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Alcohol Use during a Trial of N-Acetylcysteine for Adolescent Marijuana Cessation

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Abstract

Current adolescent alcohol treatments have modest effects and high relapse rates. Evaluation of novel pharmacotherapy treatments is warranted. N-acetylcysteine (NAC), an over-the-counter antioxidant supplement with glutamatergic properties, is a promising treatment for marijuana cessation in adolescents; however, its effects on adolescent drinking have not been examined. To that end, this secondary analysis evaluated: (1) the effect of NAC vs. placebo on alcohol use over an 8-week adolescent marijuana cessation trial and (2) the role of marijuana cessation and reduction on subsequent alcohol use.

Marijuana-dependent adolescents (ages 15–21; N=116) interested in treatment were randomized to NAC 1200mg or matched placebo twice daily for 8 weeks. Participants were not required to be alcohol users or interested in alcohol cessation to qualify.

There were no demographic or baseline alcohol use differences between participants randomized to NAC vs. placebo (ps>.05). Of the 89 participants returning for ≥1 visit following randomization, 77 reported ≥1 alcoholic drink in the 30 days prior to study entry and averaged 1.3 (SD=1.4) binge drinking days per week. During treatment, less marijuana use (measured via urine cannabinoid levels) was associated with less alcohol use in the NAC-treated group but not in the placebo-treated group (p=0.016).

There was no evidence of compensatory alcohol use during marijuana treatment. In fact, in the NAC group, lower levels of marijuana use were associated with less alcohol use, suggesting NAC effects may generalize to other substances and could be useful in decreasing adolescent alcohol use. NAC trials specifically focused on alcohol-using adolescents are warranted.

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INTRODUCTION

Alcohol and marijuana are the two most commonly used substances during adolescence and are often used concurrently (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2015). Several adverse outcomes are associated with adolescent alcohol and marijuana use, including poorer psychosocial (Miller, Naimi, Brewer, & Jones, 2007), cognitive (Jacobus et al., 2015; Meier et al., 2012; Nguyen-Louie et al., 2015; Squeglia & Gray, 2016; Squeglia, Spadoni, Infante, Myers, & Tapert, 2009), and educational outcomes (Latvala et al., 2014). Unfortunately, few adolescent substance use treatment options exist and current efforts have only been modestly effective (Jensen et al., 2011; Tripodi, Bender, Litschge, & Vaughn, 2010; Vandrey & Haney, 2009), with some studies suggesting up to 86% of youth return to alcohol or drug use within 12 months following treatment (Brown, Gleghorn, Schuckit, Myers, & Mott, 1996; Winters, Stinchfield, Opland, Weller, & Latimer, 2000).

Although several medications have been efficacious in treating adult alcohol dependence, pharmacotherapy research focused on adolescent alcohol use has been sparse (Miranda et al., 2014). This limits treatment options, as safety and efficacy of medications for adolescents cannot be inferred from adult studies (Bridge et al., 2007). Evaluation of alternative and more efficacious treatments is warranted in adolescents, particularly in regards to interventions that effectively reduce both alcohol and marijuana use given their considerable co-use.

Based on preclinical findings, glutamate has emerged as a potential pharmacotherapeutic target in the treatment of addictions (Kalivas, 2009; Kalivas & Volkow, 2011). N-acetylcysteine (NAC) is an over-the-counter antioxidant supplement that is believed to restore glutamate homeostasis disrupted by addiction (McClure, Gipson, Malcolm, Kalivas, & Gray, 2014). Part of the appeal of NAC as a treatment for youth with substance use disorders is its long-established safety and tolerability record, with pediatric and adult FDA approval since 1963 (Gray, Watson, Carpenter, & Larowe, 2010). NAC has shown potential efficacy for promoting abstinence from a number of drugs, including marijuana (Gray et al., 2012), cocaine (LaRowe et al., 2013), methamphetamines (Grant, Odlaug, & Kim, 2010), and nicotine (Froeliger et al., 2015; Knackstedt et al., 2009; Van Schooten et al., 2002). In a double-blind placebo controlled study of marijuana-dependent adolescents, youth randomized to receive NAC had more than double the odds of negative urine cannabinoid tests during treatment compared to the placebo group (Gray et al., 2012). Secondary analyses of cigarette smokers revealed that changes in marijuana use during treatment did not affect cigarette smoking (McClure, Baker, & Gray, 2014). Despite this, there is some evidence of a "substitution effect", wherein marijuana reduction or abstinence may increase the use of other substances of abuse (Chaloupka & Laixuthai, 1997; Copersino et al., 2006; Schaub, Gmel, Annaheim, Mueller, & Schwappach, 2010). Identifying medications that can reduce both alcohol and marijuana use are ideal, given the high rates of co-use of these substances during adolescence.

