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N-acetylcysteine reduces cocaine-cue attentional bias and differentially alters cocaine self-administration based on dosing order[*]

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Abstract

Background—Disrupted glutamate homeostasis is thought to contribute to cocaine-use disorder, in particular, by enhancing the incentive salience of cocaine stimuli. n-Acetylcysteine might be useful in cocaine-use disorder by normalizing glutamate function. In prior studies, n-acetylcysteine blocked the reinstatement of cocaine seeking in laboratory animals and reduced the salience of cocaine stimuli and delayed relapse in humans.

Methods—The present study determined the ability of maintenance on n-acetylcysteine (0 or 2400 mg/day, counterbalanced) to reduce the incentive salience of cocaine stimuli, as measured by an attentional bias task, and attenuate intranasal cocaine self-administration (0, 30, and 60 mg). Fourteen individuals (N = 14) who met criteria for cocaine abuse or dependence completed this within-subjects, double-blind, crossover-design study.

Results—Cocaine-cue attentional bias was greatest following administration of 0 mg cocaine during placebo maintenance, and was attenuated by n-acetylcysteine. Cocaine maintained responding during placebo and n-acetylcysteine maintenance, but the reinforcing effects of cocaine were significantly attenuated across both maintenance conditions in participants maintained on n-acetylcysteine first compared to participants maintained on placebo first.

Conclusions—These results collectively suggest that a reduction in the incentive salience of cocaine-related stimuli during n-acetylcysteine maintenance may be accompanied by reductions in cocaine self-administration. These results are in agreement with, and link, prior preclinical and clinical trial results suggesting that n-acetylcysteine might be useful for preventing cocaine relapse by attenuating the incentive salience of cocaine cues.

Keywords

n-Acetylcysteine; Cocaine; Pharmacotherapy; Self-Administration; Attentional Bias; Human

1. Introduction

Glutamate, the principal excitatory neurotransmitter in the central nervous system, is strongly implicated in the development and maintenance of cocaine-use disorder (D'Souza, 2015; Kalivas et al., 2009). Disrupted glutamate homeostasis following repeated cocaine use is thought to enhance the incentive salience of cocaine stimuli (Kalivas, 2009). Incentive salience refers to the attention-grabbing effect of cues that have become associated with rewards that may then motivate behavioral responses to obtain and consume the primary reward (Berridge and Robinson, 2016; Robinson and Berridge, 2000). Alterations in glutamate function have been linked to changes in incentive salience hypothesized to underlie compulsive patterns of drug use. Preclinical studies indicate that repeated cocaine exposure increases the salience of cocaine relative to non-drug reinforcers. This change in reinforcer salience corresponds with reductions in glutamate levels during abstinence (Baker et al., 2003; Bowers et al., 2004; Choi et al., 2011; Kalivas and Volkow, 2011; McFarland et al., 2003; Pierce et al., 1996). These studies also indicate that cue- or cocaine-induced increases in glutamate during abstinence ameliorate this deficit, thereby promoting the cyclic pattern of drug use, abstinence, and relapse that characterizes cocaine-use disorder.

n-Acetylcysteine is a cysteine prodrug used to treat chronic-obstructive pulmonary disease (COPD) and acetaminophen overdose (Repine et al., 1997; Smilkstein et al., 1988). Recent evidence suggests that n-acetylcysteine may have promise as a medication for cocaine-use disorder (Berk et al., 2013; McClure et al., 2014). Preclinical studies have demonstrated that repeated cocaine administration disrupts glutamate signaling, and that n-acetylcysteine treatment increases the expression and function of the cysteine-glutamate exchanger and the glial glutamate transporter-1, restoring glutamate homeostasis (Baker et al., 2003; Madayag et al., 2007; Moran et al., 2005; Moussawi et al., 2009). Restoration of glutamate homeostasis with n-acetylcysteine might directly attenuate the reinforcing effects of cocaine. Preclinical studies have shown that n-acetylcysteine selectively reduced cocaine-maintained responding compared to responding maintained by non-drug reinforcers and prevented the escalation of cocaine intake during extended access self-administration sessions (Baker et al., 2003; Knackstedt et al., 2010; Ward et al., 2011; but see Amen et al., 2011; Ducret et al.,

2016; Murray et al., 2012). Whether n-acetylcysteine maintenance decreases the reinforcing effects of cocaine in human drug self-administration procedures has not been determined.

Although preclinical findings suggest that n-acetylcysteine might reduce cocaine use by directly attenuating the reinforcing effects of cocaine, normalization of glutamate function might also decrease cocaine use by reducing the salience of cocaine-related stimuli. In clinical studies, repeated n-acetylcysteine treatment attenuated self-reported desire for cocaine and time spent viewing cocaine-related images in cocaine users (Amen et al., 2011; LaRowe et al., 2007). This reduction in craving and the salience of cocaine cues might promote continued abstinence. A secondary analysis of an 8-week, double-blind trial revealed that 2400 mg/day n-acetylcysteine delayed relapse in treatment-seeking cocaine users who had achieved abstinence prior to the outset of the trial (LaRowe et al., 2013). Although the primary analysis did not detect a significant effect of n-acetylcysteine treatment on cocaine-use outcomes, these secondary results suggest that n-acetylcysteine may have utility in the treatment of cocaine-use disorder. Despite the importance of these clinical findings, they do not provide direct insight into the mechanisms responsible for n-acetylcysteine's effects on cocaine use. n-Acetylcysteine might reduce cocaine use in humans by altering the incentive salience of cocaine cues, directly attenuating the reinforcing effects of cocaine as suggested by preclinical studies, or some combination of the two.

Changes in the salience of cocaine-related stimuli during n-acetylcysteine treatment may be determined in a human laboratory setting by measuring the ability of drug-related stimuli to capture and hold attention versus non-drug-related stimuli (i.e., attentional bias; see Field and Cox, 2008 for review). Attentional bias is thought to arise from classical conditioning processes by which drug-related stimuli acquire incentive-motivational properties following repeated pairings with drug rewards (Field and Cox, 2008; Robinson and Berridge, 1993) and/or may reflect the current motivational state of the individual (Klinger and Cox, 2011). Attentional bias is commonly inferred using reaction-time based measures such as the visual-probe task (Field et al., 2014). Individuals typically respond faster to probes that follow motivationally salient images compared to neutral images (Mogg and Bradley, 1998). For example, subjects with cocaine-use disorder display a robust attentional bias to cocaine cues relative to controls and individuals who abuse other classes of drugs (Leeman et al., 2014). Although the results of previous clinical studies described above suggest that n-acetylcysteine decreases time spent viewing cocaine images and self-reported cocaine craving, the impact of n-acetylcysteine maintenance on cocaine-cue attentional bias is unknown, as is the impact of acute cocaine administration on cocaine-cue attentional bias.

