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N-Acetylcysteine for Smoking Cessation Among Dual Users of Tobacco and Cannabis: Protocol and rationale for a randomized controlled trial

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Abstract

Background—Tobacco and cannabis co-use is a growing public health problem. The synergistic effects of cannabis and nicotine on neurobiological systems that mediate reward and shared environmental cues reinforcing use may make tobacco smoking cessation more difficult. N-

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Author Contributions

EH acquired funding and led the conception, design, and implementation. DP, BB, JM, SB, and MY contributed to the conceptualization of the design and MY led the data analytic plan. MMR, NR, JD, BG, and NW led the effort to implement and launch the trial. EH, MMR, BG, NR, and JD prepared the Institutional Review Board application and [ClinicalTrials.gov](https://www.clinicaltrials.gov) materials. NR and JD participated in editing and revision of the grant application. All authors contributed to the article and approved the submitted version.

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Trial status

The trial began recruitment in November 2021 and is currently recruiting. We anticipate recruitment to be completed June 2024.

Human Subjects Protections: This work is being carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All procedures received approval from the UCSF Institutional Review Board with concurrence from SFVAHCS Human Research Protection Program. Informed consent is obtained for experimentation with human subjects.

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Declaration of Competing Interest

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acetylcysteine (NAC), an FDA-approved medication and over-the-counter supplement, has shown promise in animal studies and randomized controlled trials (RCTs) in reducing tobacco and cannabis craving and use. NAC's potential efficacy in treating addiction may be attributable to its central nervous system effects in reducing excessive glutamatergic activity, oxidative stress, and inflammation. To date, no RCT has examined NAC for smoking cessation among dual users of tobacco and cannabis.

Method—In a double-blind, placebo-controlled RCT, we will examine NAC for smoking cessation among dual users of tobacco and cannabis. Sixty adult cigarette-cannabis co-users are randomized to receive NAC 3600 mg per day or placebo over 8 weeks. Participants in both groups receive 8 weekly cognitive behavioral therapy sessions addressing smoking cessation and cannabis reduction. Outcomes are assessed at Weeks 0, 4, 8, and 12. Primary aims are to determine NAC's efficacy in decreasing cigarette craving, nicotine dependence, and use; and cannabis craving and use. Exploratory aims include examination of changes in neurocognition with NAC and their potential mediational effects on cigarette and cannabis use outcomes.

Conclusion—Results will inform smoking cessation treatment among dual users of tobacco and cannabis.

Keywords

Smoking cessation; Cannabis use; Randomized clinical trial; Pharmacotherapy; Tobacco-cannabis co-use

INTRODUCTION

Cigarette use remains the leading preventable cause of death in the United States (U.S.) and is associated with cardiovascular and pulmonary disease, cancer, and premature death¹ and \$300 billion annually in healthcare and lost productivity costs². Although cigarette use has been declining overall in the U.S.³, co-use of cannabis and tobacco, which defined here as use of cannabis and tobacco separately or simultaneously in the past 30 days⁴, is common and increasing with cannabis legalization across the country. Approximately 20–50% of cigarette smokers report current cannabis use^{5–7}.

Concurrent use of tobacco and cannabis may make quitting either substance more difficult^{8,9}. Cannabis use among cigarette smokers has been shown to reinforce progression to tobacco use disorder (TUD)^{10–12} and to impede smoking cessation in adults^{13,14}. Tobacco and cannabis share multiple contextual stimuli, including inhaled route of administration, co-administration of the two substances¹⁵, and social and environmental cues⁴. At the time of this writing, there is no Food and Drug Administration (FDA)-approved medication that targets both tobacco and cannabis use. Cognitive behavioral therapy (CBT), motivational interviewing/motivational enhancement therapy, cognitive behavioral therapy, and contingency management are evidence-based psychosocial treatments for both Tobacco Use Disorder¹⁶ and Cannabis Use Disorder (CUD)¹⁷.