While no published clinical trials to date have examined the effect of NAC on alcohol use, recent preclinical findings suggests that NAC may effectively decrease alcohol consumption.

Alcohol-consuming rats who were administered NAC inhibited alcohol intake up to 70% compared to saline-treated rats ($p<.0001$). The effect of treatment was long-lasting and remained for 4 days post-treatment, showing that NAC administration generates a neurochemical effect extending well past its 1 hour half-life in rodents (Quintanilla et al., in press). Taken together with previous promising findings in marijuana dependent youth (Gray et al., 2012), exploration of this medication in reducing adolescent alcohol use is warranted. The purpose of this secondary analysis was to explore the effect of NAC on alcohol use during a marijuana cessation trial (Gray et al., 2012), thereby determining if this could be a potentially efficacious target medication for adolescent alcohol use. Specifically, this study evaluated: (1) the effect of NAC vs. placebo on co-occurring alcohol use over an 8-week adolescent marijuana treatment trial and (2) the role of marijuana use (reductions and/or abstinence) on subsequent alcohol use. This is the first exploratory analysis from a randomized treatment trial examining the effects of NAC on adolescent alcohol use and provides a unique opportunity to explore alcohol use during NAC-assisted marijuana cessation.

METHODS

Participants

Participants were obtained from a marijuana cessation treatment study ($n=116$) (Gray et al., 2012). All participants were between ages 15 and 21, met criteria for marijuana dependence, used marijuana regularly (≥3 days/week), and were interested in marijuana cessation treatment. Participants were excluded if they were enrolled in substance abuse treatment, had comorbid substance dependence (other than nicotine), had any unstable psychiatric or medical issue, were pregnant, were taking carbamazepine or nitroglycerine, or had a history of adverse reaction to NAC. Recruitment occurred primarily through community media outlets and clinical referrals. As this was a marijuana cessation trial, participants were not required to be alcohol users or interested in alcohol cessation to qualify, and were excluded from study participation if they met criteria for alcohol dependence, but not abuse. Further description of the sample and marijuana abstinence outcomes have been previously reported (Gray et al., 2012).

Procedures

Participants were randomized to receive either active treatment (NAC, 1200 mg twice daily) or matched placebo. The study treatment lasted for eight weeks, during which participants were required to attend weekly study visits. One follow-up visit occurred at 12 weeks. In addition to study medication, contingency management procedures were used to reinforce attendance at study visits and abstinence from marijuana throughout the eight-week intervention. Brief marijuana cessation counseling was provided weekly during the in-person study visit. No psychosocial treatment targeted alcohol use.

Measures

Substance use—During the 8-week treatment phase, alcohol, marijuana, cigarette, and other drug use was recorded via daily diaries. Timeline Follow-back (TLFB) methods were used to measure substance use during the 30 days prior to study enrollment and through the

follow-up period (Sobell & Sobell, 1992). Standard drinks were calculated based on NIAAA guidelines (http://rethinkingdrinking.niaaa.nih.gov/tools/Calculators/drink-size-calculator.aspx). Urine cannabinoid testing at baseline, during weekly study visits, and at post-treatment follow-up, was conducted as the primary biological measure of marijuana use.

Psychopathology—The Mini International Neuropsychiatric Interview (MINI), or MINI-KID for participants under age 18, ascertained current or lifetime history of the major DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998; Sheehan et al., 2010). None of the participants met criteria for alcohol dependence.

