The Impact of CBT-I on Cannabis Cessation Outcomes

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Research Design and Statistical Plan sections abstracted from CDA application

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2a.3. Research Design and Methods

Design Framework.

The proposed study will employ a between subjects prospective design to follow 168 Veterans with CUD and co-occurring insomnia over the course of six months while individuals complete a treatment/placebo group followed by a cannabis cessation attempt within the context of outpatient addiction treatment at the Menlo Park division of the VA Palo Alto Health Care System. Overall, this design will involve assessments during the following times: baseline (prior to the intervention and quit attempt), *over the course of the intervention,* upon completion of the treatment/placebo group conducted during week 6 (completion of the sleep [or placebo] intervention), and three follow-up assessments conducted 2-weeks, 4-weeks, and 6-months post-cessation. Veterans will be recruited through the outpatient substance abuse treatment program within the Menlo Park Division of the VA Palo Alto Health Care System. Interested participants will complete a brief phone-based screening with a trained research assistant to assess for initial inclusionary/exclusionary criteria. Eligible individuals will then be scheduled for a baseline assessment once enough individuals have been recruited to comprise three groups for the treatment/placebo group portion. Baseline assessments will consist of structured clinical interviews, questionnaires, and a lab-based physiological sleep assessment. Eligible participants will then be randomly assigned to one of three conditions: *(1) CBT-I with adjunctive sleep mobile app (CBT-I-MA); (2) CBT-I only (CBT-I); or (3) Placebo-control (PC).* The treatment/placebo groups will occur weekly for six consecutive weeks. *During this time, substance use (including cannabis) and sleep will be monitored.* Upon completion of the treatment/placebo group (week 6), individuals will complete self-report questionnaires and a sleep assessment. Individuals will then schedule their cessation attempt for the following day. Two-weeks, 4-weeks, and 6-months post-cessation (follow-up assessments) participants will complete home-based sleep assessments (actigraphy) and the same self-report and interview-based questionnaires that were administered during baseline. Assessments will be completed in person. Baseline and 6-month follow-up interviews and questionnaires will take 3 hours to complete, while 2-week and 4-week post-cessation follow-up appointments will take 1 hour. Home-based sleep assessments will occur overnight for the length of each individual's typical sleep cycle (approximately 8 hours).

2a.3.a. Limitations to the proposed procedures and alternative approaches to achieve the specific aims.

A number of design components were carefully considered in order to create the most methodologically sound design while balancing human subjects and feasibility considerations. Below is a detailed overview of these design considerations.

The first design consideration was to determine which CBT-I protocol to implement in the current investigation. This included consideration of a number of components: (1) session content, (2) mode of delivery (individual versus group), and (3) total number of sessions. Session Content: While the primary components of CBT-I are similar across protocols (i.e., sleep restriction, stimulus control, sleep hygiene, cognitive restructuring), there are subtle differences within content that had to be determined. The primary differences are observed in the administration of sleep restriction and the inclusion/exclusion of relaxation training. Specifically, within the original formulation of CBT-I (Glovinsky & Spielman, 1991; Spielman et al., 1987), sleep restriction therapy starts with a short initial time in bed (TIB) and does not include relaxation training. This form of sleep restriction has been shown to result in more efficient results compared to adapted modifications developed more recently (Edinger et al., 1992; Friedman et al., 1991; Hoelscher et al., 1988). Mode of Delivery: Next we considered individual versus group delivery of CBT-I. While clinical trials have been conducted using both individual and group-based delivery methods,