N-Acetylcysteine (NAC) is an inexpensive oral medication available as an FDA-approved mucolytic for the treatment of cystic fibrosis¹⁸ and as an over-the-counter supplement. NAC also has antioxidant and anti-inflammatory effects in acetaminophen overdose¹⁸, and

has central nervous system effects in reducing glutamatergic activity, oxidative stress, and inflammation^{19–21}. NAC is also generally well-tolerated, with oral doses up to 3000–4000 mg/day associated with few adverse effects other than mild gastrointestinal symptoms in adult populations²². NAC has shown promise both in animal models^{19–21} and as found to be safe for use in clinical populations^{23,24}, including clinical trials addressing both TUD and CUD^{25,26}. A 2021 meta-analysis of 16 RCTs evaluating the effectiveness of NAC for treating substance use disorders (nicotine, alcohol, cocaine, amphetamine, or cannabis) found that a significant decrease in craving symptoms (standardized mean difference (SMD) -0.67 ; 95% confidence interval (CI), -1.21 to 0.21), and withdrawal and depressive symptoms (SMD, -0.35 ; 95% CI, -0.64 to -0.06) were observed in the NAC treatment groups compared with the control groups²⁷.

To date, there have been five placebo-controlled RCTs examining NAC for TUD^{28–32}, including one active RCT underway examining effects in adult cigarette smokers³³. A RCT ($N=22$) comparing 3600 mg NAC daily with placebo for nicotine withdrawal symptoms during a 4-day abstinence period showed that those receiving NAC found no differences with respect to withdrawal symptoms or craving. However, in the NAC condition, participants rated cigarettes to be substantially less rewarding at post-treatment compared to the placebo control condition ($d=0.85$)²⁸. Another RCT comparing 2400 mg NAC daily to placebo in non-treatment seeking smokers undergoing a 4-day contingency management behavioral protocol ($N=16$) found that by study end, the NAC group had significantly higher abstinence, less craving, and more positive affect than the placebo control group (all large effects: $d \geq 1.58$)²⁹. In another pilot RCT, patients with treatment resistant TUD ($N=34$) (failed at least one medication for smoking cessation) all received 12 weeks of CBT and were randomized to also receive either NAC 3000 mg/day or placebo. The NAC group had significantly greater reductions in number of daily cigarettes (endpoint comparison: $d=0.64$), CO levels (endpoint comparison: $d=0.59$), and depression scores (endpoint comparison: $d=0.89$) and had a higher quit rate³⁰. A fourth RCT assigned treatment-seeking smokers ($N=29$) to 4 weeks of 2400 mg/day NAC or placebo and found no differences in craving, carbon monoxide levels, or withdrawal. Daily cigarette use by time was significantly lower in the NAC group (no effect size provided)³¹. Finally, a 14-day placebo-controlled RCT assigned 48 male smokers to receive either NAC 2400 mg/day or placebo found no treatment group differences³². Limitations of these studies include relatively small sample size and brief treatment and follow up observations.

Two RCTs have examined NAC for CUD^{23,34}. A RCT in treatment-seeking adolescents with CUD ages 15–21 ($N=116$) examined CM plus NAC 2400 mg/day for 8 weeks²³. Intent-to-treat analyses showed greater than twofold odds of bioverified cannabis abstinence in the NAC group vs. placebo at study end (odds ratio=2.4, 95% CI=1.1–5.2)²³. A similar RCT by the same team with adults with CUD found that NAC 2400 mg/day for 12 weeks did not differ from placebo³² in cannabis craving or use.

Both cannabis³⁵ and cigarettes^{36,37} have measurable adverse effects on cognition and impulse control, which can interfere with treatment response. NAC has been associated with improvements in neurocognitive functioning⁴¹ among military personnel with traumatic

brain injury⁴², cocaine users⁴³, and individuals with neurocognitive disorders such as Alzheimer's disease⁴¹.

Taken together, clinical trials to date have demonstrated promise of NAC in reducing tobacco use or cannabis use. However, no study has systematically examined the potential efficacy of NAC for smoking cessation among dual users of tobacco and cannabis, nor has any RCT provided CBT for SUD in combination with NAC to address both tobacco and cannabis use. Moreover, no study has examined measures of neurocognitive functioning as potential mediator of NAC's effect on craving and substance use.

Study Objectives and Design

The current study is a prospective, parallel groups, randomized, double-blind, placebo-controlled clinical trial among cigarette-cannabis co-users ($n=60$) to examine NAC to treat smoking cessation and cannabis reduction. This is a 12-week study, which consists of 8 weeks of treatment with NAC 3600 mg/day or placebo. Outcomes are assessed at Weeks 0, 4, 8, and 12. To ensure that participants in both groups receive evidence-based treatment, all participants receive 8 sessions of CBT for both smoking cessation⁴⁴ and substance use disorders⁴⁵ targeting cigarette and cannabis use.

