PROTOCOL TITLE:

Gender and Sex Hormone Influences on Cannabis Use Disorder Remission

PRINCIPAL INVESTIGATORS:

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1.0 Objectives / Specific Aims

Cannabis use disorder (CUD) is prevalent and associated with significant clinical sequelae. Effective treatment for CUD may be complicated by gender and sex differences in the behavioral, biological, and clinical correlates of CUD. Women demonstrate more severe withdrawal, greater sensitivity to subjective cannabis effects, more rapid progression from first use to CUD, and greater likelihood of comorbid psychiatric disorder, while men tend to initiate use earlier and have higher lifetime prevalence rates of CUD. Other substance use disorder fields, such as alcohol use disorder, have adopted clinical trial endpoints that are sex or gender-informed. To date, no work has focused on whether different clinically relevant endpoints may be needed for men and women with CUD. Cannabis reduction is increasingly seen as a viable option for CUD treatment. The amount of reduction necessary for individuals to achieve remission from CUD is unknown. Further, given that cannabis use patterns and social consequences of use differ by gender, the critical reduction threshold for CUD remission may also differ by gender.

Sex-related variables, such as ovarian hormones, may also contribute to successful cannabis reduction. A growing literature suggests that ovarian hormones play a key role in drug use. In particular, evidence from preclinical and clinical research suggests that endogenous progesterone attenuates drug sensitivity and behavior. Recent clinical studies investigating exogenous progesterone as a potential pharmacotherapy have shown that it attenuates the subjective and physiological effects of cocaine and tobacco in drug-dependent individuals. Presently, however, little is known regarding the interface of progesterone and CUD, and if fluctuations in progesterone levels may impact ability to reduce cannabis use.

The goal of this application is to identify clinically meaningful cannabis reduction levels for both men and women with CUD and to determine whether fluctuations in progesterone are associated with successful cannabis reduction. Adults (age 18+; 50% women) with CUD will be enrolled in a web-based treatment program (CBT4CBT).[1-3] Participants will engage in 8 weeks of treatment and will complete end-of-treatment, 1-, 2-, and 3-month follow-up sessions. CUD symptoms will be assessed at baseline, mid-treatment, end-of-treatment, and follow-up visits. By providing effective and standardized treatment to all participants, we anticipate a broad range of use patterns resulting in variability in CUD remission rates. Detailed self-report of cannabis use (e.g., days of use, episodes of use) will also be obtained using electronic daily diaries. Number of cannabis use days, number of episodes of cannabis use, and milligrams of Δ9-tetrahydrocannabinol (THC) in the past month prior to end-of treatment will be used to predict CUD remission. The threshold for successful remission will be computed as the number of past-month cannabis use days, episodes of use per day, and average milligrams of THC per week below which most people successfully achieve CUD remission and above which most people do not achieve remission from CUD. Remission from CUD is defined as not meeting any criteria for CUD (except for craving) in the past month. This threshold will be computed separately for men and women.

In addition, daily saliva sample collection will take place at home and will be video-recorded via a mobile app. At each in office visit during the treatment phase participants will return all

collected samples, which will be taken to the lab for analysis of progesterone. Associations between daily progesterone levels and cannabis use will be examined to determine whether natural increases in progesterone (compared to one's own mean progesterone levels) promote successful cannabis reduction.

Aim 1: Determine the threshold of cannabis use frequency and quantity associated with CUD remission at end-of-treatment and at follow-ups (a) for both men and women and (b) determine whether this threshold *differs* between men and women. *It is hypothesized that the change in frequency of cannabis use days, episodes per day, and estimated milligrams of THC necessary for successful remission will significantly differ between men and women, with women requiring more reduction for successful remission.*

Aim 2: Examine associations between endogenous progesterone and cannabis use during treatment for females. *It is hypothesized that increases in endogenous progesterone will be associated with decreased cannabis use at the daily level.*

This project will elucidate gender and sex hormone effects on successful CUD reduction. Additionally, this project will facilitate future gender-informed cannabis reduction benchmarks and will facilitate CUD treatment development and evaluation by providing definitions of successful cannabis reduction for both men and women. This study represents a crucial next step in the mechanistic examination of progesterone in CUD treatment outcomes. If individuals are more successful at reducing their cannabis use when progesterone is increased, this lends further credence to the potential therapeutic role of compounds that modify ovarian hormone levels.

2.0 Background

Significance

Sex and gender are critical considerations in treatment development for Cannabis Use Disorder. It is estimated that 8-10% of individuals who have experimented with cannabis at least once in their lifetime, and over 20% of individuals who begin cannabis use during adolescence, develop cannabis use disorder (CUD).[4-6] Among people aged 18 or older, the percentage of past year cannabis users increased from 10% (or 22 million people) in 2002 to 18% (or 45 million people) in 2019,[7] likely due to changes in legalization and societal attitudes related to cannabis.[8,9]

Importantly, prevalence of cannabis use continues to increase significantly among both pregnant and non-pregnant women.[10] Across substances of abuse, including cannabis, men are at greater risk for lifetime use disorder diagnosis.[11] However, cannabis using women show greater abuse liability[12], more rapid progression from use to disorder[13,14], and more severe withdrawal symptoms.[15-17] Gender-related factors may be responsible for lower rates of cannabis initiation, unique precipitants of use and relapse, unique social consequences, and greater barriers to treatment among women.[18] Sex-related factors, such as ovarian hormones and metabolic differences, may further contribute to observed differences in abuse liability and withdrawal. Further, there is emerging evidence that women may not respond as well to CUD treatment as men[19-21], suggesting that consideration of gender and sex should be key in design and interpretation of future CUD clinical trials.

Reduction is a viable endpoint for CUD trials. With increasing legalization and societal acceptance of cannabis, reduced cannabis use may become a more common goal than abstinence for treatment-seeking individuals with CUD. In fact, several recent studies show that interest in quitting cannabis is low and individuals who use cannabis are more interested in and likely to engage in reduction attempts versus quit attempts.[22-24] Further, abstinence may be unrealistic for many[25] and individuals are more likely to achieve outcomes that are in line with their personal goals.[26]

The Food and Drug Administration (FDA) has supported the use of non-abstinence outcomes in alcohol[27] and opioid use disorder[28] clinical trials. The FDA's movement toward non-abstinence outcomes for other substance use disorders, coupled with preliminary data showing that decreased frequency of cannabis use is associated with improved clinical functioning,[29,30] suggests that non-abstinence outcomes for CUD may be feasible. Recently, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) workgroup, consisting of representatives from the FDA, National Institutes of Health, academic institutions, and other stakeholders, concluded that cannabis reduction is a viable alternative to abstinence as a primary outcome in CUD trials, but that clarity in defining successful reduction is necessary.[31]

Amount of cannabis reduction necessary to observe clinical benefit is unclear. Reduced frequency of cannabis use (i.e., number of days or weeks when cannabis was used) has been the primary means of assessing cannabis reduction in clinical trials to date.[32] Individuals who successfully reduce the number of days on which they use cannabis have shown improvement in mental health functioning.[33] However, associations between reduced cannabis quantity and psychosocial functioning have been mixed.[30,33,34] Reduction in days of cannabis use is perhaps the most promising self-report metric to date; however, information about total cannabis exposure is lost when cannabis quantity is ignored.[35] Existing data from our group has shown that when quantity is precisely measured, it is associated with improved prediction of cannabis-related problems above and beyond days of use alone.[34]

Though several studies have examined associations between quantity/frequency of cannabis use and functioning, few studies to date have attempted to empirically quantify high versus low-risk cannabis use.[36] Here we describe two notable exceptions. One research group found that individuals who report an average of 1.2 standard joint units (defined as 0.25 grams of cannabis or 7 milligrams of THC) per cannabis use day are at greater risk for CUD.[37,38] A second research group found that individuals who use more than 0.5 grams of cannabis per day were more likely to experience cannabis-related problems.[39] To our knowledge, no studies to date have examined whether individuals who present to treatment for CUD who are able to reduce their use to below these high-risk thresholds are able to achieve CUD remission. It is critical to establish that CUD remission can be achieved when an individual transitions from high-risk (above clinical threshold) to low-risk use (below clinical threshold) because it is possible that the quantity and frequency of use that results in CUD differs from the quantity and frequency of use which can be safely used by someone in remission without risking relapse. Further, the threshold for "safe" cannabis use may vary by gender, but prior attempts have not defined gender-specific high and low risk.