The present study addressed two gaps in the literature on the potential utility of n-acetylcysteine to treat cocaine-use disorder. First, this study assessed the impact of n-acetylcysteine maintenance on the incentive salience of cocaine cues by measuring the allocation of attention to cocaine-related and neutral stimuli following acute cocaine administration using a visual-probe task. Second, human drug self-administration procedures were used to determine the effects of n-acetylcysteine maintenance on the reinforcing effects of intranasal cocaine. It was hypothesized that n-acetylcysteine maintenance would reduce cocaine-cue attentional bias and decrease cocaine self-administration. Because the effects of

n-acetylcysteine on the subject-rated and physiological effects of cocaine are also unknown, the current study evaluated the impact of n-acetylcysteine, alone and in combination with cocaine, on these measures.

2. Methods

2.1. Participants

Fourteen (N = 14) non-treatment-seeking cocaine users between the ages of 30-52 participated in this within-subject, double-blind, placebo-controlled, crossover-design study. Participants met diagnostic criteria for cocaine abuse or dependence according to a computerized version of the structured clinical interview for the DSM-IV (American Psychiatric Association, 2000), reported recent cocaine use verified by a benzoylecgonine-positive urine specimen during screening, and were required to be daily cigarette smokers to be eligible for participation. Participants had experience with alcohol and a variety of other drugs but did not meet diagnostic criteria for abuse or dependence for any of these substances, except alcohol. Two participants met diagnostic criteria for alcohol dependence and two met diagnostic criteria for alcohol abuse (see Table 1). These individuals were not excluded from participation because they were not physiologically dependent on alcohol and agreed to discontinue their alcohol use during participation. Other information on screening procedures and inclusion/exclusion criteria are provided in the Online Supplement [1]. Participants were generally in good health with no contraindications to cocaine or n-acetylcysteine. The Institutional Review Board at the University of Kentucky Medical Center approved the informed consent document and study procedures. All procedures were carried out in accordance with the guidelines established in the Declaration of Helsinki. Participants provided their written informed consent prior to enrollment and were compensated $1,360 USD upon successful completion of the study. The overall number of choices for money in the Drug Choice Procedure (see section 2.4.2.) was added to the total compensation above (up to $9 USD). Demographic information is shown in Table 1.

2.2. General Procedures

Participants enrolled as inpatients at the University of Kentucky Chandler Medical Center Clinical Services Core (CSC) for 17 days. Participants completed one practice and six experimental sessions (see Supplementary Figure 1[2]). During the consent process, participants were informed that they would receive oral n-acetylcysteine, intranasal cocaine, and placebo (orally and intranasally) alone or in combination. Beyond this general information, participants (as well as medical and research staff) were blind to the type or dose of drug administered in any given experimental session. Participants were told that the purpose of the study was to learn more about how drugs affect mood, physiology, and behavior. Otherwise, participants received no instruction of what they were supposed to do or what outcomes might be expected.

Prior to their admission to the CSC, participants were required to provide an expired breath sample that was negative for the presence of alcohol using a hand-held breathalyzer (Intoximeters, Saint Louis, MO, U.S.A.) and pass a field sobriety test. They were also required to provide a urine specimen that was screened for recent use of commonly abused drugs (see Online Supplement2 for further detail). Urine drug screens were required to be negative for all substances other than cocaine and cannabis [and negative for pregnancy in female participants] prior to admission. Following admission to the CSC, participants were allowed to acclimate to the unit for 24 h. During this acclimation period, participants were medically monitored, including observation for signs and symptoms of drug and/or alcohol withdrawal. Withdrawal was not detected in any participant during this time, or at any point during the study. Participants were also allowed to engage in recreational activities and adjust to the inpatient setting during the acclimation period.

2.2.1. Practice Session—Participants completed one practice session to familiarize them with the experimental session routine and experimental tasks. The practice session was procedurally identical to experimental sessions except that no medications were administered during this session.

2.2.2. Drug Maintenance Days—Beginning the day after the practice session, participants received maintenance medication (i.e., placebo or 800 mg n-acetylcysteine; see section 2.3. below) at 0700, 1500, and 2300 h each day for the remainder of their participation. The total daily n-acetylcysteine maintenance dose was 0 or 2400 mg. After four days under the first maintenance condition, participants completed three consecutive experimental sessions, one per day. Maintenance continued across experimental session days and the other maintenance condition began on the day following the third experimental session. Each maintenance period lasted a total of 7 days. The order of maintenance conditions was counterbalanced across participants. Medication side effects were monitored once daily with the Udvalg for Kliniske Undersøgelser scale (Lingjærde et al., 1987).

2.2.3. Experimental Sessions—Three consecutive experimental sessions were completed during each maintenance condition (6 total sessions). Participants received the appropriate maintenance dose at 0700 h, ate a standard breakfast, and were required to smoke one cigarette approximately 2 h before each session. Participants were also required to provide a urine specimen that was screened for commonly abused drugs (see Online Supplement3 for further detail) and an expired breath sample that was negative for the presence of alcohol. They also completed a field sobriety test to proceed with a session. At approximately 0900 h, participants completed baseline subject-rated measures and sampled the cocaine dose (0, 30, or 60 mg; see section 2.3. below) available during that session approximately 30 min later. Subject-rated measures were collected at 15-min intervals for 60 min following administration of the sampling dose. The Visual-Probe Task was completed once during each experimental session, after completing the 15-min post-sampling dose subject-rated measures. Participants began the Drug Choice Procedure approximately 60 min after the sampling dose. Physiological indices were monitored at 15-min intervals

throughout the session. Supplementary Figure 2[3] shows the sequence of events during experimental sessions. Experimental sessions lasted approximately 4.5 h and were separated by at least 24 h.