The project's primary aim (Aim 1) is to examine the effect of NAC on cigarette craving, nicotine dependence levels, and daily cigarette use in co-users of cigarettes and cannabis. We hypothesize that the NAC group will show greater reductions in cigarette craving than placebo, assessed by the Questionnaire on Smoking Urges-Brief (QSU)⁴⁶, at post-treatment (Week 8) and follow-up (Week 12). We also hypothesize that the NAC group will show greater decreases in nicotine dependence levels (Fagerström Test of Nicotine Dependence, FTND⁴⁷) and lower past-30-days self-reported cigarette use (TLFB⁴⁸) at post-treatment (Week 8) and follow-up (Week 12).

The secondary aim (Aim 2) is to examine the effect of NAC on cannabis craving and self-reported cannabis use among co-users. We hypothesize that the NAC group will report lower cannabis craving than placebo, assessed by the Marijuana Craving Questionnaire (MCQ)⁴⁹, at post-treatment (Week 8) and follow-up (Week 12). The NAC group will report greater decreases in CUD severity levels (Cannabis Use Disorder Identification Test-Revised, CUDIT-R^{50,51}) and mean daily cannabis use (TLFB⁴⁸) at post-treatment (Week 8) and follow-up (Week 12).

This project has two exploratory aims. First, we will examine changes in self-reported impulsivity (Barratt Impulsiveness Scale-11, BIS-11⁵²); and objective measures of cognitive functioning, including measures of mental switching (Oral Trail Making Test (OTMT)⁵³); working memory (Paced Auditorial Serial Addition Test, PASAT⁵⁴); and learning and memory (Hopkins Verbal Learning Test, HVLN-R⁵⁵) as mediators of NAC's effects on cigarette and cannabis use (Exploratory Aim 1). Second, we will examine the effect of NAC versus placebo on bioverified 7-day point prevalence cigarette abstinence and bioverified 30-day cannabis abstinence rates at Weeks 8 and 12 (Exploratory Aim 2).

In this phase 1b pilot study, measures of feasibility (recruitment rate, study drug tolerability and safety, retention) will be assessed.

MATERIALS AND METHODS

Participants, inclusion, and exclusion criteria

Inclusion Criteria: Participants include smokers ages 18 and over who: 1) have smoked an average of at least 2.5 cigarettes per day in 15 of the past 30 days, or an average of at least 1 cigarette per day for the past 30 days; 2) endorse the use of cannabis within the past 30 days, reported by Timeline Followback (TLFB), and test positive for tetrahydrocannabinol (THC) on urine immunoassay at Week 0 or up to 30 days prior to Week 0; and 3) consent to receive interventions to stop smoking cigarettes and using cannabis. Although co-users can use tobacco and cannabis simultaneously (i.e., in “spliffs”) and other forms of nicotine and tobacco, participants must smoke combustible cigarettes that are not mixed with cannabis on a regular basis to participate.

Exclusion Criteria: Individuals are excluded from participation if they endorse: 1) Psychotic disorders, bipolar disorder, cognitive disorder, or other psychiatric or medical conditions judged by the PI to be unstable in the past 30 days, based on MINI Neuropsychiatric Interview⁵⁶. 2) Concurrent participation in another addiction treatment study or pharmacological study. 3) Pregnancy or lactation at screening or at any time during the study period. 4) Non-study NAC use at enrollment or at any time during the study period. 5) Use of medications for TUD (NRT, bupropion, or varenicline) at enrollment or at any time during the study period (bupropion for depression (assessed by self-report, chart review, and/or discussion with prescriber) is permitted); 6) A suicide attempt or suicidal ideation with intent 30 days prior to enrollment. *Human Subjects Protections:* The investigative team has obtained local Institutional Review Board approval, FDA Investigational New Drug approval, and a Certificate of Confidentiality.

Recruitment, screening, and randomization

Eligibility and Recruitment: We are recruiting a sample of 60 cigarette-cannabis co-users with TUD from the San Francisco Bay Area and greater California. Approved flyers and brochures are distributed throughout the area, approved emails and social media postings are shared. We are using established methods to recruit from local hospitals and clinics. Research staff conduct brief pre-screening by phone with potential candidates to assess eligibility and schedule for screening.

