N-Acetylcysteine for the Treatment of Co-Occurring Posttraumatic Stress Disorder and Alcohol Use Disorder:

A Double-Blind, Randomized Controlled Trial

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Abstract

Objective: Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are common co-occurring conditions associated with a more severe clinical profile and poorer treatment outcomes than either disorder alone. To date, no medications have proven efficacious in the treatment of co-occurring PTSD/AUD.

Methods: This randomized, double-blind, placebo-controlled trial examined the efficacy of *N*-acetylcysteine (NAC; 2,400 mg/day) among individuals (N = 182, aged 21–65 years) who met *DSM-5* criteria for current PTSD/AUD. Participants were randomized 1:1 to receive 12 weeks of NAC (n = 93) or placebo (n = 89). All participants received weekly, individual, cognitive behavioral therapy (CBT) for AUD. Follow-up visits occurred at 3-, 6-, and 12-months posttreatment. Primary outcomes included the Clinician Administered PTSD Scale for *DSM-5* (CAPS-5), PTSD Checklist for *DSM-5* (PCL-5), Timeline Follow-Back (TLFB), and the Obsessive Compulsive Drinking Scale at 12 weeks. The TLFB evaluated the frequency and amount of alcohol consumption. A secondary measure evaluated depression symptoms.

Results: Intent-to-treat analyses showed that participants in both the NAC and placebo groups evidenced significant reductions in the CAPS-5 (B = −0.19, $P < .001$) and PCL-5 (B = −0.20, $P < .001$) during treatment, with no significant group differences. Both groups also showed significant reductions in alcohol use (drinks per drinking day [B = −0.02, $P < .001$], percent heavy drinking days [B = −0.14, $P < .001$], percent days abstinent [B = 0.29, $P = .022$]) and craving (B = −0.12, $P < .001$) during treatment, but with no significant group differences. There were no group differences in retention or adverse events.

Conclusions: Although NAC was well tolerated, it was not more effective than placebo in improving symptoms of PTSD or AUD when added to individual CBT for AUD.

Trial Registration: ClinicalTrials.gov identifier: NCT02966873.

J Clin Psychiatry 2025;86(4):25m15803

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Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are highly prevalent and debilitating psychiatric conditions, with general population lifetime prevalence rates of 7.8% and 29.1%, respectively.[1,2] Among individuals with PTSD, approximately half meet criteria for AUD[3] underscoring the substantial overlap and bidirectional nature of these conditions. Comorbid PTSD/AUD is associated with greater symptom severity, increased functional impairment, and overall worse treatment outcomes compared to either disorder alone.[4–6]

Research implicates glutamate dysregulation in both PTSD and AUD, suggesting overlapping treatment targets.[7–9] Glutamate dysregulation plays a role in stress reactivity, fear learning, and memory consolidation which are critical aspects in the development of PTSD. Chronic substance use induces frontostriatal glutamatergic circuitry adaptations, which are associated with compulsive drug-seeking behaviors and maladaptive behaviors to drug- or stress-related cues.[10–13] This evidence suggests that pharmacologic agents modulating the glutamate system may be promising candidates for treating co-occurring PTSD/AUD.

Clinical Points

- Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) frequently co-occur and are associated with numerous adverse health outcomes.
- Effective medications for co-occurring PTSD and AUD are lacking.
- In this sample of treatment-seeking community adults with co-occurring PTSD and AUD, NAC (2,400 mg/day), when added to cognitive behavioral therapy for AUD, was not more effective than placebo in reducing symptoms of PTSD or AUD.

N-acetylcysteine (NAC), an antioxidant which regulates glutamate homeostasis, has gained attention in the treatment of psychiatric disorders including PTSD and AUD.[14,15] Preclinical studies indicate that NAC significantly reduces ethanol intake and ethanol-seeking behaviors, mechanistically by restoring extracellular glutamate levels through the glial glutamate transporter 1 (GLT-1).[15–21] Animal models show that NAC reduces alcohol withdrawal symptoms and decreases stress- and cue-induced alcohol consumption.[21] While clinical findings are mixed, a meta-analysis among individuals with substance use disorders (SUDs) concluded that NAC decreased cravings and potentially reduced withdrawal symptoms.[22] Another recent systematic review and meta-analysis found that NAC reduced craving across substances,[23] and a cue-reactivity study[24] found that NAC reduced alcohol craving.

Several clinical studies have examined NAC among individuals with co-occurring PTSD and SUDs. A pilot trial of NAC in treatment-engaged veterans (N = 35) with PTSD/AUD enrolled found that NAC reduced PTSD symptoms, cravings, and depressive symptoms.[25] No group differences were observed in substance use, as assessed via urine drug screen tests. Another randomized controlled trial evaluated NAC among individuals with treatment-resistant PTSD who had previously failed to respond to a first-line treatment. AUD was not an exclusion criterion, and 34 of 104 (32.7%) randomized participants had AUD. No significant effects of NAC on PTSD symptoms were observed, but the NAC group had greater reductions in craving duration and craving resistance at follow-up compared to placebo group.[26]

The primary objective of the current study was to evaluate the efficacy of NAC in reducing PTSD and AUD severity among individuals with comorbid PTSD/AUD. A secondary objective included assessing the effects on depressive symptoms. We hypothesized that NAC, as compared to placebo, would result in greater reductions in PTSD symptom severity, alcohol use, and craving. This study aims to contribute to the growing body of evidence exploring NAC as a novel pharmacologic adjunct to psychosocial treatment for co-occurring PTSD/AUD.

