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Varenicline as a Treatment for Cannabis Use Disorder: A Placebo-Controlled Pilot Trial

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Abstract

Background.—An efficacious pharmacotherapy for cannabis use disorder (CUD) has yet to be established. This study preliminarily evaluated the safety and efficacy of varenicline for CUD in a proof-of-concept clinical trial.

Methods.—Participants in this 6-week randomized, placebo-controlled pilot trial received either varenicline (n=35) or placebo (n=37), added to a brief motivational enhancement therapy intervention. Outcomes included cannabis withdrawal, cannabis abstinence, urine cannabinoid levels, percent cannabis use days, and cannabis sessions per day.

Results.—Both treatment groups noted significant decreases in self-reported cannabis withdrawal, percentage of days used, and use sessions per day during treatment compared to baseline. While this pilot trial was not powered to detect statistically significant between-group differences, participants randomized to varenicline evidenced numerically greater rates of self-reported abstinence at the final study visit [Week 6 intent-to-treat (ITT): Varenicline: 17.1% vs. Placebo: 5.4%; RR=3.2 (95% CI: 0.7,14.7)]. End-of-treatment urine creatinine corrected cannabinoid levels were numerically lower in the varenicline group and higher in the placebo group compared to baseline [Change from baseline: Varenicline −1.7 ng/mg (95% CI: −4.1,0.8) vs. Placebo: 1.9 ng/mg (95% CI: −0.4,4.3); Δ=3.5 (95% CI: 0.1,6.9)]. Adverse events related to study treatment did not reveal new safety signals.

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CRediT authorship contribution statement

Authors McRae-Clark and Gray designed the study and wrote the protocol. Authors McRae-Clark, Gray, Sherman, Squeglia, Wagner, and Tomko participated in the conduct of the study. Author Baker undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Conclusions.—Findings support the feasibility of conducting clinical trials of varenicline as a candidate pharmacotherapy for CUD, and indicate that a full-scale efficacy trial, powered based on effect sizes and variability yielded in this study, is warranted.

Keywords

cannabis; marijuana; treatment; pharmacotherapy; varenicline; addiction

1. Introduction

The prevalence of past year cannabis use in the United States more than doubled between 2001 and 2013, from 4.1% to 9.5% of the adult population (Hasin et al., 2015). In 2019, nearly one million Americans received treatment for cannabis related problems (SAMHSA, 2020). Although a high demand for effective interventions exists, few specific treatments have been developed for cannabis use disorder (CUD). Further, current evidence-based treatments have limited efficacy, with few individuals achieving abstinence (Compton & Pringle, 2004; Kadden et al., 2007; Nordstrom & Levin, 2007; Sherman & McRae-Clark, 2016). As such, there is significant interest in exploring new strategies to improve treatment outcomes. In particular, the role that medications may play in the treatment of cannabis use disorder (CUD) has become an active area of research (Vandrey & Haney, 2009).

Varenicline, a selective nicotinic acetylcholine receptor (nACHr) partial agonist of the α4β2 subtype and a full agonist of the α7 subtype (Mihalak et al., 2006), is arguably the most effective first line pharmacotherapy for promoting tobacco cessation (Aubin et al., 2008; Eisenberg et al., 2008; Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006). Given its partial agonist profile, varenicline likely exerts its effects via dual mechanisms. First, it partially activates α4β2 receptors in the ventral tegmental area (VTA), resulting in increased dopamine levels and a reduction in withdrawal symptoms and craving (Rollema et al., 2007; Reperant et al., 2010) as well as striatal dopamine receptor binding (Crunelle et al., 2009; Crunelle et al., 2011). Further, through its antagonist properties, varenicline also blocks the ability of nicotine to further stimulate dopamine release, thereby attenuating nicotine's reinforcing effects during smoking (Coe et al., 2005). Varenicline also reliably reduces reactivity to smoking-related cues among tobacco users, via its effects on reward and cognitive circuitry (Brandon et al., 2011; Franklin et al., 2011; Hartwell et al., 2013).

Given that the mesolimbic dopamine system is a key element in the brain reward pathways and that increased dopaminergic transmission in these pathways is important for the reinforcing effects of multiple drugs of abuse (Taylor & Robbins, 1984; Koob & LeMoal, 1997; Tanda et al, 1997; Volkow et al., 2016), varenicline has been identified as a prime candidate medication for evaluation in other substance use disorders (Crunelle et al., 2010). Positive findings have been reported in regard to varenicline reducing alcohol cue reactivity (Schacht et al., 2014), reducing alcohol self-administration among heavy drinking smokers (McKee et al., 2009), improving drinking outcomes in preliminary clinical trials (Fucito et al., 2011; Mitchell et al., 2012), and reducing alcohol use in a large, placebo-controlled trial (Litten et al., 2013). Two recent meta-analyses of varenicline's impact on alcohol consumption have had mixed results, with one finding reduction in alcohol consumption

but not heavy drinking days (Oon-arom et al., 2019) and another reporting a reduction in alcohol craving but not in drinking-related outcomes (Gandhi et al., 2020). A laboratory study by Herrmann et al. (2018) demonstrated that varenicline reduced tobacco use, craving, and negative affect in tobacco/cannabis co-users, though it had no effect on cannabis relapse. However, a case series reported reductions in amount of enjoyment of cannabis and self-report of cannabis use among cannabis- and nicotine-dependent individuals receiving varenicline (Newcombe et al., 2015). In addition, a small pilot trial reported reduced cannabis craving, cannabis use, and tobacco use when varenicline was added to standard care among a sample of individuals with opioid use disorder (Adams et al., 2018).