Screening Assessments: Participants complete written informed consent, then undergo screening and baseline procedures to determine eligibility and characterize the sample. Assessments are adapted to be conducted either in person or remotely via secure teleconference (Zoom or telephone) to optimize recruitment during the COVID-19 pandemic.

Randomization and blinding: Eligible participants are randomly assigned, sequentially as they enroll, to either NAC or placebo in a 1:1 ratio per a computer-generated list

provided by a biostatistician. Randomization is stratified by combustible cigarette use (<10 cigarettes/ day and > or = 10 cigarettes/ day) and gender and is balanced using permuted blocks. Participants and study team are blinded to assignment. To maintain the blind, sealed envelopes containing the randomization list (i.e., NAC or placebo) are kept together in a limited access area that is available to the investigators should the blind need to be broken for any safety concerns. Participants in both groups are permitted to continue medical and psychiatric treatment as usual but are asked to avoid use of smoking cessation medications and open label NAC treatment during the study.

Interventions

Pharmacotherapy: Random assignment is followed by 8 weeks of treatment with NAC or placebo. Study medications are identical in appearance and are obtained from a local compounding pharmacy. NAC dosage is gradually uptitrated, starting with a dose of 600 mg orally twice daily (BID) (1200 mg per day) for 3 days, then 1200 mg BID (2400 mg per day) for 4 days, then 1800 mg BID (3600 mg per day) for Weeks 2 through 8. If a participant reports adverse events (AEs) on the weekly AE checklist, the dosage may be adjusted by the PI as needed. Participants receive the highest dose tolerated, not to exceed 3600 mg per day, but may be adjusted as determined by PI. The study pharmacist receives medications directly from the manufacturer and maintain the blind. The PI adjusts medication dose as needed based on weekly medication and AEs lists. Medication adjustments are recorded in the medical record.

Rationale for Dosing: We hypothesize that this relative higher dose of 3600 mg/day may be more efficacious than lower doses in adults with TUD and CUD, as speculated by Gray and colleagues³⁴, who found 2400 mg/day NAC effective for CUD in adolescents, but not adults.

Behavioral Treatment:

CBT-SUD: Both groups receive an 8-session CBT-SUD intervention targeting both cigarette and cannabis use^{57 44}. CBT-SUD includes 8 approximately 30-minute sessions focusing on both smoking cessation and cannabis reduction, including health education, behavioral coaching, setting goals for tobacco cessation, coping with withdrawal symptoms, and relapse prevention skills, with recommended cigarette quit date in session 5. Attention is given to tobacco-cannabis co-use behaviors and triggers, and behavioral coping skills for withstanding cravings when confronted with cues. The 8-session intervention incorporates elements of an 8 session VA smoking cessation intervention and a 12-session manualized CBT for SUD VA intervention, both used widely in VA settings^{44,57}. Sessions focus on cigarette and cannabis use only and exclude modules that address other substance use. Motivational Interviewing techniques have been incorporated to resolve ambivalence about behavior change⁵⁸. Therapists are postgraduate level clinicians under weekly supervision of the study team. All study therapists completed initial training with the supervisory team consisting of teleconference didactics, reading assignments, role-play, and supervised practice.

Measures and Schedule of Data Collection

Assessments occur at Weeks 0 (baseline), 4, 8, and 12 (See Schedule of Measures, Table 1). Outcomes are assessed at Weeks 0, 4, 8, and 12 unless otherwise stated.

Demographic and baseline characteristics—Participant demographics, medical history, medication list, drug allergies, and tobacco use history (pack years, longest time abstinent, smoking in household) are collected at Week 0.

MINI Neuropsychiatric Inventory⁵⁶ is a structured diagnostic interview for Diagnostic and Statistical Manual-5 diagnoses in the past 12 months. MINI is administered for major Axis 1 diagnoses. Modules assessing eating disorders and personality disorders are not administered. MINI is administered at Week 0 to characterize the sample and to assess for psychiatric acuity (for example, current suicidal ideation with intent).

Motivation is assessed using the Contemplation Ladder⁵⁹, a single item measure of motivation administered twice at each timepoint to assess motivation to stop 1) cigarettes and 2) cannabis.