research has demonstrated that group format CBT-I is as effective in the short and long-term as individual treatment (Bastien et al., 2004). Therefore, group format provides a cost-effective, efficient method of delivery which is as effective as individual treatment. Total Number of Sessions: Finally, we considered the most appropriate number of sessions to include within the protocol. While relatively limited research has been conducted in this area, particularly in relation to group formats, research has evaluated the dose-response effect of 1, 2, 4, and 8 CBT-I sessions conducted over 8 weeks. Here, results demonstrated 4 bi-weekly sessions resulted in the best short- and long-term follow-up results among adults with primary insomnia (Edinger et al., 2007). However, this was conducted among a psychologically healthy sample of individuals without substance use disorders. In comparison, among individuals with a substance abuse disorder, six-sessions of group CBT-I resulted in decreased drug use for up to 1-year post-intervention (Bootzin et al., 2005; et al., 2006). Finally, a dissemination effort has recently been initiated to integrate CBT-I throughout the VHA as the empirically supported first-line treatment for insomnia. Specifically, Dr. Rachel Manber (consultant on this proposal) is currently leading the training of mental health clinicians from multiple backgrounds (psychology, social work, nursing) in the effective delivery of CBT-I to Veterans with insomnia and co-occurring conditions (*with the exception of SUD)*. Based on the above research and the current roll-out of CBT-I throughout the VHA, we opted to model our CBT-I delivery after the program already being disseminated throughout the VHA. Therefore, we adopted a group-based six-week intervention including the original formulation of sleep restriction without a relaxation component (Glovinsky et al., 1991; Spielman et al., 1987). Employing the same protocol as the one currently being disseminated throughout VHA will allow this study to be highly generalizable and have the greatest likelihood of VA-wide dissemination should efficacy be established.

Second, we considered the mode of treatment delivery (outpatient versus residential). We opted to utilize outpatient (versus residential) treatment for a number of reasons. First, the majority of Veteran CUD treatment occurs in outpatient treatment centers, providing greater generalizability of study findings. Second, residential treatment removes the individual from their everyday contextual cues that often lead to use, thereby limiting the environmental stimuli that produce conditioned withdrawal effects (Budney et al., 2001). Given the strong influence of context effects on treatment, by utilizing outpatient treatment, individuals will remain in contact with environmental cues for use (e.g., life stressors, friends associated with using), thereby improving ecological validity of study findings.

Third, we carefully considered the most appropriate *experimental (and control) conditions to include*. *W*e considered two primary control options, a waitlist control or a placebo-control. We opted to utilize the placebo-control group for the following reasons: First, we believed use of a waitlist control condition was contra-indicated, as within VHA, waitlist treatment control conditions cannot be employed for ethical concerns of randomly assigning an individual to wait up to 6 months to begin their quit attempt. Second, previous work that has evaluated CBT-I has most commonly utilized a placebo-control as a comparison condition, as quasi-desensitization (described in detail below) has been shown to be an excellent placebo control for insomnia treatment (Krystal & Edinger, 2010). *We also considered the best treatment groups to include in order to determine the effect of the mobile app above and beyond traditional CBT-I. We opted to include a CBT-I only and a CBT-I with mobile app condition for the following reasons: First, this design allows for determining the impact of CBT-I on cannabis cessation outcomes, which has yet to be tested. Second, comparisons of outcomes between the CBT-I and CBT-I-MA groups will allow for determination of the additional benefit provided by the mobile app above and beyond traditional CBT-I, including understanding how a mobile app may bolster outcomes.*

Fourth, we considered the most appropriate timing of the sleep intervention in relation to the cessation attempt. Here, we considered three primary options: (a) sleep intervention precedes the cessation attempt, (b) sleep intervention occurs simultaneously with the cessation attempt, or (c) the sleep intervention occurs after the cessation attempt. We chose not to administer the sleep intervention after the cessation attempt, as insomnia symptoms have a particularly robust effect on cannabis lapse during the first 48 hours of a cannabis cessation attempt (Babson et al., 2013a; Babson et al., 2013b). Given that the proposed sleep intervention is not a single session but rather weeks in duration, we opted to position the sleep intervention prior to the cannabis quit attempt. This design also has the benefit of allowing for prospective conclusions to be drawn about the impact of insomnia treatment on cannabis cessation outcomes, conclusions which would be difficult to ascertain within the context of simultaneous administration, due to temporal effects.