METHODS

Participants

Participants (N = 182) were treatment-seeking adults between ages 18–65 years who met *DSM-5* criteria for PTSD and AUD. Participants were recruited and follow-up assessments completed between 2017 and 2022. Primary exclusion criteria included significant medical or psychiatric conditions (eg, seizures, asthma, psychosis, suicidal intent), use of contraindicated medications (eg, nitroglycerin, carbamazepine), pregnancy, or nursing. Individuals with significant alcohol withdrawal symptoms (Clinical Institute Withdrawal Assessment for Alcohol Scale–Revised[27] score of ≥10) were referred for medically managed withdrawal. Participants were allowed to take psychotropic medications but had to be on a stable dose for at least 4 weeks pretreatment. Detailed procedures are described in Back et al.[28]

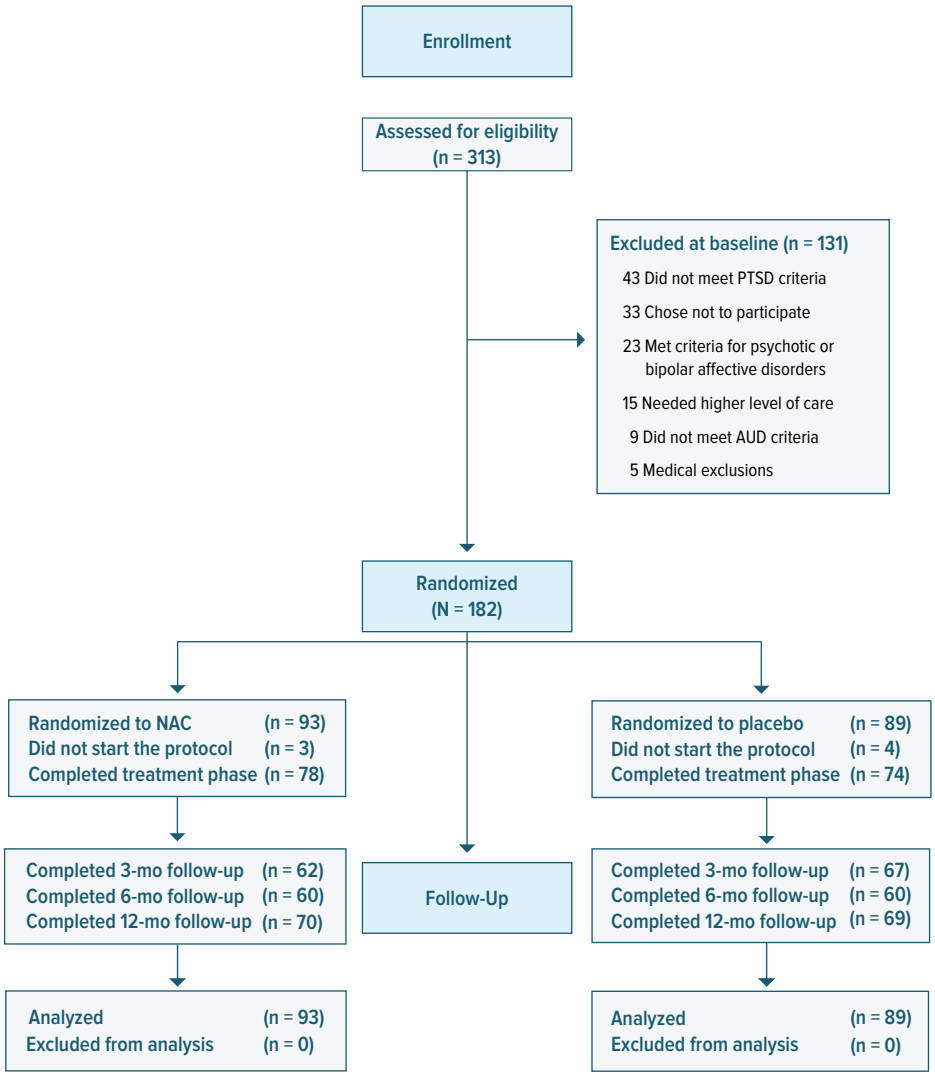
General Procedures

This study was approved by the local institutional review board, and the trial was registered at ClinicalTrials.gov (NCT02966873). Participants gave written informed consent before study procedures and were recruited from the community through social media, newspaper advertisements, flyers, and clinician referrals. Eligibility was assessed by a comprehensive baseline evaluation of PTSD severity, alcohol use, and related mental health issues.[28] Study visits and procedures could be completed either in-person or via telehealth due to the COVID-19 pandemic. Ineligible individuals were referred clinically for treatment. Eligible participants were randomized (1:1) to receive 12 weeks of NAC (2,400 mg/day) or placebo, and all participants received weekly, individual cognitive behavioral therapy (CBT) for AUD. Figure 1 presents the CONSORT diagram.

Study Interventions

Medication and dose. Dosage of NAC and treatment duration were determined based on prior studies.[29–31] NAC was administered as 1,200 mg twice daily. Placebo capsules visually matched the NAC capsules. Medication adherence was monitored by pill counts and riboflavin assay (all capsules contained 25 mg riboflavin). Side effects and adverse events (AEs) were monitored weekly. Participants were randomly assigned (1:1) to receive NAC or placebo. Stratified block randomization was employed to ensure balance in treatment group assignment based on baseline PTSD severity (high: PTSD Checklist for *DSM-5* [PCL-5][32] score ≥48) and AUD severity (high: Alcohol Use Disorders Identification Test[33] score ≥16).

Figure 1.
CONSORT Diagram



Abbreviations: AUD = alcohol use disorder, NAC = N-acetylcysteine, PTSD = posttraumatic stress disorder.