Outcomes

Total number of standard drinks consumed, number of drinking days, and number of binge drinking days (4 or more drinks for women and 5 or more drinks for men) were calculated at each weekly study visit as the primary alcohol use outcomes. When missing visits occurred between attended visits, the TLFB summary alcohol use data for the next attended visit were calculated back to the last previously attended visit. This allowed use of all of the collected TLFB data even in the presence of missing visits. To account for the variable time frame of data collection between attended visits (including variable time frame of contingnency management and cessation counseling), all models also adjusted for the number of days since the last attended visit. Out of the 89 participants included in this analysis, there were 22 informative visits with missing data (TLFB data available at the following visit); 8 were from participants randomized to the NAC group and 14 to placebo. The mean number of days between attended visits when a visit was missing was 14.0 (SD=2.6) for these 22 occurrences [NAC=13.8 (1.4); placebo=14.1 (3.2)].

Statistical analysis

The primary aim of this secondary analysis was to describe drinking behavior in adolescents during a medication-assisted marijuana cessation trial. Standard descriptive statistics were used to quantify demographic, clinical, and substance use characteristics between study randomization groups. A Wilcoxon rank sum test statistic assessed differences among continuous variables at screening while differences in categorical variables were assessed using a Pearson Chi-square test statistic. The effect of NAC versus placebo on secondary abstinence from alcohol use was analyzed over the eight-week treatment period.

Alcohol use can be thought of as a two part correlated process that includes abstinence from drinking and reductions in drinking. The data contained a preponderance of zero drinking days across the duration of the study and no requirement for alcohol use was specified for study entry. Thus, these zeros are assumed to be from a mixture of two distinct processes: 1) abstinence from alcohol in the presence of past or current use (sampling zeros) and 2) abstinence from alcohol in a non-alcohol user (structural zeros). Accordingly, several models were assessed as candidate structures to analyze the data: repeated measures log-linear (Poisson/Negative Binomial using methods of Generalized Estimating Equation), Binomial-Poisson Hurdle, as well as Random effect Zero-Inflated Poisson (ZIP) and Negative Binomial (ZINB), the latter models using methods of maximum likelihood. Since the

structural zeros likely come from more than one source, zero-inflated models were chosen as fundamentally more appropriate than Hurdle and repeated measures log-linear models. Thus, random effects zero-inflated (ZIP, ZINB) models were used to investigate the effects of treatment with NAC and concurrent marijuana use on alcohol use over time. The zero-inflated models extend the Poisson/Negative Binomial models with the inclusion of a logistic regression component that distinguishes between sampling and structural zeros (those at risk for drinking and those not at risk). The parameter estimates from the Poisson/Negative Binomial portion of the model assessed the increased or decreased effects of the independent variables on number of drinks, drinking days, and binge drinking days within the at-risk group (He, Tang, Wang, & Crits-Christoph, 2014; Lambert, 1992).

Both unadjusted and adjusted models are presented. In the adjusted models, the primary model predictors are: baseline levels of drinking intensity (average weekly drinking days, binge drinking days, or total drinks over the 30 days prior to study entry, dependent on the model outcome), randomized treatment assignment, age at study entry, week of study visit, and the number of days since last treatment visit contact. Predictors were chosen as those that may be univariately associated with the alcohol use outcomes, possible effect modifiers, or confounders of the treatment effect. Interactions between covariates and the randomized treatment assignment were investigated and noted when significant. Expanded models were used to investigate the effect of marijuana use patterns on drinking behavior during the study. Urine cannabinoid tests (UCT; qualitative cutoff 50 ng/mL) and creatinine adjusted cannabinoid levels (CC Ratio: results shown for a 1 standard deviation unit change=3.62) were collected in concert with the TLFB drinking data collection. Both visit lagged creatinine levels and concurrent UCT results were included in the regression models to assess whether prior marijuana use impacted subsequent alcohol use (chosen to best model alcohol use subsequent to marijuana use). The motivation behind the use of these measures is the hypothesis that once reduction or abstinence from marijuana occurs, substitution with alcohol could follow. Thus, we were interested in marijuana use in the weeks prior to when alcohol use was measured. Treatment interactions with model covariates were independently added to the adjusted models. Although not specifically powered to detect interactions of interest at $p<0.05$, those that reached a $p<0.15$ level were further stratified by treatment assignment to investigate treatment effect modification. Medication compliance was measured through a combination of self-report and pill counts; pill count data was the primary measure of medication compliance and self-report was used in its absence. Medication compliance was defined as taking at least 80% of the prescribed doses and was measured at each weekly study visit. In order to assess the effect of concurrent weekly alcohol use outcomes on weekly compliance, a repeated measures logistic regression model using the methods of generalized estimating equations (Zeger & Liang, 1986) was implemented with weekly compliance status as the outcome of interest. All statistical analysis were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study Characteristics and Baseline Associations