Importantly, α4β2 nACHRs in corticothalamic circuitry, which are saturated with varenicline dosing (Lotfipour et al., 2012), have also been heavily implicated in prefrontally mediated attentional and inhibitory control (Sarter & Paolone, 2011) and working memory (Vandesquille et al., 2013). In addition, α7 nACHRs are involved in hippocampal-dependent memory function (Levin et al., 2006). nACHr agonists improve frontally mediated executive function among nicotine-naïve animals (Levin et al., 2006) and humans (Froeliger et al., 2009). Varenicline has been shown to improve multiple forms of attention (Rhodes et al., 2012) including inhibitory control (Austin et al., 2014) among treatment-seeking tobacco users and in nicotine-naïve animal models (Rollema et al., 2009). Given that cannabinoid agonists inhibit cholinergic transmission (Varvel et al, 2001), the cholinergic system in particular may play an important role in cannabis-induced cognitive dysfunction. As such, varenicline, as a cholinergic modulator in prefrontal circuitry, is a promising candidate to ameliorate frontal-executive dysfunction (Sofuoglu et al., 2010).

Gonzales et al (2006) and Jorenby et al (2006) found that varenicline was superior to placebo in reducing tobacco withdrawal symptoms. Specifically, treatment with varenicline, compared to placebo, was associated with less withdrawal-related negative affect; a meta-analysis found that negative affect during tobacco cessation attempts modulates treatment efficacy (Foulds et al., 2013). These findings appear highly relevant to CUD, as cannabis withdrawal has been identified as a potentially high-yield behavioral target for CUD pharmacotherapy development (Brezing and Levin, 2018).

Although a strong theoretical framework supports the utility of varenicline for CUD, to date, varenicline has not been evaluated in a randomized clinical trial for treatment in this population. As such, the purpose of this study was to conduct a proof-of-concept pilot trial to preliminarily assess safety and initial efficacy of varenicline in cannabis using individuals.

2. Materials and methods

2.1. Design

This study was a 6-week, double-blind, 1:1, parallel group, placebo-controlled trial (NCT02892110) of varenicline (up to 2mg/day). Pre- and post-functional magnetic resonance imaging (fMRI) was completed on a subset of participants and will be reported separately. Participants were primarily recruited through media and internet advertisements. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and received approval from the Medical University of South

Carolina Institutional Review Board. All participants gave written, informed consent prior to study participation.

2.2. Participants

A total of 72 participants meeting DSM-5 criteria for CUD, aged 18 to 65 and using cannabis at least 3 days per week, were recruited from February 2017 to November 2018. Additional inclusion criteria included consent to random assignment, ability to read and provide informed consent, having a body mass index between 18 and 35 kg/m^2, and interest in CUD treatment. Exclusion criteria included women who were pregnant, nursing, or planning to become pregnant during the course of the study; having a lifetime history of DSM-5 bipolar I or II disorder, schizophrenia or other psychotic disorder; suicidal ideation or behavior within the past six months; 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 attention-deficit/hyperactivity disorder medications; contraindication to fMRI for individuals completing those procedures; and meeting criteria for any moderate or severe non-cannabis substance use disorder within the past 60 days with the exception of tobacco use disorder.

2.3. Assessments

The MINI International Neuropsychiatric Interview (MINI) was used to assess psychiatric and substance use diagnoses (Sheehan et al, 1998). A medical history, physical exam, laboratory assessment (comprehensive metabolic panel, complete blood count, and urine pregnancy test if indicated) was also completed. Self-report cannabis use for the 90 days prior to study entry was estimated using the Time-Line Follow-Back (TLFB) (Sobell et al., 1992). Cannabis use was recorded as times or “sessions” used per day, with each session being defined as cannabis use separated by an hour of no cannabis. We used previously utilized methods to standardize for different types of cannabis use (joints, bowls, blunts, etc.), as well as determine overall amount used per day (McRae-Clark et al., 2015; Gray et al., 2017). Tobacco, alcohol, and other substance use was also assessed. Cannabis withdrawal symptoms were assessed at screening and weekly using the Cannabis Withdrawal Scale (CWS; Allsop et al., 2011). The Columbia-Suicide Severity Rating Scale (Posner et al., 2011) was also completed weekly. Urine drug tests were administered twice weekly to qualitatively screen for the presence of opioids, cocaine, amphetamines, and benzodiazepines. In addition, a semi-quantitative urine cannabinoid tests [11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH)] was performed using the AXSSYM® system from Abbott Laboratories with a minimum detection cut-off value of 30.00 ng/ml (Abbott AXSYM® System package insert). Urine creatinine was also obtained, as creatinine normalization has been proposed as a method to differentiate new cannabis use from residual drug excretion (CN-THCCOOH; Huestis and Cone, 1998; Schwilke et al, 2011).

Adverse events were evaluated weekly by a clinician by asking the participant open-ended questions such as “Have you had any problems or side effects since we saw you last (such as cold, flu, nausea, headache, or any other problem)?” The type of adverse event, severity of adverse event, relationship to study medication, action taken, and outcome were recorded.

Adverse events were coded on a weekly basis using Medical Dictionary for Regulatory Activities (MedDRA) rules.