Fifth, we considered the use of *pharmacotherapy (for sleep and other disorders) in our inclusionary/exclusionary criteria. Pharmacotherapy for sleep disturbances often includes FDA-approved hypnotics as well as medications used off-label, especially benzodiazepines, trazodone, and atypical antipsychotics. In addition, the alpha-1 receptor blocker, prazosin, has enjoyed increasing support and utilization (Raskind et al 2013). At the same time, general pharmacotherapy for psychological disorders commonly includes SSRI/SNRIs associated with mild worsening of sleep (Bajor et al, 2011). We opted to include individuals using pharmacotherapy (including for sleep) for the following reasons. First, research has suggested that up to 50% of individuals seeking treatment for sleep disturbances receive a pharmacotherapy to manage sleep (Ohayon, 1996).* Based on these rates, it is likely that a number of individuals interested in the current study may be prescribed a medication to manage sleep. Therefore, inclusion of those using prescription sleep medication would increase the generalizability and feasibility of the current study. Second, research has indicated that individuals using prescription sleep medications respond to CBT-I in a similar manner as those not using prescription sleep medications (Espie et al., 2001; Espie et al., 2007; Morin et al., 2006; Verbeek et al., 1999). Therefore, inclusion of individuals using prescription sleep medications should not impact treatment outcomes from CBT-I. Third, within the roll-out of CBT-I throughout the VHA, pharmacotherapy is not an exclusionary criteria. *Therefore, we opted to include individuals using pharmacotherapy. However, we will include a medication form for participants to complete during each assessment. This will include class of medication (SSRI/SNRI, benzo, non-benzo hypnotic, trazodone, prazosin, atypical anti-psychotic), dosage, and use since the previous assessment (See Measures section). Should group-based differences on these factors emerge, we will conduct exploratory moderating analyses to investigate the role of pharmacotherapy on outcomes.*

Finally, we considered our inclusionary/exclusionary criteria in relation to co-occurring psychopathology and sleep apnea. We have sought to balance internal and external validity by including individuals with co-occurring conditions, while also developing an internally valid design. As the majority of Veterans present with co-occurring psychological conditions, for both generalizability and feasibility purposes, we chose not to exclude Veterans with comorbidities. However, we will measure co-occurring psychological symptoms during the baseline assessment. While randomization into treatment group should result in relatively consistent groups in terms of demographic, baseline, and co-occurring symptoms, prior to data analysis we will compare treatment groups in terms of baseline factors. Should baseline differences emerge, we will conduct exploratory analyses to investigate the moderating role of each factor on the outcomes. In relation to sleep apnea, to increase generalizability and to be consistent with previous work (Edinger et al., 2009), we will include individuals with sleep apnea that have an apnea hypopnea index (AHI) less than 15. The AHI cut-off of 15 was chosen as this will allow for the inclusion of individuals with minimal-mild sleep apnea (AHI under 15), while excluding

individuals with moderate to severe (AHI 15-30) apnea. Individuals with moderate-severe apnea (AHI >15) will be excluded as this level of apnea would cause significant sleep fragmentation that would impair sleep to the point that we would not expect CBT-I to result in significant treatment gains without the inclusion of treatment for the likely underlying cause of the sleep disturbance (i.e., sleep apnea).

2a.3.b. Study Settings.

The proposed study will take place in the context of outpatient substance abuse treatment within VA Palo Alto's Outpatient Addiction Consultation and Treatment Program (see letter of support from Dr. Michael Potoczniak). This program is comprised of outpatient group-based substance abuse treatment. Treatment consists of five hours of group-based substance-focused therapy per week. In addition, 75% of Veterans enrolled in this program receive three hours of therapy per week focused on comorbid psychiatric conditions; however treatment for insomnia is not provided. In FY 2011, 485 unique patients were treated through the outpatient treatment program for a CUD. The majority of individuals were self-referred to this program (75%), with a minority of individuals being legally mandated to treatment (2%). Upon admission to the program individuals are screened for co-occurring symptoms, however, they are not required to complete detoxification. The outpatient program provides treatment for a broad range of substance use disorders, including CUD. The treatment components include: psychoeducation, motivational enhancement, cognitive behavioral therapy for relapse prevention, and supportive group therapy. In conjunction with this treatment protocol, approximately 90% of individuals participate in 12-step groups such as Alcoholics Anonymous. Treatment is administered by members of the 15 person full-time staff, including two clinical psychologists. Importantly, individuals engage in components of treatment outlined above prior to their quit attempt. Within this context, a formal quit day is not determined. In the current study, this existing treatment will be augmented by including a treatment/placebo group prior to the cessation attempt and will formalize a set quit day which will occur after completion of the treatment/placebo group (see below for group details). This design will not result in a delay of VA treatment.

