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A preliminary evaluation of N-acetylcysteine's effects on patient adherence to treatment for cocaine use disorder

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Abstract

Introduction: Cocaine use disorder (CUD) is a disabling disease associated with high rates of relapse and intense cravings. Patients with CUD struggle to adhere to treatment, which contributes to relapse and frequent readmissions to residential rehab (RR) facilities. Preliminary studies suggest that N-acetylcysteine (NAC) attenuates cocaine-induced neuroplasticity and, therefore, may assist with cocaine abstinence and adherence to treatment.

Methods: This retrospective cohort study obtained data from 20 RR facilities across Western New York. Eligible subjects were 18 or older, diagnosed with CUD, and were divided based on their exposure to 1200 mg NAC twice daily during RR. The primary outcome was treatment adherence measured by outpatient treatment attendance rates (OTA). Secondary outcomes included length of stay (LOS) in RR and craving severity on a 1 to 100 visual analog scale.

Results: One hundred eighty-eight (N = 188) patients were included in this investigation: NAC, n = 90; control, n = 98. NAC did not significantly impact OTA (% appointments attended), NAC 68%; control 69%, ($P = .89$) or craving severity NAC 34 ± 26; control 30 ± 27, ($P = .38$). Subjects treated with NAC had a significantly longer average LOS in RR compared with controls, NAC 86 ± 30; control 78 ± 26, ($P = .04$).

Discussion: In this study, NAC did not impact treatment adherence but was associated with a significantly longer LOS in RR for patients with CUD. Owing to limitations, these results may not be applicable to the general population. More rigorous studies examining NAC's impact on treatment adherence in CUD are warranted.

Keywords: N-acetylcysteine, cocaine use disorder, cocaine dependence, adherence, stimulant use disorder

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Introduction

Cocaine use disorder (CUD) is a chronic relapsing disease that takes an enormous toll on those afflicted, their friends, family, and society.[1-4] Cocaine is a powerfully addictive psychostimulant that seizes control of primal dopamine (DA) pathways in the brain such as the mesolimbic "reward" system.[5] Continued cocaine use rapidly triggers neuronal adaptations that facilitate a transition to the addicted state.[6-9] For instance, repeated cocaine use decreases the expression of DA transporters and receptors and leads to excessive excitatory signaling in the brain's

corticostriatal tract. Glutamate (GLU) is the most abundant excitatory neurotransmitter in the central nervous system, and excessive GLU accumulation is found in the nucleus accumbens of individuals with CUD.[5] The nucleus accumbens is a region of the brain important for learning, memory, and cognition.[7] These drug-induced changes in the brain precipitate behaviors that are characteristic of CUD such as relapse and uncontrolled use. Indeed, individuals with CUD will seek out and use the drug despite severe financial, social, and health consequences.[10]

N-acetylcysteine (NAC) is a cysteine prodrug commonly used in the treatment of acetaminophen overdose.[11] Convergent evidence, both preclinical and clinical, demonstrates that NAC attenuates cocaine-induced neurological changes.[12-16] For instance, NAC upregulates the expression of GLU transporters in the nucleus accumbens, thereby removing excessive GLU accumulation caused by repeated cocaine administration.[17] Functional MRI studies suggest that NAC normalizes disruptions in corticostriatal signaling that are caused by repeated nicotine use and contribute to drug-seeking behavior. Despite significant interest in NAC's potential as a therapeutic for CUD, clinical studies investigating NAC's efficacy have returned equivocal results to date.[16,18-21] Evidence points to NAC's utility as an antirelapse agent, best utilized after cocaine abstinence is already achieved.[12]

Owing to a lack of economic viability from the standpoint of industry, there has been insufficient progress in the field of drug development for CUD and stimulant use disorders (STUD) in general.[22] Of the available treatment options for CUD, only bupropion, topiramate, and long-acting psychostimulants such as dextroamphetamine improve abstinence, and the evidence supporting such is weak.[23] More recently, extended-release intramuscular naltrexone plus oral bupropion were found to be effective for the treatment of methamphetamine use disorder.[24] Despite these advances, there are no FDA-approved medications for the treatment of CUD or any STUD. Meanwhile, cocaine and stimulant overdose deaths have increased in recent years across all age groups.[25] Indeed, CUD is a devastating condition that is associated with serious health risks, functional impairment, and overdose.[3] The broken pipeline for CUD demands new treatment strategies such as repurposing available therapies such as NAC.