Of the 116 participants randomized in the study, 89 (77%) returned for at least one study treatment visit and had recorded alcohol use data (even if abstinent from alcohol use) and were included in the longitudinal analysis. Of those 89, 45 were randomized to receive NAC and 44 to receive placebo; 603 of the possible 712 (85%) weekly visits had alcohol use and abstinence data available (NAC: 311 vs. placebo: 292) and each attended visit was, on average, 7.4 (SD=2.3) days apart (max=21 days). Overall, participants attended a mean of 6.8 visits (SD=2.1; Median=8.0) with no significant differences between groups [p=0.502; NAC: mean=6.9 (SD=2.1; Median=8.0) vs. placebo: mean=6.6 (SD=2.1; Median=7.5)]. Demographic, psychiatric, and use characteristics between study groups are presented in Table 1. Out of the 89 participants with study data available, 77 (87%) reported at least one drink during the 30 days prior to study entry and 69 (77%) noted at least one drink within a week of study entry; 36 (80%) in the NAC group and 33 (75%) in the placebo group (p=0.572). There were no differences between study groups with respect to age, race, sex, substance use characteristics, or psychiatric comorbidities. Compared to the portion of the cohort with no alcohol follow up data (n=27), those included in this analysis had fewer years of marijuana use [4.0 (SD=1.8) vs. 5.0 (2.0); p=0.013] and were more likely to be Caucasian [87.6% vs. 69.2%; p=0.026]. The cohorts did not differ on other demographic and use characteristics at screening (i.e., age, blood pressure, height, weight, marijuana quit attempts, MCQ scores, or previous drinking behaviors; ps>0.10; see Gray et al., 2012).

Of those who had reported recent drinking prior to study entry (within 7 days; 69/89), the average number of drinking days between weekly treatment visits was 2.2 (SD=1.8) and the average number of binge drinking days was 1.3 (SD=1.4). There were no baseline differences in the average weekly number of drinking or binge drinking days between study groups (p=0.618 and p=0.665, respectively) leading up to study participation. See Table 1.

Alcohol Use and Medication Compliance

There were 478 weekly visits with compliance and alcohol use data available. 440 of the 478 (92%) weekly medication compliance measures were considered in compliance and 365 (76%) compliance measures reflected taking *all* prescribed medication during the week. Concurrent measures of alcohol use were not associated with medication compliance during the treatment phase of the study. During weeks when any drinking was reported, 91% of weekly medication measures were considered compliant where 93% were compliant in weeks where no drinking was reported [RR=0.99 (95% CI: 0.93–1.05), χ^2_1=0.2, p=0.667]. Similarly, during weeks when any drinking was reported, 75% of compliance measures reflected taking all prescribed doses, whereas 79% reflected taking all prescribed doses in weeks when no drinking was reported [RR=0.99 (95% CI: 0.90–1.09), χ^2_1=0.0, p=0.862]. Additionally, there was no differential effect of alcohol on compliance (≥80%) between treatment with NAC or placebo [Treatment by Drinking interaction, χ^2_1=0.5, p=0.491]. Similar results are seen in the evaluation of increases in the total number of drinks [RR=0.99 (95% CI: 0.98–1.01), χ^2_1=0.2, p=0.638], drinking days [RR=0.99 (95% CI: 0.98–1.01),

χ^2_1=1.0, p=0.318] and binge drinking days [RR=1.00 (95% CI: 0.98–1.02), χ^2_1=0.0, p=0.847] between each visit.

