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A randomized placebo-controlled trial of *N*-acetylcysteine for cannabis use disorder in adults

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ABSTRACT

Background: Cannabis use disorder (CUD) is a prevalent and impairing condition, and established psychosocial treatments convey limited efficacy. In light of recent findings supporting the efficacy of *N*-acetylcysteine (NAC) for CUD in adolescents, the objective of this trial was to evaluate its efficacy in adults.

Methods: In a 12-week double-blind randomized placebo-controlled trial, treatment-seeking adults ages 18–50 with CUD ($N = 302$), enrolled across six National Drug Abuse Treatment Clinical Trials Network-affiliated clinical sites, were randomized in a 1:1 ratio to a 12-week course of NAC 1200 mg ($n = 153$) or placebo ($n = 149$) twice daily. All participants received contingency management (CM) and medical management. The primary efficacy measure was the odds of negative urine cannabinoid tests during treatment, compared between NAC and placebo participants.

Results: There was not statistically significant evidence that the NAC and placebo groups differed in cannabis abstinence (odds ratio = 1.00, 95% confidence interval 0.63–1.59, $p = 0.984$). Overall, 22.3% of urine cannabinoid tests in the NAC group were negative, compared with 22.4% in the placebo group. Many participants were medication non-adherent; exploratory analysis within medication-adherent subgroups revealed no significant differential abstinence outcomes by treatment group.

Conclusions: In contrast with prior findings in adolescents, there is no evidence that NAC 1200 mg twice daily plus CM is differentially efficacious for CUD in adults when compared to placebo plus CM. This discrepant finding between adolescents and adults with CUD may have been influenced by differences in development, cannabis use profiles, responses to embedded behavioral treatment, medication adherence, and other factors.

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1. Introduction

One in eleven adult cannabis users develops cannabis use disorder (CUD), a syndrome with well characterized physiological and behavioral symptoms and associated adverse outcomes (Budney and Moore, 2002; Hasin et al., 2015; Volkow et al., 2014). CUD is prevalent, with 2.5% United States adults meeting criteria in the past year, but only 13.2% of those with lifetime CUD participate in any treatment for the disorder (Hasin et al., 2016). For those who do, evidence-based psychosocial interventions yield modest effects, with few individuals achieving long-term cannabis abstinence, though some evidence suggests that the behavioral intervention contingency management (CM), in which tangible incentives are provided for desired behaviors (e.g., objective indicators of cannabis abstinence) may enhance outcomes (Cooper et al., 2015; Gates et al., 2016). Amid increased understanding of the neuropharmacology of CUD, recent efforts have focused on developing pharmacotherapies to complement psychosocial treatments (Copeland and Pokorski, 2016; Marshall et al., 2014). *N*-acetylcysteine (NAC), available over-the-counter as an antioxidant supplement, restores glutamate homeostasis and reduces reinstatement of drug seeking in animal models of addiction and is being evaluated clinically as a potential treatment for a variety of substance use disorders (Baker et al., 2003; McClure et al., 2014a,b). In an 8-week randomized placebo-controlled trial (RCT) for CUD in adolescents ages 15–21 ($N = 116$) receiving a CM intervention and weekly medical clinician-delivered cessation counseling, NAC compared to placebo more than doubled the odds of abstinence during treatment, reflected in negative weekly urine cannabinoid tests (OR = 2.4, 95% CI: 1.1–5.2, $p = 0.029$) (Gray et al., 2012). While these positive findings were encouraging, a similar trial in adults was deemed necessary to evaluate efficacy in this age group. The present study was designed to replicate and extend the adolescent study's general methods via a 12-week RCT (McClure et al., 2014a,b). We hypothesized that NAC-treated adults would evidence higher rates of abstinence during treatment than those receiving placebo.

2. Material and methods

2.1. Trial design

Treatment-seeking adults with CUD were randomized, in 1:1 parallel group allocation, to receive a double-blind 12-week course of NAC (1200 mg) or placebo twice daily, added to a CM intervention and medical clinician-delivered medical management. Urine specimens were collected at baseline, twice weekly throughout treatment, at end-of-treatment, and at post-treatment follow-up for urine cannabinoid testing (UCT) by dipstick, and an aliquot was collected once a week for enzyme immunoassay (Abbott Laboratories, Chicago, IL) analysis by a central laboratory (Clinical Neurobiology Laboratory, Medical University of South Carolina, Charleston SC) for the primary outcome.

The study was conducted within an approved United States Food and Drug Administration Investigational New Drug application. The institutional review boards at participating centers approved the study protocol, which was overseen by an independent National Institute on Drug Abuse-appointed Data and Safety Monitoring Board. All participants provided written informed consent.

The trial was implemented across six sites within the National Drug Abuse Treatment Clinical Trials Network (CTN): Behavioral Health Services of Pickens County, Pickens, South Carolina; CODA, Portland, Oregon; University of California Los Angeles Integrated Substance Abuse Programs, Los Angeles, California; APT Foundation, New Haven, Connecticut; University of Texas Health Science Center San Antonio, San Antonio, Texas; University of Kentucky, Lexington, Kentucky.