Despite a lack of sufficient evidence for efficacy, NAC is commonly used as an adjunctive therapy for CUD thanks to its low cost, availability, and favorable safety profile.[20] NAC is heavily prescribed at a large treatment network of residential rehab (RR) facilities across Western New York (WNY). Patients with CUD struggle to adhere to treatment, which contributes to high rates of relapse and frequent readmissions to RR.[26,27] A longer length of stay (LOS) in RR, specifically greater than 90 days, may be associated with a lower risk of relapse in patients with CUD.[27] NAC reduces cue-induced cravings of cocaine, may support abstinence, and therefore, may improve patients' ability to adhere to treatment.[28]

Given the evidence supporting NAC's utility in CUD, the prevalence of use in our region, and the need for more real-world data on the use of this treatment, we investigated NAC's impact on treatment adherence in patients with CUD.

Methods

Institutional Review Board approval was granted by the University at Buffalo and Horizon Health Services (HHS) Clinical Review Committee to conduct this retrospective cohort study. Patient data were obtained from Horizon Health Services Inc, a large nonprofit substance abuse and mental health treatment organization with more than 20 New York State Office of Alcohol and Substance Abuse Services–accredited RR treatment facilities across WNY. Patients, 18 years or older, admitted to RR from January 1, 2017, to December 31, 2018, for treatment of CUD were included in this evaluation. Patients were excluded from this study if they had a documented allergy or hypersensitivity to NAC, if their length of stay (LOS) in RR exceeded 200 days, or if they had a nonoutpatient discharge from RR such as a transfer to another RR or inpatient treatment facility. The intervention in this study was 1200 mg NAC taken by mouth twice a day during RR and after discharge. Blister packs containing 600-mg NAC capsules were provided by Parkview Health Services (a specialty pharmacy located in Buffalo, New York) and sent to each RR facility. The medication was purchased through the patient's insurance or out of pocket, depending on how payment for their stay in RR was remitted. Registered or licensed practical nurses administered two 600-mg NAC capsules to each patient at scheduled administration times twice a day while in RR. Patients received prescriptions for NAC at discharge. Control subjects received treatment as usual without NAC. The primary outcome in this study was patient adherence to treatment measured by outpatient treatment attendance rates (OTA) 0 to 6 months after discharge from RR. OTA included mental health or substance use disorder appointments such as psychiatric follow-up and group and individual counseling sessions. HHS provided OTA rates, which were calculated as a percentage by taking the number of appointments attended by the patient and dividing it by the total number of appointments they were scheduled for.

Secondary outcomes included LOS in RR in days and craving severity after discharge. Craving severity on a 1 to 100 visual analog scale (VAS) was assessed at patient's first outpatient appointment using a method previously described and validated in opioid use disorder (OUD).[29]