Treatment Administered:

The cannabis cessation attempt will be completed in conjunction with standard substance abuse treatment within the VA Palo Alto's Outpatient Addiction Consultation and Treatment Program (Described above in the "study settings" section). The unique addition offered by this study will include randomization into a behavioral sleep intervention *(with or without a mobile app)* or a placebo-control intervention for sleep, and formalization of a quit day (to occur after completion of the treatment/placebo group). These interventions are described in detail below:

Cognitive Behavioral Therapy for Insomnia Only (CBT-I). Individuals randomized into the CBT-I group will receive group-based CBT-I. CBT-I will be administered consistent with the VHA roll-out. This will include six group-based sessions (1/week) as follows: session 1: General overview/introduction; session 2: Sleep restriction (SRT) and stimulus control (SC); sessions 3-5: modify SRT guidelines as indicated, add additional components including counter-arousal methods and addressing sleep-interfering cognitions; session 6: Review of treatment content and relapse prevention.

Cognitive Behavioral Therapy for Insomnia with Adjunctive Sleep Mobile App (CBT-I-MA). Individuals randomized into the CBT-I-MA group will receive group-based CBT-I *identical to the CBT-I condition described above. However, individuals randomized to this group will also be provided with an adjunctive sleep mobile app. The mobile app has been developed by the National Center for PTSD (NCPTSD) as an adjunct to group-based CBT-I. The content of the app mirrors that provided by traditional CBT-I and includes four main interactive content areas: "My Sleep," "Tools," "Learn," and "Reminders." "My Sleep" provides individualized tracking of sleep and sleep prescriptions. Here, individuals can complete sleep diaries, update and track sleep prescriptions, and complete sleep assessments to determine patterns in sleep disruption, and*

obtain individualized suggestions for improving sleep. The "Tools" section provides (1) psychoeducation consistent with CBT-I strategies and framework including sleep hygiene tips and stimulus control instructions, (2) guided relaxation tools that can be used in the moment to assist in treatment outcomes (e.g., guided relaxation, guided worry time), and (3) individualized recommendations for relapse prevention. The "Reminders" section includes menus to customize and set reminders to (1) complete assessments, (2) set alarms for prescription bed and rise times, and (3) begin wind-down time. Finally, the "Learn" section includes psychoeducation on stages of sleep, why we sleep, additional sleep disorders, and treatment including CBT-I. In addition, a glossary of terms is provided as well as recommended good sleep habits. Participants randomized to this condition will be provided with an iPod Touch, which will be loaded with the mobile app, for the duration of the study.

Placebo Control (PC). Individuals randomized to the placebo control condition will receive six sessions of a placebo intervention modeled after quasi-desensitization within a group-based context. Quasi-desensitization is a well-established and credible non-pharmacological placebo intervention which has been successfully used in multiple clinical trials for insomnia treatment (Edinger et al., 2001; Krystal & Edinger, 2010). This placebo treatment has been shown to be a credible intervention and is associated with high expectations of positive outcomes (Edinger et al., 2001; Krystal & Edinger, 2010). In addition, CBT-I has been shown to be effective when compared to this control intervention (Edinger et al., 2001; Krystal &Edinger, 2010). Quasi-desensitization is based on the theory that symptoms of insomnia will remit as a result of desensitization to conditioned arousals during sleep. Based on this, quasi-desensitization involves the development of a hierarchy of 12 activities that occur during awakenings from sleep (e.g., watching clock). In addition, individuals also develop six imaginal scenes of themselves engaging in neutral activities during the day (e.g., reading, watching TV). Individuals are then taught to pair the neutral image with each of the 12 activities on the hierarchy. During each session, these pairings are reviewed.

2a.3.c. Recruitment Procedures.

We will implement a multi-pronged recruitment process. First, we will advertise the study to each Veteran presenting to the outpatient SUD treatment center at VAPAHCS. Second, staff within the outpatient SUD treatment center will provide study and contact information to patients beginning the program. Finally, in order to ensure enrollment of individuals with comorbid insomnia, we will also advertise within the outpatient SUD treatment center with flyers that specifically mention insomnia symptoms. Patients interested in the study will contact the research laboratory to complete a brief phone screening for initial eligibility criteria and schedule a baseline appointment. Several mentors including Drs. Trafton and Bonn-Miller have long-standing relationships with the outpatient SUD treatment center at the VAPAHCS which will facilitate recruitment and completion of this project (Also see letter from Dr. Michael Potoczniak).

2a.3.d. Participants.