2.3. Drug Administration

All drugs were administered under medical supervision in a double-blind fashion. n-Acetylcysteine doses (Bronson Laboratories, Lindon, UT) were prepared by over-encapsulating commercially available 400 mg n-acetylcysteine tablets in two size zero, opaque gelatin capsules. Previous research suggests that this dose of oral n-acetylcysteine reaches peak plasma concentrations within 1-2 h and has a terminal elimination half-life of 6.25 h (Holdiness, 1991). Similar doses have been safely administered to cocaine users, alone or in combination with cocaine (Amen et al., 2011; LaRowe et al., 2006; 2007). Placebo capsules contained only cornstarch.

Cocaine doses (0, 30, and 60 mg) were prepared by combining the appropriate amount of cocaine HCl, USP powder (Medisca, Plattsburg, NY or Mallinckrodt, St. Louis, MO) with lactose monohydrate powder to yield 60 mg of powder. The order of cocaine doses during each maintenance period was randomized and the same cocaine dose was available throughout a given session. To administer the cocaine dose, the participant was presented with a mirror, razor blade, and a 65-mm plastic straw, instructed to divide the powder into two even "lines," and then insufflate one line of powder through each nostril within 2 min. Participants were required to insufflate the entire volume of powder.

2.4. Dependent Measures

2.4.1. Visual-Probe Task—A visual-probe task (e.g., Lubman et al., 2000; Townshend and Duka, 2001) was used to measure attentional bias and was completed on a PC laptop computer running E-Prime 2.0 (Psychology Software Tools Inc., Sharpsburg, PA, U.S.A.). The visual-probe procedure was similar to previous studies with alcohol- and cocaine-related images (see Roberts et al., 2012 and Marks et al., 2014a for further detail).

The visual-probe task consisted of a total of 80 trials (40 critical trials and 40 filler trials) presented in randomized order. During critical trials of interest, cocaine-related images (n = 10) were presented adjacent to matched, non-cocaine-related, neutral images (n = 10). Immediately after presentation of the images, a visual probe (an "X") appeared in the same location as one of the images and response time (ms) to the probe was measured. Attentional bias is inferred from differences in response times to probes that replace cocaine versus neutral images during critical trials. Slower response times to probes that replace neutral images, relative to when the probe replaces a cocaine-related image, are interpreted as the participant's attention being focused on the cocaine image. An attentional bias score was calculated from response time (RT) data in the visual-probe task as described previously (i.e., $RT_{Cocaine} - RT_{Neutral}$; Marks et al., 2015) such that negative scores would suggest a cocaine-cue attentional bias. The attentional bias score served as the primary outcome measure for data analysis.

2.4.2. Drug Choice Procedure—A Drug Choice Procedure, identical to that used previously (Stoops et al., 2010), assessed the reinforcing effects of cocaine. Participants were given six opportunities at 30-min intervals to choose between the dose of cocaine that was sampled at the beginning of the session and an alternative reinforcer ($0.25 USD). Maximum number of drug choices was the dependent measure.

2.4.3. Subject-Rated Drug-Effect Questionnaires—A battery of subject-rated measures was completed on an Apple Macintosh laptop computer (Apple, Cupertino, CA, U.S.A.) in a fixed order. The measures included were the Adjective Rating Scale (Oliveto et al., 1992) and an investigator-developed Drug-Effect Questionnaire (Rush et al., 2003). Subject-rated measures were only completed after administration of the sampling dose. Data from these questionnaires were analyzed as peak effect (i.e., the maximum value observed after the cocaine sampling dose).

2.4.4. Physiological Measures—Systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), and oral body temperature (°F) were recorded using an automated digital vital-signs monitor. Data from these measures were analyzed as peak effect.

2.5. Data Analysis

Statistical analyses were performed in IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY, U.S.A.). Significant main and interaction effects were followed up with Fisher's least significant difference (LSD) post-hoc tests, where appropriate. The alpha level was set at p 0.05 for all analyses. Because visual inspection of data from the drug choice procedure revealed an orderly effect of maintenance order (placebo or n-acetylcysteine first), participants were divided into two subgroups based on maintenance order. Data from each experimental measure (see section 2.4.) were analyzed with $2 \times 2 \times 3$ mixed-factors analysis of variance (ANOVA) that included Maintenance Order as a between-subject factor and n-Acetylcysteine and Cocaine as within-subject factors. If the three-way mixed-factors ANOVA failed to reveal significant effects of maintenance order, the data were collapsed across maintenance order and analyzed using separate 2×3 repeated-measures ANOVAs with n-Acetylcysteine (0 and 2400 mg/day) and Cocaine (0, 30, and 60 mg) as the factors. Participant demographic and drug-use outcomes were compared between these subgroups of participants with independent samples t-tests but these tests failed to detect significant differences (p's > 0.08; see Table 1).

3. Results

3.1. Simple Visual-Probe Task

Figure 1 illustrates the effects of n-acetylcysteine maintenance on mean attentional bias scores ($\pm$ *SEM*) as a function of cocaine dose. Data from one participant were excluded from analysis due to a technological malfunction (resulting N = 13). There was no effect of maintenance order, (F-values < 1.73, p-values > 0.22), but in the subsequent 2×3 ANOVA a significant n-Acetylcysteine $\times$ Cocaine interaction, $F_{(2,24)} = 3.88$, $p = 0.04$, was observed. Under placebo maintenance, negative attentional bias scores (M = -18.79 ms, *SEM* = 5.71) were obtained following acute intranasal administration of 0 mg cocaine. These results

indicate faster average reaction times when the probe appeared behind cocaine-related images relative to neutral images (i.e., attentional bias towards cocaine cues). Cocaine attentional bias scores remained negative, but were lower (i.e., closer to 0) following administration of the 30 mg (M = -9.39 ms, SEM = 4.60) and 60 mg (M = -9.78 ms, SEM = 5.99) doses of cocaine. Under n-acetylcysteine maintenance, a positive mean attentional bias score (M = 8.45 ms, SEM = 8.22) was obtained following administration of 0 mg cocaine, which was significantly different than the score observed following placebo maintenance. This indicated slower reaction times when visual probes appeared behind cocaine-related images compared to neutral images. In contrast, negative attentional bias scores were observed after administration of active cocaine doses during n-acetylcysteine maintenance. The mean attentional bias scores following the 30 and 60 mg cocaine doses were -15.15 ms (SEM = 7.33) and -10.71 ms (SEM = 5.95), respectively. Post-hoc comparisons indicated that attentional bias scores did not significantly differ between placebo and n-acetylcysteine maintenance following either active cocaine dose.

