Varenicline for the Treatment of DSM 5 Cannabis Use Disorder in Adults

Study Overview and Design

Although cannabis use is widespread and basic science research on cannabinoids is well-developed, advancements in medication development for cannabis use disorder (CUD) have been limited. Varenicline, a selective nicotinic nACH receptor partial agonist of the α4β2 subtype and a full agonist of the α7 subtype, is arguably the most effective pharmacotherapy for promoting tobacco abstinence, and has also shown promise for the treatment of alcohol use disorder. Varenicline may improve cannabis use outcomes through multiple mechanisms, including interaction with the mesolimbic dopamine system, enhancement of cognitive functioning, and restoration of inhibitory control. To date, however, varenicline has not been evaluated in individuals specifically seeking treatment for CUD. Through the UG3/UH3 mechanism we proposed to rapidly yet thoroughly assess the utility of varenicline for CUD to potentially advance varenicline through the FDA's drug development approval pipeline. In the UG3 component, we conducted a six-week, placebo-controlled proof-of-concept clinical trial of varenicline for CUD, paired with pre- and post-evaluations of cognitive functioning and neural circuitry involved in cannabis cue reactivity and inhibitory control to elucidate the pharmacodynamics of varenicline as a treatment for CUD. We successfully met the pre-specified Go/No Go criteria for the UG3 study. For the the UH3 component, we will extend our promising UG3 findings by conducting a 12-week, placebo-controlled, double-blind trial to determine the impact of varenicline on cannabis use outcomes.

Specific Aim 1. To evaluate the efficacy of varenicline for cannabis use disorder (CUD). **Hypothesis 1:** A 12-week treatment course of varenicline, compared to placebo, for CUD will yield significant reduction in cannabis use.

Specific Aim 2. To examine the safety and tolerability of varenicline, compared with placebo, when used for CUD. **Hypothesis 2:** A 12-week treatment course of varenicline, compared to placebo, will demonstrate adequate safety and tolerability, as defined by non-inferiority in the frequency of treatment-emergent adverse events.

Exploratory Aim. To evaluate the effect of varenicline on negative affect, and the relationship between negative affect and cannabis use reduction, during CUD treatment. **Exploratory Hypothesis 1:** A 12-week treatment course of varenicline, compared to placebo, for CUD will yield reduction in negative affect. **Exploratory Hypothesis 2:** Reduction in negative affect during varenicline treatment will be associated with cannabis use reduction.

Participants. A total of approximately180 participants with CUD, aged 18 and over, will be recruited over a 32-month period at 2 participating sites.

Inclusion Criteria

- Meet DSM-5 criteria for cannabis use disorder and use cannabis at least 3 days per week in the last 30 days.
- Express interest in receiving treatment for cannabis use disorder and reducing use.
- Males and females at least 18 years of age.
- If female and of childbearing potential, must agree to use acceptable methods of birth control for the duration of the trial.
- Must consent to random assignment, and be willing to commit to medication ingestion.
- Must be able to read and provide informed consent.
- Must have body weight >110lbs (50kg) and have BMI between 18 and 35 kg/m^2
- Must function at an intellectual level and have knowledge of the English language to sufficiently allow for accurate completion of assessments.

Exclusion Criteria

- Women who are pregnant, nursing, or plan to become pregnant during the course of the study.