Medication adherence was measured using smartphone video recording (Tomko et al., 2019). Participants recorded themselves taking their morning and evening medication doses with a smartphone and then submitted these videos to research staff via a REDCap survey. Validity of the REDCap data was verified by concurrent data collection with MEMS® caps (medication bottle caps containing an embedded computer chip which digitally records when pill bottles are opened) and participant self-report.

2.4. Interventions

Matching varenicline and placebo tablets were provided by Pfizer, at the standard recommended dose approved for tobacco cessation 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 six-week treatment period. When necessary, medication dose was reduced to 0.5 mg twice daily for tolerability.

All participants received brief motivational enhancement therapy consisting of three individual sessions. The first session occurred during the first week of medication administration, and the second session occurred approximately one week later. Sessions incorporated use of a personalized feedback report summarizing the participant's problems related to use, reasons for quitting, and high-risk situations for use. The major goals of the first session were to build rapport, identify issues related to health behavior change, and goal setting. The second session focused on assessment/review of goals and barriers to goal achievement. The third session occurred at approximately Week 4 and was used to follow-up on action plans. We have successfully used a similar intervention in previous cannabis treatment studies (McRae-Clark et al, 2009; McRae-Clark et al, 2010; McRae-Clark et al. 2015) to provide an evidence-based treatment platform for all participants.

Participants received compensation for completion of study tasks, including completion of study assessments, imaging procedures, and uploading medication adherence videos, up to a possible total of $1375. Fishbowl contingency management was also utilized to enhance study retention, in which participants earned chances to draw a plastic chip from a prize bowl, with chips either having a motivational message ("Good job") or prizes of monetary value (range $1 to $100 per draw).

2.5. Statistics

2.5.a. Study Outcomes and Randomization—Study outcome measures were assessed at baseline and weekly during the final 3 weeks of active treatment, following the initial 2-week medication titration and the targeted quit date. CUD symptom measures included cannabis withdrawal (CWS total score), as well as CWS item scores deemed clinically related to both negative affect and cannabis craving. Negative affect scores included CWS items 5: "I felt nervous", 6: "I had some angry outbursts", 7: "I had mood swings", 8: "I felt depressed", 9: "I was easily irritated", 15: "Life seemed an uphill struggle", and 18: "I felt physically tense". Craving scores included items 1: "The only

thing I could think about was smoking some cannabis" and 10: "I had been imagining being stoned". In addition to the CWS total score, negative affect and craving scores were averaged across all items at each of the final 3 study visits. Additional cannabis use outcomes included a) cannabis abstinence; b) cannabis reduction, measured as changes in creatinine corrected urine cannabinoids taken at each weekly visit (CN-THCCOOH); and c) self-reported changes in cannabis use frequency and intensity, noted as the percentage of weekly use days (frequency) and average reported use sessions per day (intensity) from the TLFB. As abstinence was measured from 1 to 4 weeks following study medication titration, urine THCCOOH levels were not likely to reach the 50 ng/ml threshold and thus alternative markers of new-onset abstinence based on Baker et al. (2018) were included; specifically, creatinine adjusted cannabinoid decrease of 25% or greater from study baseline and urine THCCOOH levels < 200 ng/ml. Medication adherence was assessed weekly from the start of study mediation through the end of study treatment (weeks 1–6).

Participants were randomized in a 1:1 manner utilizing stratified random block design. Randomization was stratified on participant gender and cigarette smoking status. Randomization and dispensing were performed by the MUSC Investigational Drug Service, a centralized research pharmacy that compounds and manages clinical trial medications.

2.5.b Sample Size Determination—The primary focus of this study was to assess whether varenicline, compared to placebo, would evidence greater reductions in cannabis related withdrawal and negative affect during treatment. Assuming a strong correlation between withdrawal and negative affect measures taken weekly within each subject (rho=0.8), a sample of n=68 participants (34 in each treatment group) was deemed necessary for adequate power (80%) to detect a clinically relevant effect size of d=0.60 between the two groups. With the stated sample size, similar differences (d=0.60) in weekly cannabis use quantity were deemed detectible between groups. For the secondary abstinence analysis, the sample size necessary to estimate 50% of a fully powered Phase 3 clinical trial for the abstinence endpoint was determined. To show that treatment with varenicline would yield an abstinence rate at least 20% greater than placebo at the end of study treatment under the most conservative conditions, at a 15% placebo abstinence rate, a sample size of n=72 participants in each treatment assignment (N=144 total) was deemed necessary to provide 80% power with a type 1 error of 5% to detect this difference at the end of a fully powered study. The *a priori* sample size for this pilot trial was therefore n=36 per treatment condition (N=72 total).

2.5.c Statistical Methods—Baseline demographics and clinical characteristics were tabulated for study participants in the overall cohort as well as stratified by randomized treatment assignment (see Table 1). Additionally, these variables were independently assessed for association with cannabis use outcomes (i.e., abstinence and reduction). Variables that indicated association with outcomes were retained for model development ($p<.05$).

