Article

Is Cocaine Desire Reduced by *N*-Acetylcysteine?

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Objective: Animal models suggest that *N*-acetylcysteine inhibits cocaine-seeking. The present pilot study evaluated whether *N*-acetylcysteine would suppress reactivity to cocaine-related cues in cocaine-dependent humans.

Method: In this double-blind, placebo-controlled trial, 15 participants received *N*-acetylcysteine or placebo during a 3-day hospitalization. Participants were crossed over to receive the opposite condition on a second, identical 3-day stay occurring 4 days later. During each hospital stay, participants completed a cue-reactivity procedure that involved collecting psychophysical and subjective data in response to slides depicting cocaine and cocaine use.

Results: While taking *N*-acetylcysteine, participants reported less desire to use and less interest in response to cocaine slides and watched cocaine slides for less time.

Conclusions: The inhibition of cocaine cue reactivity is consistent with existing preclinical data and supports the use of *N*-acetylcysteine as a treatment for cocaine dependence.

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There is no pharmacological treatment for cocaine dependence approved by the U.S. Food and Drug Administration. Preclinical studies examining the reinstatement of cocaine-seeking behavior, an animal model of relapse, suggest that reinstatement of cocaine-seeking in animals results, in part, from down-regulated cysteine-glutamate exchange (1). Increasing glutamate exchange activity with cysteine prodrugs, such as *N*-acetylcysteine, reduces cocaine-seeking in animal models (2, 3). These data implicate *N*-acetylcysteine as a possible pharmacotherapy for relapse prevention in cocaine addiction. A double-blind-placebo-controlled crossover study was conducted to determine the effects of *N*-acetylcysteine on cue-induced craving in cocaine-dependent individuals.

Method

The participants were 15 nontreatment-seeking individuals who met DSM-IV criteria for current cocaine dependence and had no concurrent psychiatric disorder (see data supplement Methods at http://ajp.psychiatryonline.org). The participants included seven men and eight women with a mean age of 37.4 years (SD=7.1, range=23–45); 11 were African American and four were Caucasian. Of those participants, 10 were primarily crack smokers, and two primarily used nasal powder, while the remaining participants used a mixture of crack, powder, and freebase cocaine. Self-report accounts of cocaine use for the 90 days before study participation indicated that the participants used cocaine 38 of 90 days on average (SD=22, range=10 to 90), spending a daily average of $31 (SD=$12, range=$10–$47) and an average of $95 per use day (SD=$57, range=$10–$220). The participants received $900 for their participation ($100 per day in the hospital plus $300 for completion of follow-up visits). All participants were free of cocaine at the time of admission (confirmed by urine drug screen) and completed two 3-day inpatient hospitalizations separated by 4 days. The participants, who were closely monitored while hospitalized to ensure that they remained free of cocaine, received four doses of either *N*-acetylcysteine (600 mg) or placebo (lactose powder) at 12-hour intervals. Preliminary data on a portion of the subjects (N=13) have been previously reported regarding the safety and tolerability of *N*-acetylcysteine, as well as self-reports of craving and cocaine withdrawal at hospital intake and discharge (4). However, cue reactivity data were not presented in that preliminary report.

After the final dose of medication/placebo, the participants completed a cue-reactivity procedure that involved presentations of four categories of slides (cocaine, neutral, pleasant, and unpleasant). Five cocaine-related slides depicting simulated crack and powder cocaine were used. Five neutral slides (e.g., objects such as a book and a stool) served as control stimuli. In addition, five pleasant slides (e.g., amorous couples kissing, skydiving, skiing) and 10 unpleasant slides (e.g., a pointed gun, a snake) were presented as well. The neutral and affective slides were selected from the International Affective Picture System (5). The slides were presented in one of two semirandom orders that were designed to reduce the predictability of slide type.

