50] and ventricular enlargement.[55] One possibility is that the increased erythrocyte volume, which is found in alcohol dependence[19] 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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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.

[a] SD = standard deviation.

[b] IQR = 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 [n = 9]	45 (9–90, 78)
No. of Days of Cocaine Use in the Past 90 Days [n = 3]	37.0 (45.9)
No. of Days of Opiate Use in the Past 90 Days [n = 1]	1
No. of Cigarettes Used in the Past 90 Days [n = 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 *T* 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	
T Score	44.9 (11.6)
TMT-B	
T Score	45.6 (11.0)

n = 30 except where noted.

[a] n = 27 because of 3 missing data points.

[b] Because most values were undetectable at <100 ng/mL, EtG was dichotomized into <100 vs. >100 ng/mL.

[c] Because 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.

[f] Kln = log-transformed delay discounting after applying the hyperbolic function.

TABLE III

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

	HVLT-R: %Retention *T* Score	BART: Adjusted Average Number of Pumps on Unexploded Balloons	DD: Kln	TMT-A: *T* Score	TMT-B: *T* 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.

[a] Correction for extreme values did not change results, so original results are presented.

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

[a]Correction for extreme values did not change results, so original results are presented.

[b]Correction for extreme values changed results, so corrected results are presented.