A Double-Blind, Randomized, Controlled Pilot Trial of *N*-Acetylcysteine in Veterans With Posttraumatic Stress Disorder and Substance Use Disorders

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ABSTRACT

Objective: The antioxidant *N*-acetylcysteine is being increasingly investigated as a therapeutic agent in the treatment of substance use disorders (SUDs). This study explored the efficacy of *N*-acetylcysteine in the treatment of posttraumatic stress disorder (PTSD), which frequently co-occurs with SUD and shares impaired prefrontal cortex regulation of basal ganglia circuitry, in particular at glutamate synapses in the nucleus accumbens.

Methods: Veterans with PTSD and SUD per *DSM-IV* criteria (N = 35) were randomly assigned to receive a double-blind, 8-week course of *N*-acetylcysteine (2,400 mg/d) or placebo plus cognitive-behavioral therapy for SUD (between March 2013 and April 2014). Primary outcome measures included PTSD symptoms (Clinician-Administered PTSD Scale, PTSD Checklist-Military) and craving (Visual Analog Scale). Substance use and depression were also assessed.

Results: Participants treated with *N*-acetylcysteine compared to placebo evidenced significant improvements in PTSD symptoms, craving, and depression (β values < –0.33; *P* values < .05). Substance use was low for both groups, and no significant between-group differences were observed. *N*-acetylcysteine was well tolerated, and retention was high.

Conclusions: This is the first randomized controlled trial to investigate *N*-acetylcysteine as a pharmacologic treatment for PTSD and SUD. Although preliminary, the findings provide initial support for the use of *N*-acetylcysteine in combination with psychotherapy among individuals with co-occurring PTSD and SUD.

Trial Registration: ClinicalTrials.gov identifier: NCT02499029

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Posttraumatic stress disorder (PTSD) is the most common mental health disorder among veterans presenting at US Veterans Affairs (VA) hospitals,[1] and 45.7% of military personnel with PTSD remain symptomatic 3 years after discontinuing service.[2] Data from the Department of Veterans Affairs indicate that, among veterans serving in the Vietnam era or later (N = 1,001,996), 41.4% with a substance use disorder (SUD) meet criteria for current PTSD.[3] Veterans with co-occurring PTSD/SUD have poor treatment outcomes on multiple indices of functioning (eg, social problems, suicide attempts) and undergo more episodes of SUD treatment.[4]

Pharmacologic treatment for co-occurring PTSD/SUD is not well explored. Only selective serotonin reuptake inhibitors (SSRIs) have received US Food and Drug Administration (FDA) approval for the treatment of PTSD.[5,6] Investigations of pharmacologic treatments of co-occurring PTSD/SUD have had suboptimal results.[7–10] The antioxidant *N*-acetylcysteine has been used in the treatment of acetaminophen overdose for over 3 decades[11] and is being increasingly investigated as a therapeutic agent for a variety of psychiatric disorders that share impaired executive functioning, impulse control, and top-down regulation, including addiction (ie, cannabis, cocaine, nicotine), gambling, and trichotillomania.[11–13] Preclinical and clinical research suggests that *N*-acetylcysteine normalizes extracellular glutamate by restoring the activity of glutamate transporters and antiporters in the nucleus accumbens.[14] Animal models demonstrate that chronic SUD down-regulates the glial glutamate transporter (GLT-1, EAAT-2) in the nucleus accumbens, and treatment with *N*-acetylcysteine restores this transporter, thereby normalizing synaptic glutamate transmission.[12]

Accumulating research suggests that there may be shared neurobiological mechanisms underlying PTSD and SUD,[15] which might respond favorably to *N*-acetylcysteine. For example, PTSD and SUD share impaired prefrontal cortex regulation of basal ganglia circuitry, in particular at glutamate synapses in the nucleus accumbens.[16–18] Neuroimaging studies demonstrate that individuals with PTSD exhibit hypoactive executive functioning (prefrontal cortex) and hyperactive fear circuitry (amygdala) activity[19–21] and significant uncoupling between the prefrontal cortex and amygdala at rest and during symptom provocation.[22,23] Similarly, individuals with SUD also demonstrate attenuated prefrontal-amygdala functional connectivity,[18,24] which is a marker of early relapse risk.[25] This converging evidence suggests that the prefrontal cortex of individuals with PTSD/SUD is less able to disrupt maladaptive anxiety-related and drug-seeking behaviors that are driven, in part, by intrusive thoughts and/or cravings.[18,26]

