N-Acetylcysteine for Youth Cannabis Use Disorder

Study Protocol

NCT0305537

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***PROTOCOL TITLE: N*-Acetylcysteine for Youth Cannabis Use Disorder**

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OBJECTIVES/SPECIFIC AIMS

Cannabis use is particularly prevalent and problematic among youth, who are more likely than adults to initiate cannabis use, develop cannabis use disorder (CUD), and suffer lasting adverse cannabis-related consequences. Despite the clear need for youth-targeted cannabis cessation treatments, established modalities offer limited efficacy, with very few youth achieving sustained cannabis abstinence.

Among the most promising emerging youth-targeted cannabis cessation treatments is the over-the-counter antioxidant medication *N*-acetylcysteine (NAC). Our team previously demonstrated superior NAC versus placebo (PBO) abstinence outcomes in youth with CUD who concurrently received the behavioral treatment contingency management (CM). In order to optimally translate NAC to real-world clinical practice, further work is now needed to evaluate if NAC is efficacious independent of CM.

We propose a 12-week randomized placebo-controlled trial of NAC for CUD in youth (*N*=192). Participants will be randomized to double-blind NAC or PBO, yielding two equally-allocated treatment groups. All participants will receive brief weekly cannabis cessation counseling and medication management. The primary efficacy outcome will be the proportion of negative urine cannabinoid tests during the 12-week active treatment, compared between groups. We will also assess cognitive task performance at baseline, during treatment, and after treatment, examining changes in performance among participants who achieve abstinence versus those that do not.

- *Specific Aim 1*. Compare the effect of NAC versus PBO, added to brief weekly cessation counseling and medication management, on cannabis cessation in youth with CUD.
    - Hypothesis 1: NAC participants will have a higher proportion of negative urine cannabinoid tests during treatment than PBO participants.
- *Specific Aim 2*. Examine the impact of cannabis cessation on cognitive task performance.
    - Hypothesis 3: Participants who achieve abstinence will demonstrate significant improvement in attention, processing speed, verbal declarative memory, and cognitive control, compared to those who continue to use cannabis.

It is important to identify for whom NAC is likely to be an effective treatment. NAC is thought to normalize extracellular glutamate levels which may reduce compulsive cannabis use when exposed to cues. Purportedly through anti-inflammatory effects, NAC also has the potential to improve mood and reduce depressive symptoms. Many individuals report motivation to use cannabis to alleviate stress and other aversive affective states. Thus, NAC may also indirectly influence cannabis use through improvement in mood, particularly for adolescents who use cannabis in response to negative affect/stress. However, adolescents may be unaware of what drives their substance use. Shrier and Scherer (2014) found that adolescents provided different motives before and after use for 20% of all reported episodes of cannabis use. These adolescents reported their motives near in time to their actual cannabis use; therefore, we may expect that adolescents have even more difficulty when asked to retrospectively report motives or antecedents for cannabis several days or weeks later. In a two-week study of 18-21 year olds who regularly use cannabis, craving and cannabis use is measured in real-world contexts. Therefore, we can gain insight into whether an adolescent's craving increases when they are exposed to stress/negative affect or cannabis cues, suggesting that cues and/or stress may be a personalized risk factor for use. Individuals are given information on potential treatment studies following participation in this two week protocol, including the current treatment protocol. All participants beginning the current protocol will be asked if they participated in the two-week study and whether they would like to sign a release of information, allowing their data to be combined across studies. Combining data from these two protocols will allow us to examine the following research aim:

- Exploratory Aim: Estimate for whom NAC is likely to be effective at reducing cannabis use.

- Hypothesis 1: Adolescents who display increased cue-induced or negative affect-related craving in the two-week trial will show greater reduction in quantitative urine cannabinoid tests with NAC, as compared to placebo.

The identification of NAC as potential treatments for youth CUD is an important development, but to optimize translation to real-world practice and enhance youth CUD outcomes, this trial is critical. At present, it is unclear whether NAC requires a CM platform for efficacy, and regardless of psychosocial/behavioral treatment platform, the initial positive trial of NAC requires replication. The proposed study is designed with adequate power to evaluate the effect of NAC versus PBO on cannabis cessation. Further, the trial is positioned, regardless of between-group efficacy outcomes, to carefully examine potential cognitive task performance improvement with early abstinence achieved during treatment. Given the clear demonstration of potentially lasting adverse cognitive effects of frequent youth cannabis use, and given the central role of learning and academic achievement in this developmental phase, it is important to assess what domains of cognition may acutely improve during successful cannabis cessation treatment engagement.

This proposed trial is the clear "next step" in the assessment of NAC as a youth CUD treatment, and is positioned to inform researchers, clinicians, and the general public, addressing a critical need for optimization of youth CUD treatment.

BACKGROUND – Research Strategy

A. SIGNIFICANCE

Youth Cannabis Use: Prevalence and Implications

Youth are more likely than adults to initiate cannabis use, develop cannabis use disorder (CUD), and suffer potentially lasting adverse consequences of use (1,2). Amid evolving cannabis-related policies in the United States (e.g., state-level legalization for medical and recreational use), youth perceptions of cannabis-related harms are decreasing and rates of use are increasing. Currently, 44% of high school seniors have tried cannabis, 21% are current users, and 6% use daily (3).

Adolescence is a critical period of brain development. In the context of rapid neurobiological changes, the brain may be particularly susceptible to environmental influences, including drugs of abuse (4). Cannabinoid (CB_1) receptors are widely distributed in areas involved in cognition, emotion, and habit formation (5,6). Stimulation of these receptors by endocannabinoids during adolescence is known to affect the release of other neurotransmitters (7), influence short- and long-term synaptic plasticity (8,9), and contribute to neural development via influence on gene expression (10). Frequent use of cannabis during adolescence may interfere with these developmental processes by overstimulation of cannabinoid receptors, leading to potentially lasting adverse effects on behavior, emotion, and cognition (11).

Consistent with emerging neurobiological findings, a confluence of evidence suggests that heavy use and early initiation (during childhood/adolescence) are associated with generally poorer outcomes among cannabis users (2). In a dose-dependent manner, adolescent cannabis use is associated with adverse academic (12-13), cognitive (14-16), occupational (13), psychiatric (17-20), and substance use (21) outcomes.

The adverse effects of cannabis use on cognition and learning may have lifelong implications (15), as scholastic achievement in adolescence is a particularly important predictor of adult success (22). Among the most important benefits of youth-focused cannabis cessation treatment may therefore be recovery of cognitive performance and academic achievement. While research to date has helped identify cognitive domains most affected by heavy cannabis use during adolescence (e.g., attention, declarative memory, cognitive control) (16), little work has focused on identifying domains that may be most likely to recover with acute abstinence in the context of treatment (23), versus those that may persist even with extended abstinence (15).

Limitations in Current Treatments

Treatment development for youth CUD has, to date, focused almost exclusively on psychosocial treatments. Trials of motivational enhancement therapy, cognitive-behavioral therapy, community reinforcement therapy, and family therapy have revealed similarly modest outcomes, with very few youth achieving sustained abstinence (24-27), echoing results in the larger literature involving psychosocial treatments for youth substance use in general (28,29). The behavioral treatment contingency management (CM) may improve outcomes when added to psychosocial treatments, but it has not consistently translated into clinical practice (30-40). Significant efforts

are needed to enhance outcomes for youth with CUD, and development and refinement of new approaches is critical.

The Potential Role of Pharmacotherapy: N-Acetylcysteine

In the last decade, efforts to develop potential pharmacotherapies for CUD have expanded, though nearly all of this work has focused solely on adult cannabis users (41). Several human laboratory studies have been conducted to screen for medication effects on cannabis craving, withdrawal symptoms, and self-administration, yielding mixed results (42-53). A smaller number of pilot/proof-of-concept randomized controlled trials have been conducted, also yielding mixed results (54-58). Only a handful of trials with adequate power to evaluate intent-to-treat efficacy outcomes have been conducted, and almost all have yielded negative findings (59-61). Among these, only one youth-focused trial of *N*-acetylcysteine (NAC), an *N*-acetyl pro-drug of the naturally occurring amino acid cysteine, has demonstrated statistically significant intent-to-treat positive efficacy findings (62). Youth randomized to receive NAC had more than twice the odds of submitting negative urine cannabinoid tests during treatment than those randomized to receive placebo (see Preliminary Studies below); all participants in that trial received CM, regardless of treatment randomization group. A replication trial (NAC versus placebo, added to CM) in adults was recently completed, with the primary manuscript currently under review for publication (UG1DA013727—CTN0053, PI: Gray) (see Preliminary Studies below) (63).