Cognitive behavioral therapy (CBT) for AUD. All participants received weekly 1-hour sessions of protocolized CBT for AUD.[34] Topics included coping with cravings, managing thoughts and urges about drinking, and alcohol refusal skills. CBT provided a standardized behavioral platform, ensuring all participants received adequate psychosocial support, irrespective of medication arm. Study therapists were master's- or doctoral-level clinicians who received extensive training in the CBT protocol and weekly supervision throughout the trial.

Measures

Participants completed a self-report form to assess demographic characteristics (eg, age, sex, race, ethnicity, employment, and relationship status). The Clinician Administered PTSD Scale for *DSM-5* (CAPS-5[35]) evaluated PTSD diagnosis and symptom severity, and the PCL-5 measured self-report PTSD symptom severity. The Timeline Follow-Back (TLFB),[36] a self-report measure of daily substance use, evaluated the frequency and amount of alcohol consumed, and the Obsessive Compulsive Drinking Scale (OCDS)[37] measured alcohol craving. Finally, the Beck Depression Inventory-II (BDI-II[38]) evaluated depression symptoms, and the Columbia-Suicide Severity Rating Scale[39] assessed current and history of suicidal thoughts and behaviors. For more information on measurements and time points, refer to Back et al.[28]

Data Analysis and Sample Size

Statistical analyses were conducted on an intent-to-treat sample of 182 randomized participants.

Descriptive statistics characterized the sample group (see Table 1), and *T* tests and χ^2 analyses were used to compare demographic and clinical characteristics at baseline by treatment condition; no baseline characteristics significantly differed by treatment group. Primary outcomes were PTSD severity, as measured by the CAPS-5 and PCL-5; average number of standard drinks per drinking day (DDD), measured by the TLFB; and craving, as measured by the OCDS. The TLFB was also used to measure percent days heavy drinking (PDH) and percent days abstinent (PDA).

To test whether NAC treatment would result in significantly greater reductions in PTSD and alcohol-related outcomes, including quantity and frequency of alcohol use and alcohol craving, than placebo, a series of latent growth curve models were run in R version 4.3.2 using the lavaan package. Independent models were run for each of the outcome variables. Measurement models were fit to the data first to ensure that a linear (versus nonlinear) growth curve model provided the best fit to data.

Linear latent growth curve models were specified for each outcome variable such that the paths for the latent intercept were fixed to 1, which allowed the residual variances for data at each observed time point to be free. Paths for the latent slope were specified to correspond with the week during which the measurement was taken (eg, the path for the baseline data time point was set to 0, session 6 was set to 6, session 12 was set to 12, 3-month follow-up was set to 24, 6-month follow-up was set to 36, and 12-month follow-up was set to 60). For all models, data from all possible study time points were utilized. Intercepts and slopes were allowed to covary. Treatment condition (−1 = placebo; 1 = NAC) was entered as a predictor variable for the latent intercept and slope, and sex (−1 = male; 1 = female) was selected as a relevant covariate in the model. Although both the NAC and placebo conditions did not differ by sex, we chose to examine the effects of treatment condition while controlling for sex to ensure that any medication effects would not be driven by sex differences. Abstinence from alcohol reported the week prior to medication initiation was also considered as a potential covariate but was not significant across alcohol models and thus removed from the models.

The target sample size was 200 participants (100 per treatment arm). This sample would provide >95% power with α of 0.05 to detect between-group differences in the CAPS-5 and >80% power with α of 0.05 to detect between-group differences in the average number of standard DDD, assuming 25–30% attrition.[40] See Back et al[28] for more information on considerations for the data analytic plan and sample size estimates.

RESULTS

Demographic Variables and Baseline Clinical Characteristics

As shown in Table 1, there were no group differences in demographics or baseline clinical characteristics by the treatment group. Most participants (62.1%) were female, with a mean age of 40.3 years (SD = 12.7). On average, participants consumed an average of 6.76 (SD = 4.51) DDD, with 45.3% heavy drinking days. Seventeen participants (10 NAC, 7 placebo; $\chi^2 = 0.45$, $df = 1$, $P = .50$) were abstinent from alcohol for approximately 1 week prior to medication initiation.

PTSD Symptoms

Examination of change in the CAPS-5 and PCL-5 total scores during treatment revealed a significant effect of time on PTSD symptoms (see Table 2; Figures 2A, B). Results from independent linear growth curve models indicated that PTSD symptoms significantly decreased over the course of treatment and follow-up (CAPS-5: B = −0.19, $P < .001$; PCL-5: B = −0.20, $P < .001$) for the sample but were not impacted by treatment condition. For both of the PTSD models, there were no significant effects of sex on the latent intercept or slope, suggesting there were no differences in PTSD outcomes by sex. To evaluate reliable change and clinically significant change in PTSD symptoms, we compared average change in CAPS-5 and PCL-5 total scores from baseline to week 12 to previously established criteria for reliable change and clinically significant change.[41] On average, CAPS-5 total scores decreased 12.8 points from baseline to week 12, with an average CAPS-5 total score of 15.67 (SD = 11.88) at week 12. The reduction in clinician-rated PTSD symptoms was slightly below the threshold for reliable change (ie, >13 point change), but week 12 CAPS-5 scores were above the threshold for clinically significant change (<8 total score).[41] The PCL-5 total scores decreased an average of 17.0 points from baseline to week 12, with an average total PCL-5 score of 20.76 (SD = 17.67) at week 12, which represents clinically significant change (<28 total score) as well as reliable change (ie, >9–12 point change).[41,42] Together, this suggests that, on average, participants demonstrated clinically meaningful change in PTSD symptoms.