- Individuals with severe renal impairment (creatinine clearance less than 30 mL per minute).
- Lifetime history of DSM-5 Bipolar I or II Disorder, Schizophrenia or other psychotic disorder. Stably treated MDD, Dysthymia, GAD, Social Phobia, and Specific Phobia diagnoses are acceptable (i.e. same dose of medication has been prescribed for at least 2 months prior to screening and no changes in current medication expected during course of the trial).
- Past year or current posttraumatic stress disorder.
- Subjects who are actively suicidal, or who report suicidal ideation (SI) with intent or plan in the past year.
- Subjects who have a SBQ-R total score ≥8, or for whom the investigator judges that a risk assessment by a qualified medical professional is required. Subjects answering 'yes' on questions 4 or 5 of C-SSRS will be referred to assessment by a qualified mental health professional.
- Suicidal behavior within the past 10 years or a lifetime history of serious or recurrent suicidal behavior.
- Subjects who are believed to be at homicidal risk.
- Concomitant use of psychotropic medications, with the exception of stable doses (defined as no dosing adjustments in the past two months) of non-MAO-I antidepressants, non-benzodiazepine anxiolytics, and ADHD medications.
- Current use of medications prescribed for mania or psychosis.
- Current use of bupropion or nortryptiline.
- Moderate or severe non-cannabis substance use disorders within the past 60 days with the exception of tobacco use disorder.
- Past year or current moderate or severe alcohol use disorder.
- Individuals taking an investigational agent within the last 30 days before baseline visit.
- Individuals with clinically significant medical disorders or lab abnormalities.
- Any individual at screening with SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal and/or total bilirubin greater than two times the upper limit of normal.
- Individuals with clinically significant cardiovascular disease in the past 6 months (e.g., myocardial infarction, CABG, PTCA, severe or unstable angina, serious arrhythmia, or any clinically significant ECG conduction abnormality)
- Individuals with clinically significant cerebrovascular disease in the past 6 months such as TIA, CVA, or stroke
- Hypersensitivity to varenicline.
- Individuals who have participated in the clinical trial of any investigational agent within the last 60 days.
- Individuals who are on probation or under a mandate to obtain treatment.
- Individuals with plans to initiate or change frequency of attendance at self-help meetings (e.g. AA, NA).

Recruitment. Recruitment is planned to occur through both clinical referral and advertising.

Procedures.

Strategies to Ensure a Robust and Unbiased Approach: As detailed throughout this section, the proposed study will achieve robust and unbiased results via several design features including: explicit inclusion/exclusion criteria; randomization of treatment condition; placebo control; blinding; use of validated measures and methods; explicit hypotheses and corresponding planned statistical analyses; power estimates; planned handling of retention/attrition and missing data; objective adherence monitoring; and careful consideration of potential confounds.

Screening and Eligibility Assessment. Individuals will be screened by the research study intake coordinator. The consent and all screening/eligibility procedures may be completed remotely, via a secure Web-based platform such as Doxy.me or RedCap, or a combination of these platforms as appropriate. A quick screen, focused on inclusion/exclusion psychiatric diagnoses, medical status, current medication regimen, and ability and willingness to commit to completion of study procedures, will be used to initially determine study eligibility. Interested individuals will be given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form. In order to confirm and document understanding, individuals will be asked to

complete a consent quiz prior to signing the form. They will also be asked to complete a W9 during the informed consent/teleconsent process.

Diagnostic/Descriptive Assessment. The MINI International Neuropsychiatric Interview (MINI) will be used to assess psychiatric and substance use diagnoses. A detailed medical history will be taken, and subjects will be asked to complete bloodwork at the MUSC CNL or a local LabCorp of their choosing (or AnMed lab in Pickens) to ensure the individual is eligible to participate. A physical exam will be conducted only if there is an issue raised by either the medical history or bloodwork. In the event that an individual is found to be ineligible to participate in this research protocol, he or she will be given an appropriate referral for further medical care or to an appropriate treatment program.

Treatment Assignment. Individuals who meet all inclusion criteria and no exclusion criteria will be randomized to receive either varenicline or matching placebo. Randomization (stratified on tobacco smoking status and gender) and dispensing will be performed by the MUSC Investigational Drug Service. Varenicline will be provided at the standard recommended dose of 0.5mg daily for three days, then 0.5mg twice daily for four days, and then 1mg twice daily for the remainder of the 12-week treatment period. Matching placebo and varnicline (0.5mg and 1mg) capsules will be compounded by IDS utilizing Letco 00 capsules and microcrystalline cellulose filler. For the Pickens site, medication will be packaged and dispensed by MUSC IDS, and then shipped to Pickens via registered courier. On site, medication will be stored in a controlled access environment and provided to participants by appropriately trained and designated study staff, with double checks in place. In extenuating or emergency circumstances, when patient visits are not feasible or are prohibited, such as in the case of a pandemic, weekly medication may be mailed to participants.