Recommended thresholds for reduction may differ between men and women. The National Institute on Alcohol Abuse and Alcoholism has provided separate definitions of high-risk alcohol consumption for men and women. For men, a "heavy drinking day" is defined as 5 or more standard drinks. For women, 4 or more drinks on a single day is considered a heavy drinking day, suggesting that the threshold for problematic alcohol use is lower for women than for men. The FDA has supported the use of NIAAA-defined heavy drinking days as a valid endpoint in alcohol use disorder clinical trials, meaning that clinical trial endpoints are sex/gender specific.[27]

Consistent with the alcohol field, evidence-based recommendations for cannabis reduction may vary for men and women. Both national and clinical trial data suggest that women may develop cannabis-related problems at lower quantity or frequency of cannabis use. Men and women with CUD in the United States endorsed a comparable number of DSM-IV-TR dependence criteria, but women used fewer average joints per day than men.[13] Likewise, a clinical trial from our group found that men and women who were seeking treatment for CUD reported comparable quantity and frequency of cannabis use, but women reported more craving and withdrawal symptoms.[16] These studies suggest that women experience more negative consequences of cannabis use at the same quantity and frequency of use. In addition to observed gender differences, preclinical and laboratory data suggests that biological sex differences exist with females showing different responses to Δ9-tetrahydrocannabinol (THC). Females experience greater subjective effects of THC than males at the same dose[12] and require lower doses to feel effects.[40] There are also sex differences in THC metabolism[41-45], and females may more effectively convert THC to the potentially even more psychoactive metabolite, 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC).[44-46] Thus, while cannabis reduction may be a viable outcome for both men and women with CUD, the quantity/frequency threshold for women to achieve remission from CUD may be lower than that of men.

Ability to reduce cannabis use may be hormonally-mediated. Gender differences in cannabis outcomes may be exacerbated or mitigated by differences in sex hormones. A growing literature suggests that the ovarian hormones, which fluctuate naturally during the menstrual cycle, may play a key role in sex differences in substance use disorders[47] and that progesterone in particular may modulate drug responding. Vallee and colleagues[48] examined the effects of pregnenolone, a precursor to progesterone, on THC administration in rats and reported that it suppressed THC-induced effects including hypothermia, locomotor suppression, and analgesia, as well as dampened neurobiological effects in reward-related brain regions (VTA, NAc). Numerous preclinical studies have also shown progesterone administration attenuates the reinforcing effects of cocaine[49,50] and reduces drug-reinstatement and self-administration of cocaine[51,52] and nicotine.[53]

Clinical studies in substance users support these findings. Compared to placebo, exogenous progesterone has been shown to attenuate subjective and physiological effects of cocaine in female cocaine users[54-56], as well as decrease cue-induced craving and cortisol response in early abstinent cocaine-dependent women.[57] In a 12-week trial, progesterone reduced weekly cocaine use in post-partum cocaine-dependent women compared to placebo.[58] Exogenous progesterone, compared to placebo, has also been shown to attenuate craving and subjective effects of smoking[59,60], and improve cognitive performance in women but not men.[60] A recent placebo

controlled trial of progesterone treatment also found sex specific improvements in smoking outcomes, with women receiving progesterone having greater point prevalence abstinence than those receiving placebo but no effect observed in men.[61] In a pilot feasibility study conducted by our group of exogenous progesterone administered to cannabis abstaining women, a trend in reduced cannabis craving was observed.[62]

In regards to endogenous progesterone, women in the luteal phase of the menstrual cycle, when progesterone is high, show decreased subjective cocaine[63,64] and amphetamine[65] effects compared to women in the follicular phase, while female smokers randomly assigned to quit during the luteal phase had lower relapse rates than those assigned to quit during the follicular phase.[66] Previous research from our group found that increasing levels of endogenous progesterone were associated with a 37% increase in the odds of smoking abstinence in women undergoing a relatively brief 4-week course of nicotine replacement therapy.[67] Further, we have recently shown that increased levels of daily progesterone were associated with decreased cigarettes smoked per day in non-abstaining women.[68] As such, endogenous progesterone levels may be an important contributing factor to successful cannabis reduction.

Genetic variability in how people break down cannabinoids may modify our study findings. For example, people who have cytochrome P450 genetic variants known to alter THC metabolism may show increased or decreased response to THC and therefore may have differential treatment outcomes. Additionally, THC is broken down by many of the same cytochrome P450 enzymes that contribute to the bioconversion of progesterone and our previous work preliminarily suggested that young adult females with CUD may have higher rates of genetic variants associated with reduced CYP 2C9 and/or CYP 3A4 activity.

Summary. In sum, cannabis reduction is a viable alternative to abstinence, but definitions of low-risk cannabis use associated with CUD remission may differ by gender. The ovarian hormone progesterone may reduce susceptibility to cannabis-related adverse effects and play an important role in ability to reduce cannabis use. The goal of this proposal is to determine whether 1) the threshold of cannabis use necessary for successful CUD remission differs by gender and 2) whether higher endogenous progesterone levels promote successful cannabis reduction. Consistent with RFA-OD-19-029, *The Intersection of Sex and Gender Influences on Health and Disease*, this proposal examines the role of gender in CUD outcomes, while accounting for a sex-related factor, progesterone levels, and genotype. Because individuals who identify as female have lower rates of CUD, but present with more complex symptoms and comorbidity when CUD is present, gender represents a risk factor for poor CUD treatment outcomes. However, this risk is likely exacerbated when female gender is accompanied by decreases in the sex hormone, progesterone. The proposed study will examine whether thresholds for successful cannabis reduction differ by gender and will determine if increasing progesterone decreases cannabis use in the context of CUD treatment. This is consistent with the Trans-NIH Strategic Plan for Women's Health Research priority to investigate the influence of sex and gender on disease presentation, management, and outcomes.

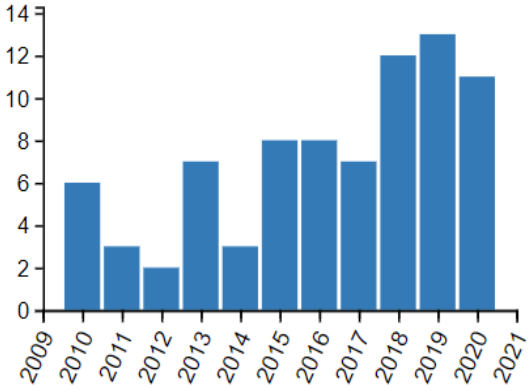
Innovation

The proposed study will test truly novel hypotheses. This proposal will be the first to our knowledge to empirically determine the threshold of cannabis reduction necessary for both men and women to achieve remission from CUD. Additionally, we plan to examine the potentially important effect that progesterone may have on cannabis use in women using remote sampling methodologies. We will use innovative mobile technology to precisely measure cannabis use, as well as to confirm daily progesterone sample measurement. This study is a critical and necessary next step in gender and sex-specific treatment development for CUD.

Detailed plans for approach

Research Team. The interdisciplinary research team is led by Dr. Tomko, whose research focuses on substance use disorder clinical trial methods refinement and remote monitoring, and Dr. McRae-Clark, an expert in CUD treatment development and sex/gender research. Drs. Tomko and McRae-Clark are accompanied by a statistician with expertise in clinical trials (Baker), a licensed psychiatrist (Gray), and a licensed clinical psychologist (Sherman), providing the full team with complementary expertise in sex/gender differences in CUD, mobile technology, statistical analysis, cannabinoid assays, psychosocial treatments for CUD, as well as extensive experience conducting randomized controlled trials evaluating behavioral and pharmacological interventions for CUD and other substance use disorders. The MPIs and Co-Is have existing working relationships and have co-published 80 peer-reviewed manuscripts from 2010-2020 (see Figure 1).