In light of the capacity of *N*-acetylcysteine to restore glutamatergic synaptic physiology in prefrontal cortex projections and to inhibit drug use in animal models and human addiction, as well as the shared prefrontal impairments identified in PTSD and SUD, we examined *N*-acetylcysteine

Clinical Points

- Posttraumatic stress disorder (PTSD) and substance use disorders (SUDs) are chronic and debilitating conditions that often co-occur.
- Substantial gaps in the treatment of PTSD/SUD exist, and little evidence is available to guide the provision of care. The pharmacologic treatment of PTSD/SUD remains largely ineffective.
- For patients with co-occurring PTSD and SUD, *N*-acetylcysteine may help reduce PTSD symptoms, craving, and depressive symptoms.

as a candidate pharmacotherapy for comorbid PTSD/SUD. We conducted a double-blind, randomized, placebo-controlled pilot trial of *N*-acetylcysteine versus placebo, plus cognitive-behavioral therapy (CBT) for SUD among US military veterans. We hypothesized that *N*-acetylcysteine treatment combined with CBT for SUD would reduce PTSD symptoms, craving, and substance use.

METHODS

Design

Treatment-seeking veterans with PTSD and SUD were randomly assigned to receive a double-blind, 8-week course of *N*-acetylcysteine or placebo, along with group CBT for SUD (ClinicalTrials.gov identifier: NCT02499029). A 1-month assessment following medication discontinuation was conducted. The Investigational New Drug application for this study was approved by the FDA. All study procedures were approved by the institutional review boards and were in accordance with the Helsinki Declaration of 1975.

Participants

Veterans (N = 35) were enrolled in the Substance Abuse Treatment Clinic (SATC) at the Ralph H. Johnson VA Medical Center in Charleston, South Carolina, between March 2013 and April 2014. Participants were 18–65 years old; were US military veterans; met *DSM-IV*[27] diagnostic criteria for the past 6 months for SUD (ie, alcohol or drug use disorder) and PTSD or subthreshold PTSD (ie, met criteria for cluster B [re-experiencing] and either cluster C [avoidance] or D [hyperarousal], as well as duration of 1 month and clinically significant impairment); and scored >21 on the Mini-Mental State Examination (MMSE).[28] Participants were excluded for unstable medical conditions, significant cognitive impairment, bipolar or psychotic disorders, seizures or asthma, prior treatment with *N*-acetylcysteine, ongoing PTSD treatment, or use of carbamazepine, phenytoin, nitrous oxide, methotrexate, or nitroglycerin within the last 14 days or any other medication felt to have a hazardous interaction if taken with *N*-acetylcysteine. Female participants could not be pregnant or lactating.

General Procedures

Veterans were recruited through clinical referral and local advertisements. After receiving a complete description of the study, participants provided written informed consent. Interested veterans completed a baseline assessment that involved diagnostic interviews, history and physical examination, self-report questionnaires, breathalyzer tests, and urine drug screen tests to assess inclusion/exclusion criteria as well as baseline characteristics and symptom severity. Eligible participants were randomly assigned after at least 1 week of abstinence from alcohol and drugs, as indicated by self-report, urine drug screen test, and breathalyzer test. Participants came into the office twice weekly for visits. Vital signs and concomitant medications were assessed weekly. Participants received $510 for completing all visits.

Interventions

Medication. Participants were randomly assigned to *N*-acetylcysteine (2,400 mg/d) or placebo for 8 weeks. The starting dose of *N*-acetylcysteine was 1,200 mg twice daily (2,400 mg/d). One participant achieved target dose at week 4 (1,200 mg/d for the first 4 weeks). Equivalent numbers of identical appearing placebo capsules were dispensed. All *N*-acetylcysteine and placebo capsules contained riboflavin 25 mg, which was used as a biomarker for medication compliance. Weekly pill counts and missed doses were recorded each week.