Alcohol Use and Craving

We examined changes in average DDD, PDH, and PDA during treatment using linear growth curve models. Results from the independent growth curve models (see Table 3) indicate that each of these variables improved significantly over the course of treatment and at follow-up for the sample: average DDD (B = −0.02, $P < .001$), PDH (B = −0.14, $P < .001$), and PDA (B = 0.29, $P = .022$). Treatment condition did not significantly predict latent intercepts or slopes across any of the alcohol use models,

Table 1.

Demographic and Clinical Characteristics

	NAC (n = 93)	Placebo (n = 89)	Total (N = 182)	*P* value
Demographic characteristics				
Age, mean (SD), y	40.87 (13.15)	39.65 (12.41)	40.27 (12.77)	0.521
Sex, n (%)	–	–	–	0.821
Male	36 (38.7%)	33 (37.1%)	69 (37.9%)	–
Female	57 (61.3%)	56 (62.9%)	113 (62.1%)	–
Employment, n (%)	–	–	–	0.216
Full time	40 (43.0%)	43 (48.3%)	83 (45.6%)	–
Part time	18 (19.4%)	16 (18.0%)	34 (18.7%)	–
Unemployed	19 (20.4%)	22 (23.9%)	41 (22.6%)	–
Volunteer	2 (2.2%)	1 (1.1%)	3 (1.6%)	–
Retired/disabled	13 (14.1%)	7 (7.9%)	20 (11.1%)	–
Military/Veteran, n (%)	9 (9.7%)	10 (11.2%)	19 (10.4%)	0.554
Race, n (%)	–	–	–	0.196
White	72 (77.4%)	66 (74.2%)	138 (75.8%)	–
Black/African American	14 (15.1%)	18 (20.2%)	32 (17.6%)	–
Asian American	4 (4.3%)	0 (0%)	4 (2.2%)	–
American Indian/Alaskan Native	1 (1.1%)	0 (0%)	1 (0.5%)	–
Native Hawaiian or other Pacific Islander	0 (0%)	1 (1.1%)	1 (0.5%)	–
Another race	2 (2.2%)	4 (4.5%)	6 (3.3%)	–
Ethnicity, Hispanic, n (%)	4 (4.3%)	4 (4.5%)	8 (4.4%)	0.949
Relationship status, n (%)	–	–	–	0.569
Single	40 (43.0%)	33 (37.1%)	73 (40.1%)	–
Married	21 (22.6%)	30 (33.7%)	51 (28.0%)	–
Separated	6 (6.5%)	7 (7.9%)	13 (7.1%)	–
Divorced	20 (21.5%)	15 (16.9%)	35 (19.2%)	–
Widowed	6 (6.5%)	4 (4.5%)	10 (5.5%)	–
Education level, n (%)	–	–	–	0.856
Some high school	3 (3.2%)	3 (3.4%)	6 (3.3%)	–
GED	5 (5.4%)	5 (5.6%)	10 (5.5%)	–
High school diploma	6 (6.5%)	5 (5.6%)	11 (6.0%)	–
Some tech school or college	30 (32.3%)	29 (32.6%)	59 (32.4%)	–
Tech school/associate degree	14 (15.1%)	17 (19.1%)	31 (17.0%)	–
4-year college degree	27 (29.0%)	21 (23.6%)	48 (26.4%)	–
Master's degree	6 (6.5%)	8 (9.0%)	14 (7.7%)	–
Doctoral degree (PhD, MD, DDS, etc)	2 (2.2%)	0 (0%)	2 (1.1%)	–
Past month income, mean (SD), $	2,913.33 (4,746.77)	2,488.82 (2083.53)	2,704.80 (3,672.59)	0.448
Alcohol use and alcohol severity				
Alcohol use disorder and drug use disorder, n (%)	21 (22.6%)	17 (19.1%)	38 (20.9%)	0.539
No. of drinks per drinking day, mean (SD)	6.81 (4.07)	6.79 (4.95)	6.76 (4.51)	0.976
Days abstinent, %, mean (SD)	32.42 (30.38)	32.16 (29.23)	32.29 (29.74)	0.952
Heavy drinking[a] days, %, mean (SD)	46.58 (35.17)	44.05 (35.21)	45.34 (35.11)	0.628
CIWA-AR, mean (SD)	2.40 (2.52)	2.40 (2.80)	2.40 (2.65)	0.991
AUDIT (total score), mean (SD)	20.62 (8.31)	20.65 (7.91)	20.64 (8.09)	0.984
OCDS (total score), mean (SD)	16.92 (7.72)	16.91 (6.94)	16.92 (7.33)	0.989
Alcohol biomarker (EtG), n (%)	48 (51.6%)	43 (48.3%)	91 (50.0%)	0.656
Trauma and PTSD				
PCL-5, mean (SD)	38.56 (16.53)	38.13 (16.20)	38.35 (16.33)	0.861
CAPS-5, mean (SD)	28.16 (9.37)	29.02 (9.80)	28.58 (9.57)	0.545
Lifetime Events Checklist	–	–	–	–
Total number of traumas, weighted, mean (SD)	27.66 (17.95)	23.72 (10.58)	25.73 (14.91)	0.072
Traumas, n (%)				
Natural disaster	70 (75.3%)	67 (75.3%)	137 (75.3%)	0.998
Fire or explosion	42 (45.2%)	44 (49.4%)	86 (47.3%)	0.563
Transportation accident	77 (82.8%)	71 (79.8%)	148 (81.3%)	0.601
Serious accident	49 (52.7%)	49 (55.1%)	98 (53.8%)	0.749
Exposure to toxic substance	23 (24.7%)	22 (24.7%)	45 (24.7%)	0.998
Physical assault	77 (82.8%)	72 (80.9%)	149 (81.9%)	0.740
Assault with weapon	63 (67.7%)	50 (56.2%)	113 (62.1%)	0.108
Sexual assault	66 (71.0%)	65 (73.0%)	131 (72.0%)	0.756

(continued)

Table 1 (continued).