3.2. Drug Choice Procedure

A three-way, mixed-factors ANOVA revealed a significant Maintenance Order × n-Acetylcysteine × Cocaine interaction, $F(2,24)$ = 5.52, p = 0.01. Figure 2 shows mean number of drug choices (± SEM) as a function of cocaine dose during placebo (circles) and n-acetylcysteine (squares) maintenance for participants who received placebo (left) or n-acetylcysteine (right) first. In participants who were maintained on *placebo first*, a subsequent two-factor ANOVA revealed a significant main effect of Cocaine, $F(2,12)$ = 32.25; p < 0.001, but the n-Acetylcysteine × Cocaine interaction was not significant, $F(2,12)$ = 2.86; p = 0.10. Post-hoc comparisons revealed that the 30 and 60 mg doses of cocaine significantly increased number of drug choices compared to the placebo-placebo control condition (i.e., open circle on the center side) during placebo and n-acetylcysteine maintenance. In participants who received *n-acetylcysteine first*, there was a significant n-Acetylcysteine × Cocaine interaction, $F(2,12)$ = 3.93; p = 0.05, as well as a significant main effect of Cocaine, $F(2,12)$ = 4.75; p = 0.03. These participants also chose active doses of cocaine significantly more than placebo-placebo control (i.e., open circle on the right side) during both maintenance periods. Post-hoc comparisons between groups showed that n-acetylcysteine significantly decreased cocaine choice at the 30 mg dose in participants who received n-acetylcysteine first relative to those maintained on placebo first. During placebo maintenance, participants who received n-acetylcysteine first also chose both active doses of cocaine significantly less than participants who were maintained on placebo first.

3.3. Subject-Rated Drug-Effect Questionnaires

The three-way mixed-factors ANOVA that included Maintenance Order as a between-subjects factor revealed a significant Maintenance Order × n-Acetylcysteine interaction for peak ratings of "Willing to Pay For," $F(1,12)$ = 4.64, p = 0.05. Participants provided higher peak ratings on this item during the first maintenance period relative to the second, regardless of cocaine dose (data not shown). However, the magnitude of ratings during each maintenance period was comparable between these groups of participants. There were no other significant main or interaction effects that included Maintenance Order. The three-way

mixed-factors ANOVAs did not reveal additional main or interaction effects beyond those obtained in the two-factor repeated measures ANOVAs reported below.

Cocaine significantly increased peak ratings on the stimulant subscale of the Adjective Rating Scale, $F_{(2,26)} = 20.57$, $p < 0.001$, and 17 items from the Drug-Effect Questionnaire relative to placebo, regardless of n-acetylcysteine maintenance dose. Significant main effects of Cocaine were obtained for the following items on the Drug-Effect Questionnaire: "Active-Alert-Energetic," "Any Effect," "Bad Effects," "Euphoric," "Good Effects," "High," "Irregular-Racing Heartbeat," "Like Drug," "Nauseated," "Nervous-Anxious," "Rush," "Shaky-Jittery," "Sluggish-Fatigued-Lazy," "Stimulated," "Talkative-Friendly," "Willing to Pay For," and "Willing to Take Again," F-values > 3.80, p-values < 0.04. Representative data for mean peak-effect ratings ($\pm$ *SEM*) of "Any Effect" (top left), "Stimulated" (top right), "Euphoric" (bottom left), and "Willing to Take Again" (bottom right) during placebo (circles) and n-acetylcysteine (squares) maintenance are shown in Figure 3.

n-Acetylcysteine maintenance modestly blunted peak ratings on 2 items from the Drug-Effect Questionnaire, regardless of cocaine dose. Two-way repeated-measures ANOVAs revealed significant main effects of n-Acetylcysteine on peak ratings of "Euphoric," $F_{(1,13)} = 4.79$, $p = 0.05$, and "Stimulated," $F_{(1,13)} = 5.89$, $p = 0.03$. There were no other significant main or interaction effects.

3.4. Physiological Measures

Figure 4 shows the mean peak effect ($\pm$ *SEM*) for systolic blood pressure (top), diastolic blood pressure (center), and heart rate (bottom) as a function of cocaine dose during placebo (circles) and n-acetylcysteine (squares) maintenance. The three-way mixed-factors ANOVA revealed a significant Maintenance Order × Cocaine interaction for oral body temperature, $F_{(2,24)} = 6.00$, $p = 0.008$, but all average peak oral temperatures differed by less than one degree Fahrenheit. There were no other significant main or interaction effects for physiological measures that included Maintenance Order.

Cocaine dose-dependently increased peak systolic and diastolic blood pressure, regardless of n-acetylcysteine maintenance dose. Separate two-factor repeated-measures ANOVAs revealed significant main effects of Cocaine for systolic, $F_{(2,26)} = 17.70$, $p < 0.001$, and diastolic blood pressure, $F_{(2,26)} = 7.84$, $p = 0.002$. Post-hoc analyses showed significant increases in systolic blood pressure relative to 0 mg cocaine during placebo maintenance (i.e., placebo-placebo control) following administration of both active doses of cocaine under placebo and n-acetylcysteine maintenance. Cocaine also significantly increased diastolic blood pressure relative to placebo-placebo control following 30 and 60 mg cocaine during placebo maintenance. During n-acetylcysteine maintenance, cocaine increased diastolic blood pressure at the 30 mg, but not 60 mg, dose.

Cocaine significantly increased peak heart rate as an orderly function of dose, regardless of n-acetylcysteine maintenance dose. There was a significant main effect of Cocaine for peak heart rate, $F_{(2,26)} = 7.99$, $p = 0.002$. Post-hoc comparisons revealed significant increases in heart rate following both active cocaine doses during placebo maintenance but only

following the high dose of cocaine during n-acetylcysteine maintenance. There were no other significant main effects or interactions.

A two-factor repeated measures ANOVA failed to detect statistically significant effects for oral body temperature, F-values < 1.85, p-values > 0.18 (data not shown).