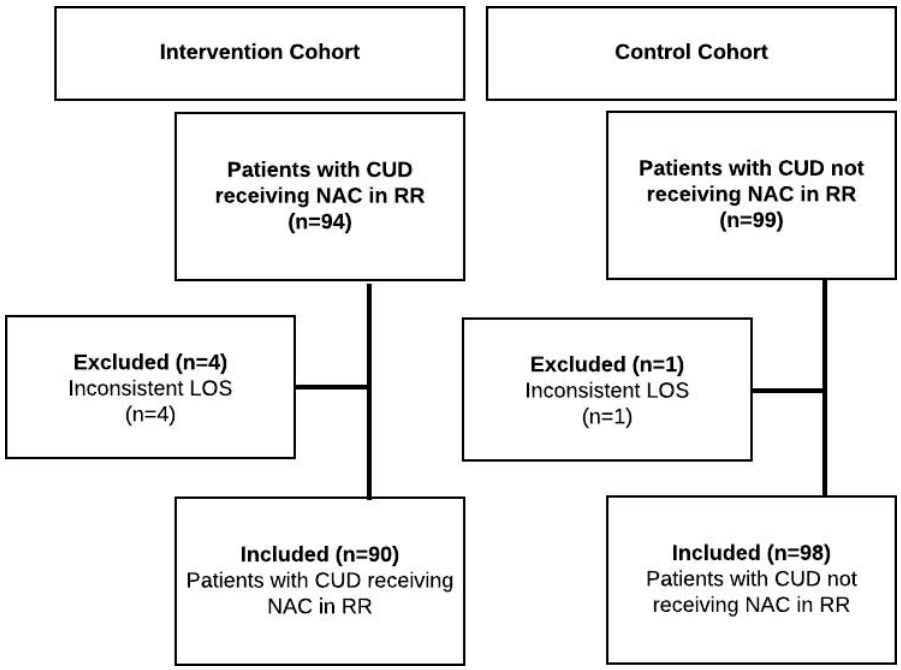

FIGURE: Flow diagram of patients evaluated **Flow diagram of patients provided by the data sponsor and patients included in our final analysis. CUD = cocaine use disorder; LOS = length of stay; NAC = N-acetylcysteine; RR = residential rehab.**

Demographic data, social, psychiatric, substance use history, legal status in RR, and other clinical characteristics were collected from the medical chart of eligible subjects to assess comparability of natural history between the groups.

Descriptive statistics were used to present the demographic data and clinical characteristics. Categorical data were analyzed using Fisher exact test, and continuous variables were analyzed with the *t* test as appropriate. All statistical analyses were performed with IBM SPSS Statistics (version 26, IBM). A *P* value of less than .05 was considered statistically significant.

Results

Data were provided for 193 patients, and a total of 188 (n = 188) were included in our final analysis (Figure). Five patients were excluded because their LOS in RR was greater than 200 days, which may be explained by a discharge from RR followed by a subsequent readmission that was not properly captured. Ninety (n = 90) patients received NAC, and ninety-eight (n = 98) served as controls. Patient demographics and clinical characteristics were similar between the groups with a few exceptions. Patients who received NAC were more likely to use cocaine daily, to report smoking the drug, to have a prior psychiatric hospitalization, and to be less likely to have OUD or to use cannabis daily (Table 1).

Treatment adherence measured by OTA was found to be similar between groups (Table 2). Patients treated with NAC attended 68% of all appointments, and controls attended 69% of appointments ($P = .89$). In contrast, a statistically significant difference in LOS between groups was observed. Subjects treated with NAC had a longer average LOS in RR compared with control subjects. The average LOS in RR for patients treated with NAC was 86 ± 30 days (mean ± SD) compared with control subjects whose average LOS was 78 ± 26 days ($P = .04$).

Treatment with 1200 mg NAC twice a day did not appear to impact craving severity in our sample. Subjects treated with NAC had an average craving severity of 34 ± 26 (1-100 VAS) compared with control subjects 30 ± 27 ($P = .38$).

Discussion

In this retrospective cohort study, treatment with NAC did not impact patient adherence or craving severity but did result in a longer LOS in RR for patients with CUD. These results are consistent with previous clinical studies in patients with CUD that have reported mixed results suggestive of a modest benefit of NAC.[19,20,28,30] To our knowledge, this is the first real-world evaluation of NAC's impact on adherence to treatment for CUD in patients that were enrolled in RR. Our results provide new data on the use of NAC in the RR patient population.

The apparent lack of benefit NAC had on OTA in this study may be explained by several factors including the existence of significant differences in natural history between our groups. Patients receiving NAC were more likely to use