The primary hypothesis that participants receiving varenicline would have superior reductions in cannabis withdrawal as compared to placebo participants during treatment was assessed using a generalized linear mixed effects framework. Cannabis withdrawal

was operationalized utilizing the CWS total score as well as subsets of items deemed clinically related to negative affect and craving, analogous to those responsive to varenicline in tobacco cessation trials (Gonzales et al., 2006; Jorenby et al., 2006). Initial models were fit including the main effects of study treatment, visit, and baseline measures. Residual normality was assessed using QQ-plot. Model based group differences and associated 95% confidence intervals (CI) were computed for all estimates

The hypothesis that participants receiving varenicline would have a higher probability of weekly abstinence and lower creatinine corrected cannabinoid levels compared to placebo participants during treatment was assessed using a generalized linear mixed effects framework. A logistic regression model with a sandwich variance estimate was used to assess the efficacy of treatment with varenicline on weekly point prevalence abstinence. To assess the potential impact of missing outcome data on abstinence parameter estimates, sensitivity analyses were completed (a) with missing data imputed to not abstinent [intent-to-treat (ITT) sample] and (b) with all available data. Results are noted as the percent of abstinent participants at each weekly visit and the overall percent of abstinent visits across the 3 final weeks of treatment.

The hypotheses that varenicline participants would have greater reductions in CN-THCCOOH, percent of days using cannabis and craving during study treatment were assessed using a generalized linear mixed effects framework similar to that developed for the analysis of cannabis withdrawal. Initial models were fit including the main effects of study treatment, visit, and baseline measures of each outcome. Correlations between changes in CN-THCCOOH and cannabis use (percent of days using and sessions of use) were assessed using a spearman rank order correlation coefficient. Additionally, cigarette smoking status at study entry was included as a predictor in all cannabis use outcome models. Further, effect modification (model interactions) and stratified analysis of the smoking subgroup was analyzed to determine, what, if any effect smoking status had on use patterns and abstinence across study groups.

The proportion of expected medication doses taken was collected daily and tabulated each week. Medication adherence was determined as those who took at least 80% of expected doses during the study week and was calculated for all actively enrolled participants. A logistic regression model with a sandwich variance estimate was used to assess differences in medication adherence between randomized treatment groups over time. Results are presented as the overall percentage adherent, as well as the percentage adherent within each treatment group.

This was a pilot trial and was not powered *a priori* to detect statistically significant differences; however, statistically significant p values are noted in results tables along-side group level and between group difference estimates (and 95% confidence intervals). For continuous outcomes, effect sizes from weekly group differences are calculated from model-based means and pooled standard deviations and noted as Cohen's *d* while overall treatment effect sizes are noted as partial eta square values ($\eta^2 p$). For binary abstinence, effect sizes are noted as relative risks and 95% confidence intervals. All models additionally control for baseline measures of each outcome. All statistical analysis was conducted using SAS

version 9.4 (SAS Institute Inc., Cary, NC, USA). Significance is noted at a level of α=0.05 and no adjustments for multiple comparisons were made.

3. Results

3.1 Study Participants

Participant demographic and baseline characteristics are presented in Table 1 and progression through study procedures is summarized in Figure 1. Of 136 individuals screened, 82 (60.3%) were eligible to participate and 72 (52.9%) were randomized, 35 to varenicline and 37 to placebo. The end of study treatment visit was attended by 65% of participants (n=47; 22 varenicline and 25 placebo). Study participants averaged 30 years of age (SD=10) and were predominately male (68%; n=49) and Caucasian (58%; n=42). Thirty-one (43%) of the participants were cigarettes smokers and averaged 9 cigarettes per day (SD=11). Study participants reported using cannabis an average of 83 of the 90 days prior to study entry (93%; SD=14%) and noted an average of 3.1 (SD=2.3) cannabis use sessions per day. There were no statistically significant differences for any baseline variables between treatment groups. During study treatment, 93% (67/72) participants remained at the prescribed dose while 7% (5/72) had dosages decreased (varenicline 11.4%; 4/35 vs. placebo 2.7%; 1/37; p=0.14); all four dose reductions in the active treatment group were due to nausea and the single dose reduction in the placebo group was due to muscle spasms. 65% of participants completed all three motivational enhancement therapy sessions (varenicline 63%; 22/35 vs. placebo 68%; 25/37; p=0.85). Median fishbowl contingency management payment over all sessions was $104.50 (IQR: $50.00, $163.00) and was not different between randomized treatment assignments [varenicline $84.00 ($37.00, $195.00) vs. placebo $111.50 ($66.50, $153.50); p=0.63].

3.2 Cannabis Withdrawal

CWS total scores measured during the active phase of study treatment are shown in table 2. Participants randomized to receive varenicline had an average CWS total score decrease of 18.3 (95% CI: 12.1,24.5) and those randomized to placebo had an average decrease of 15.0 (95% CI: 9.2,20.9); between group differences in CWS total scores were not observed [Δ=3.3 (95% CI: −5.2,11.8); Cohen's d=0.12]. Similarly, the average decrease in CWS negative affect score was similar in varenicline participants [1.0 (95% CI: −0.6,1.0)] and the placebo participants [0.6 (95% CI: −0.2,1.0)] with no between group difference [Δ=0.4 (95% CI: −0.2,1.0); Cohen's d=0.16]. The average decrease in CWS craving items was significant in both varenicline 2.4 (95% CI: 2.0,2.9) and placebo 2.6 (95% CI: 2.2,3.1) participants but no difference was noted between groups [Δ=−0.2 (95% CI: −0.8,0.4)); Cohen's d=0.12].