4. Discussion

This study determined the influence of n-acetylcysteine maintenance (0 or 2400 mg/day) on the cognitive-behavioral, reinforcing, subject-rated, and physiological effects of intranasal cocaine (0, 30, and 60 mg). Cocaine-cue attentional bias was evident following acute administration of active doses of cocaine regardless of n-acetylcysteine maintenance dose. Compared to placebo maintenance, n-acetylcysteine significantly reversed cocaine-cue attentional bias following administration of the 0 mg cocaine dose. Cocaine functioned as a reinforcer, but n-acetylcysteine significantly reduced cocaine choice across both maintenance conditions in participants who received n-acetylcysteine first. Intranasal cocaine produced prototypic positive and stimulant-like subject-rated effects. n-Acetylcysteine modestly attenuated ratings of "Euphoric" and "Stimulated". Statistically, but not clinically, significant acute increases in physiological measures were also observed following active doses of cocaine but were unchanged by n-acetylcysteine.

This is the first study to determine the impact of n-acetylcysteine maintenance and acute cocaine administration on a measure of attentional bias in cocaine users. Although attentional bias to cocaine cues was apparent during placebo maintenance following acute cocaine administration (30 and 60 mg), the absolute magnitude of cocaine-cue attentional bias obtained following active cocaine doses was lower than that observed following placebo cocaine. Two previous studies determined the influence of candidate pharmacotherapies for cocaine-use disorder on attentional bias to cocaine cues (Goldstein et al., 2010; Liu et al., 2013). Liu and colleagues (2013) showed that escitalopram (10 mg), acutely but not chronically, reduced cocaine-cue attentional bias in the Cocaine Stroop task in non-treatment-seeking cocaine-dependent individuals. Similarly, an acute oral dose of 20 mg methylphenidate reduced commission errors in a task similar to the Cocaine Stroop suggesting that methylphenidate attenuated attentional bias to cocaine-related words (Goldstein et al., 2010). The results of the current study extend previous findings to show that n-acetylcysteine maintenance may shift attentional bias away from cocaine cues following acute administration of 0 mg intranasal cocaine. This finding may suggest that n-acetylcysteine reduced the incentive salience of cocaine cues as indicated by an indirect measure of attentional bias. However, n-acetylcysteine had minimal effect on cocaine-cue attentional bias following active doses of cocaine. This may suggest that acute cocaine administration restored the incentive salience of cocaine cues. That n-acetylcysteine may reduce attentional bias towards cocaine-related stimuli during a drug-free state might partially explain the results of previous clinical studies in which n-acetylcysteine reduced self-reported desire for and interest in cocaine in cocaine-dependent individuals (LaRowe et al., 2007) and delayed relapse in abstinent treatment-seeking cocaine users (LaRowe et al., 2013).

The effects of n-acetylcysteine on cocaine self-administration in the current study parallel those of a recent clinical trial where n-acetylcysteine delayed relapse in participants who had achieved abstinence prior to beginning the trial compared to those who had not (LaRowe et al., 2013). Although the drug choice procedure used in the current study was not designed to model relapse, there were differences in cocaine-choice behavior as a function of n-acetylcysteine maintenance following a 6-day period of cocaine abstinence that was imposed by inpatient study participation. Alterations in cocaine self-administration were not observed in the current study if participants experienced the effects of cocaine within the laboratory context during placebo maintenance before being maintained on n-acetylcysteine.

That n-acetylcysteine did not completely block the reinforcing effects of intranasal cocaine in the current study is in line with recent preclinical findings. n-Acetylcysteine failed to impact escalation of cocaine intake and responding under a progressive-ratio schedule of reinforcement in rats but reduced cocaine self-administration following three sessions in which cocaine-seeking responses were punished prior to a cocaine infusion (Ducret et al., 2016). Significant reductions in cocaine choice during both maintenance periods were observed in the current study for participants maintained on n-acetylcysteine *first*, suggesting that it may have altered cocaine self-administration through mechanisms other than blocking the reinforcing effects of cocaine. The enduring decrease in cocaine choice during placebo maintenance that was observed in this subset of participants is also generally consistent with lasting reductions in cocaine-seeking behavior in rats following chronic n-acetylcysteine (Reichel et al., 2011). A sustained decrease in cocaine choice during placebo maintenance in participants maintained on n-acetylcysteine first suggests that n-acetylcysteine maintenance might have produced lasting alterations in the expression and/or function of the cysteine-glutamate exchanger or glial glutamate transporter-1, although this study was not designed to directly test this possibility. That reductions in cocaine self-administration were only observed in participants who received n-acetylcysteine first might also suggest that n-acetylcysteine exposure needs to occur during a period of cocaine abstinence in order to reduce drug-taking behavior. This may potentially explain why n-acetylcysteine prevented reinstatement of cocaine-seeking behavior in some preclinical studies (Ducret et al., 2016; Moussawi et al., 2011; Reichel et al., 2011) and delayed relapse in participants who were cocaine abstinent prior to receiving n-acetylcysteine in a recent clinical trial (LaRowe et al., 2013).

Cocaine significantly increased peak ratings on several subject-rated drug effects, but n-acetylcysteine maintenance had limited impact on the subject-rated and physiological effects of cocaine in the current study. n-Acetylcysteine decreased ratings of "Euphoric" and "Stimulated" to suggest that it may have attenuated certain stimulant-like and positive effects of cocaine. However, because peak ratings on these measures were attenuated by n-acetylcysteine irrespective of cocaine dose (i.e., a main effect of n-Acetylcysteine), the decrease in peak ratings may reflect a non-specific decrease in ratings on these items. Acute cocaine administration resulted in non-clinically significant acute increases in physiological measures such as blood pressure and heart rate but the effects of cocaine on these measures did not differ systematically as a function of n-acetylcysteine maintenance. These findings indicate that 2400 mg/day n-acetylcysteine may be safely co-administered with intranasal cocaine in active cocaine users.