2.2. Participants

The trial enrolled treatment-seeking participants ages 18–50 meeting Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for cannabis dependence and submitting a positive UCT during the initial screening visit (Fig. 1) (American Psychiatric Association, 2000). Individuals with acutely unstable medical or psychiatric disorders, DSM-IV-TR substance dependence aside from cannabis or tobacco, contraindications for NAC treatment, or recent synthetic cannabinoid use were excluded. Recruitment, conducted between January 2014 and April 2015, occurred primarily through community media advertisements. Interested individuals were prescreened by phone, and those meeting general entry criteria were scheduled for consent and screening procedures in the research clinic.

2.3. General procedures

Details of study design have been described previously (McClure et al., 2014a,b). All procedures and data collection were conducted in research clinics at participating sites. At the baseline visit, comprehensive psychiatric and substance use diagnostic assessments, medical history and physical examination, and laboratory testing (urine pregnancy and drug tests) were performed (Sheehan et al., 1998; First et al., 2004). Timeline Follow-Back methods were used to assess self-reported substance use (Sobell et al., 1988; Mariani et al., 2011).

Eligible participants were enrolled in a CM intervention, and randomized to medication treatment group. Participants were seen twice weekly during the 12-week treatment phase and a follow-up post-treatment assessment was conducted 4 weeks after treatment conclusion. During one weekly visit, the study medical clinician provided medical management and adverse event assessment, participants completed self-assessments, and UCT and CM procedures were completed. The other weekly visit was brief, consisting only of UCT and CM procedures. At multiple time points, participants and medical clinicians were asked to state whether they thought the participant was receiving NAC or placebo, to evaluate penetration of the blind. Upon the first negative UCT for a participant, the sample was additionally sent for synthetic cannabinoid testing (Soft Landing Labs, Elmhurst IL) to confirm that the participant was not substituting synthetic cannabinoids for traditional cannabis.

2.4. Interventions

2.4.1. Medication

Participants were randomized to a double-blind 12-week course of orally administered NAC 1200 mg or placebo twice daily. Randomization, conducted centrally through the CTN Data and Statistics Center, was on a 1:1 ratio, with stratification by study site and self-reported binary tobacco smoking status (yes/no), in light of prior research indicating poorer cannabis cessation outcomes among tobacco users (Haney et al., 2013; Peters et al., 2014).

United States Pharmacopeia grade NAC powder was encapsulated in 600 mg quantities (two 600 mg capsules per twice-daily dose). Matched placebo capsules were also prepared. Riboflavin 25 mg was added to all capsules (100 mg/day total) as a biomarker for medication adherence (assessed fluorometrically by the Clinical Neurobiology Laboratory, Medical University of South Carolina, Charleston SC) (Malcolm et al., 2000). All capsules were packaged in blister packs, dispensed weekly, with individual labels for time/date of each dose.

2.4.2. Embedded behavioral treatment

All participants received CM twice weekly during treatment, including escalating schedules of cash reinforcement with resets, targeting (a) visit attendance (initial attended visit $10, escalating by $2 per subsequent visit, and reset to $10 after a missed visit; maximum $30