3.3 Cannabis Abstinence and Use Reduction

Self-reported cannabis abstinence during the active phase of study treatment is shown in Table 3. Participants randomized to receive varenicline noted numerically greater rates of overall weekly self-reported abstinence [ITT sample, varenicline: 14.3% vs. placebo: 6.3%; RR=2.3 (95% CI: 0.6,8.1)]. Although abstinence differences between groups were consistent over study visits, the differences were greatest at the end of study treatment [week 6: ITT sample, varenicline: 17.1% vs. placebo: 5.4%; RR=3.2 (95% CI: 0.7,14.7)]. When

only available study visit data was included, relative risk ratios were consistent with those reported for the analysis of ITT data (Data shown in Table 2). Additionally, the creatinine corrected urine cannabinoid tests results appear consistent with self-reported use and are shown in Table 2. Within subject changes in measured CN-THCCOOH from study baseline in the varenicline group were significantly lower as at the end of study treatment visit (visit 6) and higher in the placebo group [Change in CNTHCCOOH from baseline: varenicline −1.7 ng/mg (95% CI: −4.1,0.8) vs. placebo: 1.9 ng/mg (95% CI: −0.4,4.3); Δ=3.5 (95% CI: 0.1,6.9)]. The mean within subject change from baseline CN-THCCOOH taken during the last three weeks of treatment was significantly lower in the varenicline group as compared to placebo [change in CN-THCCOOH from baseline: varenicline: −1.7 ng/mg (95% CI: −3.3, −0.1) vs. placebo: 0.9 ng/mg (95% CI: −0.6,2.5); Δ=2.6 (95% CI: 0.4,4.8)]. In the overall sample, during study weeks where participants reported abstinence, there was a median decrease in CN-THCCOOH from baseline of 71% (IQR: 33.4%, 82.1% decrease) while reported non-abstinent weeks had a median increase in CN-THCCOOH of 21% from baseline (IQR: 61% decrease, 128% increase). These numbers and ranges were similar across treatment assignments. When including biological confirmation with self-reported abstinence, participants randomized to receive varenicline noted numerically greater rates of overall weekly [ITT data: varenicline: 12.4% vs. placebo: 6.3%; RR=2.0 (95% CI: 0.5,7.2)] and end of study treatment abstinence [ITT data: varenicline: 14.3% vs. placebo: 5.4%; RR=2.6 (95% CI: 0.5,12.7)].

3.4 Cannabis Use Frequency and Intensity

Weekly measures of percent using days and reported use sessions from the TLFB are noted in Table 4. Participants in both the varenicline and placebo treated group noted statistically significant decreases in both percentage of days used and use sessions per day during study treatment as compared to baseline. Participants randomized to receive varenicline reported numerically greater overall changes in percentage of study days using as compared to placebo [change in % days using from baseline: varenicline: −41.7% (95% CI: −26.3, −57.0) vs. placebo: −27.4% (95% CI: −13.0, −41.8); Δ=14.3% (95% CI: −7.1,35.7)]. Similarly, participants randomized to receive varenicline reported numerically greater overall changes in cannabis use sessions per day as compared to placebo [change in sessions per day from baseline: varenicline: −2.1 (95% CI: −1.7, −2.5) vs. placebo: −1.8 (95% CI: −1.4, −2.1); Δ=0.3 (95% CI: −0.2,0.9)]. Decreases in CNTHCCOOH from baseline were significantly and positively correlated with decreases in both percent use days (rho=0.33; p=0.001) and weekly use sessions (rho=0.26; p=0.002).

3.5 Nicotine Co-Use

Participants that self-identified as cigarette smokers and had a positive qualitative urine cotinine test prior to study entry represented 43% of the randomized sample and reported relatively low smoking rates at study baseline [mean=9 cigarettes per day (CPD), range=1,40]. Twenty of the 31 cigarette smokers (64.5%) reported smoking less than 10 CPD in the 90 days prior to study entry. In the intent to treat analysis, smokers and non-smokers did not differ statistically in likelihood of achieving weekly cannabis abstinence [ITT sample, smokers: 8.6% vs. non-smokers: 11.4%; RR=0.8 (95% CI: 0.2,2.8)]. Similarly, changes from baseline in CNTHCCOOH [smokers 0.5 ng/mg (95% CI: −1.2,2.2) vs. non-

smokers: 0.2 ng/mg (95% CI: −1.3,2.2); Δ=0.3 (95% CI: −2.6,2.1)] and percent cannabis using days [smokers: −33.1% (95% CI: −16.9, −49.4) vs. non-smokers: −35.6% (95% CI: −21.1, −50.1); Δ=−2.5% (95% CI: −24.9,20.0)] did not differ between smokers and non-smokers. Among cigarette smokers, treatment with varenicline did not affect reported CPD as compared to placebo [varenicline: 7.8 (95% CI: 5.6,10.1) vs. placebo: 7.6 (95% CI: 5.8,9.3); Δ=0.3 (95% CI: −3.1,2.6)]. Further, weekly cannabis use rates (sessions/day) were not significantly associated with co-occurring cigarette use (CPD; β=0.0004; SEM=0.038).

3.6 Adverse Events

Adverse events were tabulated at weekly visits in all randomized participants and relatedness to study treatment established. Adverse events deemed definitely, probably or possibly related to study treatment at the time of report were included in the analysis. At the close of study treatment, 43 (60%) of the 72 participants reported at least one study-related adverse event [20 (54%) in the placebo group and 23 (66%) in the varenicline group (p=0.31)]. Participants reported a total of 106 adverse events during treatment; 47 events were reported in the placebo group and 59 in the varenicline group. The most commonly reported adverse event was nausea (total sample: 23/106, 22%; varenicline 19/59, 32%; placebo 4/47, 9%) followed by dream disturbances (total sample: 16/106, 16%; varenicline 10/59, 17%; placebo 6/47, 13%) and insomnia (total sample: 12/106, 11%; varenicline 6/59, 10%; placebo 6/47, 13%). The majority of reported adverse events were mild/moderate (105/106; 99%). The noted severe adverse event considered related to study treatment occurred in the varenicline treated group (nausea).