Interest in NAC emerged from preclinical work implicating glutamate dysregulation as an important factor in addictive processes across substances of abuse (64). Among potential glutamate-targeted pharmacotherapies, NAC is a particularly strong candidate (65-67). NAC administration stimulates cystine-glutamate exchange, thereby increasing non-synaptic glial release of glutamate (68). The NAC-induced increase in extracellular glutamate stimulates inhibitory presynaptic metabotropic glutamate autoreceptors, thereby reducing vesicular glutamate release and, in turn, reducing the reinstatement of drug seeking in animal models (68-70). Since drug self-administration down-regulates the cystine-glutamate exchanger (71), the up-regulation of the exchanger via NAC administration directly normalizes a drug-induced pathology (72). This NAC-induced normalization has been shown to provide enduring protection from relapse, even after NAC is no longer present, in multiple studies (73-75). A recent study has also shown that NAC reduces drug seeking both early and late in the development of addictive behaviors (76). While most preclinical work in this area has focused on cocaine, studies involving nicotine, heroin, and alcohol have yielded consistent findings, suggesting that NAC may play a potential therapeutic role across substances (77-80).

NAC is available over-the-counter as an inexpensive supplement and it has a well-established pediatric and adult safety record over decades of clinical use (81,82), positioning it as a highly accessible, acceptable, and affordable pharmacotherapy for youth.

The Need to Parse the Effects of N-Acetylcysteine and Contingency Management on Abstinence Outcomes

Our prior work demonstrated that NAC yielded superior abstinence outcomes compared to placebo in the context of youth with CUD receiving CM (See C1. Preliminary Studies) (62). This was a critical advance in youth CUD treatment development, but it left several unaddressed questions. If clinicians wish to recommend NAC, must it be utilized in the context of a CM intervention? It is possible that both NAC and CM possess significant independent treatment effects, such that either can be implemented on its own with positive outcomes. However, NAC has not yet been tested outside of the context of a CM platform, and we do not yet know whether CM is necessary for NAC to exert its effects on abstinence. It is possible that there is synergy between these interventions, which would support their implementation as a combination treatment approach. An adequately powered randomized controlled trial is needed to determine main effect of NAC outside of the context of a CM platform, and to compare the effects of combined versus singular treatments. This would provide necessary clarity to clinicians wishing to employ NAC and/or CM interventions to optimize abstinence outcomes among youth with CUD.

B. INNOVATION

NAC is among the most promising potential pharmacotherapies for youth CUD, and a trial to (a) replicate prior positive findings, and (b) test outside of the context of a CM platform, is strongly indicated. Particularly important is an innovative trial that is designed and powered to address a variety of clinically relevant questions. We endeavored to echo the general design features of our prior trial of NAC versus placebo, added to CM, with select enhancements. In the proposed trial, NAC will be compared to PBO, each without a CM platform.

Extension to 12 weeks of active treatment provides more clinical exposure and opportunity to yield treatment response, and also provides consistency with typical FDA standards of 12-week active treatment courses in pharmacotherapy trials. Extending post-treatment follow-up to six months from randomization allows for improved examination of the potential for lasting cessation effects of the interventions (83). Abstinence criteria are based on objective biological verification, and we will additionally gather detailed quantitative cannabis use self-report (84-85). Recruitment and retention will be bolstered by several well-established techniques our team has used successfully across multiple trials of youth CUD and other substance use disorders. The proposed sample size was chosen based upon consistently conservative estimates from prior relevant research, thereby ensuring sufficient power for hypothesis testing.

The proposed trial of NAC is timely and supported by the research team's experience with these interventions. We have already been granted Investigational New Drug (IND) approval #078927 from the FDA for youth CUD research with NAC. Aside from our prior NAC trial, to our knowledge, no other adequately powered trials of any pharmacotherapy for CUD in any age group have yielded positive intent-to-treat cessation/abstinence efficacy findings, indicating that further work with NAC should be prioritized. The proposed trial will directly impact real-world practice by providing clear information regarding the efficacy of NAC (e.g., whether prior positive NAC versus PBO findings can be replicated, and whether a CM platform is necessary for NAC to exert its effects on abstinence outcomes). Regardless of the results yielded, the innovative approach of the proposed trial will address multiple key gaps in the treatment evidence base in an area of considerable public health concern.

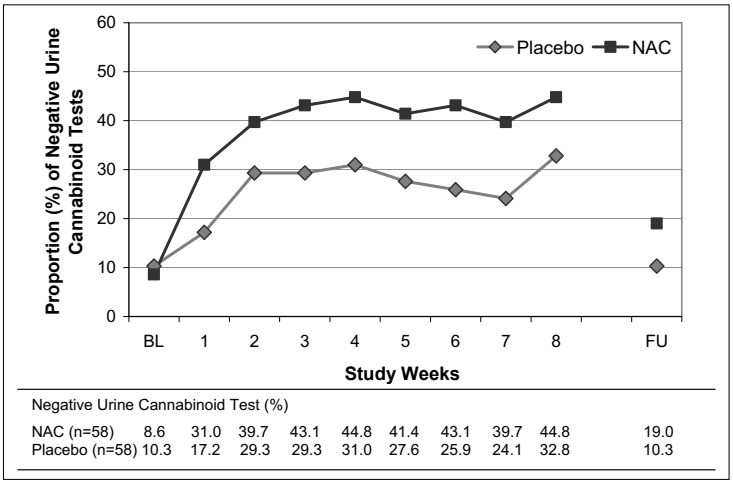
C. APPROACH

C1. Preliminary Studies

C1a. Prior NAC trial for youth CUD

Our research team recently completed a double-blind randomized placebo-controlled trial of NAC for youth CUD (62). Treatment-seeking youth with CUD (*N*=116) were randomized, in 1:1 parallel group allocation, to receive a double-blind 8-week course of NAC (1200 mg) or placebo (PBO) twice daily, added to a CM intervention and brief (≤10 minute) weekly cessation counseling. A post-treatment follow-up visit occurred 4 weeks after treatment conclusion.

The primary study hypothesis was that participants randomized to NAC would have higher odds than those randomized to placebo to submit negative weekly urine cannabinoid tests (UCTs) during treatment. An intent-to-treat (ITT) approach including all randomized participants was used. In all analyses, participants lost to follow up or absent for visits were coded as having a positive UCT at every missed visit.



Negative Urine Cannabinoid Test (%)

	BL	1	2	3	4	5	6	7	8	FU
NAC (n=58)	8.6	31.0	39.7	43.1	44.8	41.4	43.1	39.7	44.8	19.0
Placebo (n=58)	10.3	17.2	29.3	29.3	31.0	27.6	25.9	24.1	32.8	10.3

The proportion of negative UCTs in the NAC and PBO groups at each visit (ITT sample) is shown in the adjoining figure. Though there was no group difference in baseline years of cannabis use, this variable was an independent predictor of positive UCT during treatment (p=0.007) and was therefore covaried in the model. Participants randomized to NAC had more than double the odds of negative UCTs during treatment, compared with those randomized to PBO. In the adjusted model, the relationship between treatment and the odds of a negative UCT was OR=2.4 (95% CI: 1.1-5.4), p=0.021. Through the final treatment visit, 40.9% (190/464) of the UCTs among participants in the NAC group were negative, compared to 27.2% (126/464) among those in the PBO group, per ITT analysis, assuming any missing urine was positive for cannabinoids. At the post-treatment follow-up visit (four weeks after medication discontinuation), 19.0% (11/58) of the UCTs among participants in the NAC group were negative, compared to 10.3% (6/58) among those in the PBO group. While still numerically favoring NAC, the overall treatment effect lost statistical significance at post-treatment follow-up (OR=2.2 [95% CI: 0.7-6.5], p=0.155), though the trial was not powered for this outcome.

Models were examined for the possibility of confounding and effect modification of age, weight, gender, and number of previous cannabis quit attempts. None of the variables tested were significant confounders or effect modifiers (all $p>0.60$).

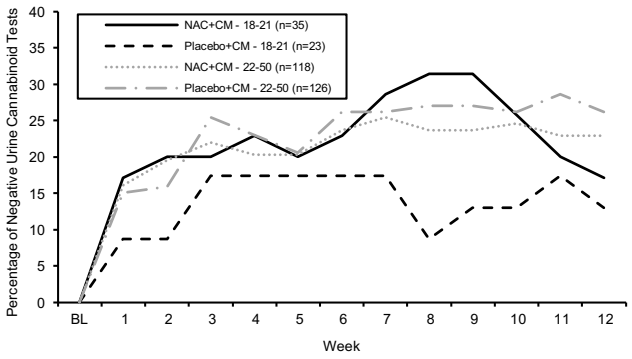
A *post hoc* sensitivity analysis was performed on odds of negative UCTs during treatment, using multiple methods to manage missing data and participant dropouts. In addition to the ITT approach noted above ($n=116$), a modified ITT analysis that examined participants who received at least one dose of study medication ($n=106$) and a per-protocol analysis using available data (n=varying) were performed. Using a modified ITT analysis, participants in the NAC group had 2.2 times the odds of submitting negative UCTs, compared to those in the PBO group (OR=2.2 [95% CI: 1.1-4.5], $p=0.04$) during the treatment phase of the study. When only examining available data (per-protocol analysis), participants in the NAC group had 2.4 times the odds of submitting negative UCTs than those in the PBO group (OR=2.4 [95% CI: 1.1-4.5], $p=0.04$). Finally, combinatorial graphical methods for assessing the impact of missing data on significance of findings were also employed, in which every permutation of missing data assignment was considered, and a subsequent logistic regression performed (86). For the majority of missing data assignments that could be reasonably expected, the odds ratio was still significant. In general, the selection of missing data handling had little effect on analytic outcomes.