Medication Management. Medication Management (MM) is a common-sense, generalizable approach to encourage adherence to medication specifically, and to a treatment plan in general. Once a week, participants will be seen for a brief MM session. Sessions will be focused on (a) developing and maintaining rapport, (b) reviewing AEs and concomitant medications, and (c) discussing progress with medication adherence and cannabis reduction/abstinence. These sessions provide an opportunity to address challenges and help participants devise strategies for success. A similar intervention was utilized in the NIDA-funded CTN0053 trial (Achieving Cannabis Cessation—Evaluating N-Acetylcysteine Treatment) to provide an evidence-based treatment platform for all participants. MM with participants at the Pickens site will be done by approved medical personnel there and, as needed, by MUSC site medical personnel via WebEx or Doxy.me, HIPAA-compliant, MUSC Information Security-approved platforms for telehealth. In extenuating or emergency circumstances, when patient visits are not feasible, safe, or are prohibited, such as in the case of a pandemic, MM at both sites may be completed remotely by telehealth/phone.

Assessments. **Table 4** provides an overview of assessments; a brief description of the instruments is provided below. In extenuating or emergency circumstances, when patient visits are not feasible, safe, or are prohibited, such as in the case of a pandemic, visits and their procedures that can be completed remotely by telehealth/phone may be. Additionally, urine drug and cotinine tests may be completed less than weekly if deemed appropriate. All of the assessments will mirror what would be done in clinic, and as such do not add risk to the participants.

Table 6. Schedule of assessments.

	Screening	BL	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	FU 1
Quick Screen	X														
MINI	X														
Urine pregnancy test	X	X				X				X				X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SBQ-R	X														
Daily Substance Use Logs and Time-Line Follow-Back	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

MCQ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine cotinine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CWS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROMIS-29	X					X				X				X	
DSM-5 Criteria for CUD	X					X				X				X	
Self-Efficacy Questionnaire	X													X	
Marijuana Problem Scale	X													X	
Reasons for Quitting Questionnaire	X														
Review of AEs			X	X	X	X	X	X	X	X	X	X	X	X	X
Pill Count			X	X	X	X	X	X	X	X	X	X	X	X	
Med Video Adherence			X	X	X	X	X	X	X	X	X	X	X	X	

Screening and Diagnostic Instruments. **Quick Screen:** This assessment will be used to quickly determine whether an individual meets inclusion or exclusion criteria for the study when they first present. The instrument is designed to assess for substance dependence and obvious psychiatric, medical, and logistic exclusions. **Mini-International Neuropsychiatric Interview (M.I.N.I.):** The M.I.N.I. is a brief structured interview that was designed to assess DSM-5 diagnoses using a series of questions in dichotomous format (yes/no) (Sheehan & Lecrubier, 2003; Sheehan et al, 1998).

Psychiatric and Functioning Assessments. **Columbia-Suicide Severity Rating Scale (C-SSRS):** The C-SSRS (Posner et al., 2011) is a brief, low-burden suicide assessment scale administered by a clinician. We have successfully used this instrument in multiple previous trials, and it is regarded as the gold standard of suicidality assessment in clinical trials. **Suicide Behaviors Questionnaire-Revised (SBQ-R):** The SBQ-R is a 4-item psychological self-report questionnaire designed to identify risk factors for suicide by assessing different dimensions of suicidality including lifetime suicide ideation and/or attempt, frequency of suicidal ideation over past 12 months, threat of suicide attempt, and likelihood of suicidal behavior in the future. **PROMIS-29:** This assessment, available through the Phen-X toolkit, includes 29 self-administered quality of life-type questions from the PROMIS® Profile 29 for adults. The quality of life questions include physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain intensity over the past 7 days. Each question, except for the pain intensity question, is measured on a 5-point scale.