A sample of 187 male and female (10%) Veterans with CUD and insomnia, self-motivated to make a cannabis quit attempt within the context of the VA outpatient SUD treatment center at the Menlo Park Division of the VA Palo Alto Health Care System, will be targeted. Allowing for 10% attrition during the baseline assessment, a sample of 187 will provide a final randomization of 168 Veterans into one of the three treatment conditions. In FY 2011, the outpatient SUD program at the VAPAHCS treated approximately 485 unique individuals meeting criteria for CUD. Based on previous research, we expect that approximately 60% of individuals with a CUD will also meet criteria for insomnia (Budney et al., 2008). Therefore, this sample will be feasible to recruit by the beginning of year 4 (see "Timeline for Primary and Secondary Research Activities").

2a.3.e. Inclusionary and Exclusionary Criteria.

Inclusion and exclusionary criteria was carefully considered in order to balance internal and external validity with minimal risk and greatest benefit to participants. To be included in the current study individuals must (1) be a Veteran 18 years or older scheduled to begin outpatient SUD treatment at VAPAHCS; (2) meet DSM-5 diagnostic criteria for cannabis use disorder; (3) meet DSM-5 diagnostic criteria for insomnia; (4) endorse a motivation to quit, evidenced by actively thinking about/or having a plan to quit in the next month; and (5) be willing to formalize and agree to a quit day which will occur after completion of the treatment/placebo group. Individuals will be excluded based on evidence of the following: (1) inability to provide fully-informed written consent to participate; (2) history of, or current, psychotic symptoms; (3) current pregnancy; (4) apnea hypopnea index (AHI) >15, indicative of moderate to severe sleep apnea; and (5) active suicidal/homicidal intent. Suicidal and homicidal intent will be assessed in the context of a structured clinical interview (see section 2a.3., "measures" subsection for details). In the case that respondents endorse active intent they will be referred immediately for treatment and will be excluded from the current study.

2a.3.f. Participant Retention.

Participant retention strategies are based on strategies successfully used in past research designs by members of this research team. Based on previous prospective designs, the risk for participant attrition may occur at 3 main time points: baseline, during treatment, and follow-up. We will specifically address each time point to limit attrition rates. First, it is expected that a small number of individuals will not complete the baseline assessment. In this case, those individuals will be excluded from data analysis and replaced with another participant. In relation to prospective retention, of those completing baseline procedures, we expect 80% of the original sample to complete all follow-up assessments (Heinz et al., 2013*;* also see section 2a.3, "Missing Data" subsection). *We will recruit 187 Veterans in order to account for 10% attrition from baseline to the group intervention, with the goal of randomizing 168 Veterans.* In addition, an intent-to-treat approach will be used for all analyses. *Within the intent-to-treat approach individuals completing at least 70% of the intervention/control group will be included in all analyses, thereby limiting the impact of the predicted 20% attrition.* Finally, we will employ a multi-pronged approach to enhance participation in all follow-up assessments. This approach will utilize financial incentives, participant contact, and session reminders.

Financial Incentives. To reduce attrition rates, a weighted compensation schedule will be employed as follows: Baseline assessment ($50), post-treatment/placebo group (6-weeks) ($50), 2-weeks post-cessation ($25), 4-weeks post-cessation ($25), and 6-months post-cessation ($25), with a $60 bonus for individuals that completed all time points. Overall, the rate of compensation was determined based on $19/hour of daytime assessment.

Contact with Participants. Throughout the course of the study, simultaneous strategies will be employed by the research team to maintain participant contact. First, during the initial intake assessment a tracking log will be completed for each participant that includes: (1) home address, (2) home/work /cell phone numbers, (3) employment or school information, and (4) contact information for two additional individuals to be used if contact with the participant is lost. This information will be kept behind VA firewalls and password-protected tracking database and continually updated (See section 4a, "Human Subjects" for more information). Further, tracking information will be collected at all follow-up interview points. Additional methods to help reduce attrition will include specialized cards such as individualized birthday cards, holiday cards, and occasional thank-you fliers, each of which will include a toll free number of the study center for subject-initiated contact. These mailings will also include a change of address and phone form. This approach has been used successfully before in prospective work (Gwadz & Rotheram-Borus, 1992), including that of Drs. Bonn-Miller and Trafton.