Additional secondary analyses were conducted to explore end-of-treatment outcomes, using a sample restricted to participants with positive urine cannabinoid tests at baseline ($n=105$). While the study was not powered for these outcomes, it was felt that these were particularly relevant to evaluate meaningful clinical impact of the intervention. We additionally explored abstinence outcomes via the Number of Beyond-Threshold Weeks of Success (NOBWOS) Analysis Method (87), quantitative self-reported cannabis use, and cumulative days abstinent during treatment (self-report), all among participants with positive baseline urine cannabinoid testing ($n=105$). We also examined concordance between UCT and self-report within the data set, yielding 88% agreement in the end-of-treatment outcome measure.

Every efficacy outcome approach explored, inclusive of both UCT and self-report data sets, consistently yielded findings numerically favoring NAC over placebo. Statistically significant differences were noted in the study's *a priori* outcome analysis (odds of negative weekly UCT over the course of treatment) and in the end-of-treatment binary UCT outcomes (last 2 weeks [OR 2.55, $p=0.036$] and last 4 weeks [OR 2.59, $p=0.045$]). The study was powered only for the *a priori* outcome, so lack of statistical significance for some of the secondary/exploratory outcomes may be attributed to low power/limited sample size. Odds ratios were greater than 2 for all end-of-treatment (last 2 and last 4 weeks) UCT and self-report outcomes (aside from those assuming the extremely unlikely case that all missing data were negative/abstinent). Furthermore, there was strong agreement between UCT and self-report. Overall, findings demonstrate consistently favorable outcomes for NAC versus PBO across a wide variety of approaches.

C1b. Prior NAC trial for adult CUD – youth subgroup results

Our team recently completed a multisite trial ($N=302$) of NAC versus PBO, added to CM, for CUD in adults ages 18-50 (UG1DA013727—CTN0053). While that trial failed to detect an overall differential NAC versus PBO treatment effect, *post hoc* exploration within participants ages 18-21 (overlapping age group with the prior adolescent NAC, added to CM, trial) revealed numerical advantage of NAC over PBO with a magnitude remarkably consistent with that of the prior adolescent trial (OR=2), suggesting that response to NAC may potentially be age-dependent. Whether this may be due to developmental differences in the course and phenomenology of CUD, 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. In light of these discrepant findings, a replication trial of NAC in adolescents with CUD is indicated.



C1c. Experience with cognitive task performance assessments in youth with CUD

Participants in our prior trial of NAC for youth CUD completed serial cognitive task performance assessments, demonstrating improvement in multiple cognitive domains (verbal memory, psychomotor performance) among participants who achieved abstinence during the trial, compared to those who continued using cannabis (23). We plan to utilize the same comprehensive cognitive task battery in the proposed trial, and the enhanced sample size will allow for significantly more power to carefully assess cognitive outcomes with abstinence versus continued use, and to (in exploratory fashion) examine potential relationships between NAC and PBO and cognitive outcomes.

C2. Research Team

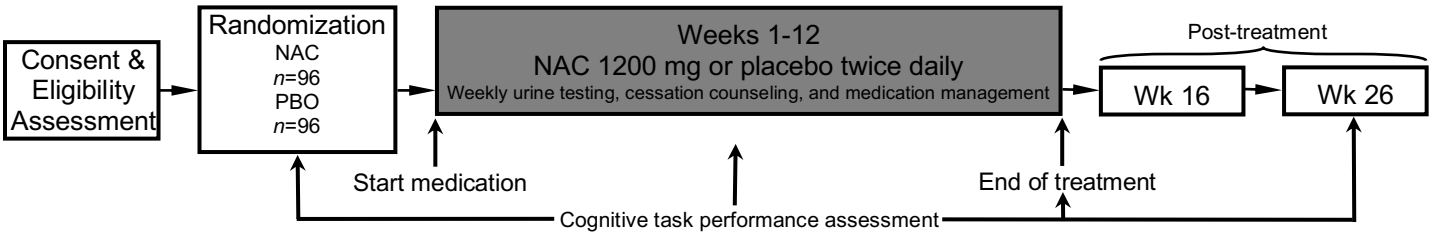
The investigative team, uniquely experienced with pharmacotherapy trials for youth substance use disorders (SUD), is ideally suited to undertake this study. In addition to having completed prior trials of NAC versus PBO, added to CM, for youth CUD (62) and adult CUD (UG1DA013727—CTN0053), the team has also conducted multiple pharmacotherapy trials targeting youth tobacco use disorder (88, U01 DA031779), and is experienced with serial cognitive task performance assessment within a CUD treatment trial (23). The multidisciplinary team is led by a board-certified child and adolescent psychiatrist with specific expertise in clinical trials targeting youth SUD. Each team member possesses expertise vital to the successful completion of the study.

The study will be conducted at a nationally recognized SUD treatment research center, assuring the ability to efficiently complete the project while maintaining the highest quality of protection of human participants and data integrity.

C3. Design and Methods of Current Proposal

C3a. Overview

We propose a 12-week trial of *N*-acetylcysteine (NAC) for cannabis use disorder (CUD) in youth (*N*=192).



C3b. Participants and Feasibility of Recruitment and Retention

Recruitment Strategies

Youth (200 consented/screened for a power analysis *N*=192) will be recruited from the community, schools, and clinical settings. We have an aggressive plan for recruitment and are confident that our previously established strategies will ensure success. Assuming an initial 3-month period for study setup, per-participant study duration of 6 months, and a concluding 3-month period for data analysis and publication, we anticipate a recruitment window of 48 months. To meet the recruitment goal, we must enroll 6 participants per month, which is feasible and realistic.

Our confidence in successful recruitment stems from a complement of strategies developed over years of experience with randomized controlled trials of pharmacotherapies and behavioral treatments for youth substance use disorders. We have had consistent success via multimedia and internet advertisements, longstanding partnerships with local schools (including the Charleston County School District [enrollment >48,000] and the College of Charleston [enrollment >11,000]), referrals from clinics, and respondent-driven sampling/participant peer referral.

In our prior trial of NAC versus PBO, added to CM, for youth CUD (R01DA026777), we combined the above strategies, enrolling 7.5 participants per month, demonstrating consistent recruitment success achieved by combining a number of innovative, aggressive strategies (62). We are currently using similar methods for a youth (same age range) tobacco cessation pharmacotherapy trial (U01DA031779), remaining consistently on track for goal enrollment.

For the proposed study, we plan to continue our established combined approach, which we are confident will be successful. In the event that we encounter unforeseen recruitment difficulty, we will broaden our school partnerships to other nearby school districts and private schools. We can additionally utilize strategies that have been successful for other MUSC studies, including (a) advertising on billboards along area highways, (b) establishing research clinics in existing suburban/rural MUSC clinics, and (c) establishing additional sites within the Southern Consortium node of the NIDA Clinical Trials Network.

Additionally, a Youth Collaborative of adolescent substance use studies within the Division has been developed that will not only allow for the cost sharing needs of advertising and study promotion but also make the process of identifying opportunities at MUSC easier for participants, parents/family, and community partners. By marketing a central point of contact for interested parties to seek additional information, callers can be triaged to the appropriate study or directed to clinical services based on their expressed interest level and/or prescreen outcomes. This is particularly appropriate for incorporation since there is a high likelihood of polysubstance use. By streamlining the referral process, it lessens the burden on the caller to duplicate their efforts and potentially become fatigued and disillusioned with the process and ultimately not receive the service delivery that they desire.

Retention Strategies

Retention, like recruitment, is a considerable challenge in youth CUD studies. Given intent-to-treat analysis (including all randomized participants and assuming that participants are using cannabis at each missed visit), poor retention may result in an underestimate of treatment effects. It also limits participant exposure to treatment, which further attenuates treatment effects.