The Minnesota Tobacco Withdrawal Scale⁶⁰ and Cannabis Withdrawal Scale⁶¹ are validated measures of tobacco and cannabis withdrawal, respectively, that are administered at each timepoint to assess for withdrawal states.

TLFB⁴⁸ is a validated instrument that uses a calendar with specific anchor dates to identify the quantity and frequency of use. TLFB is administered at each timepoint to document past 30 days of all nicotine use (e.g., combustible cigarette use, electronic nicotine delivery system use, smokeless tobacco, cigars) and cannabis use (smoked, edible, and aerosolized cannabis), and other substance use. There is substantial heterogeneity across cannabis products⁶². To ensure comprehensive accounting of use of cannabinoid products containing THC, we have adapted the Timeline Followback to categorize cannabis use: inhaled products (including vapes), oral products, sublingual tinctures, and dermal products.

Primary Outcomes:

Tobacco Outcomes: Outcomes include cigarette craving (QSU)⁴⁶, nicotine dependence levels (FTND)⁴⁷, cigarette use (TLFB⁴⁸), and bioverified smoking cessation rates (Weeks 8 and 12 only).

QSU⁴⁶ is a validated 10-item measure that assesses cigarette craving. The FTND⁴⁷ is a validated 6-item instrument to evaluate the intensity of physiological addiction to nicotine.

Cannabis Outcomes: Outcomes include measures of cannabis craving (MCQ)⁴⁹, cannabis use severity (CUDIT-R^{50,51}), and cannabis use (TLFB⁴⁸). The MCQ⁴⁹ is a validated 12-item multidimensional measure that assesses cannabis craving and the CUDIT-R^{50,51} is a validated 8-item instrument to assess severity of CUD.

Laboratory Testing: Urine toxicology testing (immunoassay) to test for THC, opioids, amphetamine, cocaine, and benzodiazepines is conducted at all timepoints, and urine

pregnancy test is performed among people of childbearing potential ages 18–55 at Weeks 0, 4, and 8. Laboratory tests may be conducted at home or in the office.

Among participants reporting abstinence, smoking cessation (tobacco) at Weeks 8 and 12 is bioverified through salivary cotinine testing, with cotinine levels less than 10 nanograms/milliliter consistent with cessation⁶³

Neurocognitive Assessment: Exploratory outcomes include measures of cognitive functioning and self-reported impulsivity as potential mediators of change in primary outcomes. A brief battery, including mental switching (OTMT⁵³); working memory (PASAT⁵⁴); and learning and memory (HVLTR⁵⁵) is being used to assess performance in cognitive domains commonly affected by chronic cannabis and/or cigarette use and contains standardized instruments with good-to-excellent norms. The assessment lasts approximately 30–45 minutes and is administered at all timepoints via phone or video conference. Participants are asked to refrain from cannabis and substance use other than tobacco for 12 hours prior to evaluation. Impulsivity is assessed through a self-report measure (BIS-11⁵²).

Treatment Fidelity: Sessions are audio recorded and approximately 10% of sessions selected and reviewed by supervisors to assess adherence.

Risks and Safety Considerations: Risks include potential AEs of NAC, distress at completing assessments, discomfort due to nicotine or cannabis withdrawal, potential loss of confidentiality. Study medication and AEs are monitored weekly by the study team and PI. NAC is a safe medication that is available as a non-prescription dietary supplement^{64,65}. It is prescribed clinically for several FDA-approved indications, including acetaminophen overdose and cystic fibrosis⁶⁶. NAC has few to no side effects in doses up to 4000 mg/day²². NAC is Pregnancy Category B; pregnant and lactating people are thus excluded. To manage nicotine and cannabis withdrawal⁶⁷, participants receive 8 weekly CBT-SUD sessions for support and coaching. Study staff are trained to triage behavioral or medical emergencies, and participants have a wallet card with the PI's contact information. A Data Safety Monitoring Board meets biannually throughout the study to ensure safety.

Stakeholder engagement: We have convened a community advisory panel, consisting of local and regional clinicians, policymakers, and content experts serving a range of clinical populations that commonly co-use cannabis and tobacco, including low-income individuals; women; and adolescents. The investigatory team meets with the panel biannually to review study procedures, discuss recruitment strategies, and ensure feasibility and acceptability for target populations.