3.7 Medication Adherence

Medication adherence was assessed using self-report, pill counts, MEMs Caps, and video diary at each of the six study weeks and reported as the total percent of doses taken. Reported medication adherence was numerically higher using self-report (87%) and pill count (86%) as compared to MEMs Cap (81%) and video diaries (72%). There were no between group differences in self-reported adherence (placebo=89% vs. varenicline=86%; p=0.58), pill count adherence (placebo=87% vs. varenicline=87%; p=.98), MEMs Cap adherence (placebo=81% vs. varenicline=80%; p=0.75) or video diary adherence (placebo=70% vs. varenicline=73%; p=0.89).

4. Discussion

Although not powered *a priori* to find statistically significant differences, this pilot trial provides preliminary data to support further evaluation of varenicline as a treatment for CUD; however, it is noted that overall cannabis abstinence in both treatment groups was low. Significant between group differences in creatinine-corrected urine cannabinoids from study baseline levels were noted, with greater reductions occurring in participants receiving varenicline. Although the study was not powered to detect group differences in self-reported cannabis use, the relative ratio for abstinence favoring the varenicline group at treatment end was similar to the odds ratio of the only positive pharmacotherapy trial abstinence outcome for CUD to date (Gray et al., 2012). However, it is important to note that different criteria for

abstinence were utilized in this study due to the shorter duration than what was used by Gray and colleagues.

All participants reported reductions in cannabis withdrawal symptoms over the course of the study, with no significant between group differences noted and effect sizes (Cohen's d) ranged from negligible to small. A confirmatory factor analysis has been performed on the Minnesota Nicotine Withdrawal Scale to allow measurement of specific withdrawal symptom clusters in tobacco trials (Toll et al., 2007). To date, however, there has not been a factor analysis of a cannabis withdrawal assessment instrument; as such, CWS items mapping on to negative affect and craving in the present trial were selected based on clinical judgment. Given this limitation, a more nuanced evaluation of cannabis withdrawal symptom subscales, as has been conducted in tobacco trials, may have utility in cannabis treatment research.

Overall, the incidence of participants reporting adverse events did not differ between study groups, although it is noted that nausea and dream disturbances, well-documented adverse effects of varenicline, occurred more commonly in varenicline than placebo treated individuals. In addition, retention was similar to that observed in other recent CUD pharmacotherapy trials (Gray et al., 2017; Levin et al., 2016). Multiple measures of adherence were utilized in this trial, and no between group differences in adherence were noted. Objectively measured adherence (video monitoring and MEMS cap) were higher than objective measurements (riboflavin) reported in previous CUD medication trials (McRae-Clark et al., 2015; Gray et al., 2017). However, it should be noted that this trial was only of six-weeks duration, as opposed to the 12-week study duration commonly utilized in CUD investigations. Previous work in this population has shown that medication adherence declines with length of treatment (McRae-Clark et al., 2015); as such, it will be important to evaluate if similar rates of adherence are seen with a full 12-week course of varenicline treatment.

Limitations of this study include the small sample size and truncated treatment duration, given its goal of feasibility testing and evaluation of preliminary efficacy to determine varenicline's suitability for a fully powered trial for CUD. Sex and gender may impact treatment response in cannabis trials (McRae-Clark et al., 2017), and women have been shown to have better response to varenicline than other smoking cessation treatments in tobacco trials (Smith et al., 2017). Due to the small sample size we were not able to conduct sex or gender analyses. Across cannabis clinical trials, challenges exist in outcome measurement due to limitations in biological and self-report measurements (Loflin et al., 2020). Finally, the video uploads of medication taking and payment to attend study appointments may not easily translate to clinical settings and smaller effect sizes may be observed in trials not utilizing such monitoring. Strengths of the trial were use of validated assessments and multiple measures of cannabis outcomes and medication adherence. Although preliminary, these findings suggest future research is warranted to determine if varenicline improves cannabis use outcomes.

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HIGHLIGHTS

- Varenicline was evaluated for cannabis use disorder (CUD) in a placebo-controlled, pilot trial.
- Greater reductions in urinary cannabinoids were observed with varenicline vs placebo.
- Additional research is warranted to determine if varenicline improves cannabis use outcomes.