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

Substance-Related Instruments. **Time-Line Follow-Back (TLFB):** The TLFB (Sobell & Sobell, 1992) is a calendar-based instrument designed to assess daily substance consumption. Although initially designed to assess alcohol use, we have successfully modified this instrument to assess for other drug use. Upon review of the participant's daily substance use logs, cannabis use will be recorded as times used per day, with each time being defined as cannabis use separated by an hour of no cannabis use, in order to standardize for different types of cannabis use (joints, bowls, blunts, etc.), as well as recorded as amount used per day. Nicotine and other substance use will also be assessed. **Urine Drug Testing:** The urine drug tests will be screened qualitatively for the presence of opioids, cocaine, amphetamines, and benzodiazepines. Urine cannabinoid tests will be performed using the AXSSYM® system from Abbott Laboratories. This assay is semi-quantitative with a

detection cut-off value of 30.00 ng/ml (Abbott AXSSYM® System package insert). Urine creatinine will also be obtained, as creatinine normalization has been proposed as a method to differentiate new cannabis use from residual drug excretion (Huestis and Cone, 1998; Schwilke et al, 2011). **Urine Cotinine:** Nicotine is metabolized to cotinine by the liver. Cotinine has a longer half-life than nicotine, and thus serves as a more reliable biomarker of cigarette smoking (Zevin et al., 2000). Urine will be screened qualitatively at each visit (detection cut-off value of 200 ng/ml). **Marijuana Craving Questionnaire (MCQ):** The MCQ (Heishman et al, 2001) is a Likert-based self-assessment of cannabis craving shown to be a valid and reliable instrument for measuring cannabis craving. The 12-item MCQ will be used, which has been constructed by selecting the three items from each factor of the full 47-item MCQ that exhibited the most within-factor reliability (Heishman et al, 2009). **Cannabis Withdrawal Scale:** The Cannabis Withdrawal Scale (Allsop et al, 2011) is comprised of 19 items for which participants rate severity of symptoms in the previous 24 hours. **Marijuana Use Summary Sheet/Self-Efficacy Questionnaire/Marijuana Problem Scale/Reasons for Quitting Questionnaire:** These worksheets, created by Stephens and colleagues (2000), will be used to gather information from participants to prepare personalized feedback reports (PFRs) for use in the motivational enhancement sessions. **DSM-5 Criteria for CUD:** DSM-5 criteria will be assessed at four time points to determine changes in severity of cannabis use disorder.

Safety Assessment. **Review of Adverse Events:** Adverse events (AEs) will be assessed weekly by study personnel. The type of AE, severity of AE, and the relationship to study medication will be recorded. AEs will be coded on a weekly basis using Medical Dictionary for Regulatory Activities (MedDRA) rules.

Adherence. During the 12 weeks of treatment, participants will be asked to record and upload twice-daily videos of medication-taking at home or in a private location of their choosing. These videos will be taken remotely and submitted via REDCap surveys to confirm medication adherence. Participants may use their personal mobile phones for video submission. If they do not have a smartphone, one will be loaned to them during the first week of study. Video submissions may only be completed on a smartphone (cannot be completed on a computer). A survey link will be sent to the participant via text message. Video capture will occur as part of the REDCap survey. Videos are automatically stored on Android smartphones, and participants will be informed of that so they can delete the files, if necessary. Participants using iPhones (and using loaner iPhones from our group) will not have stored videos on their phone and nothing will need to be deleted. These procedures were used successfully in the prior UG3 study. To complement these procedures, pill counts will be completed at each clinic visit during active treatment.

Follow-up plan. Following the study, participants will be referred for appropriate substance use management. In the event that an AE occurs during the study, a participant will be followed until resolution.

Statistical Analysis

Data Management Plan. All data will be entered into a standard software package (REDCap). Macro programs will be written to check the data for logical consistency and values out of possible range. Quarterly database management and data integrity audits will be conducted.