Our team has been successful with optimizing participant retention via a number of well-established strategies. Our research clinic is centrally located and open for extended (including after-school) hours, with free parking immediately in front of the building. We maintain active communication with participants between visits via their preferred mode of contact (e.g., text message, telephone, e-mail). We also strictly maintain confidentiality, a particularly significant issue in studies focused on interventions for illicit substance use in youth. The PI is a board-certified child, adolescent, and general psychiatrist, well versed in managing communication with youth and parents/guardians while maintaining appropriate bounds of confidentiality and managing issues of safety; the resultant trust and rapport supports participant adherence and retention. Additionally, we strive to reinforce participants appropriately for attending visits and completing study procedures. It is clear that higher magnitude reinforcement is associated with significantly improved retention (89-91), and cash rewards (relative to gift cards or other tokens) are associated with improved session attendance (92). Adult and youth studies reveal that high-magnitude rewards are generally not used to purchase cannabis or other substances of abuse (92,93). Participants will be compensated $20 for each visit attended, with an additional $20 each for lengthier visits involving cognitive task performance assessment (screening/assessment, randomization, mid-treatment, end-of-treatment, and last post-treatment follow-up visit). In the event of a visit being completed remotely, participants will receive the same compensation rate for completing all visit needs, to include the at home collection and return of a urine sample. If urine needs are not possible (either participant declines or collection/storage is not feasible, the participant will receive $10 for the remote visit. If an Unscheduled Visit is required during study participation, the participant will be compensated $10/visit for time and travel demands. If the participant is enrolled directly from the Youth Collaborative Intake (PRO 94743) with data from that protocol being utilized for the current aims, this study may be responsible for the $40 Intake Screening compensation. Payments will be made in cash or via ClinCard.

In our prior NAC trial, with the above-mentioned strategies in place, among participants presenting for ANY visits after medication initiation, 84% completed the entire course of treatment. We maintain similar success in our ongoing youth tobacco cessation pharmacotherapy trial (U01DA031779).

<u>Inclusion Criteria</u>

a) Age 13 – 21 years
b) Must be able to understand the study and provide written informed consent (for participants under 18 years old, a parent/legal guardian must be able to provide consent and the participant must be able to provide assent)
c) Must meet current (within last 30 days) DSM-5 criteria for cannabis use disorder
d) Must express interest in treatment for cannabis use disorder

e) Must submit a positive urine cannabinoid test during screening
f) Females must agree to use appropriate birth control methods during study participation: oral contraceptives, contraceptive patch, barrier (diaphragm or condom), levonorgestrel implant, medroxyprogesterone acetate, complete abstinence from sexual intercourse, or hormonal contraceptive vaginal ring
g) Must have successfully completed the YC Intake Protocol (PRO# 94743) within approximately 30 days of formal study screening

Exclusion Criteria

a) Allergy or intolerance to *N*-acetylcysteine
b) Females who are pregnant, contemplating pregnancy over the next 6 months, or lactating
c) Current use of *N*-acetylcysteine or any supplement containing *N*-acetylcysteine (must agree not to take any such supplement throughout study participation)
d) Use of carbamazepine or nitroglycerin within 14 days of randomization or expectation of future use during protocol participation
e) Current enrollment in treatment for cannabis use disorder or expectation of other treatment during protocol participation
f) Any use of synthetic cannabinoids (such as K2/Spice) in the 30 days prior to screening or expectation of future use during protocol participation
g) Current moderate or severe substance use disorder, other than cannabis or tobacco
h) Medical history of severe asthma (uncontrolled with medication)
i) History of seizure disorder
j) Any other medical or psychiatric condition or other significant concern that in the Investigator's opinion would impact participant safety or compliance with study instructions, or potentially confound the interpretation of findings

Age Range

The participant age range for the proposed study (13-21 years old) was chosen for multiple reasons. Broad agreement exists to support this range. The Maternal Child Health Bureau defines adolescence as age 11-21, and the Center for Disease Control and Prevention defines it as ages 10-24. Given considerable developmental variability from age 10-24, though, a sample inclusive of this range might be overly heterogeneous. Additionally, while many youth initiate cannabis use between ages 10-13, few exhibit sufficient symptoms of cannabis use disorder to merit study inclusion (only 1% of 8th graders use cannabis daily) (3). Given the potential identification of individuals 22-24 as adults, we opted to exclude this age range as well. Additionally, our prior trial of NAC versus PBO, added to CM, for youth CUD included ages 14-21, and sample consistency between that study and the proposed trial will help avoid confounding of between-study outcome comparisons.

We do recognize that the developmental context varies considerably even within the narrowed range of 13-21. To address this, we plan to stratify randomization by age (at time of randomization), ensuring that equivalent proportions of those age 13-18 and those age 19-21 are represented in the treatment randomization groups. Given our prior success, we anticipate recruiting similar proportions of youth across these strata, and will adjust strategies if the proportions become skewed. This stratified approach will convey the added opportunity to compare outcomes (in exploratory fashion) between younger and older adolescents.

C3c. Intake and Randomization

Pre-Screening Assessment

Individuals responding to recruitment materials or otherwise referred to the study will be pre-screened on the phone or in person to ascertain preliminary eligibility status. A series of questions will determine preliminary eligibility, and formal screening appointments will be scheduled for those who meet these eligibility criteria. No information obtained during the pre-screening will be used as research data. All study related procedures will take place either on the MUSC campus within the designated office areas of the Addiction Sciences Division located at 125 Doughty Street, Suite 190, or remote/ hybrid via doxy.me, WebEx, or Zoom.

Informed Consent Procedures

Prior to the initiation of any study procedures, written informed consent and HIPAA authorization will be obtained by the designated research staff. Informed consent/assent may be obtained remotely via REDCap and doxy.me, WebEx, or Zoom. Parents/guardians of participants under 18 years old will participate with the adolescent in the screening, evaluation, and informed consent/assent procedure. Participants 18 years and older will be able to provide their own informed consent. The informed consent process will include a thorough discussion of potential risks associated with participation, including potential adverse effects of study medication. The complex issues of informed consent and assent, and related limitations of confidentiality, as they apply to adolescents and their parents/guardians, are understood by the PI and will be communicated clearly during the telephone screening and assessment visit. In the case of adolescents in South Carolina Department of Social Services custody, state guidelines regarding consent for clinical research participation will be followed.

Potential participants (and parents/guardians, as appropriate) will be given a copy of the IRB-approved consent form and asked to read the document with ample opportunity to take their time in its review. The participant (and parent/guardian, as appropriate) will have the consent documents reviewed with delegated study personnel and have all questions and concerns addressed to their satisfaction. Anyone who cannot demonstrate appropriate understanding of the study or who expresses an unwillingness to participate in the protocol will be ineligible to participate and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form and proceed with the screening assessments. As part of the informed consent procedures, participants will be asked to provide or decline consent to be contacted for future studies. Copies of the signed consent documents will be given to the participants for their reference and resource.

Screening/Baseline Assessment

After consenting to participate in the study, participants will start the screening/baseline assessment phase. Ideally, the screening/baseline assessment procedures will be completed in one visit, but they can be completed in more visits if necessary. Participants will provide general demographic information and complete a locator form to optimize between-visit contact and communication. The comprehensive assessment will include a medical history and physical examination, urine drug testing, semi-structured psychiatric diagnostic interview (94,95), and detailed assessment of cannabis and other substance use history. Should a participant have screen failed for protocol #80921, N-Acetylcysteine for Youth Alcohol Use Disorder, the data/information that was completed as part of that protocol could be incorporated into this protocol if the participant presented as a likely eligible candidate. Additionally, the data collected as part of successful completion of protocol #94743, Youth Collaborative Assessment: Youth Treatment Trends, may also be incorporated as part of the inclusionary requirement. The participant would need to confirm interest and consent to such participation and data sharing. The screening procedures of these protocols closely mirror each other and this data sharing would remove the need for duplication of procedures as well as undue burden and testing fatigue.

Randomization

Following completion of screening/baseline assessments and determination of study eligibility, participants who return for the randomization visit and continue to be eligible will be randomly assigned, in double-blind fashion, to one of two conditions (NAC or PBO) for 12 weeks of treatment. Random assignment will be on a 1:1 ratio. Randomization will be stratified by age (≤18 versus ≥19) and by current tobacco/nicotine use status (yes/no). The age stratification will ensure that both younger and older adolescents will be equally represented across groups. The tobacco use stratification will help equalize distribution across treatment groups, as co-occurring tobacco use may impact cannabis use disorder treatment outcomes. We considered additional stratification variables (e.g., gender, severity of cannabis use disorder, history of attention-deficit/hyperactivity disorder), but, amid concern over excessive division of participants among multiple cells, judged that these could be adequately explored as covariates during efficacy analyses.

Mr. Baker, the study statistician, will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. Randomization assignments will not be conveyed to staff or participants. Mr. Baker will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization slot, once used, will not be re-allocated.

C3d. Treatment

Psychosocial Intervention

All participants will receive psychosocial intervention in the form of brief weekly non-manualized skills-based cannabis cessation counseling (designed to match the intervention provided in the prior NAC trial, and to mimic what may be feasibly conducted in a busy clinical practice setting).

Pharmacological Intervention

Consistent with our established procedures, United States Pharmacopeia (USP) grade NAC powder will be encapsulated in 600 mg quantities (two 600 mg capsules per dose). Matched placebo capsules will also be prepared. All capsules will be packaged in blister packs, with individual labels for time/date of each dose (e.g., Tuesday morning October 5th). This date- and time-labeled blister pack method has demonstrated superior participant adherence, compared to traditional packaging, and offers the additional advantage of tracking the timing of any missed doses (96-99). We successfully used identical methods for medication/placebo preparation and dispensing in our prior NAC versus PBO, added to CM, study.