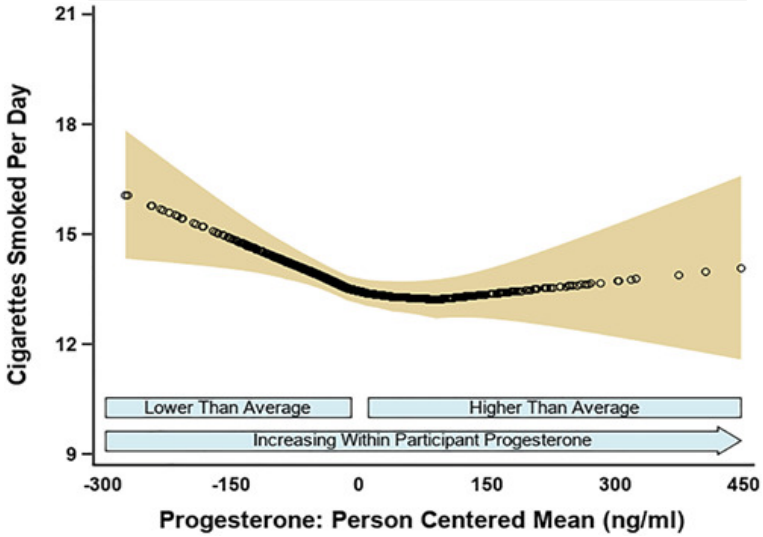
Figure 1. Research Team Co-Authored Publications From 2010-2020 (N=80) from NIH's iCite Database



Preliminary Studies. *Experience conducting clinical trials for CUD*. We have successfully conducted multiple NIH-funded studies involving individuals with CUD (K23DA15540, PI: McRae-Clark; R21DA018221, PI: McRae-Clark; R21DA022424; PI: McRae-Clark; R01DA026782, PI: McRae-Clark; R21DA034089, PI: McRae-Clark; UH3DA04323, MPIs McRae-Clark/Gray; U54DA016511, MPIs McRae-Clark/Brady; K12HD055885 to Tomko). Although substance using individuals are sometimes difficult to engage, our CUD clinical trials (six completed trials to date, with collective *N*=480) have consistently enrolled and retained participants well ahead of goal rates (recently ≥6 participants per month). As such, we do not anticipate any issues with successful recruitment of the proposed study sample.

Sex/gender differences in CUD. Our research group has conducted multiple studies examining sex and gender differences in CUD. Dr. McRae-Clark is PI of MUSC's Specialized Center of Research Excellence on Sex Differences (U54DA016511), which is focused on stress-mediated relapse in cannabis and opioid use disorders. Drs. Tomko, Gray, Sherman, and Baker are all Co-Is in this center. As discussed previously, we have demonstrated important sex and gender differences in clinical characteristics of cannabis users[16], treatment response[19,20], and predictors of cannabis outcomes.[21,69,70] For example, women presenting to CUD treatment reported greater withdrawal intensity than men[16] and the association between depressive symptoms and cannabis use was stronger among women than men.[70]

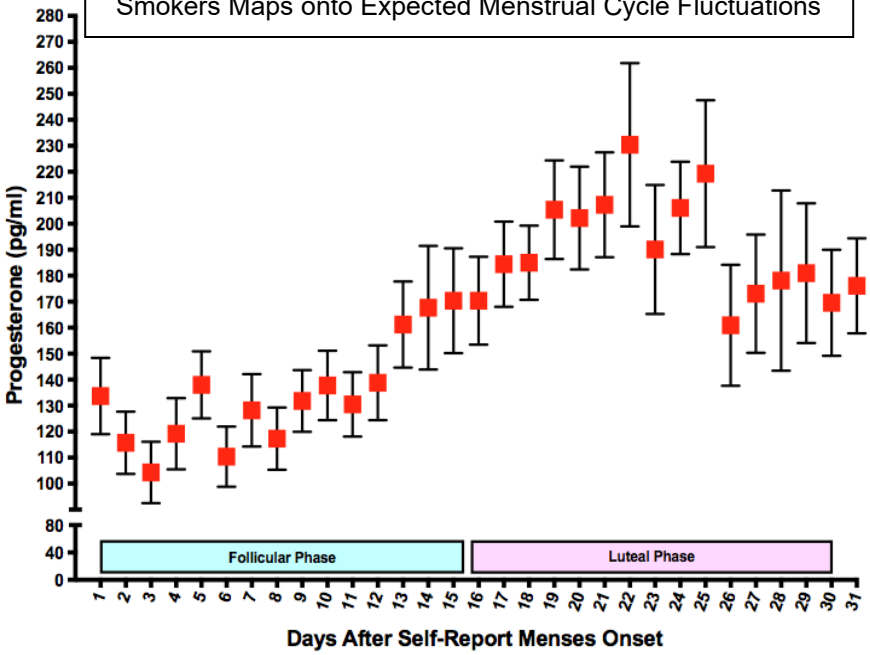
Figure 2. Associations Between Progesterone and Cigarettes Per Day Among Female Cigarette Smokers



Effects of progesterone on substance use disorder treatment outcomes. We completed a small pilot trial (n=8) comparing progesterone to placebo administration in cannabis using women during cannabis withdrawal.[62] Conduct of this trial allowed us to validate the feasibility of conducting remote daily progesterone measurements in a cannabis using population. Preliminary data also provided suggestive evidence of a potential treatment by time interaction (p=0.071) in regard to cannabis craving, with women received progesterone reduced cannabis craving compared to women receiving placebo over the five-day period.

Additionally, our group showed that that male and female cigarette smokers could provide daily at-home saliva samples for analysis of hormones. In this study, we found that non-treatment seeking female smokers (N=104) smoking as usual naturally showed elevated average cigarettes per day when endogenous progesterone levels were lower than their own average[68] (see Figure 2). Importantly, these at-home saliva samples showed progesterone levels that mapped onto the average menstrual cycle in free-cycling women, providing evidence of validity (Figure 3). Our research team is currently conducting an outpatient trial among individuals with a CUD (ages 18-50) as part of MUSC's SCORE in which participants are asked to serially collect daily salivary samples for progesterone analysis, which they refrigerate and return to the lab, as well as conduct

Figure 3. At-Home Salivary Progesterone in Female Cigarette Smokers Maps onto Expected Menstrual Cycle Fluctuations



twice daily video-record qualitative oral fluid THC testing. To date, 85 participants have been randomized, and 78 participants have completed the three-week study. Overall, we have collected 92% of expected progesterone samples. These results demonstrate that, among cannabis users, remote data collection is both feasible and acceptable. However, administration of exogenous progesterone as well as the non-treatment seeking status of the SCORE study population precludes examination of the aims of the current proposal.

Cannabis assessment. In several adult CUD trials conducted by our research team, we demonstrated that new abstinence is difficult to detect using weekly semi-quantitative urinary THCCOOH samples, with maximum correct classification of 76.6% (95% CI: 71.6–81.3) when using a cut-off of 200 ng/mL or a 25% reduction in semi-quantitative THCCOOH.[71] However, we also showed that trials that financially-reinforced abstinence showed less agreement between urinary THCCOOH and self-report, suggesting that erroneous self-report may be more frequent when there are incentives for abstinence.[71] Therefore, participants in the current study will not be contingently reinforced for abstinence (i.e., contingency management will not be part of treatment) to avoid reducing accuracy in self-report.

In addition to challenges in assessing abstinence in clinical trials, the assessment of cannabis reduction is complex.[33] We have also previously demonstrated that obtaining detailed information about estimated cannabis quantity in addition to days of use, as measured via a proxy substance, significantly strengthens associations between cannabis use consumed and problems associated with cannabis use.[34] These data suggest that careful consideration of cannabis quantity, in conjunction with frequency of use, may serve as a better predictor of cannabis-related problems than cannabis use days alone.

In this same CUD trial conducted by our group, participants used a scale to estimate the physical weight of a proxy substance to aid in estimation of herbal cannabis.[34] A limitation of this method is that estimation of herbal cannabis is not a direct measure of the amount of the primary psychoactive component, THC. Very few participants used non-herbal forms of cannabis in this prior trial, making the scale estimation procedure a viable option for measurement. However, since completion of the trial in 2015, a larger proportion of individuals are using non-herbal cannabis (e.g., wax, dabs, concentrates) which cannot be estimated using our proxy substance via a scale. For example, participants in our ongoing SCORE study (U54DA016511; PI: McRae-

Clark/Brady) record their cannabis use several times daily (sampled at random) on a mobile app. Seventy-three (73)% of recorded cannabis use sessions sampled to date involved use of herbal, combustible cannabis (Mean=0.74 grams; SD=0.82), 30% of sessions involved use of wax, oil, dabs, edibles, or concentrates (Mean=49 mg THC; SD=44.9), and a small percentage of sessions involved the use of both combustible herbal cannabis and non-herbal products. We can convert grams of herbal cannabis to estimated milligrams of THC using estimates of THC content derived from confiscated cannabis samples in the United States (9.4% THC).[72] We estimate that the average milligrams of THC in herbal cannabis used at each session to date is 69 mg (SD=77.5). Conversion of grams to milligrams is consistent with NIDA and cannabis researchers call for a "standard cannabis unit" in terms of milligrams of THC.[73,74]

Daily diary assessment of substance use and video uploads. We have developed procedures for using REDCap, a secure web application and database management system, to send a text-based daily diary for substance use assessment.[75] We have also established procedures for conducting secure video uploads via REDCap[75], which will allow remotely collected saliva samples to be video-confirmed to ensure the identity of the participant, the quality of the sample, and the timing of the sample collection. In sum, the research team is familiar with issues related to mobile phone privacy/security, phone operating systems, teaching participants how to use technology for study purposes, and loaning out mobile devices to participants.