The current findings should be interpreted in the context of several limitations. First, a limited range of doses of n-acetylcysteine was tested in the current study. Although the dose used in this study (2400 mg/day) was selected on the basis of several clinical trials that have tested the same dose (LaRowe et al., 2007; 2013), higher doses of n-acetylcysteine (3600 mg/day) have been tested in cocaine-dependent individuals without untoward effects (Mardikian et al., 2007). Second, an indirect measure of attentional bias was used in the current study. The results of previous work in our laboratory suggest that more sophisticated, direct measures (i.e., fixation time as measured with eye-tracking technology) may be a more sensitive and reliable measure of attentional bias than indirect measures like reaction time (Marks et al., 2014a; Marks et al., 2014b). Future studies should incorporate the use of direct measures of attentional bias because they may be more sensitive to changes in attentional bias resulting from pharmacological manipulations. Third, because the sub-group analysis of n-acetylcysteine maintenance order yielded small sample sizes (N = 7/group), the influence of individual differences cannot be ruled out and these findings should be considered preliminary. Lastly, the drug choice procedure used in the current study was not designed to provide information about relapse. Given that the results of several preclinical and clinical studies suggest that n-acetylcysteine may effectively decrease the likelihood of relapse, future studies using procedures that are specifically designed to model relapse are needed (e.g., Donny et al., 2004).

5. Conclusions

The current study addressed an important gap in the literature concerning the potential therapeutic efficacy of n-acetylcysteine to treat cocaine-use disorder. Previous clinical trials with n-acetylcysteine have not provided information regarding the mechanism(s) by which n-acetylcysteine might reduce cocaine use in humans. The current findings suggest that n-acetylcysteine may reduce cocaine use by attenuating some of the reinforcing and positive subjective effects of cocaine and/or by altering the incentive salience of cocaine. Although these preliminary findings do not suggest that reductions in cocaine-cue attentional bias are causally linked to changes in cocaine self-administration in humans, they suggest that changes in the incentive salience of cocaine stimuli may be accompanied by a reduction in cocaine self-administration. These results are in agreement with, and link, prior preclinical and clinical trial results suggesting n-acetylcysteine might be useful for preventing cocaine relapse by attenuating the incentive salience of cocaine cues. Collectively, these results suggest that chronic treatment with compounds that ameliorate disruptions in glutamate homeostasis during cocaine abstinence may improve treatment outcomes (e.g., McClure et al., 2014).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- n-Acetylcysteine reduced cocaine-cue attentional bias following 0 mg cocaine.

- Cocaine choice was blunted in participants that received n-acetylcysteine first.

- n-Acetylcysteine attenuated some of the positive subjective effects of cocaine.