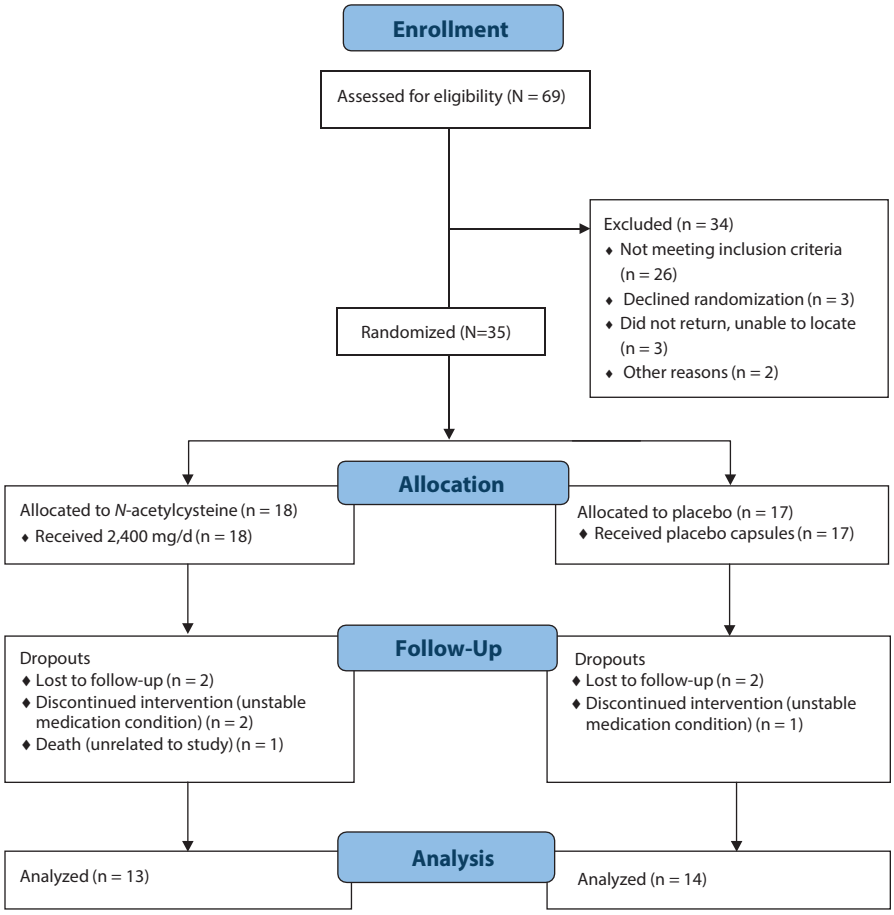
Study medications (United States Pharmacopeia [USP]-grade *N*-acetylcysteine and matched placebo capsules) were compounded by Pitt Street Pharmacy in Charleston, South Carolina, and dispensed weekly by study staff. Treatment assignment followed a prearranged randomization scheme and was carried out by study personnel at the pharmacy to preserve the double-blind design.

Cognitive-behavioral therapy. All participants received group CBT through the VA intensive outpatient program. This ensured that all participants, regardless of medication arm, received adequate psychosocial support, and it restricted variability resulting from varied types of behavioral interventions thereby enhancing statistical power.[29] Structured group therapy was provided 5 days per week and focused on SUD topics including cognitive restructuring, coping with cravings, drink refusal skills, and relaxation skills.

Measures

At baseline, participants completed a demographic form, the MMSE,[28] and the Mini-International Neuropsychiatric Interview (MINI)[30] to assess SUD and other psychiatric diagnoses. The Clinician-Administered PTSD Scale (CAPS) assessed trauma history, PTSD diagnosis, and symptom severity.[31] CAPS total and subscale scores (Re-experiencing, Avoidance, Hyperarousal) were obtained at baseline, week 4, week 8, and follow-up. The PTSD Checklist-Military (PCL-M), a 17-item self-report measure, assessed weekly PTSD symptoms.[32] The Timeline Follow-Back (TLFB),[33] a self-report, calendar-based instrument, measured the amount and frequency of substance use at baseline (past 60 days) and weekly during the study. Visual Analog Scales assessed craving over the past week. Participants rated 3 items

Figure 1. Enrollment and Study Flow of Veterans With PTSD and SUD Assigned to *N*-Acetylcysteine or Placebo



Abbreviations: PTSD = posttraumatic stress disorder, SUD = substance use disorder.

(amount, intensity, and frequency) using anchors of 0 ("not at all") to 10 ("extreme" or "all the time"). Urine drug screen tests for cocaine, marijuana, opiates, methamphetamines, amphetamines, and benzodiazepines were collected weekly. Alcohol breathalyzer tests measured blood alcohol concentration each week.