If assessment procedures reveal that a participant meets inclusion criteria and none of the exclusion criteria, the participant will be randomized to NAC or matched placebo in a double-blind fashion. The participant will be given or mailed a supply of medication, with instruction to take 1200 mg twice daily, in approximately twelve-hour intervals. This dose was chosen due to its demonstrated tolerability and evidence of effect on cannabis use in our prior trial. Subsequent medication supply will be given out or mailed a week in advance to decrease the risk of the participant running out of study medication. Participants will be expected to continue taking study medication until they complete the End of Treatment Visit.

Study personnel will review daily reports and uploaded medication-taking videos (see *C3e.* below), and perform pill counts weekly throughout treatment to monitor medication adherence. Medication tolerability and effects will be systematically assessed. Medication supply will be refreshed for ongoing use over the following week. Participants will be encouraged to contact study personnel between visits to address any immediate concerns regarding adverse effects. If a participant experiences intolerable medication-related adverse effects at any point during the study, a dose reduction to 600 mg twice daily may be undertaken. The dosage may be increased back to 1200 mg twice daily at the discretion of the medical clinician. However, if a participant is unable to tolerate the reduced dose, medication will be discontinued, and the participant will continue to compete study visits.

Post-Treatment Follow-Up

Post-treatment follow-up visits will be conducted at approximately 16 weeks and 26 weeks from initial randomization. Should a participant determine to withdraw from ongoing study participation or it is determined by the PI/medical clinicians that the discontinuation is in the best interest for the participant, an Early Termination visit (following the schedule of events for a Week 26 visit) will be completed. If the participant does not wish to return for a final visit, a "phone visit" will be completed to gather basic health and safety details in addition to current cannabis status.

Incidental Visits

Unscheduled Visits/ Meetings – Unforeseen incidents may occur that would require a participant to return to the office or set up a remote meeting outside of the routine schedule of events. Such incidents could include: technological issues with loaned study equipment, medication dispensation if medication becomes lost/damaged, or an AE that requires immediate attention for proper assessment. It is not expected that these brief visits (likely 15 minutes in duration) would occur with any frequency and the majority of study participants would not require the additional meeting/return to the office.

Remote Visits – All visits can be conducted entirely remotely via REDCap and WebEx or Zoom. The participant will receive a shipment in the mail with the supplies required to complete an offsite/at home urine collection should they be willing to follow the proper collection and storage of a sample. Study medication will also be shipped in proper packing with tracking to protect medication as well as participant privacy. Prior to the mailing of any materials, ongoing participant interest in continued study participation will be confirmed, dosing instructions and safety needs will be reviewed, and depending on the ability to physically return study medication/blister packs, appropriate destruction measures will be provided. If such remote measures are employed, participants will be directed to have more extended visualization of their medication blister packs in

their video recording of study medication dosing to allow study personnel to properly monitor medication accountability.

C3e. Instruments/Measures/Materials

Clinical Assessments

Timeline Follow-Back, inclusive of detailed quantification of cannabis use, will be conducted at baseline and throughout the trial to characterize self-reported cannabis and other substance use (84,85,106). The MINI International Neuropsychiatric Interview will be conducted at the initial assessment visit to evaluate for psychiatric and substance use disorders (94-95). Throughout the study, a variety of self-report clinical measures will be collected, including Current Quality of Life (107), Marijuana Problem Scale (108), Marijuana Craving Questionnaire (109-111), Cannabis Withdrawal Scale (112), Obsessive Compulsive Drug Use Scale (113), Beck Depression Inventory (114), Beck Anxiety Inventory (115), ADHD Rating Scale (116), Pittsburgh Sleep Quality Index (117), Barratt Impulsiveness Scale (118), and Short UPPS-P Impulsivity Scale (119). Suicidality will be evaluated using the Columbia Suicide Severity Rating Scale (120). Among tobacco users, nicotine dependence will be assessed via the Modified Fagerström Tolerance Questionnaire (mFTQ) (121). For those using electronic cigarettes (e-cigs), nicotine dependence will be assessed via the Penn State Electronic Cigarette Dependence Index (122). Additionally, a clinician completed CUD Outcomes assessment will be completed. Adverse events will be documented, rated for severity and relatedness, coded in Medical Dictionary for Regulatory Activities (MedDRA) terms, and managed/reported appropriately via established procedures (see Human Subjects section). To evaluate penetration of the blind, participants and the primary study personnel who interact with the participant will be asked at multiple time points whether they think the participant is receiving NAC or PBO.

Participants will be asked to complete daily report surveys through REDCap (Research Electronic Data Capture – a secure, web-based application designed exclusively to support data capture for research studies) during the study. The daily report will ask about marijuana and any other drug or alcohol use on the day prior, as well as (during the 12 weeks of treatment) times of medication dosing. Participants will be asked to begin completing daily reports following their screening visit. Links to access the daily report will be sent to participants through their mobile phone and their email address. Participants may complete daily reports on either their smartphone or on a computer.

During the 12 weeks of treatment, participants will be asked to record and upload twice-daily videos of medication-taking at home or in a private location of their choosing. These videos will be taken remotely and submitted via REDCap surveys to confirm medication adherence. Participants may use their personal mobile phones for video submission. If they do not have a smartphone, one will be loaned to them during the first week of study. Video submissions may only be completed on a smartphone (cannot be completed on a computer). A survey link will be sent to the participant via text message. Video capture will occur as part of the REDCap survey. Videos are automatically stored on Android smartphones, and participants will be informed of that so they can delete the files, if necessary. Participants using iPhones (and using loaner iPhones from our group) will not have stored videos on their phone and nothing will need to be deleted.

Laboratory Tests

Urine pregnancy tests will be conducted with female participants. Weekly urine samples will be tested both qualitatively via dipstick as well as analyzed by the laboratory for quantitative urine cannabinoid level (with cutoff of <50 ng/mL signifying a cannabinoid-negative urine). Quantitative urine creatinine will also be obtained, to allow for evaluation of creatinine-normalized urine cannabinoid levels for quantitative comparisons (123,124).

Cognitive Task Performance Assessments

CNS Vital Signs, a computer-administered battery of performance tests, assessing subtle changes in mental acuity, learning and memory, psychomotor speed, complex attention, impulsivity, planning and sequencing, and other aspects of performance, will be administered at baseline, during treatment, at treatment conclusion, and at post-treatment follow-up (125). A training/practice session will be conducted during screening. The

performance battery, validated among adolescents, requires approximately 45 minutes to complete and includes the following components: *Verbal Memory Test (Part 1), Visual Memory Test (Part 1), Finger Tapping Test, Symbol Digit Coding, Stroop Test, Shifting Attention Test, Continuous Performance Test, Perception of Emotions Test, Reasoning Test, Four Part Continuous Performance Test, Dual Task Test, Verbal Memory Test (Part 2), Visual Memory Test (Part 2)*. We have utilized this battery in our prior work with NAC and CM in youth with CUD, demonstrating evidence of performance changes in some cognitive domains with abstinence versus continued use (23), though the proposed trial will provide superior power to assess a variety of cognitive outcomes.

For a subset of participants having participated in PRO#82347 – Cannabis Use in Adolescents' Natural Environments (CANE), that have consented to shared linked data, the study data sets will be combined to investigate predictors of treatment outcome in the present study. Specifically, measures from the CANE study of cue-induced or negative affect-related craving will be examined as predictors of reduction in quantitative urine cannabinoid test results during treatment in the present study.