3.0 Intervention to be Studied

The goal of this study is not to test the efficacy of an intervention for CUD and a standardized intervention will be provided to all participants. The first session will consist of a brief goal setting session with a clinician in which motivational enhancement strategies will be used and participants will be introduced to the online treatment platform. The online treatment platform is based on cognitive behavioral therapy (CBT). The web-based treatment platform (CBT4CBT) teaches cognitive behavioral skills, such as decision-making, assertiveness, and coping skills, that can help individuals with CUD to gain control over their use of cannabis. CBT4CBT includes 7 modules with interactive, online exercises illustrating CBT concepts.

4.0 Study Endpoints

Type	Endpoint	Time Frame	Brief Description
Primary	Cannabis Use Disorder Remission	Week 4, Week 8, Week 12, Week 16, Week 20	Clinician Administered semi-structured diagnostic interview of DSM-5 cannabis use disorder symptoms to assess past month symptoms (MINI)
Primary	Cannabis Use (Any)	Daily during Weeks 1-8	Any cannabis use (binary yes/no variable) will be assessed via daily diaries and missing data will be filled in via Timeline Followback

Primary	Cannabis Use (Number of Episodes)	Daily during Weeks 1-8	Number of cannabis use episodes per day will be assessed via daily diaries and missing data will be filled in via Timeline Followback
Secondary	Milligrams of THC	Daily during Weeks 1-8	Via daily diary and Timeline Followback, participants will report quantity of cannabis in grams (of leaf/bud material) or milligrams of THC, depending on their method of use; grams of leaf bud material will be converted to milligrams of THC to create a common metric for all methods

5.0 Inclusion and Exclusion Criteria / Study Population

Adult (ages 18+; 50% women) cannabis users (N=225) will be recruited for the current study.

Participants having completed a separate research study (PRO #94743) who have consented to future contact and meet study criteria will be offered participation.

Inclusion Criteria.

a) Ages 18 and older.
b) Willingness to participate in a research study (otherwise, will be referred to appropriate clinical services if seeking clinical care).
c) Meet current (within last 30 days) DSM-5 criteria for cannabis use disorder.
d) Submit a positive urine cannabinoid test during screening.
e) Interested in treatment for cannabis use disorder.
f) Completion of an Intake Visit (PRO #94743) within approximately 30 days of Week 1 Visit.

Exclusion Criteria.

a) Significant or acutely unstable medical or psychiatric problems (i.e., psychosis, mania) that would contraindicate research procedures, interfere with safety, compromise data integrity, or preclude consistent study participation.
b) The presence of any SUD requiring a higher level of care.
c) Significant risk of homicide or suicide.
d) Pregnant, trying to become pregnant, or breastfeeding.

6.0 Number of Subjects

We propose to enroll 225 participants.

7.0 Setting

The research will be conducted in the offices of the Addiction Sciences Division. These clinical spaces include several private interview rooms to conduct participant visits, including informed consent procedures with the participant. The consent procedure may be conducted remotely via REDCap or doxy.me. In addition, certain procedures may be conducted in-office via doxy.me or Zoom Pro with the participant located in the private interview room and a member of research staff in a separate, private office. All participants must complete their Week 1 Visit in office. If a participant is unable to come into the office for a subsequent visit, an exception might be made for partial remote visits via doxy.me or Zoom Pro. During these visits, participants will complete direct entry REDCap longitudinal assessments remotely and will also meet with a clinician via doxy.me or Zoom Pro to conduct all clinical assessments. For these partial remote visits, biospecimen collections (e.g. urine, pregnancy test) and vitals will not be collected. Thus, this option will only be used in the event that the participant cannot attend an in-person visit to allow for partial data collection. If a remote visit is conducted during the treatment phase, participants will be asked to return all collected saliva samples when they come into the office for their next in person visit. If a participant runs out of saliva sample collection supplies and not able to come into the office to pick up any, staff will ship supplies to participants via USPS, UPS, or FedEx

8.0 Recruitment Methods

Our team is highly experienced in recruiting and retaining individuals with CUD in clinical research. Adults with CUD will be recruited from a pool of participants who have completed an Intake study (PRO #94743). Participants who have completed this protocol, have consented to future contact, and who appear to meet eligibility criteria will be offered participation in this protocol. Individuals who participate in the Intake consent for their data to be carried forward into the study in which they ultimately enroll. The Intake includes, but is not limited to, a comprehensive substance use history assessment and a structured diagnostic interview for psychiatric conditions, including assessment of CUD and other substance use disorders. After completion of the Intake, participants who are eligible for the current study will be offered participation. They will consent to sharing data collected across both protocols for analysis.
To achieve the proposed sample size, an average of 5-7 participants per month will be recruited over 38 months, commensurate with recruitment rates in our recent studies.

9.0 Consent Process

Prior to the initiation of any study procedures, the MUSC Institutional Review Board (IRB) written and approved Informed Consent (IC) and HIPAA authorization will be obtained by IRB-approved, trained, designated research staff in a private interview room. Participants will be given the opportunity to read the consent prior to review with research staff. The informed consent process will include a thorough discussion of potential risks associated with participation. The complex issues of informed consent, and related limitations of confidentiality, are understood by the PI and will be communicated clearly during the telephone screening and assessment visit. Consent can be obtained in person at the research office or remotely

using REDCap . Specifically, potential participants will have the option to complete consent 1) via MUSC's doxy.me system (tele consent) or 2) via REDCap electronic consent (e-consent) combined with a phone or video. These procedures for consenting remote study participants have been established in prior studies at MUSC (e.g., Pro# 19201). All doxy.me signed consent forms will be saved as PDF files within our study records. Signatures on the consent form may be obtained electronically via REDCap/doxy.me.

Potential participants 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 will have the consent documents reviewed with delegated study personnel and have all questions and concerns addressed to their satisfaction. Participants will be asked to explain important aspects of the study to the researcher to demonstrate their understanding of the study. 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 resources appropriate for their needs. 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 assessment visit. 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.

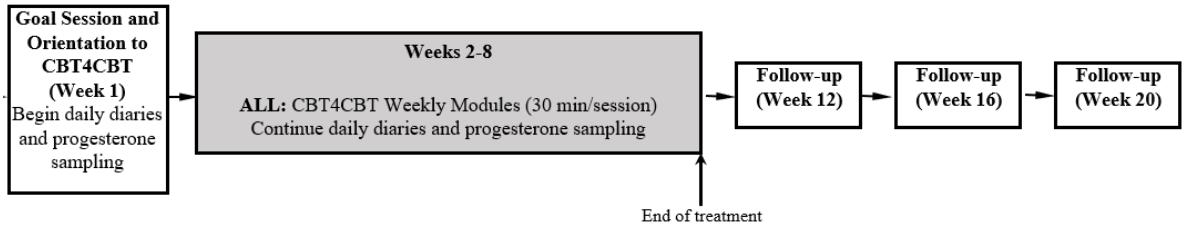
Informed consent is viewed as an ongoing process, so participants will be given the opportunity to ask questions about their participation throughout the course of the visit. The consent document will contain a thorough review of potential risks associated with participation, including breach of confidentiality and privacy concerns.

10.0 Study Design / Methods

Overview

For the proposed study, voluntary treatment-seeking adults with CUD (N=225) will be enrolled in an 8-week treatment program, with the goal of achieving 224 eligible and analyzable participants. All participants will receive the same, standardized psychosocial treatment (motivational goals session plus computerized CBT4CBT). Duration of time spent on each CUD module as well as date of completion of the module will be recorded. Detailed cannabis assessments (biological and self-report) will be conducted throughout treatment and at 1-, 2-, and 3-months post-treatment completion. Daily electronic diaries will be administered via text message to record detailed logs of cannabis use quantity and frequency as detailed below. Salivary samples will be collected (and video observed) daily throughout treatment to analyze for progesterone. See Figure 4 for an overview of the experimental design.