The Beck Depression Inventory, second edition (BDI-II), a 21item self-report questionnaire, measured depressive symptoms.[34] The Columbia-Suicide Severity Rating Scale (C-SSRS) was conducted at baseline for study eligibility.[35] Adverse events were assessed weekly using a 6-item checklist measuring the most common adverse events as indicated on the FDA-approved label for *N*-acetylcysteine (Ajinomoto North America Inc).

Statistical Analyses

Analyses were conducted using SPSS Version 22 (IBM Corporation). Demographic characteristics were compared using χ^2 tests for categorical variables and *t* tests for continuous variables. The primary hypothesis was that *N*-acetylcysteine would significantly decrease PTSD symptoms and craving. Secondary analyses examined the effect of *N*-acetylcysteine on substance use and depression. A series of hierarchical linear regression analyses were conducted to examine the effects of treatment group (*N*-acetylcysteine or placebo) on PTSD symptomatology, craving, substance use, and depression. The primary outcome measure was entered as the criterion variable. Baseline levels of the respective outcome measures were entered in Step 1 of the model to adjust for any baseline differences. Treatment group was entered as the predictor in Step 2. This was a pilot study with adequate power to detect within-group changes on key outcome measures. Thus, we conducted a series of paired samples *t* tests to examine within-group changes in PTSD symptoms, depressive symptoms, craving, and substance use. The significance threshold was set at a *P* value of .05 (2-sided) for all statistical tests.

RESULTS

Study Retention and Medication Compliance

Figure 1 illustrates the flow diagram based on the Consolidated Standards Of Reporting Trials (CONSORT). Sixty-nine participants completed the baseline assessment for eligibility and 35 participants were randomly assigned (18 to *N*-acetylcysteine, 17 to placebo). The majority of participants (77%) completed the 8-week treatment phase,

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Placebo (n = 14) n (%)	*N*-Acetylcysteine (n = 13) n (%)	Total (N = 27) n (%)
Gender, male	14 (100.0)	12 (92.3)	26 (96.3)
Race, white	4 (28.6)	4 (30.8)	8 (29.6)
Race, African-American	10 (71.4)	9 (69.2)	19 (70.4)
Relationship, married	3 (21.4)	3 (23.1)	6 (22.2)
Education, at least some college	6 (42.9)	9 (69.2)	15 (55.5)
Unemployed/retired/disabled	9 (64.3)	12 (92.3)	21 (77.7)
Trauma history			
Military, combat	2 (14.3)	3 (23.1)	5 (18.5)
Military, noncombat	4 (28.6)	5 (38.5)	9 (33.3)
Civilian-related event(s)	8 (57.1)	5 (38.5)	13 (48.1)
Substance use disorders			
Alcohol use disorder	12 (85.7)	10 (76.9)	22 (81.5)
Cocaine use disorder	9 (64.3)	11 (84.6)	20 (74.1)
Opioid use disorder	1 (7.1)	0 (0.0)	1 (3.7)
	Mean (SD)	Mean (SD)	Mean (SD)
Age, y	49.9 (8.1)	48.2 (8.6)	49.0 (8.2)
Substance use severity[a]			
Average drinks per day[b]	4.9 (4.5)	3.7 (3.5)	4.3 (3.9)
Average drinks per drinking day[b]	12.9 (5.7)	9.77 (6.8)	11.5 (6.2)
Age at onset of alcohol use disorder, y	22.8 (6.7)	26.8 (10.4)	24.9 (8.9)
Average dollar amount of cocaine used per day,[c] US $	17.3 (10.4)	20.3 (14.6)	18.9 (12.4)
Average dollar amount of cocaine used per using day,[c] US $	72.5 (32.6)	72.6 (38.9)	72.6 (34.1)
Age at onset of cocaine use disorder, y	29.9 (4.5)	30.4 (9.5)	30.2 (6.9)
PTSD severity			
PCL-M total score	43.4 (18.6)	45.7 (14.6)	44.5 (16.5)
CAPS total score	68.6 (23.7)	58.8 (21.2)	63.8 (22.6)
Re-experiencing subscale	21.9 (7.3)	18.8 (9.5)	20.4 (8.4)
Avoidance subscale	25.5 (12.5)	18.3 (8.3)	22.0 (11.1)
Hyperarousal subscale	21.2 (6.97)	21.8 (7.5)	21.5 (7.1)
Depression			
BDI-II total score	22.8 (13.1)	19.1 (6.7)	21.0 (10.5)