Reminders: Trained research staff will place reminder calls to participants the day before their scheduled appointments to provide a reminder and address any questions or concerns that

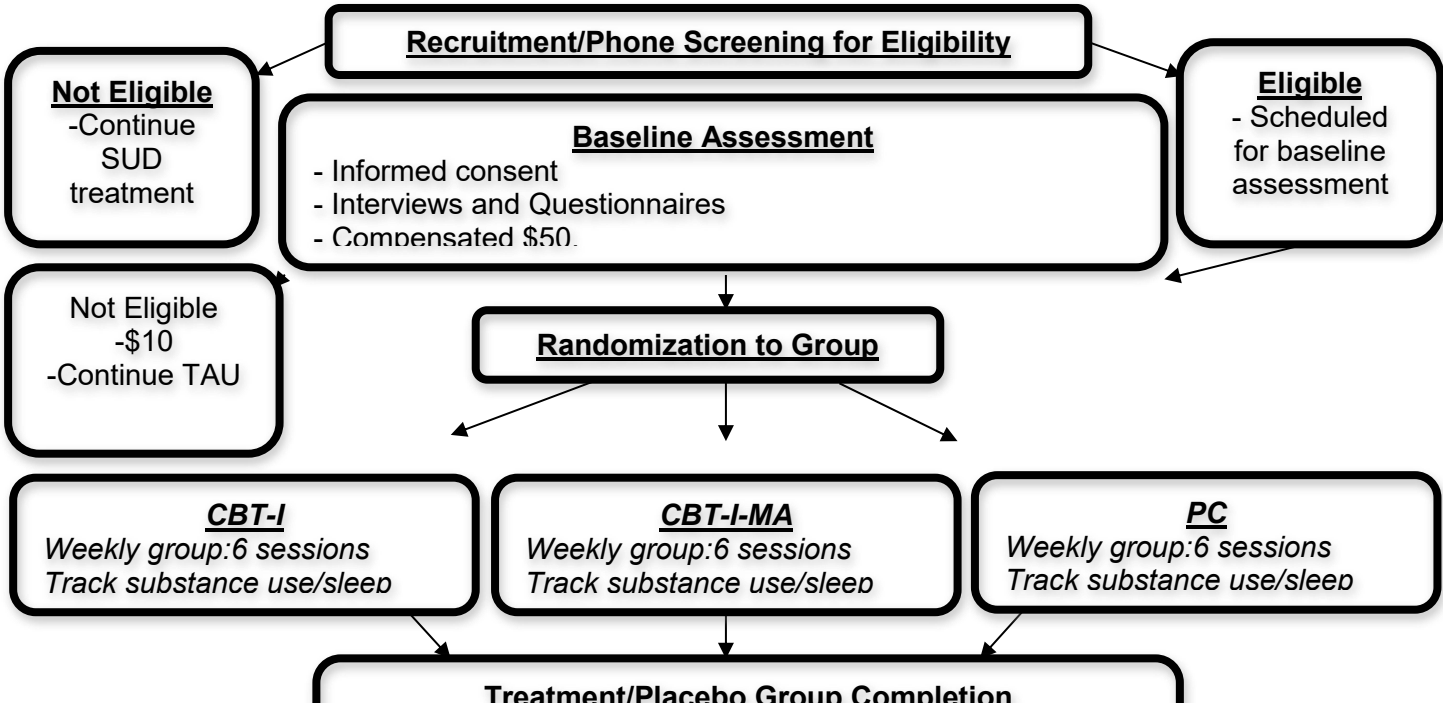
have arisen. Reminder calls will be placed for the baseline appointment as well as the 2-week, 4-week, and 6-month post-cessation follow-up appointments.

2a.3.g. Data Collection Procedures.