Efficacy of NAC on Drinking Outcomes: Main Effects

Overall weekly mean drinking days, weekly binge drinking days, and weekly total standard drinks; their associated standard errors; and unadjusted model *p*-values (count portion) are listed in Table 1. During the study, there was no main effect of NAC treatment on the odds of abstinence (zero versus any drinks), the absence of any drinking days, or binge drinking days between weekly visits during the study [any drinks: RR=0.94 (95% CI=0.72–1.22), t_{86}=−0.42, p=0.673]. In those who were at-risk for drinking, NAC did not affect the expected rate of drinking days [Unadjusted: RR=1.17 (0.58–2.34), t_{86}=0.45, p=0.657; Adjusted: RR=1.24 (0.71–2.17), t_{86}=0.78, p=0.438] or binge drinking days [Unadjusted: RR=1.23 (0.60–2.50), t_{86}=0.57, p=0.569; Adjusted: RR=1.08 (0.65–1.82), t_{86}=0.33, p=0.742]. Similarly, treatment with NAC did not affect the cohort wide expected rate of the total drinks consumed between visits [Unadjusted: RR=1.00 (0.98–1.01), t_{86}=−0.24, p=0.814; Adjusted: RR=1.00 (0.99–1.02), t_{86}=0.39, p=0.698].

The Relationship between Marijuana Use and Drinking Outcomes: Interactive Effects

It was also hypothesized that changes in marijuana use patterns would be associated with drinking behavior. Concurrent UCT results (yes/no) and prior visit (lagged) creatinine adjusted cannabinoid (CC) ratios were independently added into the Poisson portion of the model to assess if recent (prior week) reductions/abstinence in marijuana use were associated with concurrent self-reported alcohol consumption. Having a negative UCT was not associated with the number of reported drinking days [RR=1.06 (0.85–1.33), t_{86}=0.57, p=0.570] or binge drinking days between visits [RR=1.08 (0.82–1.43), t_{86}=0.56, p=0.577]. Although there was no significant association between UCT results and the number of drinking days/binge drinking days, negative UCTs were moderately associated with less concurrent weekly total standard drinks [RR=1.11 (1.01–1.22), t_{86}=2.23, p=0.029]. Examination of CC ratio model data indicated that 1 of the 512 available data points was considered significantly larger than the remainder of the data and models were run both with and without the data point [Median CC Ratio (IQR)= 0.89 (0.00–3.42); outlying data point=47.57 with extraordinarily high urine cannabinoid level (12174 ng/ml)]. Data are presented with the outlier excluded from the analysis. Similar to the UCT results, decreases in lagged CC ratios were not significantly associated with drinking days [RR=1.06 (0.97–1.15), t_{86}=1.33, p=0.186] or binge drinking days [RR=1.06 (0.97–1.15), t_{86}=1.35, p=0.180]. Similar to UCT results, lower CC ratios were associated with fewer drinks consumed within the week [RR=1.11 (1.06–1.19), t_{86}=3.83, p<0.001]. Additionally, less marijuana use (CC Ratio and UCT) was associated with fewer total drinks per week in the NAC treatment group but not in the placebo group [UCT: interaction t_{86}=2.43, p=0.017; CC: Interaction t_{86}=1.55, p=0.136]. This relationship indicates that abstinence and lower levels of marijuana use are more strongly related to alcohol consumption in the NAC-treated group [UCT: RR=1.28 (1.09–1.49), t_{43}=3.33, p=0.002; CC: RR=1.15 (1.06–1.25), t_{43}=3.51, p=0.001] than in the placebo treated group [UCT: RR=1.01 (0.89–1.14), t_{42}=0.12, p=0.907; CC: RR=1.07 (0.98–1.17), t_{42}=1.62, p=0.112]. Among those who have a risk of drinking, those with negative

UCTs (and lower CC ratios) in the NAC groups are likely to drink fewer total drinks between visits than those that have a positive UCT (or higher CC ratio).