[a]Only 3 substances (ie, alcohol, cocaine, and opioids) were endorsed by participants.
[b]Average number of standard drink units consumed per day, or per drinking day, during the past 60 days.
[c]Average dollar amount of cocaine used per day, or per using day, during the past 60 days.
Abbreviations: BDI-II = Beck Depression Inventory, second edition; CAPS = Clinician-Administered PTSD Scale; PCL-M = PTSD Checklist-Military; PTSD = posttraumatic stress disorder.

and there were no group differences in retention (13/18, *N*-acetylcysteine; 14/17, placebo). Similarly, 12 (67%) of 18 in the *N*-acetylcysteine group and 12 (71%) of 17 in the placebo group completed the follow-up. Of the 8 participants who did not complete the study, 4 were lost to follow-up, 3 were excluded due to unstable medical conditions, and 1 died of cardiovascular collapse, judged to be unrelated to the study. Medication compliance (ie, ≥ 1,000 ng/mL of riboflavin and greater than baseline at ≥ 2/3 assessment time points) was 82.9% and did not differ by group. This resulted in 13 participants in the *N*-acetylcysteine group and 14 in the placebo group who were included in the final per-protocol analyses.

Demographics

Table 1 presents the demographic characteristics for the sample. Participants were primarily male (96.3%), and the majority of participants were diagnosed with alcohol use disorder (81.5%) and/or cocaine use disorder (77.8%).

PTSD Symptoms

Self-report PTSD symptoms. The PCL-M was reduced by 32% in the *N*-acetylcysteine group versus 3% in the placebo group from baseline to week 8 (Table 2). The adjusted regression model examining *N*-acetylcysteine versus placebo on PCL-M scores at week 8 accounted for 73.8% of the variance ($F_{2,24} = 33.89$, $P < .001$), with the *N*-acetylcysteine group having significantly lower scores at week 8 than the placebo group ($\beta = -0.36$, $P < .01$). Examination of follow-up revealed a trend toward a significant between-group difference ($\beta = -0.70$, $P = .06$). Significant within-group effects were observed in the *N*-acetylcysteine group on the PCL-M from baseline to week 4 ($d = 1.84$, $P < .01$) and week 8 ($d = 1.30$, $P < .001$), reflecting large effect sizes.[36] In contrast, no significant within-group effects on the PCL-M were observed in the placebo group.

Clinician-rated PTSD symptoms. The CAPS was reduced by 46% in the *N*-acetylcysteine group versus 25% in the placebo group from baseline to week 8 (Table 2). Examination of between-group differences in the CAPS total and subscales scores revealed no statistically significant differences. Significant within-group effects in the *N*-acetylcysteine group on the CAPS total score from baseline to week 8 ($d = 1.27$, $P < .001$) and to week 12 ($d = 1.48$, $P < .05$) were observed. Further, significant within-group effects on the Re-experiencing, Avoidance, and Hyperarousal subscales

Table 2. Efficacy of *N*-Acetylcysteine Treatment on Symptoms of PTSD, Depression, and Craving[a]

	Placebo (n = 14) Within-Group Outcomes Weeks			*N*-Acetylcysteine (n = 13) Within-Group Outcomes Weeks			Between Groups
Measure	0	4	8	0	4	8	Weeks 0–8
PCL-M	43.4 (18.6)	41.9 (21.7)	41.9 (22.8)	45.7 (14.6)	33.8 (10.6)[b]	31.2 (9.7)[b]	−0.355[c]
CAPS	68.6 (23.7)	52.8 (36.9)[b]	51.5 (43.1)	58.8 (21.2)	38.7 (20.0)[b]	32.0 (23.5)[b]	−0.127
CAPS-R	21.9 (7.3)	15.6 (10.2)[b]	12.4 (13.1)[b]	18.8 (9.5)	12.6 (6.9)[b]	10.1 (8.1)[b]	−0.119
CAPS-A	25.5 (12.5)	21.6 (16.1)	20.4 (19.6)	18.3 (8.3)	10.5 (9.1)[b]	10.7 (9.2)[b]	−0.330
CAPS-H	21.2 (6.9)	15.6 (11.9)	13.6 (13.0)	21.8 (7.5)	15.6 (8.3)[b]	11.8 (9.5)[b]	−0.194
BDI-II	22.8 (13.1)	18.5 (14.8)	19.3 (15.8)	19.1 (6.7)	10.9 (6.4)	9.9 (6.7)[b]	−0.325[c]
Craving-A	4.1 (3.1)	2.8 (2.6)	2.8 (2.8)	3.7 (3.4)	1.8 (1.9)[b]	0.7 (0.7)[b]	−0.413[c]
Craving-F	4.2 (3.2)	2.4 (2.3)	3.0 (2.9)	3.6 (3.0)	1.8 (2.0)[b]	1.0 (0.9)[b]	−0.387[c]
Craving-I	3.7 (3.0)	2.9 (2.8)	2.8 (3.1)	3.7 (3.1)	1.8 (2.1)	1.3 (1.9)[b]	−0.288