- n-Acetylcysteine may have utility in the treatment of cocaine-use disorder.
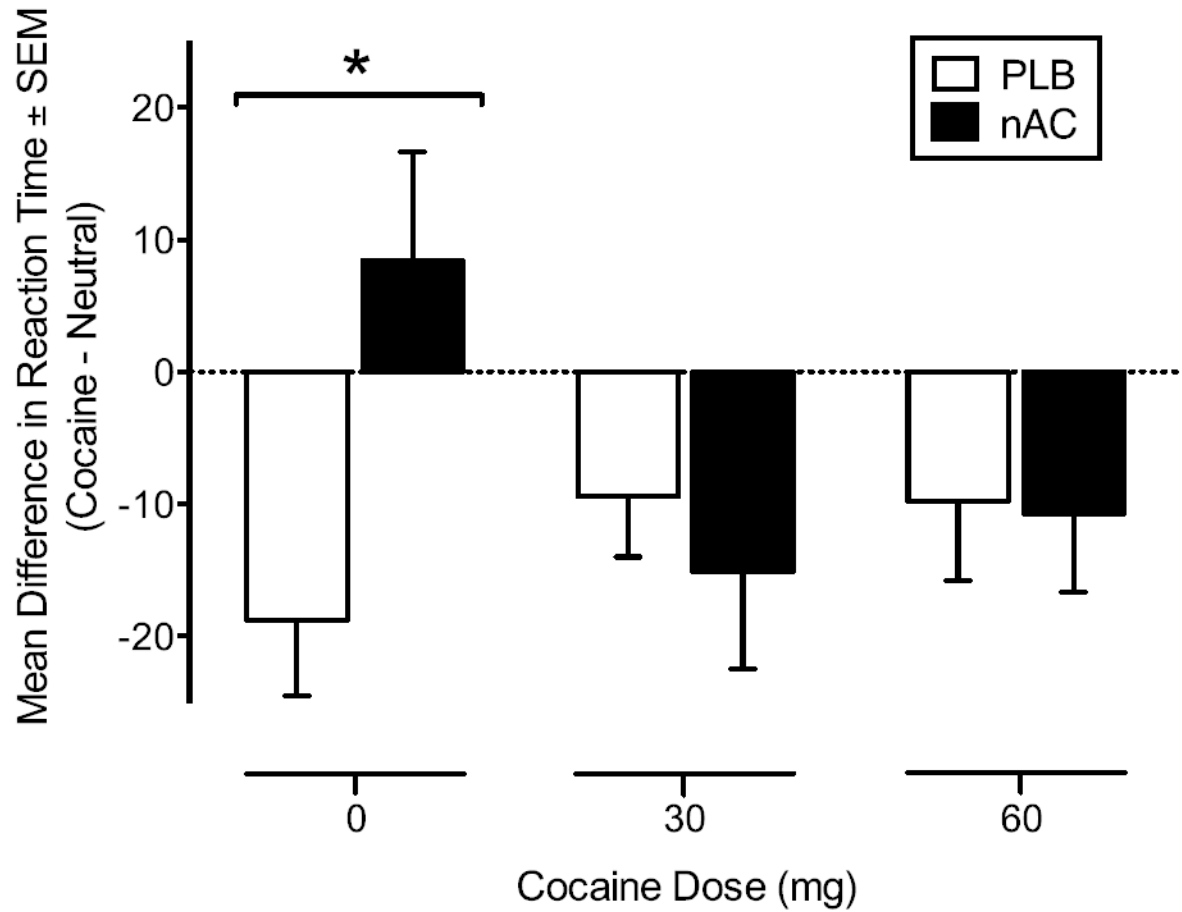
Figure 1.
Mean difference in reaction time in milliseconds (± *SEM*) during placebo (PLB; open bars) and n-acetylcysteine (nAC; filled bars) as a function of intranasal cocaine dose (0, 30, and 60 mg) from the Visual-Probe Task. Data represent the mean difference score (Cocaine - Neutral) for thirteen individuals (N = 13). An asterisk (*) indicates a significant difference between placebo and n-acetylcysteine maintenance ($p < 0.05$).
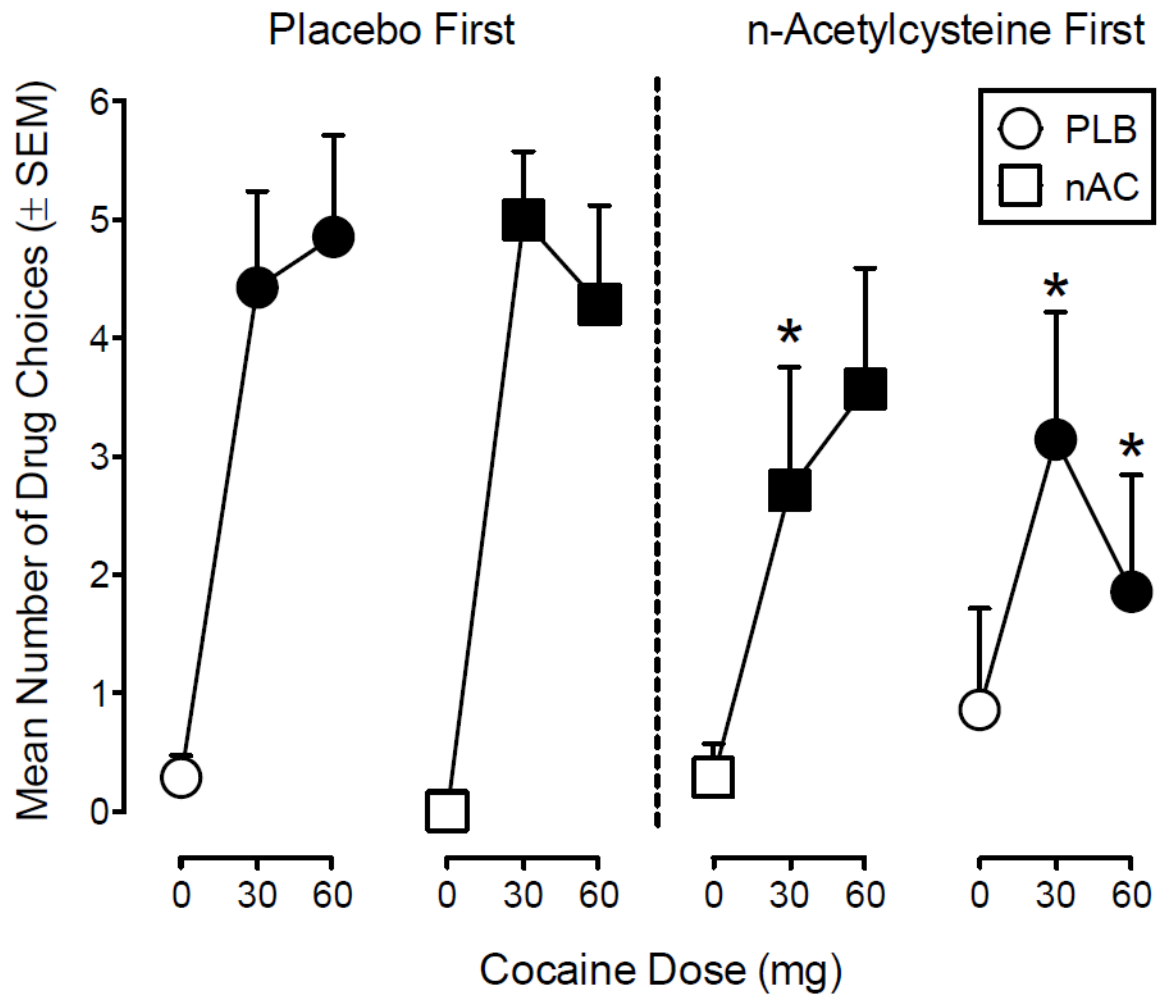
Figure 2.
Mean number of drug choices (± *SEM*) as a function of intranasal cocaine dose (0, 30, and 60 mg) from the Drug Choice Procedure under placebo (open circles) or n-acetylcysteine (open squares) maintenance. Data on the left represent participants who were maintained on placebo first (n = 7) and data on the right correspond with those who received n-acetylcysteine first (n = 7). Filled symbols indicate a significant within-group difference from 0 mg cocaine during placebo maintenance (*p* < 0.05). An asterisk (*) indicates a significant difference between participants maintained on placebo or n-acetylcysteine first at a given dose of n-acetylcysteine and cocaine.
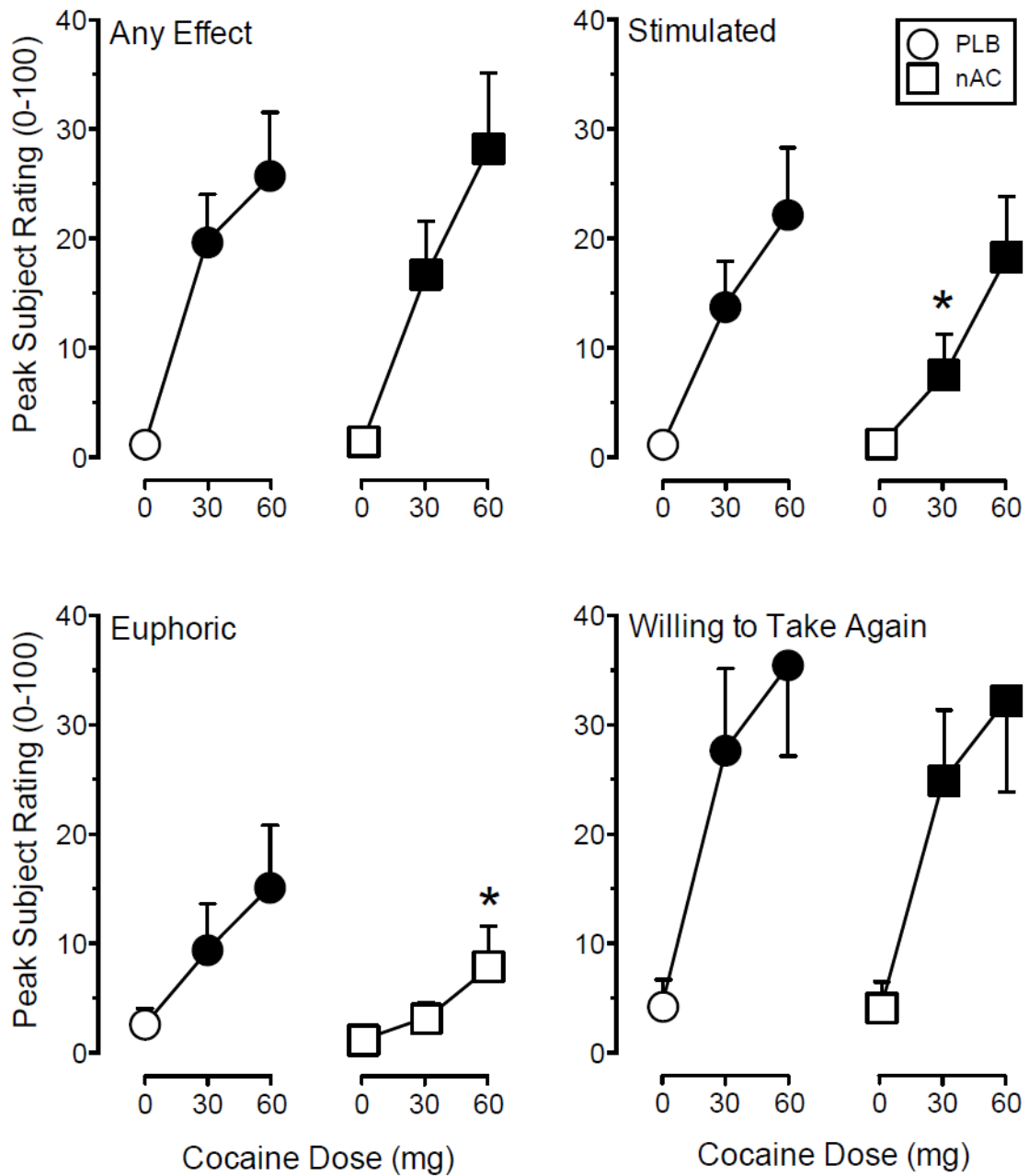
Figure 3.
Mean peak subject rating (± *SEM*) as a function of intranasal cocaine dose (0, 30, and 60 mg) from the Drug-Effect Questionnaire under placebo (PLB; open circles) or n-acetylcysteine (nAC; open squares) maintenance. Filled symbols indicate a significant difference from 0 mg cocaine during placebo maintenance ($p < 0.05$). An asterisk (*) indicates a significant difference between n-acetylcysteine maintenance conditions at a given dose of cocaine ($p < 0.05$).
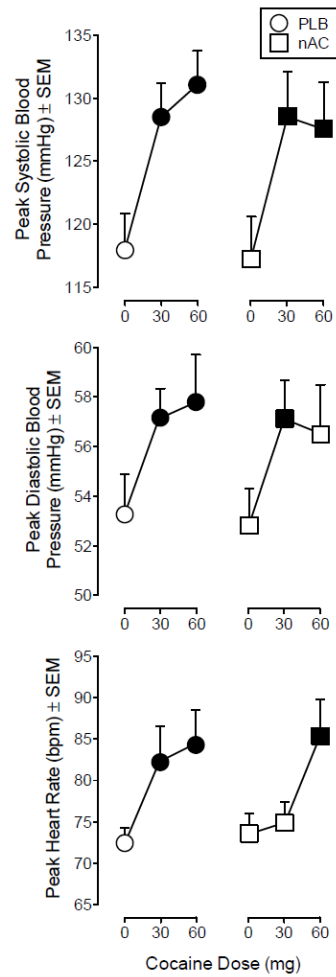
Figure 4.
Mean peak effect (± *SEM*) for systolic blood pressure, diastolic blood pressure, and heart rate as a function of intranasal cocaine dose (0, 30, and 60 mg) during placebo (PLB; open circles) and n-acetylcysteine (nAC; open squares) maintenance. The remaining details are the same as those for Figure 3.