Study Timetable

	SC	Double-Blind Medication Phase													FU	
Week →	SC	0ø	1	2	3	4	5	6&	7	8	9	10	11	12	16	26/ET
Informed Consent	X															
Locator Form and Updates	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demographics	X !⌂															
"Study Motivation"																X
Technology Survey			X													
Beliefs about Medications & Medication Adherence Video Feedback Form														X		X>
Medical Assessments																
History and Physical	X%!															
Height, Weight, Blood Pressure, and Pulse	X%!							X						X		X
Adverse Events	X%	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Meds	X%!	X$	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Penetration of Blind Assessment								X						X		X
Clinical Global Impression of Severity Scale (CGI-S)	X%							X						X		X
Psychological Assessments																
M.I.N.I.	X%!⌂															
CUD Outcomes	X							X						X		X
Barratt Impulsiveness Scale	X!															
Short UPPS-P Impulsivity Scale	X!⌂															
Current Quality of Life	X!	X						X						X	X	X
Beck Depression Inventory	X!	X						X						X	X	X
Beck Anxiety Inventory	X!	X						X						X	X	X
ADHD Rating Scale		X						X						X	X	X
Pittsburgh Sleep Quality Index	X!⌂	X						X						X	X	X
Columbia Suicide Severity Rating Scale	X!	X$						X						X	X	X
Cognitive Task Performance Testing	X#!	X						X						X		X
Substance Self-Report																
Cannabis and Other Substance Use History	X!⌂															
Cannabis Quantification	X															
TLFB/Substance Use Daily Reports	X%!⌂	X$	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cannabis Withdrawal Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Marijuana Craving Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Marijuana Problem Scale	X							X						X	X	X
Obsessive Compulsive Drug Use Scale	X							X						X	X	X
Modified Fagerström Tolerance Questionnaire (mFTQ) and/or Penn State Electronic Cigarette Dependence Index	X⌂!															
Motivation and Confidence to Quit	X	X														
Lab Samples/Testing																
Urine drug test (dipstick)	X^!⌂	X^	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Cannabinoids & Creatinine assay	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test‡	X⌂	X$	X*	X*	X*	X*	X*	X	X*	X*	X*	X*	X*	X		
Psychosocial Procedures																
Medication Adherence Assessment (Pill Count, Daily Reports, and REDCap Video Review)			X	X	X	X	X	X	X	X	X	X	X	X		
Cessation Counseling/ Medication Management		X	X	X	X	X	X	X	X	X	X	X	X			
Medication Dispensation		X	X	X	X	X	X	X	X	X	X	X	X			
Estimated Visit Length (hours) →	2-3	1.5	.75	.75	.75	.75	.75	1.5	.75	.75	.75	.75	.75	1.5	1	1.5

SC=Screening/Assessment, FU=Follow-Up, ET=Early Termination

ø the week 0 visit is the Randomization Visit, **‡** females only, ***** PRN for safety/precautionary measure**, ^** Urine drug test should be performed at screening/baseline and again before randomization to ensure eligibility, **$** should be completed prior to randomization to ensure eligibility. **&** If week 6 visit is missed, assessments that are only completed at that visit should be performed at the next attended visit, as long as the window for the end-of-treatment (week 12) visit has not yet opened. **%** These assessments may be performed at the randomization (week 0) visit, as long as they occur prior to randomization to ensure eligibility. **#** Training/practice cognitive task performance session. ; ! data sharing of completed protocol procedures from PRO#80921 as a result of screen failure, > at ET if completed during treatment phase of protocol; ^ data sharing of completed protocol procedures from PRO#94743

C3f. Statistical Methods

Power and Sample Size

This study is powered on the hypothesis that there is a clinically significant difference in proportions of negative urine cannabinoid tests (UCTs) among participants receiving NAC versus PBO.

Our previous findings demonstrated proportions of negative UCTs of 41% with NAC+CM and 27% with PBO+CM, but given that CM is itself a powerful treatment, we anticipate more modest proportions without a CM platform (62). Based on our other prior work using pharmacotherapy without a CM platform, we anticipate the proportion of negative UCTs in the PBO group will be between 6% and 10% (61). Although we have no prior clinical results for estimates of the efficacy of NAC alone, we anticipate that it will be at least as efficacious as CM in the proportion of negative UCTs (~27%), resulting in an overall anticipated effect of NAC versus PBO of 25% vs. 10%. With 12 weekly observations taken on each participant, a conservatively estimated autocorrelation as high as ρ=0.90, and a first order autoregressive covariance pattern, we will have greater than 80% power with two-sided α=0.05 to detect the stated difference of 15% in proportions of negative UCTs with 67 participants per treatment group (*n*=134 total). Based on performance of past studies, we anticipate a 30% attrition rate during the study treatment period. The inflated samples size of 96 randomized participants per group (*N*=192 total) will thus provide superior power to detect the stated difference in the main effect of NAC versus placebo in the presence of up to a 30% attrition rate.

Based on our previous research we anticipate approximately 25% percent of participants will have negative UCTs at cognitive task performance assessment visits (23). Similarly, our data indicate that negative UCTs were associated with increased verbal memory and psychomotor speed scores at both 4 and 8 weeks during a cannabis cessation trial using NAC + CM versus CM alone (Cohen's *d*=0.90 and *d*=0.60; respectively). The randomized sample size of *N*=192 will provide superior power (99% and 82%, respectively) with an adjusted α=0.01, to detect similar effect sizes across cognitive outcome measures taken at mid-treatment, end-of-treatment, and post-treatment follow-up.

Statistical Analysis

Categorical clinical and demographic variables will be assessed by chi-square tests of independence, while continuous variables will be assessed using Student's *t*-test. In addition to baseline group differences, preliminary analysis of baseline characteristics with cannabis use outcomes of interest will examine significant correlates of abstinence in the study population. Characteristics found to be significantly associated with cannabis use outcomes will be included as covariates in the initial stages of model development. The primary measure of interest will be the proportion of self-reported abstinence confirmed with negative weekly UCTs (< 50 ng/mL) during the 12 weeks of active treatment. The main effect of NAC on negative weekly UCTs will be assessed with a repeated measure logistic regression using a general estimating equations framework (GEE) (126). Models will be computed both unadjusted and adjusted for significant covariates and confounders found in the preliminary analysis. Working correlation structures will be independently compared using the quasi-likelihood under the independence model criterion statistic (127). All randomized participants will be included in the primary analysis (intent-to-treat; ITT) and participants will be deemed non-abstinent at any missed visit (drop-out/loss-to-follow up included). Model based means will be used to construct the pairwise comparisons of groups (NAC versus PBO). In addition to the longitudinal analysis of negative UCT rates during treatment, rates will be compared between treatment groups at each post-treatment follow-up visit using logistic regression models. Similarly, creatinine adjusted cannabinoid levels will be examined between groups over the course of the treatment and at the post-treatment follow-up visits using linear mixed effects models. We will also, in exploratory fashion, examine group differences in other cannabis-related outcomes (e.g., self-reported cannabis use [Timeline Follow-Back], craving [Marijuana Craving Questionnaire], withdrawal [Cannabis Withdrawal Scale], and associated problems [Marijuana Problem Scale]). In distinct models, the effect of co-occurring tobacco use disorder on cannabis cessation outcomes will be examined. The main effect of co-occurring tobacco use

disorder, as well as the interaction between tobacco use disorder and each treatment assignment (NAC and CM), will be added to the primary efficacy model.

Cognitive task performance will be assessed at pre-treatment, mid-treatment, end-of-treatment, and post-treatment follow-up. Task performance at the post-baseline time points will be compared between those who have and have not achieved abstinence at that time points using generalized linear mixed models with outcome appropriate distributions (Gaussian, Poisson, etc.). In addition to a binary indicator of UCT at each cognitive task measure visit, duration of abstinence will be examined as a predictor of cognitive performance. In exploratory fashion, we will also assess potential NAC versus PBO effects on cognitive task performance, as NAC possesses potential cognitive enhancing properties (128).

All analysis will be conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Missing Data and Attrition

Missing data in longitudinal studies can be a very problematic feature but can be mitigated through study design considerations. Attrition may introduce bias in the treatment group parameter estimate and reduce power, precision, and generalizability. In order to minimize missing data and study attrition, study simplification and enhanced communication between study coordinators and participants will be emphasized. We will make every effort to prevent attrition, e.g., telephone/text/e-mail reminders prior to visits, meeting with participants in community if needed, and reinforcing attendance at each visit. However, these methods do not ensure that all data will be collected and appropriate analysis methods will be employed to accommodate missing data. Mixed-effects models yield valid inferences assuming ignorable attrition (i.e., attrition is accounted for by covariates or the dependent variable measured prior to dropout). We propose a sensitivity strategy to examine the ignorability assumption. A pattern mixture model will be used to examine treatment response among participants with various dropout patterns and will be implemented in the mixed-effects framework (129-131) in which participants are classified by attrition pattern (e.g., early dropout, middle dropout, late dropout, completer). In addition, in keeping with the ITT Principle, we will make every effort to continue assessments for the entire course of randomized treatment, even among those who fail to adhere to randomized assignment or stop participating in the study assigned intervention.

C3g. Clinical Management Issues

Subject Discontinuation/Stopping Rules

Every effort will be made to retain participants in the trial. If a participant experiences intolerable adverse effects with study medication that are not remedied by a dose reduction, the medication may be discontinued while the participant continues to participate in all non-medication study interventions and procedures.

Clinical Deterioration "Rescue" Plan

A clinical deterioration "rescue" plan will be in place for participants that experience psychiatric or substance use deterioration during the study. Symptoms will be monitored closely throughout the trial to assess for deterioration. Appropriate intervention will be arranged for any participant demonstrating gross clinical deterioration. The rescue measures will include immediate assessment by the medical clinician for a comprehensive psychiatric and substance abuse evaluation and referral for appropriate clinical intervention. The PI has full medical and psychiatric admitting privileges at the MUSC Medical Center.

Referral for Participants Needing Continuing Treatment

At the end of study participation, if a participant requires or requests continuing treatment for CUD, an appropriate treatment referral will be made.