TABLE 1: Patient demographics and clinical characteristics

Demographic Information	NAC 1200 mg Twice a Day (n = 90)	Control (n = 98)	*P* Value
Age, mean ± SD (range), y	33 ± 9 (20-60)	34 ± 9 (21-60)	.43
Sex, male/female	57/33	70/28	.28
Duration of CUD diagnosis, mean ± SD	12 ± 8 years	14 ± 9 years	.16
Social history			
Ethnicity, n (%)			
Caucasian	79 (88)	81 (83)	.41
African American	4 (4)	7 (7)	.54
Native American	1 (1)	4 (4)	.37
Other	6 (7)	6 (6)	1
Sexual orientation, n (%)			
Straight	80 (89)	93 (95)	.18
Gay	2 (2)	1 (1)	.61
Lesbian	2 (2)	1 (1)	.61
Bisexual	6 (7)	3 (3)	.32
Marital status, n (%)			
Never married	69 (77)	73 (74)	.72
Divorced	8 (9)	8 (8)	1
Separated	4 (4)	10 (10)	.17
Married	9 (10)	5 (5)	.27
Widowed	0 (0)	2 (2)	.5
Educational attainment, n (%)			
No HS	2 (2)	0 (0)	.23
Some HS	14 (15)	15 (15)	1
HS diploma or GED	39 (43)	49 (50)	.38
Some college	28 (31)	21 (21)	.14
Associate degree	4 (4)	7 (7)	.54
Bachelor's degree	2 (2)	5 (5)	.45
Graduate degree	1 (1)	1 (1)	1
Gambling problem, n (%)	9 (10)	20 (20)	.07
RR court mandated, n (%)	17 (19)	22 (22)	.59
History of cocaine use			
Frequency of use, n (%)			
Daily	46 (51)	34 (35)	.03
3-6 times per week	10 (11)	5 (5)	.18
1-2 times per week	6 (7)	17 (19)	.03
1-3 times per month	11 (12)	15 (15)	.67
No use in past month	17 (19)	27 (28)	.17
Age use was initiated (mean ± SD)	21 ± 6 years	21 ± 6 years	.36
Route of administration, n (%)			
Smoking	45 (50)	31 (32)	.01
Injection	28 (31)	38 (39)	.29
Insufflation	17 (19)	29 (30)	.09
History of substance use			
Prior intravenous drug use, n (%)	64 (71)	69 (70)	1
Opioids, n (%)			
Lifetime use	31 (34)	41 (42)	.37
Daily use	35 (39)	47 (48)	.24
Opioid use disorder	56 (62)	79 (81)	.01

TABLE 1: Patient demographics and clinical characteristics (continued)

Demographic Information	NAC 1200 mg Twice a Day (n = 90)	Control (n = 98)	*P* Value
Cannabis, n (%)			
Lifetime use	87 (97)	92 (94)	.50
Daily use	30 (33)	47 (48)	.05
Cannabis use disorder	27 (30)	39 (40)	.17
Alcohol, n (%)			
Lifetime use	75 (83)	84 (86)	.69
Daily use	19 (21)	17 (17)	.58
Alcohol use disorder	35 (39)	44 (45)	.46
Medication assisted therapy, n (%)			
buprenorphine/naloxone	40 (44)	48 (49)	.56
naltrexone	32 (36)	29 (30)	.42
Psychiatric medical history			
Prior psychiatric hospitalization	37 (41)	24 (24)	.02
Attempted suicide	4 (4)	4 (4)	1
Major depressive disorder	36 (40)	34 (35)	.55
Generalized anxiety disorder	24 (27)	26 (27)	1
Attention deficit/hyperactivity Disorder	14 (16)	12 (12)	.53
Schizophrenia or schizoaffective disorder	6 (7)	4 (4)	.52
Post-traumatic stress disorder	46 (51)	36 (37)	.06
Any trauma	86 (96)	86 (88)	.07
Depression & anxiety rating scales			
PHQ-9, mean ± SD	6 ± 6	5 ± 6	.13
GAD-7, mean ± SD	7 ± 6	6 ± 6	.09

CUD = cocaine use disorder; GAD-7 = Generalized Anxiety Disorder 7-item; HS = high school; PHQ-9 = Patient Health Questionnaire 9-item.

cocaine daily, to report smoking the drug, and to have a prior psychiatric hospitalization. Smoking cocaine is associated with faster onset and offset of drug effects and may be associated with poorer treatment outcomes.[31] Therefore, NAC may have provided some benefit given that OTA and cravings were no different than for control subjects who had less frequent use, preferred insufflation, and had fewer prior psychiatric hospitalizations. This might also suggest that patients with more severe CUD are more likely to be prescribed NAC. Control subjects were more likely to have OUD and use cannabis daily. Therefore, control subjects may have had other drug use that eclipsed their cravings for cocaine. We were unable to obtain the number of appointments that each patient was scheduled for. If patients were not scheduled for the same number of outpatient appointments, this would increase the risk of bias in our findings on OTA. Other factors such as location of appointments, transportation, and social factors also may have affected OTA.