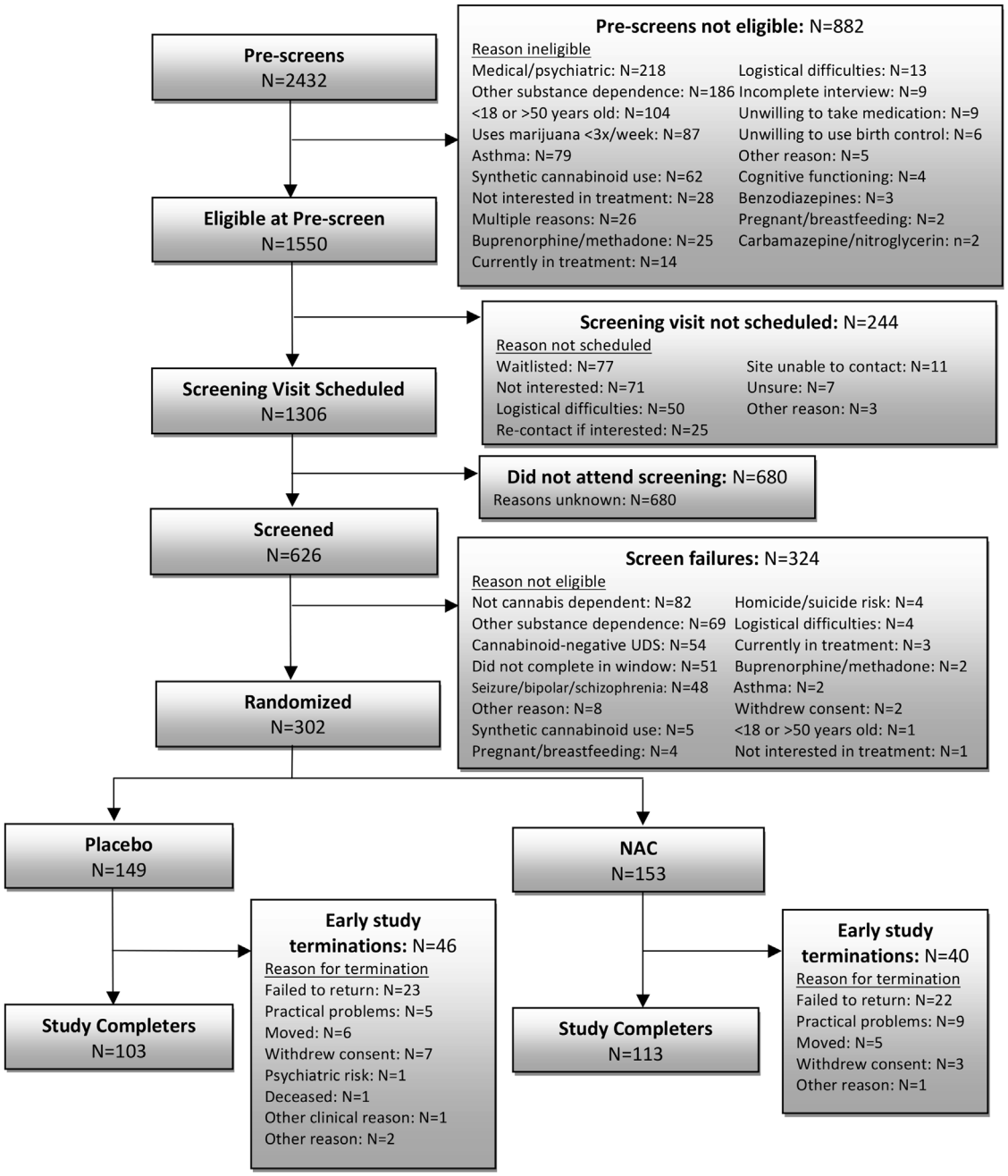

Fig. 1. CONSORT Diagram.

per visit), and (b) cannabis abstinence, confirmed by urine dipstick test (initial abstinent visit $5, escalating by $2 per subsequent visit, and reset to $5 after a non-abstinent or missed visit; maximum $25 per visit). Medical management, a low-intensity supportive intervention emphasizing cannabis abstinence, medication adherence, and study retention, was conducted by the medical clinician weekly throughout treatment (Volpicelli et al., 2001). This intervention was selected to closely match psychosocial procedures in the prior adolescent trial, and to reflect care that could be delivered in real-world medical settings.

2.5. Outcomes

2.5.1. Efficacy

UCT (< 50 ng/mL considered negative) measured by the central laboratory during weekly clinic visits and at post-treatment follow-up, was conducted as the primary biological measure of cannabis use.

2.5.2. Safety/Tolerability

Adverse events were assessed at all study visits, including severity and relatedness to study drug or study procedures. Vital signs monitoring and urine pregnancy testing were additionally conducted.

2.5.3. Adherence

Pre-defined criteria for medication adherence included taking ≥80% of prescribed study medication per study week (assessed via weekly medication diaries and blister pack pill counts), confirmed by urine riboflavin level > 1500 ng/mL, after subtracting pre-randomization riboflavin level (Herron et al., 2013).

2.6. Statistical analyses

The primary study hypothesis was that participants randomized to NAC would be more likely than those randomized to placebo to have

negative UCTs during treatment. An intent-to-treat approach including all randomized participants was used. All missing UCTs (missed visit/dropout/lost-to-follow-up) were imputed as positive, a method that does not make the missing-at-random assumption and has been employed in substance use disorder treatment trials (Avants et al., 2000; Bickel et al., 1988; Budney et al., 2006; Johnson et al., 2007; Trivedi et al., 2017; Winhusen et al., 2014). A sensitivity analysis using various single imputation approaches was also performed to evaluate the impact of various deviations from the missing-at-random assumption. The scenarios included imputing missing UCTs as negative, using surrounding UCTs to impute missing intermittent UCTs, and the worst-case scenarios in which the UCT result is imputed based on treatment assignment (i.e., all missing UCTs in the NAC group imputed as positive and all those in the placebo group imputed as negative, and vice-versa).

Based on findings from the prior adolescent trial, in which cannabis abstinence rates varied from 20% to 50% in the placebo arm, and consideration of a 6-site model, a sample size of 300 was determined to provide 80% power to detect an odds ratio of 2 at the two-sided 5% level of significance for the primary outcome, as well as evaluation of 2- and 4-week end-of-treatment abstinence outcomes, which were judged as clinically important for evaluation.

For the primary outcome measure, a repeated-measures logistic regression model was used to evaluate the odds of a negative UCT as an indicator of abstinence across all 12 weeks of treatment. At each week, the primary outcome was an indicator of whether the UCT at that visit was negative (< 50 ng/mL). Because each participant contributed up to 12 outcomes to the model, generalized estimating equations (GEEs) were used to adjust for this correlation (Liang and Zeger, 1986). The primary longitudinal model included the main effects of treatment, time, site, and baseline tobacco smoking, as well as a time-by-treatment interaction. Testing of the treatment difference evaluated the overall treatment effect by considering the average treatment effect over all time points via a Score test. Any variables in this model that were not statistically significant were dropped from all further analyses. Wald-based odds ratios (OR) and asymptotic 95% confidence intervals (CI) were computed. Efficacy analyses were repeated within the subgroup of participants meeting pre-defined criteria for medication adherence. Pre-specified secondary analyses examined whether abstinence rates differed across clinical sites, baseline tobacco use status, sex, ethnicity, and/or race, and whether these variables were effect modifiers for the relationship between NAC and abstinence.

Pre-specified logistic regression models were used to analyze the odds of cannabis abstinence over 2- and 4-week end-of-treatment periods and at the post-treatment follow-up visit. GEEs were used to test for differences in the proportion of self-reported days using throughout treatment.