Other Predictors of Drinking Behavior

Greater baseline drinking behavior [Drinking Days: RR=1.49 (1.25–1.76); t_{86}=4.62, p<0.001; Binge Drinking Days: RR=1.99 (1.63–2.42); t_{86}=6.99, p<0.001; Total Drinks: RR=1.46 (1.11–1.93); t_{86}=2.73, p=0.008] and the number of days since last visit contact [Drinking Days: RR=1.12 (1.08–1.15); t_{86}=4.60, p<0.001; Binge Drinking Days: RR=1.11 (1.07–1.16); t_{86}=5.12, p<0.001; Total Drinks: RR=1.09 (1.07–1.10); t_{86}=12.2, p<0.001] were the greatest predictors of higher rates of drinking during the treatment portion of the study. Older age at study entry was also moderately associated with increased drinking and binge drinking days [Drinking Days: RR=1.10 (0.99–1.22); t_{86}=2.90, p=0.088; Binge Drinking Days: RR=1.20 (1.02–1.46); t_{86}=2.23, p=0.028;] but not with total weekly drinks [Total Drinks: RR=1.08 (0.72–1.62); t_{86}=0.38, p=0.703].

DISCUSSION

The primary goal of this study was to understand if NAC, an over-the-counter antioxidant supplement with glutamatergic properties, could be a potentially efficacious target medication for adolescent alcohol use. In the parent study, marijuana-dependent youth randomized to NAC were nearly 2.5 times more likely than the placebo group to have a negative urine cannabinoid test during treatment (Gray et al., 2012). Secondary analyses were run to determine if promising marijuana-related effects generalized to co-occurring alcohol use. No evidence was found of compensatory alcohol use during this marijuana cessation trial, suggesting participants were not substituting alcohol during marijuana cessation, which is consistent with tobacco findings (McClure, Baker, et al., 2014). In fact, in the group receiving NAC, marijuana abstinence and reductions in marijuana use were associated with less alcohol use. In the NAC group, participants with reduced marijuana use also consumed reduced number of drinks per week; there was no relationship between alcohol and marijuana use in the placebo group. Medication compliance was high (92%) and was not affected by alcohol use during this trial. This hypothesis-generating finding suggests NAC effects may generalize to other substances and could be useful in decreasing adolescent alcohol use specifically. Findings are notable considering this sample was not attempting to reduce their alcohol use and were not receiving a combined behavioral treatment for alcohol use.

These findings are considered in the context of other promising preclinical alcohol-related NAC findings. In a recent study, rats who were consuming alcohol chronically and were administered NAC inhibited alcohol intake up to 70% compared to saline-treated rats (p<. 0001) (Quintanilla et al., in press). Additional preclinical data suggests NAC may also be useful for alcohol withdrawal (Schneider et al., 2015). NAC is thought to work through restoring glutamate homeostasis disrupted by addiction, a finding replicated across multiple substances of abuse (McClure, Gipson, et al., 2014; Olive, Cleva, Kalivas, & Malcolm, 2012); however, to date, no human alcohol clinical trials have been published. The presented

findings, in combination with promising preclinical results, suggest NAC may be a promising target medication for adolescent alcohol use.

This study is a preliminary look at the effect of NAC on adolescent alcohol use; limitations exist. The primary study provided pharmacological and behavioral treatment for marijuana dependence; no participants met criteria for alcohol dependence and youth were averaging only 2 drinking days per week, with one being a binge drinking episode. Future studies focused on alcohol dependent youth are warranted to better understand the role of NAC in reducing more problematic levels of drinking. The majority of the participants were Caucasian males over the age of 17. Younger, more diverse populations should be included in future studies to better understand the role of age, sex, race, and ethnicity on treatment effects. This study relied on youth self-report of alcohol use. Incorporating real time measures (via smart phone technology) and biological markers of alcohol use would greatly improve the accuracy of reporting. While NAC's over-the-counter availability, low cost, and established safety profile make it highly desirable for eventual dissemination, these characteristics may prompt patients or providers to prematurely consider NAC as a standalone treatment. More research is warranted to understand how NAC might affect alcohol use in adolescents, particularly youth with more severe substance use or psychological issues.