C3h. Operational Plan and Research Timetable

Funding for five years is requested. The first three months will be used for training personnel, submitting regulatory documents, and preparing for study initiation. Fifty-four months will be needed for participant recruitment (48 months) and data collection (additional 6 months for last enrolled participants). The final three months will be used for data analysis and manuscript preparation. At a targeted recruitment rate of 4 participants per month, an adequate sample will be obtained within the time allotted.

C4. Conclusion

Youth are more likely than adults to initiate cannabis use, develop CUD, and experience potentially lasting and impairing cannabis-related adverse consequences. Currently disseminated treatments for youth CUD convey generally small to modest effect sizes, with very few youth achieving sustained abstinence, indicating that work is needed to enhance treatments to address the public health burden of youth CUD. The most promising youth CUD pharmacotherapy to emerge from research is NAC, but to date it has not been evaluated without an embedded CM platform. The proposed trial addresses this issue in a manner that allows evaluation of the main effect of NAC, outside of the context of CM. This work is a critical step in optimizing treatments to disseminate into real-world practice. The multidisciplinary research team, uniquely experienced with NAC n this population, is ideally suited to conduct this trial, and is dedicated to contributing to the evidence base to address the serious issue of youth CUD.

Human Subjects Research

1. Risks to Human Subjects

1.1 Human Subjects Involvement and Characteristics

The PI and Co-Is have all completed the University of Miami computer-based CITI Human Subjects Research Education Course. A total of 200 male and female youth between 13 and 21 years old with cannabis use disorder will be recruited over 48 months for a target sample size of 192. The sample size was determined based on statistical power analysis (Section C3f). Participants will be recruited from the local community. A multimedia advertisement campaign will be used for study recruiting. The inclusion/exclusion criteria are as follows:

Inclusion Criteria

- Age 13 – 21 years
- Must be able to understand the study and provide written informed consent (for participants under 18 years old, a parent/legal guardian must be able to provide consent and the participant must be able to provide assent)
- Must meet current (within last 30 days) DSM-5 criteria for cannabis use disorder
- Must express interest in treatment for cannabis use disorder
- Must submit a positive urine cannabinoid test during screening
- Females must agree to use appropriate birth control methods during study participation: oral contraceptives, contraceptive patch, barrier (diaphragm or condom), levonorgestrel implant, medroxyprogesterone acetate, complete abstinence from sexual intercourse, or hormonal contraceptive vaginal ring
- Must have successfully completed the YC Intake Protocol (PRO# 94743) within approximately 30 days of formal study screening

Exclusion Criteria

- Allergy or intolerance to *N*-acetylcysteine
- Females who are pregnant, contemplating pregnancy over the next 6 months, or lactating
- Current use of *N*-acetylcysteine or any supplement containing *N*-acetylcysteine (must agree not to take any such supplement throughout study participation)
- Use of carbamazepine or nitroglycerin within 14 days of randomization or expectation of future use during protocol participation
- Current enrollment in treatment for cannabis use disorder or expectation of other treatment during protocol participation
- Any use of synthetic cannabinoids (such as K2/Spice) in the 30 days prior to screening or expectation of future use during protocol participation.
- Current moderate or severe substance use disorder, other than cannabis or tobacco
- Medical history of severe asthma (uncontrolled with medication)
- History of seizure disorder
- Any other medical or psychiatric condition or other significant concern that in the Investigator's opinion would impact participant safety or compliance with study instructions, or potentially cofound the interpretation of findings

Demographics

United States Census data from 2013 reveal that the population in South Carolina is 68.3% White (63.9% White, not Hispanic or Latino), 27.9% Black or African American, and 5.3% Hispanic or Latino. No other minority group comprises more than 2% of the population. Among a nationally representative sample of individuals meeting criteria for cannabis use disorder within the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), 37% were female (132). In our prior placebo-controlled trial of *N*-acetylcysteine, added to

contingency management, for youth cannabis use disorder, 27% of enrolled participants were female, 13% were Black or African American, and 1.7% were Hispanic or Latino (62). Given these numbers, we anticipate enrolling a sample that is a) 68% male and 32% female, b) 80% White, 20% Black or African American, and 3% Hispanic or Latino.

1.2 Sources of Materials

Research materials obtained from participants include responses to questionnaires, psychiatric and physical examination results, and urine tests (drug metabolites, creatinine, and pregnancy). Materials will be obtained specifically for research purposes. There will be no use of existing specimens, records, or data. Every effort will be made to maintain participant confidentiality, in accordance with HIPAA.

1.3 Potential Risks

Questionnaires and interviews are all non-invasive and, as such, involve minimal physical risk to participants. Potential risks incurred by participants include:

1. Adverse events related to study medication
2. Loss of confidentiality

1.31 Adverse events related to study medication

N-acetylcysteine has a generally benign adverse effect profile. A meta-analysis of studies evaluating long-term oral treatment with *N*-acetylcysteine for prevention of chronic bronchitis found that *N*-acetylcysteine was well tolerated, with generally mild, most commonly gastrointestinal adverse effects that did not require treatment interruption (82). Our experience to date with *N*-acetylcysteine at the same dose proposed in this trial in youth with cannabis use disorder suggests a benign adverse event profile (62).

Some patients who have taken intravenous *N*-acetylcysteine for the treatment of acetaminophen overdose have had more serious reactions. Allergic reactions have occurred in about 5% of patients taking intravenous *N*-acetylcysteine (133). These reactions may be mild, consisting of flushing, rash, and itching. Less common side effects include trouble breathing, low or high blood pressure, fever, and hives. If untreated, such a reaction could lead to death. Even more rare serious side effects of intravenous *N*-acetylcysteine are irritability, confusion, and seizures. These reactions (severe allergic reaction or seizures) have never been reported when *N*-acetylcysteine is taken orally, as it will be in this study. As a precaution, the medical clinician team will remain highly attentive to the issue of asthma, and will exclude potential participants with severe asthma as defined by those uncontrolled by medication. We will also exclude individuals with a history of seizure disorder.

1.32 Loss of confidentiality

Any communication of personal information carries the potential risk of breach of confidentiality.

2. Adequacy of Protection Against Risks

2.1 Recruitment and Informed Consent

Recruitment of the participants will be from the local community. The Medical University of South Carolina (MUSC) Institutional Review Board (IRB) approved Informed Consent (IC) will be obtained prior to the initial assessment. The consent will be explained orally and in the written form, and will be documented by the signature of the participant on the IC. For participants under 18 years old, a parent/legal guardian will provide consent and the participant will provide assent. The consent document will contain a thorough review of potential risks associated with trial participation, including potential medication-related risks.

For re-consenting purposes for those participants under 18 years of age whose parent/legal guardian is not available to attend a study visit, we would conduct the re-consent process over the phone. We understand the importance of parental/guardian presence in the initial consenting procedures of study participation due to potential risks associated with study medication. The issue that may arise, however, is that it may become intrusive and demanding for them to return for a re-consent need when in most cases the IC revisions are minor and generally editorial and administrative in nature. We would not want their child's study participation to potentially negatively impact the parent/guardian's employment, nor do we want such a need to be a barrier in the child's study participation.

The process that study personnel would follow includes: Discussion with the parent/guardian by trained/approved study personnel would be completed prior to the next scheduled visit where a re-consent is to

take place. When possible, study personnel will have forwarded the new ICF (electronic or hard copy) to the parent/guardian so he/she could have the document in front of him/her during the re-consent discussion. Study personnel would clearly document the conversation detailing the changes in the ICF. If the parent/legal guardian expresses understanding of the study changes and approves the child's continued participation and the ICF is available to the parent/legal guardian, he/she will sign and date the ICF accordingly, returning it for the minor's assent and study personnel's signature at the subsequent visit. If the parent/legal guardian does not have access to the ICF at the time, then the document will be sent home with the minor after their next completed study visit where the assent and staff's signature was obtained. The parent will sign the form accordingly and it will be returned to the study site at the following study visit. A copy of the fully signed document would be provided to the parent/legal guardian either by hardcopy (postal mail or minor's delivery) or electronically (email or fax) per the parent/legal guardian's preferred method. If the parent/legal guardian does not feel comfortable with the changes, requesting to have additional in person discussion with study personnel, then the minor's next visit would be cancelled/rescheduled for a date when the parent/legal guardian is able to attend the visit. At that time, routine in person/ remote consenting procedures would occur.

Absence of Coercion: Participation in the study is voluntary. All participants will be compensated $40 for the completion of initial assessment, $40 each for completion of the other study visits that include cognitive task performance assessment, and $20 each for study visits completed that do not include cognitive task performance assessment. Participants will also be eligible for as much as $20 per week during the twelve weeks of active treatment for completion of remote data entry via smartphone, including video uploads confirming twice-daily medication adherence. A bonus of $40 is available for reaching and completing Week 12 to address the use of the participant's personal phone or for the safe return of loaned study equipment. $20 will be available to those participants who do not reach and complete Week 12 in exchange for their personal phone use or the return of study equipment. Participants will be eligible for a maximum of $700 for uninterrupted completion of all study visits and tasks. The informed consent agreement that will be read to each volunteer (and parent/guardian as applicable) prior to enrollment in the study explains the following:

a) Compensation is supplied at each study visit.
b) Participants may discontinue participation in the study at any point.
c) Withdrawing from the study will not result in any adverse consequences to the participants.