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Table 1

Demographic Characteristics

	Total ($N = 14$) M (SD)	Placebo First ($n = 7$) M (SD)	nAC First ($n = 7$) M (SD)	t	p
Age	42.6 (5.4)	42.4 (6.8)	42.7 (4.2)	-0.1	0.93
Sex (n)					
Men	11	6	5		
Women	3	1	2		
Race (n)					
African-American	9	3	6		
Caucasian	4	3	1		
Hispanic	1	1	0		
Education (years)	12.1 (1.0)	12.3 (1.0)	11.9 (1.1)	0.79	0.44
Weight (kg)	89.4 (44.7)	107.7 (55.7)	71.0 (21.0)	1.63	0.13
Cocaine Use					
Total Lifetime Uses	4600.6 (4262.1)	5043.6 (5958.6)	4157.7 (1842.7)	0.38	0.71
Past Week (days used)	3.7 (2.0)	3.7 (1.8)	3.7 (2.3)	0	1
Past Month (days used)	16.0 (9.1)	16.3 (8.6)	15.7 (10.3)	0.11	0.91
DAST score	8.5 (5.2)	8.6 (4.7)	8.4 (6.2)	0.05	0.96
Alcohol Use	24.0 (22.8)	21.0 (18.5)	27.0 (27.6)	-0.47	0.64
Drinks/week	8.4 (9.0)	6.0 (6.9)	10.9 (10.7)	-1.04	0.32
MAST score	7.3 (5.8)	6.4 (4.0)	8.1 (7.5)	-0.54	0.6
AUDIT score					
SCID Result (n)	2	2	0		
Cocaine Abuse	12	5	7		
Cocaine Dependence	2	1	1		
Alcohol Abuse	2	1	1		
Alcohol Dependence					
Cannabis Use					

	Total (*N* = 14) *M* (SD)	Placebo First (*n* = 7) *M* (SD)	nAC First (*n* = 7) *M* (SD)	*t*	*p*
Past Month (days used)	7.9 (10.7)	12.7 (11.8)	3.1 (5.4)	1.94	0.08
Tobacco Use					
Cigarettes/day	14.0 (7.1)	13.9 (7.9)	14.0 (6.8)	-0.02	0.99

Note. nAC = n-acetylcysteine. *M* = Mean. *SD* = Standard Deviation. *t* = *t*-values from independent samples *t*-tests. DAST = Drug Abuse Screening Test (Skinner, 1982). MAST = Michigan Alcoholism Screening Test (Selzer, 1971). AUDIT = Alcohol-Use Disorder Identification Test (Saunders et al., 1993). SCID = Structured Clinical Interview for the DSM-IV.