All statistical analyses were conducted using SAS version 9.3 or higher (SAS Institute Inc. Cary, NC, USA). Significance was set at a 2-sided p-value of 0.05.

3. Results

3.1. Enrollment and baseline characteristics

Of 626 individuals formally screened, 302 met criteria and were randomized (Fig. 1–**CONSORT Diagram**). Baseline demographics and clinical characteristics are presented in Table 1; the randomization groups did not differ in these key variables, aside from education ($p = 0.037$) and employment status ($p = 0.004$). Baseline urine cannabinoid levels were higher in this sample than in the prior adolescent trial (1075.1 ± SD 1430.1 versus 417.0 ± SD 522.3 ng/mL, $p < 0.0001$). Additionally, participants in this sample had used cannabis 15.1 ± SD 9.2 years, compared to 4.2 ± SD 1.8 years in the prior adolescent trial ($p < 0.0001$). In the 30 days prior to initial assessment, participants in this sample had used cannabis on 26.0 ± SD 6.2 days, compared with 23.1 ± SD 6.1 days in the prior adolescent study ($p < 0.0001$) (Gray et al., 2012).

3.2. Efficacy

The proportion of negative UCTs in the NAC and placebo groups at each visit (intent-to-treat sample) is illustrated in Fig. 2. While there was a significant effect of time on abstinence ($p = 0.001$), there was no statistically significant difference between the NAC and placebo groups in the average odds of cannabis abstinence over time (OR = 1.00, 95% CI: 0.63–1.59, $p = 0.984$). Overall, 22.3% of UCTs in the NAC group were negative, compared with 22.4% in the placebo group. The proportion of missing UCTs at study visit ranged from 12% at week 1–32% at week 12, resulting in 23% of all expected UCTs being imputed. Of the various missing data scenarios considered in the sensitivity analysis, only the two worst-case scenarios of imputation by treatment assignment yielded statistically significant treatment differences ($p < 0.001$). For all other scenarios, the p-values were greater than 0.8. End-of-treatment and post-treatment analyses, as well as comparisons of self-reported cannabis use, similarly yielded no statistically significant evidence that NAC and placebo differentially affected abstinence. All tests for synthetic cannabinoids ($n = 107$) were negative.

Subgroup analyses: While there was no clinical site by treatment interaction ($p = 0.429$), site was a non-significant trend-level predictor of cannabis abstinence ($p = 0.054$). Baseline tobacco smoking status was a strong indicator of cannabis outcomes, with tobacco smokers being half as likely as non-tobacco smokers to achieve cannabis abstinence during treatment (OR = 0.52, 95% CI: 0.31–0.88, $p = 0.008$), but there was no tobacco-by-treatment interaction ($p = 0.883$) (Fig. 3). Sex was not a significant predictor of cannabis abstinence, and there was no sex-by-treatment interaction. Hispanic/Latino participants were half as likely as non-Hispanic/Latino participants to test negative for cannabinoids during treatment (OR = 0.52, 95% CI: 0.27–1.00, $p = 0.030$), but there was no ethnicity-by-treatment interaction ($p = 0.881$).

For analyses of race, three participants were excluded: two who refused to report their race and one whose race was unknown. Further, to optimize power, only two groups were used: White participants ($n = 176$) and racial minority participants ($n = 123$). The latter category included Black/African American ($n = 84$), multiracial ($n = 19$), Asian ($n = 3$), American Indian/Alaskan Native ($n = 2$), Native Hawaiian/Pacific Islander ($n = 1$), and Other ($n = 14$). There was a trend-level race-by-treatment interaction, suggesting that while racial minority participants had overall lower proportions of negative UCTs, they differentially responded more favorably to NAC than to placebo (White NAC versus PBO (OR = 0.81, 95% CI: 0.46–1.44; racial minority NAC versus PBO OR = 1.97, 95% CI: 0.84–4.63; race-by-treatment interaction, $p = 0.083$)) (Fig. 4). There was no association between race and tobacco smoking status ($p = 0.757$).

The study's primary outcome measure was examined *post-hoc* within participants ages 18–21 ($n = 35$ in the NAC group and $n = 23$ in the placebo group), overlapping with the prior adolescent trial's age range of 15–21. While the small sample size notably limited statistical power, within this age group NAC participants, compared to placebo participants, had numerically (but not statistically significantly) doubled rates of abstinence (OR = 2.03, 95% CI: 0.70–5.86, $p = 0.187$), a magnitude consistent with that noted in the prior adolescent trial (Gray et al., 2012).

3.3. Safety/Tolerability

Adverse events were generally infrequent, without clinically significant between-group differences in the rates of overall or specific events. In sum, 26.8% of NAC participants and 34.2% of placebo participants reported any treatment-emergent adverse events. Of the 7 reported serious adverse events, 6 occurred in the placebo group and 1 occurred in the NAC group, and none were deemed to have a causal

Table 1
Demographics and baseline characteristics.