2.2 Protection Against Risk

2.21 Adverse events related to study medication

The informed consent process will be used to thoroughly educate participants and parents/guardians about potential medication-related risks, including adverse events. This discussion will include thorough review of adverse events associated with oral *N*-acetylcysteine treatment. Rigorous screening procedures and strict exclusion criteria are designed to exclude potential participants at elevated risk for adverse events. The study medical clinician will conduct serial adverse events monitoring as part of medication management. Participants and parents/guardians will have access to the study medical clinician 24 hours, 7 days a week for emergencies. Participants experiencing intolerable adverse events will have the opportunity to reduce dose or discontinue medication altogether, while remaining in the study for ongoing monitoring. The PI has full hospital admitting privileges in the event of an adverse event requiring hospitalization. Urine pregnancy tests will be conducted at baseline and serially during treatment for female participants.

2.22 Loss of confidentiality

The research team has established procedures in place to minimize the risk of any confidentiality breach. Participant records are stored in locked files within locked offices that are locked during holidays, weekends, and non-working hours. Information contained in computer databases is password protected, maintained by participant number only, and devoid of specific identifiers. No specific or general participant information will be left in public access areas, and no oral communication regarding participants with identifiers will be made in any public areas. Research staff members have had extensive training in HIPAA regulations and in maintaining confidentiality.

3. Potential Benefits of the Proposed Research to the Participants and Others / Importance of the Knowledge to be Gained

Despite considerable public health implications, insufficient research has focused on optimizing efficacious youth cannabis use disorder treatments. Testing *N*-acetylcysteine will fill a critical evidence gap, providing key information to guide clinical practice.

Participants in this study, regardless of randomization to active or placebo medication, will benefit by receiving a) comprehensive medical and psychiatric evaluation, and b) weekly cannabis cessation counseling throughout active treatment.

4. Data and Safety Monitoring Plan

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan."

4.1 Summary of the Protocol

This application proposes a randomized controlled trial (*N*=192) of *N*-acetylcysteine for youth cannabis use disorder. Treatment-seeking youth with cannabis use disorder will be recruited from the local community, and enrolled participants will be randomized to receive a 12-week course of *N*-acetylcysteine or placebo, added to weekly cannabis cessation counseling and medication management. The primary efficacy outcome of interest is the proportion of negative urine cannabinoid tests during treatment, compared by treatment group. Cognitive task performance will be assessed prior to, during, and after treatment, to investigate whether participants achieving abstinence exhibit cognitive task performance improvement relative to participants who do not achieve abstinence. Inclusion and exclusion criteria are outlined above. Power and sample size calculations are in Section C3f.

4.2 Trial Management

All aspects of the study will be run through the MUSC Department of Psychiatry and Behavioral Sciences, where the PI holds his faculty appointment. The target population is described in Section C3b, Human Subjects Section 1.1, and the adjoining Planned Enrollment Table. The timetable is as follows:

	Year 1 (months)	**Year 2** (months)	**Year 3** (months)	**Year 4** (months)	**Year 5** (months)
Refine all procedures	1-3				
Procure supplies	1-3				
Refine recruitment methods	1-3				
Train Personnel	1-3				
Study Enrollment					
Cumulative *N* to enroll*	(36)	(84)	(132)	(180)	(192)
First Participant Enrolls	4				
First Participant Completes	10				
Last Participant Enrolls					51
Last Participant Completes					57
Data Analysis					58-60
Manuscript Preparation					58-60

All numbers reflect months within total study duration (*with the exception of cumulative *N*)

4.3 Data Management and Analysis

Data will be collected by the appropriate individual (research assistant, PI, Co-I) using standardized paper forms and will only be identified with the study's ID of the participant. The codes linking the name of the participant to the study ID will be kept confidential in an electronic file password protected by research staff. Collected forms will be securely transported to the PI's data entry center. Research assistants will enter data in REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data

capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). When possible, participant direct entry into REDCap (rather than paper forms) will be utilized. The data analysis plan is outlined in Section C3f.

4.4 Quality Assurance

Accuracy and completeness of the data collected will be ensured by weekly review. A 10% random sample of the primary source document will be crosschecked with the database on a quarterly basis. If inaccuracies exceed 4%, then a second 10% will be randomly chosen for audit. The REDCap system does not accept outliers, illogical response patterns, etc. The PI and program coordinator will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection or entry. The statistician will periodically examine the database for potential irregularities. Initial data analyses will examine distributions of variable scores and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality protections are outlined above.

4.5 Regulatory Issues

Prior to the start of the study, the protocol will be registered on the clinical trials registry (clinicaltrials.gov). All serious adverse events will be reported to the MUSC Institutional Review Board (IRB) within 24 hrs. Follow-up of all serious adverse events will be reported as well. All adverse events are reviewed weekly by the PI and yearly by both the Data and Safety Monitoring Board (DSMB; see 4.9) and the IRB. Any significant actions taken by the local IRB, including significant protocol changes, will be relayed to NIDA. We anticipate the serious adverse event rate to be extremely low. If monitoring indicates otherwise, we will convene a special meeting of the DSMB.

4.6 Trial Safety

The potential risks and benefits and methods to minimize these risks are outlined in Sections 1.3 and 2. Guidelines have been developed for managing and reporting of adverse events (AEs), including serious adverse events (SAE; defined as any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or in the opinion of the investigators represents other significant hazards or potentially serious harm to research subjects or others). Dr. Gray will serve as the Program Manager for AEs. The Adverse Event Log will be used to document all AEs. If an AE is non-serious (self-limited with no intervention needed), no further action will be necessary. However, in the case of a serious, unresolved event, an AE follow-up log will be completed. The clinician will then call Dr. Gray with initial reports within 24 hours of the start of the SAE. The clinician will record the information on SAE Notification Form. The clinician will forward hard copies of the complete report (SAE Notification Form, Concomitant Medication Log, and AE Log) to Dr. Gray, who will, in turn notify the IRB, DSMB, and NIH about the SAE. Additionally, Dr. Gray will communicate summary reports of DSMB discussion of the SAE, or any deliberations of IRB regarding the review of the SAE or the trial itself, to NIH. If the event is “Serious, Unexpected and Associated” (an SAE is considered unexpected if it is not described in the Package Insert), Dr. Gray will complete Food and Drug Administration (FDA) Form 3500A and will forward it to the FDA. Dr. Gray also will inform the IRB and the study participants (and parents/guardians, as appropriate) about the SAE. In all of these reviews and reports, strict patient confidentiality will be maintained.

AEs will be coded on a weekly basis using Medical Dictionary for Regulatory Activities (MedDRA) rules and entered into a database. For each weekly study meeting, the research assistants will prepare a summary of all AEs, including their severity and presumed relation to study medication. The PI will review this at the weekly study meeting (or before if more urgent).

Study procedures will follow as much as possible the FDA’s Good Clinical Practice Guidelines. We will encourage participants (and parents/guardians as appropriate) to notify their physicians that a) they are in a randomized controlled research study evaluating *N*-acetylcysteine and contingency management for youth cannabis use disorder, and b) the physician should contact the PI directly if the physician has any questions.

The research assistants will be instructed not to reveal whether a person is a participant in the study and will report to the PI any outside requests for information about a participant or any breaches in confidentiality. All requests by participants' physicians and other medical providers will be referred directly to the PI.

4.7 Trial Efficacy

The DSMB (see 4.9) may request a blinded interim efficacy report (blinded to the PI and research team) for review while the trial is ongoing. Final (fully unblinded) efficacy analysis will occur after all participants have completed all visits.

4.8 Data and Safety Monitoring Plan Administration

The PI will be responsible for monitoring the trial. The statistician will examine the outcomes database quarterly for missing data, unexpected distributions or responses, and outliers. The PI will weekly check the adverse event database prepared by the research assistants immediately prior to the lab meeting to a) see if any particular MedDRA categories are being endorsed more frequently than anticipated, and b) determine if any adverse event symptom checklist scores are higher than expected. A DSM report will be filed with the IRB and NIDA on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of adverse events, significant/unexpected adverse events and serious adverse events. We will report efficacy at the end of the trial.

4.9 Data and Safety Monitoring Board

We will create a DSMB, comprised of multidisciplinary faculty with expertise in pharmacotherapy and behavioral treatment trials (youth and/or addiction-related). The DSMB will meet annually (more frequently as needed for emergent situations) to review any AEs related to the study, as well as review any data management related errors. The board may be called at any point if needed for serious adverse events, etc. Modification will be made in the procedures and/or the protocol if necessary based on the findings of the board.

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