[a]Values given as mean (SD).
[b]$P < .05$ indicates a significant within-group difference as compared to baseline (week 0).
[c]$P < .05$ indicates a between-group difference at the end of treatment (week 8) as compared to baseline (week 0).
Abbreviations: BDI-II = Beck Depressive Inventory, second edition; CAPS = Clinician-Administered PTSD Scale total score; CAPS-A = CAPS Avoidance subscale; CAPS-H = CAPS Hyperarousal subscale; CAPS-R = CAPS Re-experiencing subscale; Craving-A = amount of craving; Craving-F = frequency of craving; Craving-I = intensity of craving; PCL-M = PTSD Checklist-Military, PTSD = posttraumatic stress disorder.

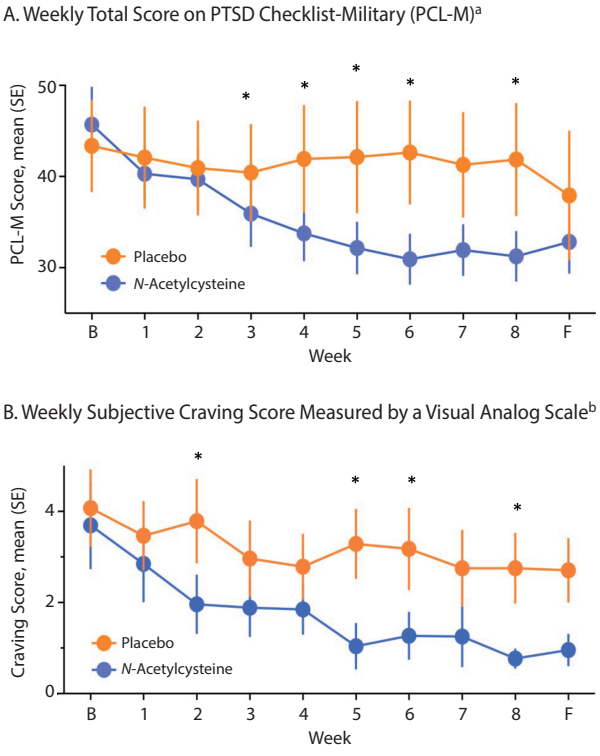
were observed in the *N*-acetylcysteine group from baseline to week 8 ($d = 1.01$, $d = 1.03$, and $d = 1.16$, respectively; P values $< .01$) and week 12 ($d = 1.04$, $d = 1.34$, and $d = 1.57$, respectively; P values $< .01$). Among the placebo group, no significant within-group effect on the CAPS total score was observed, but a within-group effect on the Re-experiencing subscale score was observed from baseline to week 8 ($d = 0.73$, $P < .05$) and week 12 ($d = 0.67$, $P < .05$).

Comparisons of responders. *Responders* were defined as participants who demonstrated ≥ 1 standard deviation (SD) difference on the outcome measure of interest from pretreatment to posttreatment (baseline to week 8). Chi-square analyses were conducted to investigate differences in responders by treatment group (*N*-acetylcysteine vs placebo). For the PCL-M, *responders* were defined as having a pre-post reduction of ≥ 16 points. For the CAPS, *responders* were defined as having a pre-post reduction of ≥ 23 points. A significant χ^2 was observed for the *N*-acetylcysteine group (61.5% responders) compared to placebo (21.4% responders) on the PCL-M ($\chi^2 = 4.49$; $P = .03$). Although in the same direction, no statistically significant difference was observed for the *N*-acetylcysteine group (53.9% responders) compared to placebo (35.7% responders) on the CAPS ($\chi^2 = 0.90$; $P = .34$).