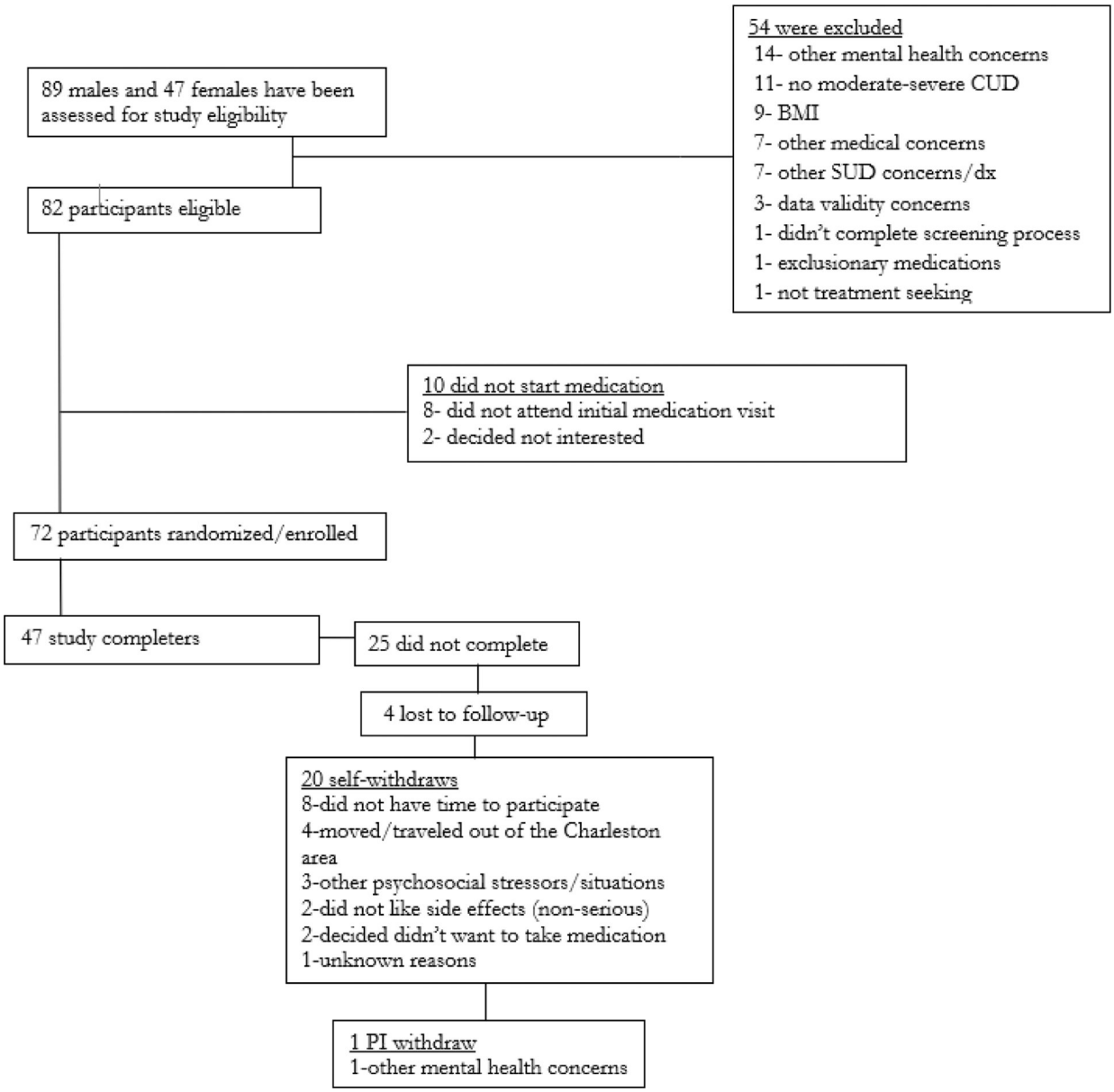

Figure 1.
Study CONSORT flow chart

Table 1.

Demographics and Cannabis Use Characteristics.

Demographics and Cannabis Use Characteristics	Cohort N=72	Treatment Assignment	
		Placebo n=37	Varenicline n=35
Age (yrs)	30.2 (10.1)	29.7 (8.3)	30.8 (11.8)
Male n (%)	49 (68.1)	27 (73.0)	22 (62.9)
Caucasian n (%)	42 (58.3)	23 (62.2)	19 (54.3)
Smoker n (%)	31 (43.1)	19 (51.4)	12 (34.3)
CPD (smokers only)	9.0 (11.3)	8.6 (11.8)	9.7 (10.8)
Baseline Cannabis Use Characteristic			
Percent of days using (90 day TLFB)	92.9 (13.5)	95.3 (10.4)	90.4 (15.9)
Cannabis Use Session/day (90 day TLFB)	3.1 (2.3)	3.4 (2.5)	2.8 (2.0)
Cannabinoids (ng/ml)	457 (738)	365 (436)	555 (958)
Cannabis Withdrawal Scale	34.9 (26.8)	36.9 (29.5)	32.7 (23.7)
Psychiatric Comorbidities			
Alcohol Use Disorder, current	3 (4.2)	1 (2.7)	2 (5.7)
Alcohol Use Disorder, past	6 (8.3)	5 (13.1)	1 (2.9)
Other Substance Use Disorder, past	4 (5.6)	2 (5.4)	2 (5.7)
Major Depressive Disorder, past	10 (13.9)	4 (10.8)	6 (17.1)
Generalized Anxiety Disorder, current	1 (1.4)	1 (2.7)	0 (0.0)
Other Axis 1 disorder, current	4 (5.6)	3 (8.1)	1 (2.9)

Data are shown as Means (standard deviations) unless otherwise noted. Continuous characteristics are compared across treatment assignments using Wilcoxon Rank Sum test and categorical characteristics are compared across treatment assignment using a Pearson chi square test statistic CPD=Cigarettes per day, TLFB=Timeline-follow-back.

* $p<0.05$

Table 2.

Summary data of Cannabis Withdrawal Scale.