Clinical studies evaluating NAC's impact on cravings have returned somewhat mixed but generally positive results.[16,30] However, these studies used different methods to assess cravings, such as measuring patients' physiologic response to different stimuli and performing a variety of cue-reactivity assessments. Contrary to these studies, we found no difference between patients treated with NAC and controls when looking at average craving severity scores on

TABLE 2: Primary results[a]

Outcome	NAC 1200 mg Twice a Day	Control Group	*P* Value
OTA (% of appointments attended)	68%	69%	.89
LOS in RR (mean ± SD)	86 ± 30 days	78 ± 26 days	.04
Craving severity 1-100 VAS (mean ± SD)	34 ± 26	30 ± 27	.38

LOS = length of stay; NAC = N-acetylcysteine; OTA = outpatient treatment attendance rates; RR = residential rehab; VAS = visual analog scale.

[a]Treatment with 1200 mg N-acetylcysteine twice a day during RR did not impact OTA or craving severity but was associated with a statistically significant longer LOS in RR.

1 to 100 VAS at the first outpatient appointment. Another explanation for the similarities observed with OTA and cravings between groups is that adherence to NAC may have been higher while patients were enrolled in RR compared with after discharge. We were unable to verify medication administration records or pharmacy data to assess patients' adherence to NAC while in RR and after discharge. However, in RR, NAC doses were administered at scheduled times by nurses, so we believe that adherence was likely to be higher in RR compared with after discharge. Although acute NAC dosing produces measurable neurochemical changes in the brain, chronic administration may be necessary for sustained effects.[12] Therefore, assessing NAC adherence before and after discharge would have been more illuminating.

The ideal LOS in RR for patients suffering substance use disorders is not well defined. Early research on CUD demonstrated that an LOS in RR less than 90 days was associated with relapse and readmission to RR.[28] On the other hand, a more recent study evaluated veterans undergoing treatment in RR for various substance use disorders and found that LOS was not associated with improved outcomes.[32] The patients treated with NAC in our sample stayed on average 8.5 days longer in RR compared with controls. While the use of NAC may have contributed to the longer LOS we observed, a variety of other factors may also explain this finding. Whether to discharge a patient from RR can be a complex decision that involves weighing risks and benefits and may involve input from the patient, his or her loved ones, and members of the treatment team. Any desire for reintegration into the community must be weighed against the risk that premature discharge may have on potential relapse, psychiatric decompensation, and/or readmission. Still, it is interesting that the patients treated with NAC in our sample stayed longer in RR, compared with controls, therefore extending the duration of their treatment. Patients treated with NAC also appeared to have more severe CUD, which may have warranted longer treatment time in RR and would also explain the difference in LOS observed. Owing to the retrospective nature of this study, we were not able to assess whether this extended stay had any impact on more meaningful patient outcomes such as time until relapse, readmission, or negative urine toxicology.

This study was limited by its retrospective nature, small sample size, use of proxy outcome measures that are open to multiple lines of interpretation, and potential for bias and confounding. The 5 individuals excluded from our analysis could have unknown consequences on the validity of our findings. Also, there were significant intergroup differences in daily cocaine use, smoking as preferred method of use, prior psychiatric hospitalization, OUD, and daily cannabis use, and the impact of these differences on our findings was not directly evaluated. Due to data limitations, we were unable to assess medication adherence or the number of appointments involved in the calculation of OTA. The nature of discharge planning at this RR treatment program also limits the generalizability of our findings about LOS.

In this study, treatment with 1200 mg NAC given orally twice a day did not improve adherence to outpatient treatment appointments or craving severity but may have helped promote a longer LOS in RR for individuals with CUD. NAC also appears to be prescribed to individuals with more severe CUD.

Future studies should continue to evaluate NAC's impact on various aspects of treatment in CUD. Convergent evidence supports NAC's potential as a treatment for CUD, and although efficacy is not clear, clinical value may still exist in areas yet to be determined by investigators. If NAC continues to be used as an adjuvant for CUD, this use should be evaluated to improve the quality of care delivered. Larger more-controlled studies are warranted to further evaluate the role of NAC in the treatment of CUD.

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