Demographic/Characteristic	NAC (n = 153)		Placebo (n = 149)		Total (n = 302)	
Age	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Years at Randomization	29.8	8.74	30.8	9.32	30.3	9.03
Gender	*Number*	*%*	*Number*	*%*	*Number*	*%*
Male	117	76.5	99	66.4	216	71.5
Ethnicity	*Number*	*%*	*Number*	*%*	*Number*	*%*
Hispanic/Latino	31	20.3	34	22.8	65	21.5
Race	*Number*	*%*	*Number*	*%*	*Number*	*%*
American Indian or Alaska Native	0	0	2	1.3	2	0.7
Asian	1	0.7	2	1.3	3	1.0
Black or African American	44	28.8	40	26.8	84	27.8
Native Hawaiian or Pacific Islander	1	0.7	0	0	1	0.3
White	84	54.9	92	61.7	176	58.3
Other	8	5.2	6	4.0	14	4.6
Multiracial	13	8.5	6	4.0	19	6.3
Unknown	1	0.7	0	0	1	0.3
Participant chose not to answer	1	0.7	1	0.7	2	0.7
Education Completed	*Number*	*%*	*Number*	*%*	*Number*	*%*
Less than high school diploma	16	10.5	12	8.1	28	9.3
High school graduate	44	28.8	22	14.8	66	21.9
GED or equivalent	10	6.5	13	8.7	23	7.6
Some college, no degree	48	31.4	59	39.6	107	35.4
Associate's degree: occupational, technical, or vocational program	10	6.5	7	4.7	17	5.6
Associate's degree: academic program	5	3.3	5	3.4	10	3.3
Bachelor's degree	16	10.5	30	20.1	46	15.2
Master's degree	4	2.6	1	0.7	5	1.7
Employment	*Number*	*%*	*Number*	*%*	*Number*	*%*
Working now	65	42.5	90	60.4	155	51.3
Only temporarily laid off, sick leave, or maternity leave	1	0.7	2	1.3	3	1.0
Looking for work, unemployed	58	37.9	33	22.1	91	30.1
Retired	1	0.7	0	0	1	0.3
Disabled permanently or temporarily	2	1.3	3	2.0	5	1.7
Keeping house	2	1.3	1	0.7	3	1.0
Student	17	11.1	18	12.1	35	11.6
Other	7	4.6	2	1.3	9	3.0
Marital Status	*Number*	*%*	*Number*	*%*	*Number*	*%*
Married	19	12.4	20	13.4	39	12.9
Divorced	12	7.8	10	6.7	22	7.3
Separated	4	2.6	4	2.7	8	2.6
Never married	102	66.7	91	61.1	193	63.9
Living with partner	16	10.5	24	16.1	40	13.2
Tobacco Use	*Number*	*%*	*Number*	*%*	*Number*	*%*
Self-reported smoking tobacco	60	39.2	56	37.6	116	38.4
Cannabis Use	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Number of Days of Cannabis Use in 30 days Prior to Informed Consent	25.7	6.72	26.4	5.65	26.0	6.21
Marijuana Craving Scale Score Heishman et al., 2009)	49.8	18.18	50.7	16.01	50.2	17.12
Urine Cannabinoid Level	1113.4	1477.63	1035.2	1382.89	1075.1	1430.14
Years Since First Cannabis Use	14.5	8.94	15.7	9.43	15.1	9.19
Years since First Cannabis Dependence	9.1	7.57	9.9	8.83	9.5	8.21

relationship with study medication. Body mass index, heart rate, and blood pressure did not change significantly over time, regardless of treatment group.

3.4. Blinding, retention, and adherence

Among participants assigned to NAC, 46.5% guessed they were receiving NAC and 53.5% guessed they were receiving placebo, and the medical clinician guessed that 52% were receiving NAC and 48% were receiving placebo. Among those assigned to placebo, 53.7% guessed they were receiving NAC and 46.3% guessed they were receiving placebo, and the medical clinician guessed that 57.3% were receiving NAC and 42.7% were receiving placebo. These differences were not statistically significant, and the participant and medical clinician agreed on guesses more often than by chance ($p < 0.0001$).

Among randomized participants, 71.9% in the NAC group and 68.5% in the placebo group were retained through the end of active treatment. Availability of the primary outcome measure (UCT) generally mirrored weekly visit attendance, decreasing gradually over time, with 68.6% in the NAC group and 67.1% in the placebo group available at the end-of-treatment visit.

Attendance-based contingent compensation (maximum possible total $610) was received by 95.4% of NAC participants (mean total $428, median $550) and 94.6% of placebo participants mean total $435, median $580). Abstinence-based contingent compensation (maximum possible total $490) was received by 35.3% of NAC participants (mean total $86, median $0) and 35.6% of placebo participants (mean total $71.80, median $0).

Following the pre-specified criteria for medication adherence, only a small subset of participants (n = 31 in the NAC group and n = 26 in the placebo group) was deemed adherent. *Post-hoc* examination of adherence based only on pill counts and self-report (taking ≥80% of expected medication ≥80% of the 12 weeks, regardless of riboflavin testing results), yielded n = 87 NAC participants and n = 78 placebo participants meeting criteria. The primary efficacy outcome was analyzed in exploratory fashion within these small, underpowered