Study Visit	Cannabis Withdrawal			Effect Size ǂ	
	Placebo	Varenicline	Difference	Cohen's d	η^2_p
BL	39.7 (26.3,53.0)	31.7 (20.8,42.7)		--	--
4	21.4 (14.9,28.0) *	20.1 (13.2,27.0) *	1.4 (−8.2,10.9)	0.06	--
5	20.9 (14.3,27.6) *	17.4 (10.5,24.2) *	3.6 (−6.0,13.1)	0.15	--
6	18.8 (12.3,25.4) *	13.8 (6.8,20.9) *	5.0 (−4.7,14.6)	0.21	--
Overall ǂ	20.4 (14.5,26.2) *	17.1 (10.9,23.3) *	3.3 (−5.2,11.8)	0.14	0.001

Values are noted as model-based means and associated 95% Confidence intervals adjusted for baseline values of CWS.

ǂOverall treatment difference noted as the model based mean treatment effect during weeks 4–6 adjusted for baseline values.

ǂEffect sizes are noted as Cohen's d and are calculated using adjusted model based mean differences and pooled standard deviations. Partial eta squared values are presented for the overall main effect of treatment adjusted for baseline differences.

*Notes significant within group changes from study baseline levels ($p<.05$).

Table 3.

Summary of Self-Reported Cannabis Abstinence and creatinine corrected cannabinoids (ng/mg).

Study Visit	ITT Data			Available Data		
	Placebo	Varenicli ne	RR (95% CI)	Placebo	Varenicli ne	RR (95% CI)
4	8.1% (3)	14.3% (5)	1.8 (0.5,6.8)	12.0% (3)	22.7% (5)	2.0 (0.5,7.3)
5	5.4% (2)	11.4% (4)	2.1 (0.4,10.8)	8.3% (2)	17.4% (4)	1.7 (0.4,7.2)
6	5.4% (2)	17.1% (6)	3.2 (0.7,14.7)	8.0% (2)	27.3% (6)	2.7 (0.7,10.0)
Overall[†]	6.3% (7)	14.3% (15)	2.3 (0.6,8.1)	9.5% (7)	22.4% (15)	2.1 (0.7,6.8)

	Creatinine Corrected Cannabinoids (ng/mg)			Effect Size[≠]	
	Placebo	Varenicline	Difference	Cohen's d	η^2_p
BL	4.9 (2.2,7.7)	4.8 (2.2,7.4)	0.1 (−3.6,3.9)	--	--
4	4.3 (2.0,6.7)	2.7 (0.2,5.1)	1.7 (−1.7,5.1)	0.33	--
5	6.2 (3.7,8.7)	3.6 (1.2,6.0)	2.6 (−0.9,6.1)	0.38	-
6	6.7 (4.4,9.0)	3.2 (0.7,5.6)	3.5 (0.1,6.9)[**]	0.55	--
Overall[†]	5.8 (4.2,7.3)	3.1 (1.6,4.7)	2.6 (0.4,4.8)[**]	0.42	0.026

Abstinence noted as self-reported abstinence from cannabis use since the last weekly visit % (n)

Creatinine corrected cannabinoid values are noted as model-based means and associated 95% Confidence intervals adjusted for baseline values.

[†]overall treatment difference noted as the model based mean treatment effect during weeks 4–6 adjusted for baseline values.

[≠]Effect sizes are noted as Cohen's d and are calculated using adjusted model based mean differences and pooled standard deviations. Partial eta squared values are presented for the overall main effect of treatment adjusted for baseline differences.

[*]Notes significant within group changes from study baseline levels (p<.001).

[**]Notes significant between group differences in changes from study baseline levels (p<.05).

Table 4.

Summary data of cannabis use frequency and intensity.

Study Visit	% Days Use			Effect Size ≠	
	Placebo	Varenicline	Difference	Cohen's d	η^2_p
BL	95.3 (90.1,100)	88.6 (83.0–94.1)	6.8 (−0.8,14.33)	--	--
4	66.4 (51.3,81.4) *	52.5 (36.4,68.6) *	13.8 (−8.5,36.2)	0.36	--
5	64.8 (49.6,79.9) *	47.5 (31.5,63.5) *	17.3 (−5.1,39.6)	0.49	--
6	65.0 (49.8,80.2) *	53.2 (37.2,69.3) *	11.8 (−10.7,34.2)	0.32	--
Overall ǂ	65.4 (51.0,79.8) *	51.1 (35.7,66.4) *	14.3 (−7.1,35.7)	0.39	0.007
	Use Sessions per day			**Cohen's d**	η^2_p
	Placebo	**Varenicline**	**Difference**		
BL	3.22 (1.80,3.20)	2.76 (1.47,2.74)	0.46 (−0.80,1.71)	--	--
4	1.33 (0.96,1.70) *	0.93 (0.54,1.33) *	0.40 (−0.14,0.94)	0.40	--
5	1.19 (0.82,1.56) *	0.89 (0.50,1.28) *	0.30 (−0.24,0.84)	0.40	--
6	1.21 (0.84,1.58) *	0.89 (0.50,1.29) *	0.32 (−0.22,0.86)	0.33	--
Overall ǂ	1.24 (0.89,1.60) *	0.91 (0.53,1.28) *	0.34 (−0.18,0.86)	0.36	0.009

Values are noted as model-based means and associated 95% Confidence intervals adjusted for baseline values of percent of days used or use sessions reported per day.

ǂOverall treatment difference noted as the model based mean treatment effect during weeks 4–6 adjusted for baseline values.

≠Effect sizes are noted as Cohen's d and are calculated using adjusted model based mean differences and pooled standard deviations. Partial eta squared values are presented for the overall main effect of treatment adjusted for baseline differences.

*Notes significant within group changes from study baseline levels (p<.001).

**Notes significant between group differences in changes from study baseline levels (p<.001).