	NAC (n = 93)	Placebo (n = 89)	Total (N = 182)	*P* value
Other unwanted/uncomfortable sexual experience	66 (71.0%)	57 (64.0%)	123 (67.6%)	0.319
Combat/war-zone exposure	21 (22.6%)	19 (21.3%)	40 (22.0%)	0.841
Captivity	23 (24.7%)	17 (19.1%)	40 (22.0%)	0.359
Life-threatening illness/injury	55 (59.1%)	44 (48.4%)	99 (54.4%)	0.189
Severe human suffering	48 (51.6%)	35 (39.3%)	83 (45.3%)	0.096
Sudden violent death	62 (66.7%)	56 (62.9%)	118 (64.8%)	0.597
Sudden accidental death	53 (57.0%)	53 (59.6%)	106 (58.2%)	0.726
Serious injury, harm, or death you caused to someone else	16 (17.2%)	20 (22.5%)	36 (19.8%)	0.373
Other traumatic event	37 (39.8%)	34 (38.2%)	71 (39.0%)	0.880
Associated features				
BDI-II, mean (SD)	22.66 (11.26)	22.39 (10.61)	22.52 (10.91)	0.868
Lifetime major depressive disorder, n (%)	66 (71.0%)	60 (67.4%)	126 (69.2%)	0.685
Lifetime suicide attempt (CSSR), n (%)	17 (18.3%)	24 (27.0%)	41 (22.5%)	0.184

[a]Heavy drinking defined as 5 or more standard drinks per day for males and 4 or more standard drinks per day for females.
Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, BDI-II = Beck Depression Inventory-II, CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, CIWA-AR = Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised, cov = covariate, CSSR = Columbia-Suicide Severity Rating Scale, EtG = ethyl glucuronide, GED = general educational development high school equivalency credential, NAC = *N*-acetylcysteine, OCDS = Obsessive Compulsive Drinking Scale, PCL-5 = PTSD Symptom Checklist-5.

Table 2.

Results From Linear Latent Growth Curve Models Examining PTSD and Depressive Symptoms

Model	Estimate	SE	z-value	*P*-value	std.lv	std.all
CAPS-5 model						
Intercept	19.420	1.119	17.356	0.000	2.066	2.066
Treatment condition	−0.406	1.074	−0.378	0.705	−0.043	−0.043
Sex	1.334	1.119	1.193	0.233	0.142	0.136
Slope	−0.189	0.018	−10.594	0.000	−2.274	−2.274
Treatment condition	0.008	0.017	0.454	0.650	0.094	0.093
Sex	−0.012	0.018	−0.682	0.495	−0.146	−0.140
Intercept-slope cov	−0.090	0.201	−0.449	0.653	−0.119	−0.119
PCL-5 model						
Intercept	24.986	2.229	11.208	0.000	1.574	1.574
Treatment condition	1.294	2.126	0.609	0.543	0.082	0.081
Sex	1.095	2.245	0.488	0.626	0.069	0.065
Slope	−0.198	0.035	−5.591	0.000	−1.133	−1.133
Treatment condition	0.006	0.034	0.182	0.856	0.035	0.035
Sex	−0.017	0.036	−0.491	0.624	−0.100	−0.095
Intercept-slope cov	−0.892	0.571	−1.562	0.118	−0.325	−0.325
BDI-II model						
Intercept	15.879	1.940	8.186	0.000	1.288	1.288
Treatment condition	0.475	1.940	0.245	0.807	0.039	0.039
Sex	1.168	1.983	0.589	0.556	0.095	0.093
Slope	−0.122	0.026	−4.743	0.000	−0.974	−0.974
Treatment condition	0.008	0.026	0.311	0.756	0.064	0.064
Sex	−0.012	0.026	−0.441	0.659	−0.093	−0.091
Intercept-slope cov	−0.968	0.353	−2.739	0.006	−0.637	−0.637

Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, BDI-II = Beck Depression Inventory-II, cov = covariate, Estimate = parameter estimate, PCL-5 = PTSD Symptom Checklist-5, std.lv = estimate standardized for latent variables, std.all = estimate standardized for latent and observed variables.

indicating that NAC did not result in greater reductions in alcohol use than placebo (see Figure 2). In the model examining PDH, a significant effect of sex on the slope emerged (B = 0.06, $P = .04$), suggesting that males exhibited greater reduction in PDH than females. No other effects of sex on intercepts or slopes were observed. To examine clinically meaningful change in substance use, we compared average change in PDA from baseline to week 12 for the current sample to previously established criteria for reliable change.[43] On average, PDA increased from 32.3% (SD = 29.74) at baseline to 65.7% (SD = 33.10) at week 12, which is above the threshold for reliable change demonstrated in other research (ie, change of 30% in days of substance use[43]). To our knowledge, no other research has examined reliable change or clinically significant change for other metrics of substance use (eg, average DDD or PDH); however, in the current sample, average DDD decreased from 6.79 (SD = 4.51) at baseline to 2.74 (SD = 2.90) at week 12, and PDH decreased from 45.3% (SD = 35.11) at baseline to 10.4% (SD = 22.76) at week 12.