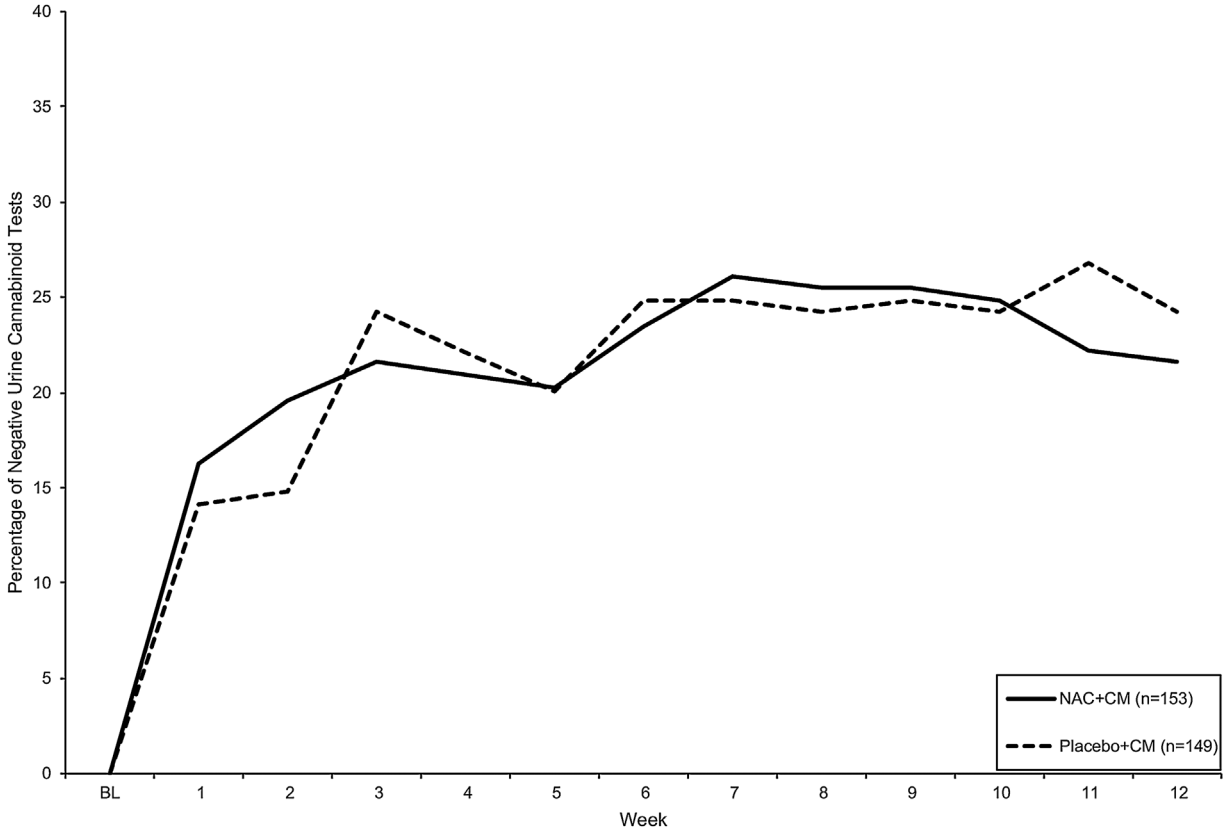

Fig. 2. Intent-to-treat urine cannabinoid test results.
BL = Baseline; NAC = *N*-acetylcysteine