See Figure 2 for a graphical depiction of the study procedures. Recruitment will target Veterans with CUD and co-occurring insomnia, within the Outpatient Substance Use Treatment Center at the Menlo Park Division of VAPAHCS. A research assistant will conduct a brief phone screen with interested individuals to assess for eligibility criteria. Once a recruitment sample large enough to comprise *three* groups is obtained, eligible individuals will then be scheduled for an in-person baseline session. During the baseline assessment, participants will provide written informed consent. Second, a more detailed assessment of inclusionary/exclusionary criteria will be conducted. Should an individual not meet inclusionary criteria during this more in depth session, they will be compensated $10 and will continue with treatment within the outpatient substance use treatment center, but will not be included in the current study. Individuals meeting all criteria will be administered structured clinical interviews, questionnaires, and an objective (lab-based) and self-report sleep assessment to collect baseline levels of responding, *and assess for sleep apnea*. Participants completing all portions of the baseline assessment will be compensated $50 and randomly assigned to one of three groups: *(1) CBT-I with adjunctive sleep mobile app (CBT-I-MA); (2) CBT-I only (CBT-I); or (3) Placebo-control (PC).* The treatment/placebo groups will occur weekly for six consecutive weeks *during which time substance use (including cannabis) and sleep will be monitored*. Upon completion of the treatment/placebo group (week six), individuals will complete a series of self-report questionnaires and a sleep assessment (post-treatment/placebo group assessment). Upon completion of this assessment, individuals will be compensated $50 and will be instructed to make a serious cannabis cessation attempt the following day. Follow-up assessments will be conducted at 2-weeks, 4-weeks, and 6-months post-cessation. During this time, participants will complete home-based sleep assessments (actigraphy) and the same self-report and interview questionnaires that were administered during baseline. Assessments will be completed in person at the Menlo Park division of VAPAHCS. Participants will be compensated $25 for completion of each follow-up assessment (plus an additional $60 bonus for completion of all time points). Baseline and 6-month follow-up interviews and questionnaires will take three hours to complete, while 2-week and 4-week post-cessation follow-up appointments will take 1 hour. Home-based sleep assessments (actigraphy) will occur overnight for the length of each individual's typical sleep cycle (approximately 8 hours). Upon completion of the study individuals will be debriefed and provided with referral information.

2a.3.h. Data Collection Procedures Overview.

Figure 2. Overview of Procedures.



Method: *Overview.* A multi-modal method of assessment will be utilized to measure all variables in the current study. This will include the use of the following forms of assessment: self report questionnaires, clinical interviews, and psychophysiological measures. All assessments will be administered by a trained research assistant blinded to condition. The measures to be employed are outlined below in relation to the construct being assessed. Interested participants will be contacted by the research team at which point a brief phone screen will be conducted and eligible participants will be scheduled for a baseline assessment once enough individuals are recruited to generate *three* groups for the treatment/placebo group portion. This appointment will include verification of inclusionary/exclusionary criteria and completion of all baseline assessments. The estimated length of the baseline assessment is 3 hours plus a lab-based overnight sleep assessment. Please see Table 1 for an overview of the measures and the timing of administration.

2a.3.i. Measures

Measures: ***Descriptive Characteristics of the Sample.***

Demographics: A brief self-report demographics questionnaire will be administered. This questionnaire will obtain information related to sex, age, ethnicity/race, education level, employment, and era of service.

Measures: ***Inclusionary/Exclusionary Criteria and Axis I Psychopathology.***

Cannabis Use Disorder, Insomnia Disorder, Psychiatric Diagnoses, Suicidality: The Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1995) will be administered at baseline to assess for current Axis I diagnoses, including CUD, insomnia disorder, and active suicidal intent. Questions for the CUD and insomnia disorder sections will be modified to be consistent with criteria for DSM-5 (APA, 2013). These modified sections will be used to determine eligibility criteria for CUD and insomnia disorder, respectively. Active psychosis and suicidal intent will also be determined based on this interview. Individuals endorsing these criteria will be excluded from the current study, and those endorsing active suicidal intent will be referred for appropriate care (See "*Human Subjects*" section for details). Finally, the SCID-I will also be used to document current (past 6 month) comorbid Axis-I psychopathology to provide information about sample characteristics.

Motivation to Quit: Motivation to quit cannabis will be assessed using an adapted version of the Contemplation Ladder (CL) developed for tobacco cessation (Prochaska & DiClemente,

1983). The CL is a visual analogue scale comprised of 10 steps, each with a corresponding statement assessing motivation to quit cannabis. *The CL will be used to assess both inclusionary (those planning to quit within the next 30 days), and exclusionary (those with little to no motivation to quit) criteria.*