Craving and Substance Use

Craving. As illustrated in Figure 2, amount of craving was reduced 81% in the *N*-acetylcysteine group as compared to 32% in the placebo group from baseline to week 8. The adjusted regression equation model examining the efficacy of *N*-acetylcysteine versus placebo on reduction of amount of craving from baseline to week 8 accounted for 32.7% of the variance ($F_{2,24} = 18.34$, $P < .001$), with the *N*-acetylcysteine group having significantly lower amount of craving than the placebo group ($\beta = -0.41$, $P < .05$). Tests of within-group effects revealed a significant effect for amount of craving in the *N*-acetylcysteine, but not placebo, group from baseline to week 8 ($d = 1.03$, $P < .05$) and week 12 ($d = 0.75$, $P < .05$).

Figure 2. Change in PTSD Symptoms and Drug Craving Over Time by Treatment Condition



[a]*N*-acetylcysteine showed a significant treatment effect to reduce PTSD symptoms over the 8-week treatment period. Follow-up measure was obtained 4 weeks after discontinuing *N*-acetylcysteine or placebo (ie, week 12 of the study).
[b]*N*-acetylcysteine showed a significant treatment effect to reduce drug cravings over the 8-week treatment period.
*$P < .05$.
Abbreviations: B = baseline, F = follow-up, PTSD = posttraumatic stress disorder.

Frequency of craving was reduced by 72% in the *N*-acetylcysteine group versus 29% in the placebo group from baseline to week 8. The adjusted regression equation model examining the efficacy of *N*-acetylcysteine versus placebo on frequency of craving from baseline to week 8 accounted for 30.3% of the variance ($F_{2,24} = 6.65$, $P < .001$), with the *N*-acetylcysteine group having significantly lower level of frequency of craving than the placebo group ($\beta = -0.39$, $P < .05$). There was a significant group difference in frequency of craving at follow-up, with the adjusted regression equation model accounting for 27.9% of the variance ($F_{2,24} = 4.057$, $P < .05$) and with the *N*-acetylcysteine group demonstrating significantly lower frequency of craving at week 12 than the placebo group ($\beta = -0.40$, $P < .05$). Tests of within-group effects revealed a significant effect for *frequency* of craving in the *N*-acetylcysteine, but not placebo, group from baseline to week 8 ($d = 1.03$, $P < .05$) and week 12 ($d = 0.79$, $P < .05$).

Treatment condition was not a significant predictor of *intensity* of craving at week 8 ($\beta = -0.28$, $P < .05$) or week 12 ($\beta = -0.51$, $P < .05$) in the between-group analyses. However, significant within-group effects from baseline to week 8 ($d = 1.06$) and to week 12 ($d = 0.82$) were revealed in the *N*-acetylcysteine but not placebo group.

Substance use. Substance use was low in both groups, and no significant between-group differences were revealed using the TLFB (ie, frequency and amount of use for each substance assessed). A linear regression was computed to examine *N*-acetylcysteine versus placebo and a trend was observed ($F_{2,24} = 3.60$, $\beta = -0.36$, $P = .07$), with *N*-acetylcysteine having slightly fewer positive urine drug screen tests during the course of treatment.

Depression

The BDI-II was reduced by 48% in the *N*-acetylcysteine versus 15% in the placebo group from baseline to week 8. The adjusted regression equation examining the impact of treatment group on BDI-II score at week 8 accounted for 57.1% of the variance ($F_{2,24} = 18.34$, $P < .001$), with the *N*-acetylcysteine group having significantly lower BDI-II scores ($\beta = -0.33$, $P < .05$). Significant within-group effects in the *N*-acetylcysteine group on the BDI from baseline to week 8 ($d = 1.62$, $P < .001$) and week 12 ($d = 0.71$, $P < .05$) were observed. Among the placebo group, no significant within-group effects were observed from baseline to week 8; however, a significant within-group effect was found at week 12 ($d = 0.71$, $P < .05$).