Baseline Analysis. Categorical clinical and demographic variables will be assessed for balance between groups with chi-square tests of independence, while continuous variables will be assessed using Student's *t*-test. In addition to baseline group differences, preliminary analysis of baseline characteristics with cannabis use outcomes of interest will examine significant correlates of use reduction and abstinence. Characteristics found to be significantly associated with cannabis use outcomes will be included as covariates in the initial stages of adjusted statistical model development.

Primary Analysis. The primary aims for the UH3 portion of the protocol are to test the efficacy and safety of varenicline for CUD during a 12-week placebo-controlled trial. **Specific Aim 1:** The primary efficacy outcome is cannabis use reduction as measured by daily substance use logs and examined as the total number of use sessions at each weekly visit (primary interest weeks 6-12). Group differences in reported session use will be examined utilizing a generalized mixed effects models using a log-linear framework for count data. A Poisson distribution will be assumed with a logarithm link function will be used to assess the effects of varenicline treatment, time, and the appropriate interaction. Overdispersion in discrete count models can have a significant

impact on parameter inference, thus when detected, a negative binomial distribution will be specified and model fit will be compared to the Poisson model. An offset variable will be included in the models to account for possible differences in between visit timing. Models will be computed both adjusted for design variables and for significant covariates and confounders found in the preliminary analysis. Working correlation structures will be independently compared using the quasi-likelihood under the independence model criterion statistic (QIC). Model based means will be used to construct the pairwise comparisons between groups. All design adjusted models will include baseline average use sessions, study visit, treatment group assignment and randomization stratification variables (smoking status and gender). Additional exploratory approaches (e.g., analysis excluding participants with <80% medication adherence, per protocol analysis, completers analysis) will be undertaken. **Specific Aim 2:** We will also compare the frequency of treatment-emergent AEs between treatment groups using a non-inferiority analysis. Of particular interest will be AEs leading to medication discontinuation and the occurrence of treatment-related serious AEs (SAEs). We will specifically compare neuropsychiatric AEs and suicidality (C-SSRS) ratings by treatment group. We hypothesize that treatment with varenicline will not cause undue adverse events and will be non-inferior to the placego group by a margin (δ) of no more than a 10% using the Farrington-Manning score test for non-inferiority.

Exploratory Analysis. **Exploratory Aim 1:** Negative affect will be measured weekly during study treatment and compared between groups using generalize linear mixed effects regression models. Model based means will be used to construct the pairwise comparisons between groups and treatment by time interactions will be included to assess differential response over time. **Exploratory Aim 2:** Further, we will assess the time varying relationship between changes in negative affect and cannabis use sessions. Cross lagged panel models will be used to assess the lagged effect of changes in negative affect on cannabis use and visa-versa. Models will also include the autoregressive and synchronous relationships between these variables over time. Models will evaluate the influence of study treatment and medication adherence on the relationship between negative affect and cannabis use through the inclusion of time variable and time invariate effects. If significant treatment effects exist, additional stratified analysis will be conducted to elucidate the magnitude and direction of the effect.

Additional Data Analysis. Logistic regression models will be used to assess end of study abstinence (7 day point prevalence abstinence at week 12 and continuous abstinence from week 6 to 12); primary analysis models will be reported both as design adjusted results as well as adjusted for significant clinical covariates. To comprehensively examine the longitudinal efficacy of varenicline, weekly cannabis abstinence will also be analyzed over the entire treatment course using generalized linear mixed effects regression models under a GEE framework. Between study visit cannabis use will be based on daily substance use diaries confirmed via Time-Line Follow-Back procedures. The number of treatment visits attended will be compared between groups using Poisson regression models, while the number of days retained will be assessed using Cox Proportional Hazards regression models. Medication adherence (REDCap video capture of medication-taking; pill counts), tobacco smoking status, and gender will be explored as potential moderators of study outcomes through model interactions. Craving and withdrawal from cannabis will be assessed between groups over time using generalized linear mixed effects models.