Analytic plan

Preliminary analyses: Prior to hypothesis testing, data will be examined for anomalous and missing values and described in detail. Description of the data is a key aspect of this work as it informs future studies. Data will be evaluated to determine whether assumptions of parametric tests have been violated. If necessary, appropriate transformations will be applied to mitigate non-normal distributions. We will use stratified randomization to ensure that the experimental (NAC) and control (placebo) groups are equivalent in terms of

proportion of females. Other demographic variables and baseline clinical characteristics will be compared between treatment groups (NAC vs. placebo) using ANOVA or Chi-squared test, as appropriate. Baseline variables that differ between treatment groups will be used as covariates in subsequent analyses. Results will be reported using CONSORT guidelines⁶⁸. For hypothesis testing, all model assumptions will first be tested and, if necessary, appropriate transformations/modifications will be performed. All models will include fixed effects for week, treatment group (NAC and placebo), and the interaction between treatment group and week.

Intent-to-treat and as-treated analyses: Primary analyses will utilize an intent-to-treat approach, which includes all randomized participants regardless of treatment adherence or dose. As-treated analyses will also be conducted to examine change in primary outcomes as a function of treatment adherence, thereby reducing variance in abstinence related to treatment dose. The procedure for as-treated analyses is generally identical to that for intent-to-treat; however, we will also include intervention adherence variables (i.e., medication adherence, CBT-SUD attendance) and their interactions with treatment condition as predictors in the models. Gender and baseline levels of anxiety (Beck Anxiety Inventory⁶⁹) and depression (Beck Depression Inventory⁷⁰) symptoms will be initially included in models as covariates and moderators for all main study outcomes. When non-significant, interaction terms (i.e., moderators) will be removed in order to minimize type II error and to provide the most parsimonious model that fits the data⁷¹. Effect sizes for all significant condition differences were calculated in accordance with Feingold's⁷² recommendations for calculating and reporting effect size in a generalized linear mixed model framework.

Cigarette and Cannabis Daily Use (Hypotheses 1b and 2b).—Generalized linear mixed modeling (GLMM) will be employed to analyze daily cigarette and cannabis use over time (TLFB⁴⁸), using a logistic linking function. Considering the scheduled quit day in Week 5 and treatment end at Week 8, we expect a discontinuous (non-linear) growth curve. The piecewise model will include three phases to model change in point prevalence abstinence (*Exploratory Hypothesis 2*): Weeks 0–5 (early intervention, prior to quit day); Weeks 6–8 (late intervention, after quit day); and Weeks 9–12 (post-intervention). If confirmed by initial analysis of linearity, change over time will be modeled as linear within each phase. Study group (NAC vs. placebo) will be included as a predictor of slope across each study phase as well as a predictor of the phase change points.

Cigarette and Cannabis Craving (Hypotheses 1a and 2a), Nicotine Dependence (Hypothesis 1b), and CUD Severity (Hypothesis 2b).—Multilevel linear models (MLM), using maximum likelihood estimation, will be used to examine condition differences in key continuous variables, including cigarette craving (QSU⁷³), cannabis craving (MCQ⁴⁹), nicotine dependence (FTND⁴⁷), and CUD severity (CUDIT-R⁵¹). To examine condition differences in changes over time in these outcomes, we will test a series of two-level models with repeated measures of the dependent variable (DV) nested within conditions. Models will determine rates of improvement (Level 1: Time; a repeated

effect) in self-reported levels of craving, dependence, and severity, as a function of treatment condition (Level 2: NAC vs. placebo).