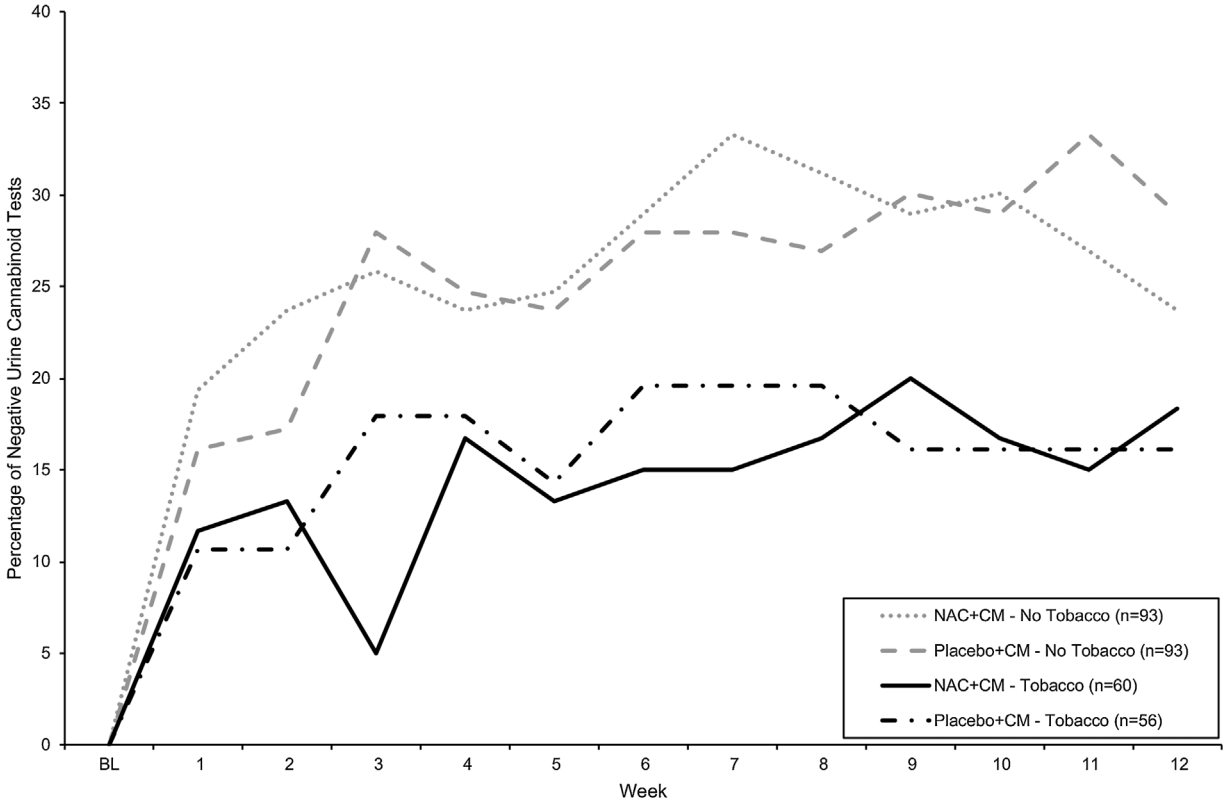

Fig. 3. Baseline tobacco use status and intent-to-treat urine cannabinoid test results.
BL = Baseline; NAC = *N*-acetylcysteine

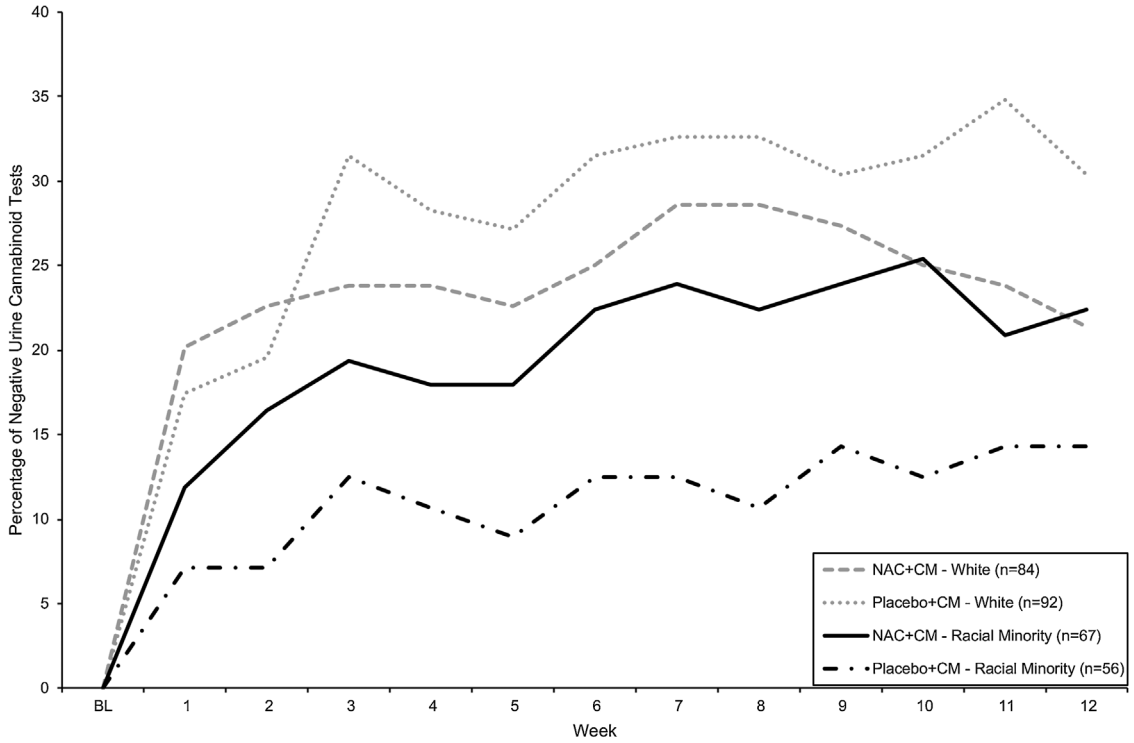

Fig. 4. Race and intent-to-treat urine cannabinoid test results.
BL = Baseline; NAC = *N*-acetylcysteine

subgroups meeting adherence criteria, revealing no significant differential outcomes by treatment group. Pill counts and self-report indicated that 73% of dispensed NAC doses and 72% of dispensed placebo doses were taken, compared to 95% and 93% taken in the prior adolescent trial (Gray et al., 2012).

4. Discussion

This is the largest-enrollment and first national multisite pharmacotherapy RCT for CUD, demonstrating the feasibility of executing these methods to evaluate candidate CUD treatments. The present results yielded no statistically significant evidence that NAC 1200 mg twice daily is differentially efficacious compared to placebo, when added to CM, for cannabis cessation among adults with CUD. This contrasts with the significant positive findings yielded in a similarly-designed prior trial in adolescents with CUD (Gray et al., 2012). In the present trial, 22.3% of UCTs in the NAC group and 22.4% in the placebo group were negative, compared to 40.9% and 27.2%, respectively, in the prior adolescent trial. Response to NAC for CUD may potentially be age-dependent, with adolescents benefiting, and adults not yielding benefit at the 1200 mg twice daily dose. Whether this may be due to developmental differences in the course and phenomenology of CUD and cumulative cannabis exposure, differential effects of NAC based on stages of brain development, potential need for dose adjustment based on age, and/or other factors remains unclear, and is deserving of further examination. It is notable that participants in the present study presented with higher dosing, frequency, and chronicity of cannabis use compared to those in the prior adolescent trial.