Figure 4. Timeline of Study Procedures.



Procedures

Week 1 visit.

After consent is obtained, the Week 1 visit will be completed in office. This visit will include an orientation to study assessments that they complete independently outside of the office. See Table 1 for a full list of assessments conducted at this visit. Participants will be taught how to collect saliva on their own and how to record and upload a video of the process. Participants will receive a Twilio text message with a timed link to REDCap for them to upload their video. They will complete a practice video in session at their Week 1 Visit. Participants who choose to use their own mobile device for research procedures will be instructed, and if needed will be shown how, to delete the videos from their phones if necessary. They will be given supplies for 14 days of saliva sample collection at each visit to ensure ample collection tubes are available in the event that they miss or need to reschedule their next in-person visit. Participants will also be provided with a small tube rack and refrigeration pack for self-storage of samples between visits. Should participants lack a reliable mobile device for completion of daily diaries and video uploads, one will be loaned to them consistent with our prior protocols (PRO 54499, PRO 82347). Participants will be loaned a study phone and can earn a bonus at the end of their study participation for returning the phone.

Instruments/measures (see **Table 1, Study Timetable** for an overall summary). Proposed instruments were selected with numerous considerations. We focused on inclusion of measures that are standardized for this population, have good psychometric properties, are part of the PhenX Toolkit to yield comparable data to national datasets, or have been used with success by our research team. See **Table 1** for a list of assessments.

The following data will be obtained from the participant's enrollment in the Intake only and shared with research staff. Additional data collected as part of the Intake protocol may be shared with research staff as appropriate:

1. The *Demographic Form* was designed by our research team to assess basic demographics, including age, gender, sex at birth, race, and social history.

2. The *Health and Substance Use History Questionnaires* were designed to assess basic health functioning and lifetime substance use exposure.

3. The *MacArthur Social Status Ladder* is a brief, 2-item measure with good psychometric properties (Operario, Adler, & Williams, 2004). It is designed to assess how individuals perceive their relative status in their community and nationally.

4. *Thoughts About Abstinence Scale (e.g., Substance Use Goals; Hall et al., 1991)* assesses whether participants are interested in total abstinence, reduced use, or no change in substance use behavior for each of the following substances: alcohol, cannabis, e-cigarettes/nicotine vaping, regular cigarettes. There are 4 items in total (one for each substance).

5. *Reasons for Quitting Marijuana Scale (Steinberg et al., 2005)* is a 27-item scale designed to assess common reasons for wanting to quit using cannabis. The scale will be modified to reflect quitting or reducing cannabis use and will only be administered to participants who report an abstinence or reduced use goal for cannabis on the "Thoughts About Abstinence Scale". Note that only items 1-27 will be administered.

6. The *Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998; Sheehan et al., 2010)* is a semi-structured interview designed to assess current, past, or lifetime history of major DSM 5 psychiatric and substance use disorder diagnoses.

7. The *Timeline Follow Back* (TLFB; Sobell & Sobell, 1992) is a calendar-based assessment designed to enhance retrospective recall of substance use for the past 30 days. Quantity and frequency of tobacco/nicotine products (cigarettes, ENDS, other tobacco/nicotine products), cannabis, alcohol, and other drug use will be assessed. Grams of cannabis will be estimated. *Cannabis Methods.* This assessment is conducted concurrently with the TLFB and includes a series of questions to determine which routes of administration participants are employing to use cannabis.

Longitudinal Assessments

(The following measures will be administered at intake and shared with research staff and/or administered longitudinally throughout the study):

1. The *Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001)* is a 9-item scale used to assess DSM-IV symptoms of depression.

2. The *Generalized Anxiety Disorder scale (GAD-7; Spitzer et al., 2006)* is a 7-item measure used to assess symptoms of generalized anxiety.

3. The *Marijuana Assessment Problem Inventory (MAPI; Johnson & White, 1989)* is a 23-item scale assessing consequences of cannabis use.

4. *The Cannabis Withdrawal Scale (CWS)*[51] is a 19-item measure used to assess symptoms of cannabis withdrawal.

5. *Marijuana Craving Questionnaire (MCQ; Heishman et al., 2001)* is a 47-item measure designed to assess cannabis craving related to compulsivity, emotionality, expectancy, and purposefulness.

6. The *Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998; Sheehan et al., 2010)* is a semi-structured interview designed to assess current, past, or lifetime history of major DSM 5 psychiatric and substance use disorder diagnoses. The CUD module will be administered longitudinally.

7. The *Pittsburgh Sleep Quality Index (PSQI; Buysee et al., 1989)* is a brief instrument designed to assess typical duration and quality of sleep.

8. The *Timeline Follow Back* (TLFB; Sobell & Sobell, 1992)/*daily electronic diaries* will be used to assess daily substance use as described in the procedures.

9. The *Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES; Miller & Tonigan, 1996)* is a 19-item questionnaire designed to assess readiness to change drug use. Instructions will be modified for cannabis and alcohol use.

10. *The Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF)* is a 16 item self-administered questionnaire that captures life satisfaction over the past week. Each question is rated on a 5 point scale from 1 (Very Poor) to 5 (Very Good).

11. The *Marijuana Motives Measure (MMM; Simons et al., 1998)* is a 25 item self-report questionnaire designed to assess common motivations for using cannabis: coping, conformity, enhancement, social, and expansion. Participants rate how often they are motivated to use cannabis for a variety of reasons on a 5 point scale from 1 (almost never/never) to 5 (almost always/always). Only 10 items corresponding to the coping and enhancement subscales are administered for our study purposes. This assessment was added after study initiation and was not administered to all participants.

12. *Self rating of treatment progress*. Participants are asked to rate their current satisfaction with their cannabis use relative to their initial goals. This assessment was added after study initiation and was not administered to all participants.

Clinical assessments.

Primary outcome. The **MINI International Neuropsychiatric Interview (MINI)** CUD module will be used to assess past month CUD symptoms throughout treatment.[76] Throughout the study, a variety of self-report and clinician-administered measures (summarized in **Table 1, Study Timetable**) will be collected, including the MINI CUD module. The primary outcome of interest is DSM 5 CUD remission, as measured by the MINI clinician interview. The MINI will be administered by a trained interviewer. Participants will be asked whether they are comfortable with the clinician-administered CUD module being audio recorded via a Digital USB recorder. Participants must sign a separate line on the consent form indicating their approval for audio-only recording and agreement to recording will ***not*** be required for participation. Ten (10%) of recorded sessions will be randomly selected and played by another clinician/therapist to determine interrater reliability. In general, the other clinical measures will be used to assess and track mental health and substance use-related problems over the course of study participation.

Adverse events will be documented, rated for severity and relatedness, and managed/reported appropriately via established procedures.

Table 1. Study Timetable

Visit→	Intake♦	Weeks 1-3	Week 4	Weeks 5-7	Week 8	Week 12	Week 16	Week 20
Informed Consent	X							
Locator Form and Updates	X							
Demographics	X							
MacArthur Scale of Subjective Social Status Ladder[77]	X							
Medical Assessments								
Brief Medical History	X							
Adverse Events		X	X	X	X	X	X	X
Prior/Concomitant Meds	X	X	X	X	X	X	X	X
Body Mass Index/Vital Signs	X		X		X	X	X	X
Psychological and Substance Use Assessments								
MINI International Neuropsychiatric Interview[76], including past year and past month CUD	X	X*°	X*°		X*°	X*°	X*°	X*°
Quality of Life Enjoyment and Satisfaction[78]	X		X°		X°	X°	X°	X°
Patient Health Questionnaire (PHQ-9)[79] [depression]	X	X#°	X°	X#°	X°	X°	X°	X°
Generalized Anxiety Disorder Scale (GAD-7)	X	X#°	X°	X#°	X°	X°	X°	X°
Pittsburgh Sleep Quality Index[80]	X		X°		X°	X°	X°	X°
TLFB or Substance Use Daily Diaries + TLFB[75,81,82]	X	X°	X°	X°	X°	X°	X°	X°
Marijuana Assessment Problem Inventory (MAPI)[83,84]	X		X°		X°	X°	X°	X°
SOCRATES Drug Use Questionnaire (Modified for Cannabis)[85]	X		X°		X°	X°	X°	X°
Substance Use Goals/Reasons for Quitting Marijuana Questionnaire	X							
Cannabis Withdrawal Scale[86]		X	X°	X°	X°	X°	X°	X°
Marijuana Craving Questionnaire- Short Form[87]		X	X°	X°	X°	X°	X°	X°
Marijuana Motives Measure- Enhancement and Coping Subscales		X^			X			X
Treatment Progress- Self-Evaluation		X^	X		X			X
Lab Samples/Testing								
Qualitative Urine Drug Test	X							
Urinary Cannabinoid (THCCOOH) Testing		X±	X±	X±	X±			
Urine Pregnancy Test‡	X	X±	X±	X±	X±			
Blood Draw for DNA Analysis (Optional)		X^						