Neurocognitive Functioning (Exploratory Aim 1).—Treatment-related changes in aspects of self-reported impulsivity (BIS-11⁵²) and neurocognitive functioning, including mental switching, working memory, and learning and memory (OTMT⁵³, PASAT⁵⁴, HVLTR⁵⁵ respectively), will be examined for both main effects of treatment and their potential mediational roles in NAC’s effects on primary outcomes. Initial analyses of main effects will use an MLM approach identical to that above. To enhance causal interpretation, mediation analyses will be conducted via cross-lagged panel analysis⁷⁴ to test the mediating effect of neurocognitive variables on the primary nicotine/cannabis use outcomes: craving and daily use of both cigarettes and cannabis, nicotine dependence, and CUD severity. The cross-lagged panel strategy accounts for temporal order of effects between mediator and outcome by lag-transforming the proposed mediator (e.g., impulsivity at Week 4) by one time point, so that it predicts the outcome (e.g., cigarette use at Week 8) at the next timepoint. To provide an even more rigorous test of mediation, analyses will control for the outcome variable at its previous timepoint (e.g., cigarette use at Week 4). The asymmetric distribution of products test will be used to test the size and significance of the neurocognitive and impulsivity mediators^{74–76}. Mediational effect sizes will be estimated via “proportion mediated” calculation, which represents the proportion of the total effect of NAC on primary outcomes⁷⁷.

Power and sample size—The primary aim of this pilot study (stage 1b) is to gather preliminary support and effect size estimation for a stage II clinical trial⁷⁸. Therefore, the sample size of 60 was determined primarily by practical and clinical reasons rather than driven by estimated effect sizes. We do plan to evaluate the key outcomes, however, so we estimated the minimally detectable effect sizes for those tests. Results indicate that intent-to-treat analysis of a total sample of at least 60 participants, with planned contrasts as described above, should provide adequate power to detect large effect sizes.

DISCUSSION

Tobacco-cannabis co-use is likely to continue to escalate as cannabis is legalized across the country and cigarette use persists among high-risk groups. This trend of increasing tobacco and cannabis co-use is concerning in light of the additive risks of these substances in combination and additional challenges with smoking cessation in the setting of cannabis use⁷⁹. Innovative, scalable treatments to address this growing public health problem. NAC has shown promise in the treatment of other SUD²⁷, and our study is the first to target both cigarette smoking and cannabis use among tobacco-cannabis co-users.

Limitations primarily pertain to sample size and duration of the intervention. Given the pilot nature of this study, design and sample size are partially driven by resource and time constraints to ensure feasibility. That said, our study design has several strengths. First, we have selected a dose of NAC on the higher end of the dosing range used in clinical trials for addictive disorders, and we believe this higher dose will increase bioavailability and optimize the potential to observe treatment effects earlier in treatment. We chose the

3600 mg dose because of NAC's low bioavailability (below 5%), which suggests the need for higher dose treatment strategies than the 1800–2400 mg daily used in most previous NAC trials. Our team successfully implemented 3600 mg/day dose in the pilot study with no significant AEs reported. With respect to the behavioral treatment, we are delivering a CBT intervention for SUD that targets both substances to ensure that both cigarette and cannabis use are addressed during treatment. Second, although young adult co-users may not initially endorse high levels of motivation to quit cannabis at baseline⁸⁰, we feel that a study population that consents to interventions to quit smoking cigarettes and stop using cannabis, but are not required to express high levels of motivation to quit both at baseline, is both feasible and suitable to achieve study aims. Third, CBT for SUD has a strong evidence base for the treatment of addictive disorders⁴⁰, including tobacco and cannabis. We chose to deliver 8 weeks of treatment to provide both NAC and placebo groups have behavioral support should they experience nicotine and/or cannabis withdrawal and because it is possible that cognitive gains with NAC treatment may enhance treatment response to CBT.

In sum, this project will allow us to examine NAC's effect on cigarette and cannabis use and craving, motivation, and explore potential neurocognitive mechanisms that may influence treatment outcomes. Given the widespread co-use of cigarettes and cannabis and the lack of FDA-approved pharmacotherapies to target both substances, this project will investigate a novel intervention to treat tobacco-cannabis co-use.

Dissemination plan

Results will be shared through conference abstracts, presentations and manuscripts. If promising, findings will serve as pilot data for clinical trials.

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Data availability

No data was used for the research described in the article.

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Table 1.