White participants had higher placebo response rates than racial minority participants, possibly reflecting previously observed racial differences in response to CM (Montgomery et al., 2012, 2015). Racial minority participants' poorer response to CM may have allowed NAC effects to emerge, as suggested by a two-fold NAC versus placebo difference in abstinence outcomes. Without a known biological mechanism to explain a race by treatment interaction, it is possible that race served as a proxy for socioeconomic or other demographic factors. Regardless of treatment group, participants who self-reported as tobacco smokers at baseline were less successful than non-tobacco smokers in achieving cannabis abstinence during study participation. This relationship, consistent with prior research, demonstrates that this may be a particularly challenging group to treat (Haney et al., 2013; Peters et al., 2014). Hispanic/Latino participants were also less likely to achieve cannabis abstinence during treatment than non-Hispanic/Latino participants. Further work is needed to address racial and ethnic disparities in CUD treatment outcomes, and to enhance outcomes among individuals with co-occurring tobacco use.

The present study included CM, a powerful behavioral treatment platform. Attendance-based CM likely contributed to study retention, and may be employed in future trials. Response to abstinence-based CM, particularly notable among White participants, may have obscured potential NAC versus placebo effects. It may be that adults with CUD (particularly White adults) are more responsive to abstinence-based CM than adolescents, leaving less opportunity for a complementary pharmacotherapy to provide added benefit. To date, NAC has not been tested in CUD in a randomized placebo-controlled trial without a CM platform.

While the present study included a number of strengths in design and execution, findings must be considered in light of limitations. While participant retention was high, medication adherence was poorer than in the prior adolescent trial, notably compromising the potential to test for efficacy in adults. Additionally, overall abstinence rates were low, especially for a trial that included high-magnitude CM cash rewards for abstinence, potentially reflective of the challenging nature of treating CUD and/or reflective of a particularly treatment-refractory sample. It may be that a sample with less chronicity and frequency of cannabis use would yield greater variance and thus greater potential for detecting between-group differences in outcomes. Another limitation is that approximately 23% of the expected UCTs were missing due to missed visits, droupout, and loss to follow-up. Single imputation approaches were implemented under varying assumptions about the degree of deviation from the missing-at-random assumption with no changes in conclusion except in the most extreme circumstances. While this

approach allows non-ignorable missingness, the single imputation approach treats imputed values as observed and thus may underestimate the true variance.

CUD is a significant health problem with few efficacious treatments, yielding overall modest outcomes. Across RCTs of psychosocial and pharmacological treatments for CUD, most participants fail to achieve and sustain abstinence (Marshall et al., 2014; Gates et al., 2016). More work is needed to develop novel treatments to enhance outcomes, particularly among racial and ethnic minorities and among those with co-occurring tobacco use. Additionally, medication adherence should be more reliably enhanced and monitored, potentially via smartphone-delivered text prompts and video capture of medication-taking (Molton et al., 2016; Peterson et al., 2016). While the present study does not refute NAC's position as the only pharmacotherapy with positive intent-to-treat efficacy findings in adolescents with CUD (a finding in need of replication), it does demonstrate that, with the present dosing and embedded CM treatment in both arms, there is no statistically significant evidence that NAC is efficacious in adults with CUD.

5. Conclusions

Results suggest that prior efficacy results for NAC added to CM in adolescents may not extend to adults with CUD. In light of these discrepant findings, a replication trial of NAC in adolescents with CUD is indicated. Additional work is needed to identify and optimize novel treatments for CUD, to enhance medication adherence in pharmacotherapy trials, and to understand developmental and health-disparity factors that may influence differential CUD treatment outcomes by age, ethnicity, and race.

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Trial registration

clinicaltrials.gov NCT01675661.
https://clinicaltrials.gov/ct2/show/NCT01675661

Conflict of interest

Gray has received research support (medication only) from Pfizer. McRae-Clark has served as a consultant for Insys Pharmaceuticals and has received research support (medication only) from Pfizer. Walsh has received research support from Cerecor, Inc., and Braeburn Pharmaceuticals; has served as a consultant for AstraZeneca, Braeburn Pharmaceuticals, Camurus, Daiichi Sankyo, DURECT, Eli Lilly & Co., INSYS, Lightlake Therapeutics, KemPharm, Neurocrine, Novartis, Pfizer, Sun Pharma, and US WorldMeds; and has received speaker's honoraria from PCM Scientific through unrestricted grants from Gilead, Indivior, and Merck. Lofwall has served as a consultant for Braeburn Pharmaceuticals, CVS Caremark, and PCM Scientific, and has received research support from Braeburn Pharmaceuticals. Vandrey has served as a consultant for Zynerba Pharmaceuticals, Battelle Memorial Institute, and CW Botanicals, and has served on an advisory panel for Insys Therapeutics. Levin has served as a consultant for GW Pharmaceuticals and Major League Baseball, and has received research support (medication only) from US WorldMeds. Sonne, McClure, Ghitza, Matthews, Carroll, Potter, Wiest, Mooney, Hasson, Babalonis, Lindblad, Sparenborg, Wahle, King, Tomko and Haynes report no competing interests.

Contributors

Gray had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design

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Acquisition of data

Gray, Sonne, McClure, Ghitza, Matthews, McRae-Clark, Carroll, Potter, Wiest, Mooney, Hasson, Walsh, Lofwall, Babalonis.

Analysis and interpretation of data

All authors.

Drafting of the manuscript

Gray.

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All authors.

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