Visit→	Intake♦	Weeks 1-3	Week 4	Weeks 5-7	Week 8	Week 12	Week 16	Week 20
Salivary Progesterone		X	X	X	X			
Treatment Administration								
Motivational/goals session + 7 CBT4CBT sessions (30 minutes/ session)		X°	X°	X°	X°			
Estimated Visit Length (hours) →	3-3.5	1-1.5	1.5-2	1-1.5	1.5-2	1.5	1.5	1.5

♦ Screening Visit for Eligibility Determination. ‡ Females only *Past month CUD criteria only. #Administered on even-numbered weeks to assess past two-week symptoms. °Can be administered remotely Weeks 2-20. ± Only on weeks 1, 2, 4, 6, 8. ^Week 1 only

Cannabis use assessments. Cannabis use will be assessed via a combination of methods: Timeline Followback (TLFB)[82], daily substance use diaries, and urinary cannabinoid tests.

1. ***Timeline Followback.*** This calendar-based assessment designed to aid in recall of substance use will be administered at baseline to characterize cannabis and other substance use during the past 30 days. Prior to administering the TLFB, participants will complete a cannabis quantification task. For each method of cannabis used, participants will report the "typical dose" in grams of herbal cannabis or milligrams of THC, as most relevant. For herbal/plant-based methods of use, a proxy substance will be used to aid in estimation of grams[81], consistent with our prior procedures.[34] Grams will be converted to milligrams of THC, consistent with a recent proposal to define a "standard cannabis unit" in terms of milligrams of THC.[73] Because the actual THC content of participants' herbal cannabis is unknown and cannabis users are often poor reporters of THC content or potency[88-90], the average potency of confiscated cannabis within the United States[72] at the time of data collection will be used to convert grams of herbal cannabis to milligrams of THC. Of note, recreational and medical cannabis is not legalized in South Carolina, so we expect herbal cannabis used by our participants to primarily be obtained via the illicit market and therefore similar in potency to confiscated cannabis in the United States. Following completion of the quantification task, participants will report for each calendar day: 1) number of distinct episodes of cannabis use per day, 2) method of use, 3) grams of cannabis product, using the scale to assist as needed, or milligrams of THC for each product, 4) alcohol standard drinks, 5) cigarettes smoked, 6) other substance use.
2. ***Daily substance use diaries.*** Using REDCap/Twilio™ integration, a survey link will be sent via text message to participants every morning at the same time for all participants. [75] Participants will be asked to record their substance use from the previous day (referred to as "daily diaries"). The daily diary includes detailed self-report information on cannabis methods, and quantity (in episodes of use, grams of total product, milligrams of THC, as appropriate). In addition, participants will report on other past-day substance use (e.g., nicotine, alcohol, opioids). Participants will have until 1 PM to complete the daily diary and up to 2 reminders will be sent to encourage completion. A traditional TLFB will also be conducted during laboratory visits to fill in missing daily diary data as shown to be feasible in our

prior work.[91] A third-party text message vendor, Twilio™ interacts with REDCap to send text messages (SMS) for the purposes of remote data collection via mobile devices while minimizing data disclosure. The Twilio platform retains the participant's number only for the duration needed to send the SMS and then this information is discarded.

Biological Assessments. Urine samples will be obtained from all participants in order to conduct pregnancy tests (females only) and qualitative urine drug screens. For females, the pregnancy test will be completed first and a positive pregnancy test will immediately stop all subsequent procedures. The Clinical Neurobiology Laboratory (CNL) will analyze urine samples for 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH; immunoassay, mass-spectrometry-confirmed semi-quantitative tests) and creatinine. A urine sample will be collected during intake and a positive THCCOOH result (at least 50 ng/mL) will be required for study inclusion. Urine samples will also be collected at Week 1, 2, 4, 6, and 8 visits for THCCOOH analysis. THCCOOH values will be creatinine-normalized for analyses. These data will be used to ensure general accuracy of self-report and in secondary data analyses.

Progesterone collection. Participants will be instructed to collect an oral fluid sample each morning during the treatment phase (30 minutes after awakening) for assessment of endogenous progesterone levels. Samples will be placed in freezer and stored until the next laboratory visit. These daily home collection and storage procedures have been used in numerous previous studies with excellent participant adherence and sample quality[92,93], including our own completed and ongoing studies (P50DA016511, U54DA016511, K12HD055885).

Cytochrome P450 DNA analysis. Among participants who consent to optional genetic analysis, a blood sample will be used to determine the presence of genetic variants associated with modified THC and/or CBD metabolism, including CYP2C9 alleles (e.g., *2,*3,*8,*11), CYP2C19 alleles (e.g., *2,*3,*17,*27), and CYP3A4 alleles (e.g., *18,*22). In most cases, the blood sample will provided at the Week 1 visit and will be collected by certified phlebotomists at MUSC's Research Nexus. However, the blood sample can be taken at any time, including after completion of all other study procedures. The DNA analysis is not part of the original federally funded project, was optional for all participants, and was added after the initiation of data collection. Participants who have completed study procedures prior to the addition of the optional blood draw component will be recontacted and asked to participate in one additional visit to collect a blood sample for genetic analysis.

Participant Visits. Participants will come to the laboratory weekly during active treatment (Weeks 1-8). During Weeks 1, 2, 4, 6, and 8 visits, they will provide a urine sample for THCCOOH analysis. If the weekly CBT4CBT module has not yet been completed, they will be provided with a quiet space in the clinic to complete the module. However, participants will be given the opportunity to complete the module at home on their own time prior to the visit. Any incomplete daily diaries will be completed retrospectively with staff administration of the TLFB. Additional assessments will be conducted as outlined in Table 1. At each visit, participants will be asked to bring their saliva samples. Samples will be taken to MUSC's Research Nexus for progesterone analysis. Participants will meet with a medical clinician as needed to assess any medical adverse events or co-occurring medical symptoms. Participants must complete their

Week 1 visit in office. Exceptions can be made with PI's approval for partially remote visits if a participant can not come into the office for a visit during Weeks 2-20. Participants will still be able to complete all direct entry REDCap longitudinal assessments and the clinician administered cannabis related interview. For that partial remote visit an exception will be made to not collect biospecimen collection. This will be used only in the event that in-person visits are not possible to minimize the amount of missing data. If a remote visit is conducted during the treatment phase, participants will be asked to return all collected saliva samples when they come into the office for their next in person visit.

Participant Compensation. Participants will be compensated $40 for the Weeks 1, 4, and 8 visits. They will compensated $40 for Weeks 12, 16, and 20 visits. They will be compensated $20 for all other visits (Weeks 2, 3, 5, 6, 7). For any partial remote visit, participants will receive $10 less than the visit compensation listed due to not providing a urine sample and/or vitals, commensurate with the reduced time burden. Participants will receive up to a $40 weekly bonus (Weeks 2-8) for completing daily diaries, recording videos of saliva samples, and returning the corresponding samples to the lab at their next visit. They will receive up to a $10 weekly bonus (Weeks 9-20) for completing daily diaries post-treatment. The amount of the bonus will be pro-rated if <90% of expected daily diaries, videos, or saliva samples are received. Participants who participate in the optional blood draw will receive $50 for their participation. All participants will be eligible for an end-of-study data usage or equipment return bonus of $25. If participants borrow a phone, this bonus is contingent upon returning the device. For others, this bonus is to offset any data usage charges accrued during their participation. The total that a participant can receive in this study is $815.