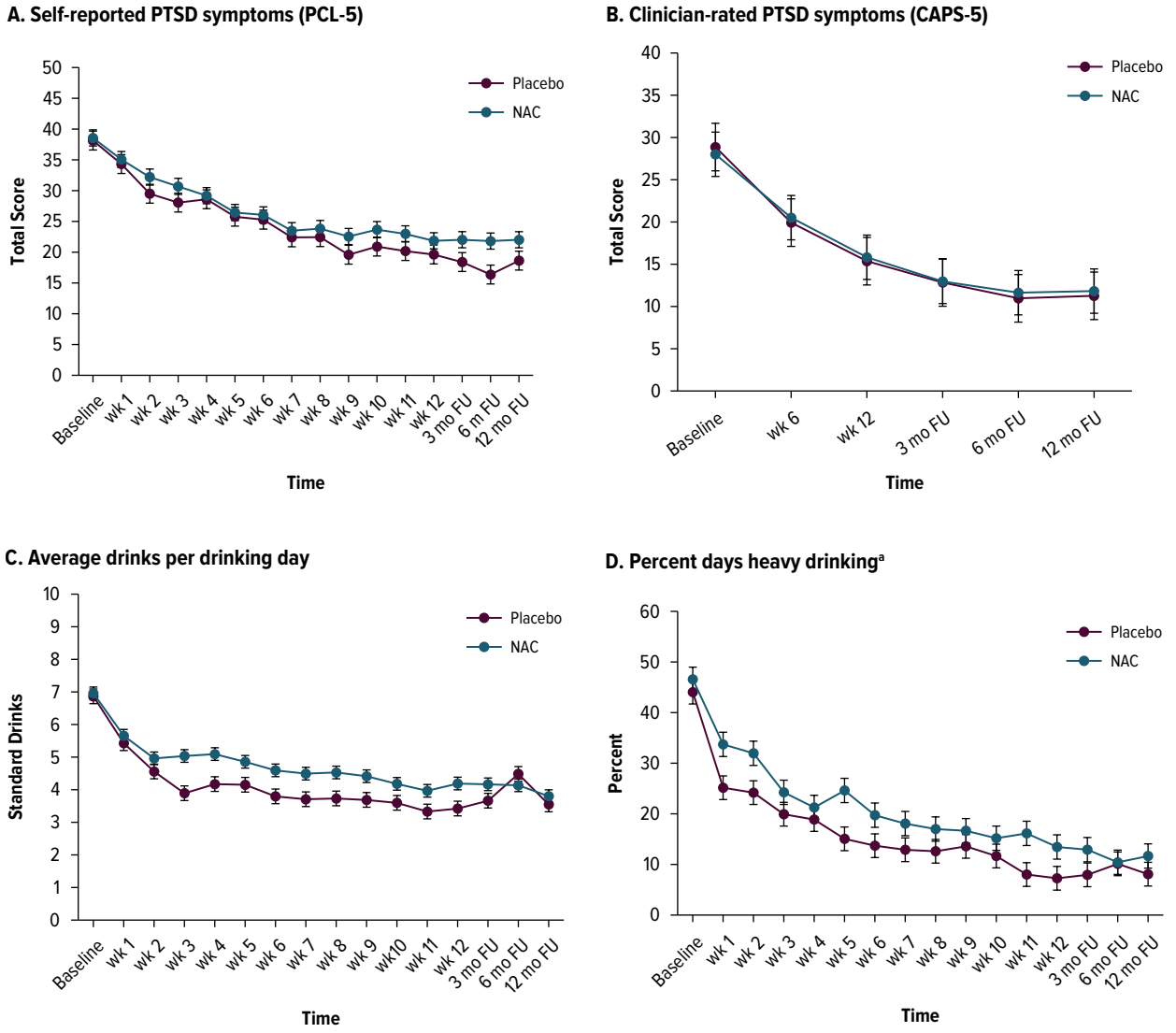
Craving, as measured by the OCDS, significantly decreased during treatment for the sample (B = −0.12, $P < .001$) but did not differ by treatment group, suggesting that there was no effect of NAC on craving (see Table 3). Further, no effects of sex were observed in this model. On average, craving scores on the OCDS decreased from 16.92 (SD = 7.30) at baseline to 9.12 (SD = 7.04) at week 12.

Depressive Symptoms

Examination of the BDI-II revealed that depressive symptoms decreased significantly over time for the sample (B = −0.12, $P < .001$; see Table 2). Treatment group was not significantly associated with the intercept or slope in this model, indicating no differences in NAC vs placebo group on depressive symptoms. No differences by sex were observed. Average BDI-II scores decreased from 22.53 (SD = 10.91) at baseline to 12.60 (SD = 11.82) at week 12, suggesting that on average, participants started treatment in the moderate depression range and ended in the minimal range.[38]

Figure 2.

Changes in PTSD Symptoms and Alcohol Use Over Time by Medication Group



[a]Heavy drinking defined as 5 or more standard drinks per day for males and 4 or more standard drinks per day for females.
Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, FU = follow-up (assessment time point), NAC = N-acetylcysteine, PCL-5 = PTSD Symptom Checklist-5.

Retention, Medication Compliance, and Penetration of the Blind

Retention was strong and 83.5% of participants (n = 152/182) completed the 12-week treatment phase. There was no difference between treatment groups in retention (n = 78 NAC, n = 74 placebo; $\chi^2 = 0.017$; $df = 1$, $P = .89$). Consistent with existing literature from pharmacotherapy trials of PTSD/AUD,[44] treatment completers were defined as participants completing week 12, whether or not they remained on the medication. Medication compliance data, as measured via riboflavin assay in urine, were missing for 44 participants due to the COVID-19 pandemic when the study transitioned to primarily telehealth visits, and this analysis could not be obtained. Among participants from whom riboflavin was able to be analyzed, 36 exhibited full medication compliance (ie, positive riboflavin urinalysis at both week 6 and 12), 83 exhibited partial compliance (ie, positive riboflavin urinalysis at either week 6 or 12) or inconclusive results (eg, riboflavin analysis conducted at only 1 time point), and 19 exhibited noncompliance (ie, negative riboflavin urinalysis at both weeks 6 and 12). There were no differences between treatment groups in medication compliance ($\chi^2 = 2.675$, $df = 3$, $P = .44$). One hundred forty-one participants completed a penetration of the blind assessment. Of these, 82 participants

Table 3.