Schedule of Measures

	Week 0	Week 4	Week 8	Week 12
Staff Measures				
Demographic Questionnaire	X			
Tobacco/Cannabis Use History	X			
Timeline Follow-Back (TLFB)-- <i>Weekly</i>	X	X	X	X
Adverse Events— <i>Weekly</i>	X	X	X	
Medication List—Weekly		X	X	X
Medical History				
Medical and psychiatric history	X			
Medication List	X			
Clinical Assessment				
M.I.N.I. Neuropsychiatric Interview	X			
Clinician Administered Cognitive Testing				
Hopkins Verbal Learning Test	X	X	X	X
Oral Trail Making Test	X	X	X	X
Paced Auditory Serial Addition Test	X	X	X	X
Labs				
Urine pregnancy tests (people of childbearing potential, ages 18–55)	X	X	X	
Urine Drug Screen	X	X	X	X
Salivary Cotinine **			X	X
Self-Report Participant Measures				
Tobacco-Related Measures				
Contemplation Ladder—Tobacco Smoking *	X	X	X	X
Questionnaire of Smoking Urges Fagerstrom Test of Nicotine Dependence	X	X	X	X
Fagerstrom Test of Nicotine Dependence	X	X	X	X
Minnesota Tobacco Withdrawal Scale	X	X	X	X
Cannabis-Related Measures				
Contemplation Ladder—Cannabis Smoking *	X	X	X	X
Marijuana Craving Questionnaire	X	X	X	X
Cannabis Use Disorder Identification Test	X	X	X	X
Cannabis Withdrawal Scale	X	X	X	X
Other				
Barratt Impulsivity Scale-11	X	X	X	X
Beck Depression Inventory	X	X	X	X
Beck Anxiety Inventory	X	X	X	X

* Measures will be administered for both cigarettes and cannabis.

** Cotinine to be completed with participants reporting smoking cessation only.

Table 2.

Smoking Cessation Manual

Session 1
Provide Treatment Overview and Emphasize Autonomy
Assess Tobacco Use, Reasons for Quitting Smoking, and Prior Abstinence Attempts
Provide Empathic Support and Encouragement in Quitting Smoking
Orient To Behavioral Counselling Treatment Plan
N-Acetylcysteine
Provide Guidelines for Setting a Cigarette Smoking Quit Date
Provide Guidelines for Setting a Personalized Goal Regarding Cannabis Use
Discuss Goal Assignments and Schedule Session
Session 2
Orient Patient to Session 2
Set Smoking Quit Date
Identify Smoking Triggers
Identify Cannabis Triggers
Introduce Strategies for Reducing Smoking
Introduce Strategies for Reducing Cannabis Use
Rudimentary Skills for Coping With Smoking Triggers & Cannabis Triggers
Discuss Goals and Assignments and Schedule Session 3
Session 3
Orient Patient Session 3
Review Progress
Teach Principles for Coping with Smoking and Cannabis Triggers
Develop an Action Plan for Coping with Triggers
Assess Adherence to Smoking Cessation Medications
Discuss Goals Assignments and Schedule Session 4
Session 4
Orient Patient to Session 4
Review Progress
Implement Behavioral Changes to Prepare for Quit Day
Identify Sources of Social Support
Discuss Goals Assignments and Schedule Session 5
Session 5
Orient Patient to Session 5
Review Progress
Actions to Take on Quit Day
Introduce Principles of Relapse Prevention
Discuss Goal Assignments and Schedule Session 6
Session 6

Orient Patient to Session 6
Assess Smoking Status and Quit Day Experiences
Procedures for Abstinent Patients
Procedures for Patients who have Continued to Smoke Cigarettes and/or use Cannabis
Assess and Resolve Problems Encountered in Quitting (and/or Anticipated Threats to Abstinence)
Discuss Goal Assignments and Schedule Session 7
Session 7
Orient Patient to Session 7
Assess Smoking Status and Quit Day Experiences
Procedures for Abstinent Patients
Procedures for Patients who have Continued to Smoke Cigarettes and/or Use Cannabis
Assess and Resolve Problems Encountered in Quitting (and/or Anticipated Threats to Abstinence)
Discuss Goal Assignments and Schedule Session 8
Session 8
Assess Smoking Status and Quit Day Experiences
Procedures for Abstinent Patients
Procedures for Patients who have Continued to Smoke Cigarettes and/or use Cannabis
Assess and Resolve Problems Encountered in Quitting Smoking (and/or Anticipated Threats to Abstinence)
Continued Support Options
Reference Material
Appendixes
Requirements and Suggestions for Telehealth-Delivery of the Manual
Notes on Adapting Protocol for Patients Attempting to Quit Other Forms of Tobacco and/or cannabis
N-Acetylcysteine (NAC) Side Effects
Tobacco and Cannabis Withdrawal
Patient Workbook