Despite alcohol being the most commonly used substance during adolescence (Johnston et al., 2015), pharmacotherapy research focused on adolescent alcohol use has been sparse. This study, in the context of recent preclinical findings, suggests NAC may be a promising candidate pharmacotherapy for adolescent alcohol use. Previously reported NAC-related reductions in marijuana use could generalize to other substances including alcohol. Effective interventions during adolescence could have substantial long-term implications by reducing acute and enduring negative social, academic, and cognitive consequences related to binge adolescent drinking (Squeglia & Gray, 2016). Evaluation of novel candidate treatments, including NAC, is warranted in adolescents, particularly in regards to interventions that effectively reduce alcohol given its high use rates during adolescence.

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Research Highlights

- N-acetylcysteine (NAC) is a promising target medication for treating addiction.
- In the NAC-treated group, less marijuana use was associated with less alcohol use.
- This relationship was not found in the placebo group.
- More research is warranted to understand the effect of NAC on adolescent alcohol use.

Table 1

Demographic, psychiatric, and substance use characteristics for the overall study sample and compared between those randomized to receive NAC and Placebo.

Baseline	Overall (n=89)		Placebo (n=44)		NAC (n=45)		P Value
	Mean or % (N)	SD	Mean	SD	Mean	SD	
Demographics Characteristics							
Age (years)	18.8 (1.6)	1.6	18.8	1.6	18.8	1.6	0.967
Caucasian %	87.6 (78)		93.2 (41)		82.2 (37)		0.116
Male %	69.7 (62)		75.0 (33)		64.4 (29)		0.279
Use Characteristics							
Alcohol Use 7 days prior to study %	77.5 (69)		75.0 (33)		80.0 (36)		0.572
Alcohol Use 30 days prior to study %	86.5 (77)		86.4 (38)		86.7 (39)		0.967
Drinking Days per Week **	2.2	1.8	2.3	1.9	2.1	1.7	0.618
Binge Drinking Days per Week **	1.3	1.4	1.2	1.4	1.3	1.7	0.665
Drinking Days per Week *	2.5	1.7	2.7	1.7	2.4	1.6	0.477
Binge Drinking Days per Week *	1.5	1.4	1.4	1.4	1.5	1.4	0.664
Years of marijuana use	4.0	1.8	3.9	1.8	4.0	1.7	0.625
# of Quit attempts (Marijuana)	2.0	2.3	2.1	2.4	1.8	2.2	0.625
% Smoke cigarettes	58.4 (52)		59.1 (26)		57.8 (26)		0.900
Years Smoking Cigarettes *	2.5	2.2	2.4	2.1	2.6	2.3	0.868
Cigarettes per Day *	5.5	6.4	5.6	7.0	5.3	6.0	0.626
Psychiatric Comorbidity							
ADHD % (N) - yes	5.6 (5)		9.1 (4)		2.2 (1)		0.203
CD/ODD % (N) - yes	6.7 (6)		9.1 (4)		4.4 (2)		0.382
MDD % (N) - yes	6.7 (6)		11.4 (5)		2.2 (1)		0.086
Meets Alcohol Abuse Criteria % (N)							0.723
Current	11.2 (10)		6.7 (6)		4.5 (4)		
Past	28.1 (25)		14.6 (13)		13.5 (12)		

Baseline	Overall (n=89)		Placebo (n=44)		NAC (n=45)		P Value
	Mean or % (N)	SD	Mean	SD	Mean	SD	
Treatment Use Outcomes							
Drinking Days per Week †	1.6	1.9	1.5	1.9	1.6	1.9	0.657
Binge Drinking Days per Week †	1.0	1.4	1.0	1.4	1.0	1.3	0.569
Total Drinks †	10.0	13.8	9.9	13.9	10.1	13.7	0.814

P-values reported from Wilcoxon Rank-Sums test for continuous characteristics and Chi-Square test for categorical or ordinal characteristics.

* In those reporting at least 1 drink in the 30 days prior to the study.

** All Participants.

† Reported P-Values from unadjusted primary analytic models.

ADHD = Attention-Deficit/Hyperactivity Disorder

CD = Conduct Disorder

ODD = Oppositional Defiant Disorder

MDD = Major Depressive Disorder