Each participant underwent two slide presentations. During the first presentation, the slides were presented for 6 seconds each while skin conductance and heart rate measures were collected. During the second presentation, motivational measures were collected. The participants viewed each slide ad libitum (20 seconds maximum each), and viewing times were recorded. Cue-induced motivation to seek cocaine was assessed by having the participants rate how much craving, desire to use cocaine, and interest was evoked by each slide on a 21-point Likert scale (see data supplement Methods). Multiple motivational measures were used because craving is a multidimensional concept that may not be accurately measured with single-item assessments (6). All motivational measures were simultaneously incorporated into a lin-

TABLE 1. Data for the Cue-Reactivity Procedure: Motivational and General Measures[a]

	N-Acetylcysteine				Placebo			
	Cocaine		Neutral		Cocaine		Neutral	
Motivational Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD
N-Acetylcysteine								
Craving	5.81	4.29	1.32	2.41	7.25	5.27	1.09	2.34
Desire to use	6.19[b]	4.41	1.01	1.66	8.32	5.13	1.79	3.09
Interest	7.85[b]	5.28	2.81	2.61	9.65	6.03	3.30	3.49
Time viewed (seconds)	3.92[b]	1.70	2.86	1.40	4.86	2.27	2.58	1.33

[a] Means represent raw unadjusted means (i.e., not estimated marginal means) and standard deviations collected during the procedure.
[b] Data for cocaine slides within *N*-acetylcysteine condition significantly less than cocaine slides within placebo condition ($p<0.05$).

ear mixed-model analysis with measure (craving, desire to use, interest, and time viewed), category (cocaine versus neutral), and medication condition (*N*-acetylcysteine versus placebo) as repeated measures and medication order (*N*-acetylcysteine first versus *N*-acetylcysteine second) as a between-subjects measure. This allowed for a simultaneous test for medication effects and verification that the cocaine slides evoked greater craving and desire to use relative to the neutral category (for a larger analysis that included all four categories, see data supplement Methods). It was hypothesized that the participants would report less craving, desire to use, and interest and would view slides for less time while taking *N*-acetylcysteine relative to placebo and that this would be specific to cocaine slides, as indicated by a significant medication-by-category interaction. Following the initial analysis, separate analyses were performed to determine medication effects for cocaine slides alone, examining each motivational measure separately with a 2×2 (medication condition by medication order) linear mixed-model analysis.

Results

Physiological measures did not reflect any medication effects (see data supplement Methods). Means and standard deviations for motivational ratings for cocaine and neutral slides are presented in Table 1 (for data pertaining to pleasant and unpleasant slides, see data supplement Table 1). The initial analysis for the cue reactivity procedure showed an overall medication effect ($F=7.40$, $df=1, 193$, $p<0.01$) and verified that cocaine slides evoked higher ratings of craving, desire to use, and interest, as well as longer viewing times relative to neutral slides ($F=133.76$, $df=1, 193$, $p<0.001$). The medication-by-category interaction approached significance ($p=0.052$). The overall means for cocaine slides were 5.94 (SD=4.28) and 7.57 (SD=5.11) within the *N*-acetylcysteine and placebo conditions, respectively, and they were 2.00 (SD=2.20) and 2.18 (SD=2.77) for neutral slides within the *N*-acetylcysteine and placebo conditions, respectively. The means for motivational ratings for cocaine and neutral slides are reported in Table 1. Secondary analyses that examined the medication effects for cocaine slides alone revealed that during the *N*-acetylcysteine treatment, the participants provided reduced ratings of desire to use ($F=5.07$, $df=1, 13$, $p<0.05$) and interest ($F=5.07$, $df=1, 13$, $p<0.05$) and spent less time viewing cocaine slides ($F=4.79$, $df=1, 13$, $p<0.05$). No significant medication-related effects were noted for craving, although means for craving within the *N*-acetylcysteine condition were lower than those in the placebo condition (Table 1).

Conclusions

In the presence of cocaine-related cues, *N*-acetylcysteine reduced the desire to use cocaine, interest in cocaine, and cue viewing time. Although the present study is, to our knowledge, the first that has examined *N*-acetylcysteine's impact on cue-induced motivation to use cocaine in cocaine-dependent humans, these data are consistent with the capacity of *N*-acetylcysteine to inhibit cocaine-seeking in cocaine-dependent rodents (2, 3) within the animal model of cocaine reinstatement. It was somewhat unexpected that no significant effects were observed for ratings of craving. However, the pattern of means for craving was consistent with that observed for desire to use and interest, which were highly correlated to craving (See data supplement Methods) and suggests that differences in craving may also have been significant had more subjects been included. In sum, the reduced subjective reports of desire to use and interest in cocaine indicate that *N*-acetylcysteine may be a promising new treatment and that cysteine-glutamate exchange may be a potential pharmacotherapeutic target for treating cocaine dependence.

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