Results From Linear Latent Growth Curve Models Examining Alcohol Use and Alcohol Craving

Model	Estimate	SE	z-value	*P*-value	std.lv	std.all
DDD model						
Intercept	4.421	0.404	10.935	0.000	1.876	1.876
Treatment condition	0.551	0.307	1.794	0.073	0.234	0.234
Sex	−0.442	0.384	−1.115	0.250	−0.188	−0.170
Slope	−0.023	0.006	−3.573	0.000	−0.322	−0.320
Treatment condition	−0.008	0.006	−1.361	0.173	−0.116	−0.116
Sex	0.008	0.006	1.259	0.208	0.106	0.106
Intercept-slope cov	−0.087	0.046	−1.905	0.057	−0.542	−0.542
PHD model						
Intercept	15.179	2.039	7.444	0.000	0.747	0.747
Treatment condition	1.824	1.694	1.077	0.281	0.090	0.090
Sex	−0.017	1.812	−0.009	0.993	−0.001	−0.001
Slope	−0.139	0.036	−3.881	0.000	−0.410	−0.410
Treatment condition	−0.037	0.029	−1.291	0.197	−0.109	−0.109
Sex	**0.063**	**0.030**	**2.104**	**0.035**	**0.185**	**0.180**
Intercept-slope cov	−4.446	1.583	−2.809	0.005	−0.663	−0.663
PDA model						
Intercept	59.387	6.683	8.886	0.000	2.167	2.167
Treatment condition	−1.102	5.885	−0.187	0.851	−0.040	−0.020
Sex	−3.390	6.702	−0.506	0.613	−0.124	−0.057
Slope	0.286	0.125	2.294	0.022	0.774	0.774
Treatment condition	−0.091	0.106	−0.856	0.392	−0.246	−0.123
Sex	−0.011	0.121	−0.092	0.926	−0.030	−0.014
Intercept-slope cov	−5.635	1.299	−4.339	0.000	−0.562	−0.562
OCDS model						
Intercept	12.618	0.866	14.574	0.000	2.029	2.029
Treatment condition	−0.897	0.827	−1.085	0.278	−0.144	−0.144
Sex	0.436	0.870	0.501	0.616	0.070	0.067
Slope	−0.117	0.017	−6.922	0.000	−1.203	−1.203
Treatment condition	0.002	0.016	0.097	0.922	0.016	0.016
Sex	0.007	0.017	0.383	0.701	0.067	0.064
Intercept-slope cov	−0.219	0.107	−2.044	0.041	−0.367	−0.367

Abbreviations: cov = covariate, DDD = average drinks per drinking day, Estimate = parameter estimate, OCDS = Obsessive Compulsive Drinking Scale, PDA = percent days abstinent; PHD = percent heavy drinking days, SE = standard error, std.all = estimate standardized for latent and observed variables, std.lv = estimate standardized for latent variables.

reported their belief that they received NAC (n = 42 NAC, n = 40 placebo), and 59 participants reported their belief that they received placebo (n = 27 NAC, n = 32 placebo), with no significant differences between treatment groups in penetration of the blind assessment ($\chi^2 = 0.41$, $df = 1$, $P = .52$), suggesting that the blinding in the protocol was effective.

Safety and AEs

AEs were assessed at weekly visits during the treatment phase and through the 1-year follow-up. Common AEs included gastrointestinal discomfort such as diarrhea or constipation (24.8% NAC, 15.0% placebo), infections (14.8% NAC, 18.0% placebo), muscle or joint pain (7.7% NAC, 11.9% placebo), and psychiatric symptoms (12.6% NAC, 13.0% placebo) with no between-group differences (294 total AEs among participants randomized to NAC and 239 total AEs among those randomized to placebo; $\chi^2 = 36.78$, $df = 1$, $P = .53$). Ten serious adverse events (SAEs) occurred during the study among 9 participants (7 NAC group; 3 placebo group; 1.01^2, $df = 1$, $P = .31$). The most common SAEs were hospital admissions for medical reasons (eg, cardiac disorders, infection, surgical procedures) or psychiatric reasons (eg, suicidality) and were unrelated to study participation. There was 1 all-cause mortality in the placebo group, unrelated to study participation.

DISCUSSION

The current study evaluated the efficacy of NAC, an antioxidant with glutamatergic modulating properties, versus placebo, when added to CBT for AUD, for the treatment of adults with co-occurring PTSD/AUD. This is the largest randomized controlled trial of NAC conducted to date among individuals with comorbid PTSD/AUD. Although significant reductions were observed in PTSD symptoms, alcohol use amount and frequency, and alcohol craving, there were no significant between-group treatment differences. Contrary to the hypothesis, NAC was not more effective than placebo in reducing PTSD or AUD severity in this sample. Depressive symptoms also improved during the treatment phase for both treatment groups, but no group differences between the NAC and placebo groups were observed. NAC was safe and well tolerated, with low rates of AEs and high rates of retention.