Treatment

Psychosocial intervention. All participants will receive computerized cognitive behavioral therapy (CBT4CBT[3,94]). Prior to beginning CBT4CBT, all participants will meet with a therapist trained in motivational interviewing (Branson, Gex, Tomko, Sherman), for a brief discussion of goals and an orientation to the CBT4CBT online platform. This session will last approximately 30 minutes and is designed to enhance motivation to engage with the online platform. The formal treatment will consist of 7 weeks of CBT4CBT modules delivered in a computerized format. Participants will receive one CBT4CBT lesson per week with each taking approximately 30 minutes to complete (see Figure 5 for lesson topics). Participants will be encouraged to complete these modules on their own time before attending a visit. These lessons each focus on a specific CBT skill (e.g., coping with craving, refusal/assertiveness skills), include video demonstrations of the skill in practice, and provide opportunities for practice exercises in-between lessons. CBT4CBT has been shown to be as effective as clinician-delivered CBT for substance use disorders with potentially greater retention and sustained treatment benefit.[3] In a treatment-seeking sample (N=137) with approximately half of patients presenting with cannabis as their primary problematic substance, computerized CBT4CBT was shown to improve substance use outcomes.[3] In addition to reducing substance use days, this study found promising initial evidence that CBT4CBT was associated with remission of DSM-IV substance dependence in two-thirds of patients (compared to 52% in clinician-delivered CBT and 43% receiving treatment-as-usual; though, differences between groups was only trend-level, p=0.06).[3] Though this study included non-CUD substance use disorders as well, a study of clinician-delivered CBT

for CUD specifically found roughly comparable rates of CUD remission (40-47% of patients remitted).[95] Though CBT4CBT has been shown to be at least as good or better than clinician-delivered CBT in reducing days of substance use and substance dependence symptoms, rates of cannabis abstinence were low among cannabis users who received CBT4CBT, clinician-delivered CBT, or treatment-as-usual, as evidenced by only 15-20% of cannabis users providing a negative urine cannabinoid test at end-of-treatment.[3] This provides further support that a) rates of cannabis abstinence are low even when other indicators of treatment success are positive and b) CUD remission may occur without complete abstinence.

11.0 Specimen Collection and Banking

Urine will be collected, analyzed for cannabinoids, and discarded consistent with the laboratory's current policy.

Saliva will be collected, analyzed for endogenous progesterone levels, and discarded following analysis.

Blood will be collected from individuals who consent to DNA analysis. While the immediate research question will result in analysis of genotypes associated with THC breakdown (e.g., 2C9, 2C19, 3A4), participants will be asked to provide additional consent for sample storage and future DNA analysis, which could include whole genome sequencing.

12.0 Data Management

All data will be managed via REDCap. Research staff and participants will enter data in REDCap; 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); 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). See below for additional information regarding data storage and confidentiality protection.

Primary Statistical Analysis. The primary aim of this proposal is to determine the amount of cannabis use associated with remission of CUD symptom severity in men and women. Cannabis use will be assessed at study baseline and summarized weekly during the study using daily diary data, supplemented with traditional TLFB as necessary to fill in missing data.[91] Baseline demographic and clinical measures will be examined using standard statistical methods. Characteristics that are associated with CUD remission, CUD severity, or are known to be predictive of cannabis use will be assessed for final model inclusion.

Aim 1. Determine the threshold of cannabis use frequency and quantity associated with CUD remission at end-of-treatment and at follow-ups (a) for both men and women and (b) determine whether this threshold *differs* between men and women. Past month CUD severity and remission will be assessed at study baseline, week 4, week 8, and follow up visits. Additionally, weekly

cannabis use frequency and amounts (use days per week, episodes per day, and milligrams of THC per week) will be measured. Individuals will be considered remitted from CUD if they no longer endorse symptoms of CUD (with the exception of craving, consistent with DSM 5). Initially, generalized linear mixed effects regression models will be used to model the estimated reduction in cannabis use associated with both decreases in severity and complete remission of CUD. Normality of residuals will be tested (QQ plot) and when found in error, appropriate transformations or non-parametric methods will be employed. Model-based mean reductions in use days and use amounts as well as associated standard errors will be reported. The interaction between remission and gender will be examined and when evidence exists of a clinically important effect, gender stratified analysis will be conducted. Classification Analysis. To estimate a classification cut-point of decreased cannabis use associated with CUD remission, bootstrapped logistic regression models will be utilized. The primary response variable will be outcome grouping based on CUD remission status (binary; remitted versus non-remitted) and the primary predictor variable will be reduction in cannabis use amount and use frequency from baseline. One-thousand bootstrap samples will be used to produce estimates of the cut-point (c) using the training set. The remaining out-of-bag sample will be used to evaluate the classifier accuracy (validation). Each bootstrap sample will fit a logistic regression model with changes in cannabis use as the primary predictor and the maximum concordance probability[96] will be used to determine the optimal cut-point, *c*. Following, each bootstrap sample, *c* will be aggregated to a mean optimal cut point (*c*'). Additionally, the bootstrap aggregate will be used to determine the variance and confidence interval of the optimal cut point using the infinitesimal jackknife method.[97] The out-of-bag samples from each bootstrap resample will be fit utilizing the parameters developed from the bootstrap sample to provide internal cross-validation. Overall model fit will be assessed through interpretation of the confusion matrix as well as the misclassification rate, sensitivity, specificity, and receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) of the cut-off(s) in the out-of-bag data sets. Following the initial analysis, additional features including baseline use amounts, baseline CUD severity, age, and race as well as any baseline characteristics that are significantly associated with CUD remission will be included. Both overall and gender stratified analysis will be presented; specifically comparing misclassification rate, sensitivity, and specificity.

Aim 2. Examine associations between endogenous progesterone and cannabis use during treatment. Salivary progesterone and cannabis use rates (any use, number of episodes, milligrams of THC) will be measured daily. Generalized linear mixed effects models will be used to assess the association between daily progesterone and cannabis use in all participants. To account for between subject variation in salivary progesterone, values will be standardized within each participant and examined as relative changes from subject specific means. Person mean salivary progesterone will be included as a covariate in all models. Eight weeks of daily data should provide at least one full menstrual cycle for female participants, allowing for the examination of periods of increasing and decreasing progesterone. Statistical analysis will be performed in three steps. First, the relationship between progesterone and self-reported cannabis use will be assessed assuming a linear relationship using a generalized linear mixed effects model. Models will be fit including a random intercept term and within participant correlation structure will be chosen based on minimization of Akaike Information Criterion (AIC). Second, nonlinear relationships between cannabis use and progesterone levels will be examined through locally estimated scatterplot smoothing (LOESS) utilizing predicted values from the generalized linear

model. LOESS methods will determine if the relationship between progesterone and cannabis use is different at varying levels of the hormone. If the LOESS modeling indicates a non-linear relationship, generalized nonlinear mixed effects models will be used to estimate the location of the change in association. Resulting change point locations will be included in a piecewise regression model allowing for correlated measures within each participant as well as random intercepts while estimating distinct slopes and standard errors for each regression segment.

Analysis of follow-up data. Secondary analysis of study follow-up data will be used to determine durability of the relationship between decreases in cannabis use and remission of CUD severity symptoms. Generalized linear mixed effects models will be utilized to determine if overall and gender specific changes in cannabis use remain associated with symptom remission 1, 2 and 3 months following the completion of study treatment.