Missing Data and Attrition. Missing data in longitudinal studies can be a problematic feature but can be mitigated through study design considerations. In order to minimize missing data and study attrition, design simplification and enhanced communication between study staff and participants will be emphasized. We will make every effort to prevent attrition (e.g., phone/text visit reminders, participation compensation, reinforcing adherence to the study protocol). To assess the potential impact of missing data on the primary study hypothesis, sensitivity analysis will be completed (a) with all available data and (b) using methods of multiple imputation (Rubin, 1987). Multiple imputation will be implemented using fully conditional specification. Due to the possibly high rate of missing data near the end of the study treatment period (>10%), 100 imputation data files will be created to assure reasonable relative efficiency (Von Hippel, 2018).

Power and Sample Size. The proposed study is powered on the primary efficacy hypothesis that varenicline treatment, relative to placebo treatment, will yield reduced cannabis use during the cruicial stages of study treatment (weeks 6-12). The UG3 portion of this study showed a moderate self-reported reduction of weekly use days between the varenicline and placebo group (Cohen's d=0.43). We intend to improve the granularity of this measure by assessing, in more detail, the number of use sessions occurring on a daily basis using daily

substance use report logs. We anticipate the increased information will allow better precision in the estimated effect between randomized study groups. Assuming this, coupled with the more extended 12-week treatment compared with the truncated treatment phase in the prior UG3 proof-of-concept trial, results in a slightly increased effect size of *d*=0.5, a high correlation between measures taken over time on the same participant (ρ=0.95) and a 5% type 1 error rate, 57 participants are necessary in each treatment arm to achieve adequate power (80%). Additionally, the UG3 noted a higher than expected attrition rate of 35%, thus we anticipate that, despite our best efforts and revised approach, attrition during the study could reach 35%. Thus to ensure that we have the appropriate sample, we will enroll and randomize **approximately 90 participants per group for a total sample size of approximately n=180**. This will allow us to detect a difference in cannabis use session of at *least d*=0.5 between randomized study groups while accounting for up to 35% study attrition. Similar to adult varenicline phase III studies (Gonzales et al., 2006), for the primary safety analysis we will compare the frequency of all treatment-emergent AEs (defined as any AE occurring between treatment initiation and one week following treatment conclusion), SAE's between varenicline and placebo groups. A non-inferiority analysis will be utilized (Piaggio et al., 2006). With an estimated placebo treatment-emergent AE rate of 75% (Gonzales et al., 2006), 90% power and two sided α = 0.05, within our proposed sample of **approximately 180 randomized participants** we will be able to detect a 10% non-inferiority margin in AE frequency between treatment groups if it exists.

Design considerations. *Comorbid tobacco use disorder.* Individuals using both cannabis and tobacco have worse cannabis use treatment outcomes. Although data from a large RCT in alcohol using individuals found an effect of varenicline on drinking outcomes regardless of tobacco use status (Litten et al., 2013), it is possible that a differential effect of varenicline will be found among tobacco and non-tobacco using individuals with CUD. Therefore, we propose to stratify randomization on this variable, and to examine comorbid tobacco use as a potential moderator in the statistical analysis as well as the impact of varenicline on tobacco use in this population. *Consideration of gender as a biological variable.* In contrast to findings for stimulant drugs, there does not appear to be a strong effect of menstrual cycle phase in response to cannabis (for review, see Terner and de Wit, 2006). However, our previous work revealed a significant gender by treatment interaction in individuals with CUD, with women randomized to buspirone having fewer negative urine cannabinoid tests than women randomized to placebo (p=0.007), and men randomized to buspirone having significantly lower creatinine adjusted cannabinoid levels as compared to those randomized to placebo (p=0.023) (McRae-Clark et al., 2015). These findings support the need to consider gender as a critical variable in treatment investigations; as such, gender will be explored as a potential moderator of treatment response.

Timeline. Following administrative review, two months are anticipated for transition to the UH3 component to allow for study start-up activities. 32 months will be needed for participant recruitment and data collection. The final two months will be used for data analysis. At a recruitment rate of approximately five to six participants per month (a rate achieved in our prior CUD pharmacotherapy trials), we should meet our target sample size.