The findings differ from a previous randomized pilot study of NAC in which military veterans (N = 35) received NAC (2,400 mg/day) or placebo plus intensive (5 days/week) outpatient treatment for SUDs at the VA.[25] In that study, veterans who received NAC had significantly greater reductions in PTSD symptoms, craving, and depression, but no difference in substance use, as compared to veterans who received placebo. Several important differences between the studies may contribute to the discrepant findings. First, the pilot study was comprised of predominantly male (96.3%), African American (70.4%) veterans who had cocaine use disorder (74.1%), were abstinent from alcohol and drugs for at least 1 week prior to randomization, and were enrolled in an intensive outpatient SUD program. In contrast, the current study was comprised of predominantly white females from the community with AUD, who received 1 weekly therapy session each week and were not required to be abstinent prior to participation.

The current study considered whether alcohol outcomes differed by individuals who were or were not abstinent 1 week prior to medication initiation, and the findings were not significant. However, the current study

was not designed to investigate the influence of pretreatment abstinence on the effects of NAC, nor was abstinence required for study enrollment. Only 9% of participants were abstinent before starting the trial, and although they were evenly distributed across treatment groups, the number of individuals was small, limiting our ability to more thoroughly examine the influence of pretreatment abstinence. One previous study examining NAC among individuals with cocaine use disorder found a positive effect of NAC on reducing craving and delaying time to relapse among individuals who were already abstinent for 1 to 2 weeks before starting the trial.[30] NAC may be most helpful to support individuals in early abstinence rather than to facilitate the induction of abstinence, but future research designed to rigorously evaluate this important question is needed.

The findings from the current study are consistent with other recent community-sample findings[26] examining NAC (2,700 mg/day) among a sample of 105 adults (58% female; average age = 43.0) with treatment-resistant PTSD. Approximately one-third of the sample also had comorbid AUD, and 14% had a drug use disorder. As in the current trial, participants in that study were not required to be abstinent prior to enrolling in the trial. While the study found high retention rates (77%) and NAC was well tolerated, their results were also not significantly better for PTSD or depression outcomes compared to placebo, supporting the idea that NAC may not be as effective in nonabstinent individuals. Additional research is also needed to better understand how alcohol use during NAC treatment may impact efficacy on AUD and PTSD symptoms. It is possible that ongoing alcohol use may disrupt or attenuate the glutamatergic mechanisms targeted by NAC. Thus, research is needed to examine the potential effects of drinking status both at pretreatment and during treatment on the therapeutic effects of NAC.

Several limitations of the current study warrant consideration. Although the dosage was selected based on prior research, it is possible that a higher dose (within safety limitations) would have generated more positive outcomes. Moreover, the COVID-19 pandemic impacted our recruitment for this study, and we reached 91% (182/200) of the target sample size. However, retention was higher than anticipated, suggesting that the findings were not solely due to the sample size. Additionally, the telehealth option limited the ability to confirm medication adherence using riboflavin or blood samples, and to measure biological outcomes (eg, ethyl glucuronide). It is conceivable that these modifications may have impacted the findings. The sample lacked racial/ethnic diversity, limiting broader generalizability. Future research should include more diverse populations, perhaps by increasing community engagement methods.

Despite these limitations, strengths of the study include the large sample size, stratified block randomization, placebo-controlled design, weekly assessments, manualized psychosocial treatment platform, long-term outcomes (1 year), and high retention. Over 80% of participants completed the 12-week treatment phase, which is notable given the challenges of retaining individuals with comorbid PTSD/AUD in longer clinical trials. Importantly, there were no significant differences in retention or AEs between the NAC and placebo groups, indicative of NAC's favorable safety profile.

In summary, this study adds to the growing evidence on NAC's potential in treating co-occurring PTSD/AUD. The largest investigation to date of NAC for the treatment of co-occurring PTSD/AUD, this study found no significant differences between NAC and placebo in clinical outcomes. Although limited, the findings fill a notable gap in the PTSD/AUD literature and provide information to help inform the next steps in this line of inquiry. Thus far, the preclinical findings of NAC's potential therapeutic value have not been translated to the specific contexts in which NAC has been applied clinically. While preclinical studies strongly support GLT-1 upregulation by NAC, it is possible that the translation of these effects to clinical improvement may depend on several factors (eg, pretreatment abstinence, substance use during treatment). For this study, we did not observe evidence of efficacy of NAC when applied at this dose and when added to this behavioral platform for patients with PTSD/AUD. Robust preclinical data support the role of NAC in modulating glutamatergic dysregulation; however, it is possible that the clinical translation of these effects may require more tailored approaches, particularly with regard to the intensity and timing of psychotherapy relative to substance use abstinence. Future analyses will explore potential moderators and mediators of potential outcomes. Continued work is essential to improve pharmacologic and integrated treatment approaches for PTSD and AUD.

Article Information

Published Online: August 27, 2025. https://doi.org/10.4088/JCP.25m15803

Submitted: January 20, 2025; accepted June 11, 2025.

To Cite: Back SE, Gray K, Jarnecke AM, et al. *N*-acetylcysteine for the treatment of co-occurring posttraumatic stress disorder and alcohol use disorder: a double-blind, randomized controlled trial. *J Clin Psychiatry* 2025;86(4):25m15803.

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Relevant Financial Relationships: There are no relevant financial relationships or conflicts of interest for any of the authors.

Funding/Support: This research was supported by the National Institute on Alcohol Abuse and Alcoholism (R01AA025086 and R01AA025086-03S1) and the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1 TR001450).

Role of the Sponsor: The funding sources were not involved in the study design, the collection, analysis, and interpretation of data, the writing of this manuscript, or the decision to submit this manuscript for publication.

Acknowledgments: The authors thank the following individuals for their assistance with recruitment, study implementation, and manuscript edits: Anjinetta Yates-Johnson, PA; Stacey Sellers, MS; and Hailey Britt, MS. There are no conflicts of interest to declare for individuals acknowledged.

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