Adverse Events

There were 31 adverse events, with the most common being dry mouth and heartburn. Adverse events were reported in 66.7% of participants (n = 12) in the *N*-acetylcysteine group and 47.1% (n = 8) in the placebo group. Three participants experienced a serious adverse event during the trial, which involved cardiac arrhythmia, pancreatitis, syncopal episode, and hospitalization for suicidality. Of these serious adverse events, 1 was conservatively estimated as possibly related to the study (syncopal episode).

DISCUSSION

This is the first double-blind, randomized, placebo-controlled trial to investigate *N*-acetylcysteine as a pharmacologic treatment for comorbid PTSD/SUD. Results showed that *N*-acetylcysteine combined with CBT significantly reduced PTSD symptoms and craving. *N*-acetylcysteine produced reductions in craving that were more than 2.5 times the magnitude of placebo. In addition, participants treated with *N*-acetylcysteine experienced significant reductions in depression, which may be due to overlap between PTSD, SUD, and depression symptoms.[37]

Although group differences in craving were observed, there was a lack of significant between-group differences in substance use (ie, frequency and amount of alcohol or drug use). Both groups demonstrated low use of substances during the trial. The observed "floor effect" may be due, in part, to the fact that all participants were enrolled in an intensive outpatient treatment program for SUD. Nonetheless, the findings add to the extant literature and suggest that the effects of *N*-acetylcysteine may not be specific to a particular psychosocial platform, but rather generalizable to disorders involving impaired regulation of compulsive, intrusive thinking.[18,38–41]

Several randomized clinical trials have examined pharmacotherapies for comorbid PTSD/SUD, all with a focus on alcohol use disorder, and the findings reveal mixed results.[7–10,42] For example, Petrakis and colleagues[42] found desipramine to be more efficacious than paroxetine in reducing alcohol use, but no differences were observed in PTSD improvement. Brady and colleagues[8] found no overall benefits of sertraline, as compared to placebo, in reducing alcohol use, but observed a trend toward lower PTSD symptoms in the sertraline group and greater benefits among participants with primary PTSD. Foa et al[9] found naltrexone to be effective in reducing drinking but not PTSD. At follow-up, patients who received naltrexone plus exposure therapy demonstrated the best alcohol use outcomes. More recently, Batki and colleagues[7] found topiramate to be more effective than placebo in reducing alcohol use and craving and observed a trend toward greater reduction of PTSD arousal symptoms. Previous trials demonstrate some efficacy for *N*-acetylcysteine in treating SUD, and *N*-acetylcysteine is currently under investigation for treating PTSD (ClinicalTrials.gov identifier: NCT01664260), but the current study is the first to assess the effects of *N*-acetylcysteine on comorbid PTSD and a broad range of SUDs. The 8-week treatment with *N*-acetylcysteine significantly reduced PTSD symptoms and led to a qualitative shift to subdiagnostic PTSD symptom presentation (< 50 CAPS score) for many participants. In combination with animal research and human imaging studies showing impaired corticostriatal regulation in SUD and PTSD, we postulate that by normalizing corticostriatal transmission, *N*-acetylcysteine reduces intrusive thinking and restores top-down control in disorders sharing this endophenotype.

There are several limitations of this pilot study that warrant attention. Mainly, the sample size was small, limiting statistical power and generalizability. Individuals with both alcohol and/or drug use disorders were included, which expands prior research and enhances ecological validity but may limit the specificity of the findings. Given the limited scope of the study, a psychotherapy-only arm was not included. Finally, no assessment of quality of life was included. Despite these limitations, the study represents an important first step in the investigation of *N*-acetylcysteine in the treatment of PTSD/SUD.

CONCLUSION

The findings provide encouraging preliminary support for combining *N*-acetylcysteine and cognitive-behavioral therapy for SUD among patients with PTSD and SUD. The wide availability, low cost, and low side effect profile of *N*-acetylcysteine make it a potentially promising pharmacologic intervention for PTSD/SUD. A larger trial and additional research are warranted to disentangle specific mechanisms through which *N*-acetylcysteine promotes symptom reduction among individuals with comorbid PTSD/SUD.

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Drug names: carbamazepine (Tegretol, Epitol, and others), desipramine (Norpramin and others), methotrexate (Trexall and others), naltrexone (ReVia and others), nitroglycerin (Nitro-Bid and others), paroxetine (Paxil, Pexeva, and others), phenytoin (Dilantin, Phenytek, and others), sertraline (Zoloft and others), topiramate (Topamax and others).
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