PROTECTION OF HUMAN SUBJECTS

RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

Admission into the study is open to men and women and to all racial and ethnic groups, age 18 and over. Approximately one hundred and eighty individuals (across two participating sites) with cannabis use disorder will be recruited primarily through clinical referrals and internet and newspaper advertisements. Inclusion/exclusion criteria that apply to all participants are listed below:

Inclusion Criteria

- Must meet DSM-5 criteria for cannabis use disorder and use cannabis at least 3 days per week in the last 30 days.
- Express interest in receiving treatment for cannabis use disorder and reducing use.
- Must be at least 18 years of age.
- If female and of childbearing potential, must agree to use acceptable methods of birth control for the duration of the trial.

- Must consent to random assignment, and be willing to commit to medication ingestion.
- Must be able to read and provide informed consent.
- Must have body weight >110lbs (50kg) and have BMI between 18 and 35kg/m2
- Must function at an intellectual level and have knowledge of the English language to sufficiently allow for accurate completion of assessments..

Exclusion Criteria

- Women who are pregnant, nursing, or plan to become pregnant during the course of the study.
- Individuals with severe renal impairment (creatinine clearance less than 30 mL per minute).
- Lifetime history of DSM-5 Bipolar I or II Disorder, Schizophrenia or other psychotic disorder. Stably treated MDD, Dysthymia, GAD, Social Phobia, and Specific Phobia diagnoses are acceptable (i.e. same dose of medication has been prescribed for at least 2 months prior to screening and no changes in current medication expected during course of the trial).
- Past year or current posttraumatic stress disorder.
- Subjects who are actively suicidal, or who report suicidal ideation (SI) with intent or plan in the past year.
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- Subjects who are actively suicidal, or who report suicidal ideation (SI) with intent or plan in the past year.
- Subjects who have a SBQ-R total score ≥8, or for whom the investigator judges that a risk assessment by a qualified medical professional is required. Subjects answering 'yes' on questions 4 or 5 of C-SSRS will be referred to assessment by a qualified mental health professional.
- Suicidal behavior within the past 10 years or a lifetime history of serious or recurrent suicidal behavior.
- Subjects who are believed to be at homicidal risk. Concomitant use of psychotropic medications, with the exception of stable doses (defined as no dosing adjustments in the past two months) of non-MAO-I antidepressants, non-benzodiazepine anxiolytics, and ADHD medications.
- Current use of medications prescribed for mania or psychosis.
- Current use of buproprion or nortryptiline.
- Moderate or severe non-cannabis substance use disorders within the past 60 days with the exception of tobacco use disorder.
- Past year or current moderate or severe alcohol use disorder.
- Individuals taking an investigational agent within the last 30 days before baseline visit.
- Individuals with clinically significant medical disorders or lab abnormalities.
- Any individual at screening with SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal and/or total bilirubin greater than two times the upper limit of normal.
- Individuals with clinically significant cardiovascular disease in the past 6 months (e.g., myocardial infarction, CABG, PTCA, severe or unstable angina, serious arrhythmia, or any clinically significant ECG conduction abnormality.
- Individuals with clinically significant cerebrovascular disease in the past 6 months such as TIA, CVA, or stroke.
- Hypersensitivity to varenicline.
- Individuals who have participated in the clinical trial of any investigative compound within the last 60 days.
- Individuals who are on probation or under a mandate to obtain treatment.
- Individuals with plans to initiate or change frequency of attendance at self-help meetings (e.g. AA, NA).

b. Sources of Materials

Research material obtained from individual participants includes questionnaires and in-person and remote interviews with study personnel, and blood and urine samples. To ensure confidentiality, all participant data will be letter/number coded, and only the investigators will have access to the master lists of codes. The research material will be obtained specifically for research purposes. Written research material obtained will be stored in the Addiction Sciences Division at MUSC or at Behavioral Health Services of Pickens County in Pickens, SC, in an office that is locked when not in use. Urine samples from MUSC site will be stored in the Clinical Neurobiology