Power and sample size. The primary aim of the proposed study is to determine changes in cannabis use frequency and quantity associated with remission of CUD at the end of treatment (week 8) and follow up. Although direct study of this relationship has yet to be performed, a recently completed treatment trial of participants with CUD (UG1 DA013727; PI: Gray) measured changes in cannabis use days and the associated change in Marijuana Problem Scale (MPS) total score. In the study, participants that had complete remission of marijuana problems noted an average decrease of 4.0 (SD=2.7) cannabis use days per week as compared to only 1.9 (SD=2.5) use days per week decreases in those without complete remission of marijuana problems (Δ=2.1, SD=2.6; Cohen's d=0.8). When stratified by gender, women required a greater reduction in cannabis use days to achieve remission of MPS as compared to men (Women Δ=2.7, SD=2.5; d=1.1 vs. Men Δ=1.9, SD=2.6; d=0.7). We assume a robust reduction in CUD severity in our sample as everyone will receive CBT treatment and anticipate up to 50% with complete remission of CUD (~40% complete MPS remission in preliminary study at end of treatment). This estimated rate is similar to a prior CUD clinical trial utilizing cognitive-behavioral therapy which found CUD remission rates between 40-47%.[95] To detect a significant difference in use frequency and quantity between those that have CUD symptom remission and those that do not during study treatment, n=52 participants will need to be enrolled. Further, to detect the anticipated gender-specific effects (i.e., a significant difference in changes in cannabis use frequency/quantity and CUD severity calculated separately by gender), n=66 male and female participants (n=132 total) will need to be enrolled to have 80% power. This sample size will provide 80% power to detect the anticipated effect in males and >80% power to detect the anticipated effect in females. Further, a total sample size of n=190 (n=95 men and n=95 women) will additionally provide 80% to detect the differences between men and women. Because we anticipate attrition rates between study enrollment and the end of the 8-week treatment to be no greater than 15%, we will enroll at least n=224 total participants (at least 112 men and women, respectively). The total sample of 112 female participants (95 study completers) with up to 56 measured progesterone sample each (ICC=0.98) will provide 80% power with a type 1 error rate of 5% to detect a linear correlation between progesterone and cannabis use amounts of ρ=0.25. Though this analysis is powered for female sub-group analyses, analyses will also be conducted in the full sample. Thus, a randomized sample of n=224 participants will provide sufficient power for Aims 1 and 2.

Missing Data. Initial analysis will be performed using all available study data. However, missing predictor or outcome data may distort the study results by introducing bias into parameter estimates. Missing data will be imputed using the K nearest neighbor (KNN) approach with continuous features replacement chosen using distance weighted mean estimation and discrete data replacement chosen using the mode. For study Aim 1, available data and imputed data results will be compared by percent improvement in prognostic accuracy. For study Aim 2, data will be compared by the difference in the parameter estimate and associated variance.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

All aspects of the study will be run through the MUSC Department of Psychiatry and Behavioral Sciences. Consistent with the guidelines of the MUSC IRB, an internal Data and Safety Monitoring Plan (DSMP) will be used. An internal DSMP is appropriate for this study because 1) it does not involve a multi-site trial and 2) it presents minimal risks to participants.

Data and Safety Monitoring Board. We will create a Data and Safety Monitoring Board, comprised of multidisciplinary faculty with expertise in pharmacotherapy and behavioral treatment trials (adolescent 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.

Data will be collected by the appropriate individual (PI, Co-Is and/or IRB-approved designated research staff) and will only be identified with the study's ID of the participant. All PHI will be kept confidential in a secured cabinet by the PI or password-protected data file. Only the PI and IRB-approved designated research staff will have access to these files. Collected forms will be securely transported to the offices of the PI and IRB-approved designated research staff for data entry. Research staff will enter data in REDCap.

<u>Reporting Events</u>
Data and safety monitoring for the human participants aspects of the research will be the shared responsibility of all investigators. Final responsibility will rest with the PI, Dr. Tomko. Dr. Tomko will be responsible for reporting any relevant serious adverse event information, changes to the study's risk/benefit ratio, and/or acceptability of study continuation to the MUSC IRB. The data and safety monitoring plan will address the following areas: 1) the progress of the research study, including assessments of data quality and participant recruitment; 2) review of outcome and adverse event data to determine whether there is any change to anticipated benefit-to-risk ratio of study participation, and whether the study should continue as originally designed, should be changed, or should be terminated; 3) assessment of external factors or relevant information; 4) review of study procedures designed to protect the privacy of the research participants and the confidentiality of their data.

14.0 Withdrawal of Subjects

Participants will be informed that they may discontinue the study at any time during the visit without penalty and that they will be pro-rated for completed research activities. Participants may also be withdrawn from the study by the PI if it is determined that it is in the participant's best interest (e.g., safety concern, requiring intervention). Finally, participants may withdraw consent of use of their biospecimen samples for additional purposes at any time.

15.0 Risks to Subjects

The risks associated with participation in this study include adverse events related to cannabis withdrawal and the potential loss of confidentiality. Potential risk details are described below and the PI will ensure that all risks are clearly defined for study participants and are thoroughly understood during the informed consent process and throughout the study period.

In the unlikely event that participants are significantly distressed by any aspect of study participation, they will be offered the opportunity to discuss these issues with one of the PIs and/or the designated medical clinician (Kevin Gray) and may withdraw from the study at any point. If the distress is more serious and requires psychiatric attention, they will meet with a designated medical clinician on the study team. If participants require longer-term intervention, they will be referred to psychiatric treatment at MUSC, where they will pay the standard fee. Should any participant report suicidal ideation at any time during study participation, they will be immediately referred to a PI or medical clinician to determine the appropriate course of action. Suicidal ideation as measured via the PHQ-9 will automatically trigger an email alert in REDCap to go to the PIs and Kevin Gray (medical clinician) for follow-up. Events of this nature are not expected to occur at greater frequency because of the current protocol, but procedures will be in place to ensure the safety of all study participants.

Cannabis Withdrawal. Participants enrolled in the study will receive cannabis cessation treatment and may reduce or abstain from cannabis use during the study period. Participants will be regular cannabis users, and as such, they may experience cannabis withdrawal symptoms and/or discomfort during their quit attempt. Cannabis withdrawal symptoms may include: anxiety, depressed mood, irritability, restlessness, sleep difficulty, strange dreams, nausea, headaches, tension, difficulty concentrating and general physical discomfort. Participants will be informed of the potential discomfort they may experience during this brief period and will be advised to contact research staff if they feel that their withdrawal symptoms worsen during the study.

Loss of Confidentiality. There is the risk of breach of confidentiality. The research team has procedures in place to minimize the risk of any confidentiality breach. Videos are stored on a secure server and deleted at the end of the study. Mobile phones will be password-protected and loaned mobile phones will be wiped prior to loaning to the next participant. Participant records are stored in locked files within locked offices, or in password-protected databases. Much of the data collected is de-identified and uses a participant ID. 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 been given extensive training in maintaining confidentiality as well as HIPAA regulations. Participants will

be informed of these potential risks during the informed consent process and will have the option to leave the study at any point.

The research team has established procedures in place to minimize the risk of any confidentiality breach. To minimize this risk, all data will be stored in secure locations, including locked file cabinets and password-protected computers and databases. Videos are stored on a secure, HIPAA-compliant server (REDCap) and deleted at the end of the study. Mobile phones will be password-protected and loaned mobile phones will be wiped prior to loaning to the next participant. iPhones will be used exclusively when participants are not using their own device because the recorded video is never stored on the device itself. Any adverse events will be reported to the IRB, NIH, and others, as appropriate, to ensure the safety of study participants. Research staff are given extensive training in maintaining confidentiality as well as HIPAA regulations.

Blood Draw: Risks associated with drawing blood from participants' arms include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting is possible, although unlikely.

Genetic Research: Genetic research studies may present unique risks to human subjects and their relatives. These involve medical, psychosocial, and economic risks, such as the possible loss of confidentiality (private information), loss of insurability and employability, paternity, and social stigmas. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members. Genetic research raises difficult questions about informing participants of any results, or of future results.

South Carolina law mandates that genetic information obtained from any test or from this research, be kept confidential. State law prohibits an insurer using this information in a discriminatory manner against the participant or participant's family in issuing or renewing insurance coverage. Our state law further prohibits sharing of genetic information with anyone except in a few narrow circumstances, one of these being a research project of this type, approved by the Institutional Review Board, and then all steps to protect participant's identity will be taken. Participants will be informed of a federal law, called the Genetic Information Nondiscrimination Act (GINA), which generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against participants based on their genetic information. Limitations of GINA will also be described to participants.

16.0 Potential Benefits to Subjects or Others

Potential benefits of participation in this study may include a reduction in cannabis use. However, there is no guarantee or promise that participants will receive any benefit from participation in this study. All participants in this study will receive standard substance use disorder treatment, in the form of computerized Cognitive-Behavioral Therapy.

The establishment of gender-specific reduction endpoints will have both real-world clinical treatment implications as well as enable future studies to more rigorously test promising candidate treatments for CUD. Further, this study will help determine if the necessary reduction

required for CUD remission differs between men and women and whether the sex hormone progesterone mitigates female-specific difficulties in cannabis reduction.

17.0 Sharing of Results with Subjects

Aggregated study results can be shared with subjects or others in the form of peer-reviewed manuscripts, as relevant, upon request.

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