Urine samples from the Pickens site will be stored at Behavioral Health Services of Pickens County and then sent to MUSC CNL for analysis in batches.

c. Potential Risks
The varenicline package insert details adverse events associated with the medication. Specifically, it reports that "the most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting." Meta-analyses of the four main adverse events in varenicline versus placebo groups in adult trials yielded relative risks (RRs) of 3.21 (95% CI 2.71, 3.80) for nausea, 1.50 (95% CI 1.26, 1.79) for insomnia, 2.79 (95% CI 2.09, 3.72) for abnormal dreams, and 1.20 (95% CI 1.00, 1.45) for headache (Cahill et al., 2009). While post-marketing anecdotal reports of psychiatric adverse events led to an FDA "black box" warning for varenicline, a reanalysis of controlled trials revealed no evidence that varenicline is associated with neuropsychiatric adverse events (Thomas et al., 2015). There is a potential risk of loss of confidentiality.

ADEQUACY OF PROTECTION AGAINSTS RISKS
a*. Recruitment and Informed Consent*
Participants will primarily be recruited through clinical referrals and the use of advertisements (internet, newspaper). Medical records will not be reviewed to identify potential study participants unless patients have requested to be contacted through a research permissions registry. A study PI, Co-I, or other qualified study staff will obtain informed consent. The informed consent form includes a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The informed consent form will be explained to participants in easy-to-understand language, and participants will be instructed to read the form carefully prior to signing it. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent.

b. Protections Against Risks
All study participants will be closely monitored for psychiatric and medical stability. All study procedures will be conducted under the supervision of experienced personnel. If crisis intervention is necessary during screening or study enrollment, senior staff will be available to evaluate the subject and provide an intervention or referral. In regards to suicidality, any participant endorsing suicidality on the C-SSRS (either during screening or at a subsequent study visit) will be assessed for safety by a psychiatrist or other qualified licensed clinician. If hospitalization is indicated, the patient will be hospitalized through MUSC or Behavioral Health Services of Pickens County, or an appropriate referral will be made. All participants will be fully informed that they may withdraw from the study at any time without penalty.

To ensure confidentiality, all participant data will be coded by name and/or numbers, and only the investigators will have access to the master lists of codes. In specific instances, participant PHI may be available to other entities, such as for ClinCard registration/payment purposes. All participant records will be kept in a locked cabinet in an office that will be locked at times when not in use. The research staff understands the importance of maintaining confidentiality, and this method of maintaining confidentiality has been used for several years by our research group and has been effective. All electronic databases are stored on HIPAA-compliant servers with restricted access. RedCap video clips will only be viewed by approved research staff and will be deleted when the study has ended and data analysis is complete. All co-investigators and study personnel have completed (or will complete upon hiring) training in Good Research Practices as mandated by the MUSC IRB.

Participants will be taught about potential side effects of varenicline and will be closely followed by psychiatrists, physicians, a PharmD, a NP, and other members of the research team. Pregnancy tests will be performed prior to medication initiation and monthly during the study. Participants will be excluded if they have a known hypersensitivity to varenicline. Adverse events will be assessed at each clinic visit, and all participants will be provided with an after-hours emergency contact number in the event that an adverse event occurs when the clinic is closed.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECT AND OTHERS

Possible risks to study participants include adverse reactions to varenicline. Benefits include detailed assessment of cannabis use and receipt of a medication and medication management that may help reduce cannabis use. The minimal risks are reasonable in relation to the potential benefits to be gained from the investigation.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may help accelerate approval of varenicline for treatment of cannabis use disorder. Presently, there are no FDA-approved medications for cannabis use disorder. The moderate risks of the investigation are considered reasonable in relation to the expected knowledge to be gained.

CLINICALTRIALS.GOV REQUIREMENTS

In accordance with Public Law 110-85, this project will be registered at the ClinicalTrials.gov Protocol Registration System Information Website prior to study initiation.

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