Obstructive Sleep Apnea: Initial screening for obstructive sleep apnea (OSA) will be conducted using the Berlin Questionnaire (Netzer et al., 1999). This measure assesses known risk factors for OSA, and consists of self-report questions indexing snoring (5 questions), daytime sleepiness (3 questions), history of high blood pressure (1 question), and information on age, sex, body mass, neck circumference, and ethnicity. Based on responses to these symptom categories, level of risk for OSA is determined based on the following criteria: Category 1: "high risk" includes persistent symptoms (>3 to 4 times/week) in 2 or more questions about snoring. Category 2: "high risk" includes persistent symptoms (>3 to 4 times/week) of sleepiness, drowsy driving, or both. Category 3: "high risk" includes history of high blood pressure or a BMI of more than 30 kg/m^2. In order to meet criteria for "high risk," individuals must qualify for at least 2 of the above high risk categories. Those not meeting these criteria are deemed "low risk." Objective confirmation of OSA will be conducted during the intake polysomnography assessment (see below for details). Consistent with methods of scoring set forth by the American Academy of Sleep Medicine, apneas will be defined as complete absence of airflow, while hypopneas are defined as a greater than 50% reduction in chest excursion and a 3% oxygen desaturation, or greater than 50% decrease in chest excursion and arousal. AHI will be calculated. Consistent with published guidelines, the following scoring scheme will be employed: mild OSA (AHI: 5-14.9), moderate OSA (AHI:15-29.9), and severe (AHI >/= 30). *Individuals with an AHI of 15 or greater will be excluded.*

Measures: *Cannabis Use.*

Cannabis Use Frequency and Relapse: Timeline follow-back (TLFB; Sobell & Sobell, 1992) will be used to assess past 3 month cannabis use at baseline and at the 2-week, 4-week, and 6-month follow-ups. The TLFB procedure has demonstrated good reliability and validity in past work across diverse samples (Sobell & Sobell, 1992). Cannabis use information obtained from the TLFB will be used as outcome variables for Aim 1. Research has demonstrated that TLFB is as effective as biochemical measures of substance use (Hjorthøj et al., 2012; Hjorthøj, Fohlmann, et al., 2012).

Measures: *Sleep Disturbance.*

Sleep Diary: The Consensus Sleep Diary (CSD; Carney et al., 2012) will be used to prospectively monitor self-reported sleep. The sleep diary has been deemed the "gold standard" self-report assessment of sleep (Carney et al., 2012). The CSD is a new standardized sleep diary based on expert consensus and qualitative patient input, developed for use across a range of clinical and research settings. The CSD is the primary self-report sleep assessment being used to monitor responses to CBT-I within the VHA roll-out of this treatment. The CSD will be completed daily throughout the course of this study.

Objective Sleep Assessment: Lab-Based Polysomnography (PSG): Lab-based overnight polysomnography will be conducted through the use of the Nihon Kohden Trackit Sleepwalker system to objectively measure sleep and assess for severity of sleep apnea (AHI) during the baseline assessment. This system is a 16-channel, level 2 ambulatory monitoring system that acquires the following signals: EEG (at F3, F4, Cz, Pz), horizontal electroculogram (EOG), chin electomyogram (EMG), Electrocardiogram (ECG), chest circumference (impedance plethysmography), abdominal circumference, nasal pressure, left and right leg movement (via accelerometry), oxygen saturation (SpO_2), and body position (right lateral, left lateral, prone, and supine). Based on these signals we will obtain data on obstructive sleep apnea, sleep staging, body position, total sleep time, and sleep efficiency. Assessment will take place within the sleep

lab of the NCPTSD.

Objective Sleep Assessment: Actigraphy (ACT): wActiSleep+Monitor actigraphy devices will be used to measure objective sleep at baseline, post-group (intervention/control), and all follow-up assessments. This noninvasive objective assessment device provides accurate and reliable measurements of sleep and wake including the following: amount of sleep, number and duration of awakenings, sleep efficiency, amount and intensity of physical activity, energy and activity, and sleep position.

Measures: ***Potential Moderating Factors:***

Due to randomization procedures we expect baseline equivalence between groups on potential confounding factors. However, prior to conducting the primary analyses, we will assess for group-based differences on baseline levels of potential confounding factors. *Should group-based differences emerge, these variables will be investigated as potential moderators of outcomes within exploratory analyses (See 2a.3.j. Planned Data Analysis).* The potential confounding factors described below were chosen based on prior research (Budney et al., 2003; Degenhardt, & Hall, 2012; Degenhardt, Hall, & Lynskey, 2001; Matthews, Hall, & Gartner, 2011; Roehrs & Roth, 2001; Tsuno, Besset, & Ritchie, 2005; Wetter, Fiore, Baker, & Young, 1995).

Psychological Diagnoses: The current diagnostic status of Axis I psychological disorders will be assessed at baseline using the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1995). Sections will be modified to be consistent with criteria for DSM-5 (APA, 2013).

Anxiety and Depressive Symptoms: General levels of anxiety and depression will be measured with the Inventory of Depression and Anxiety Symptoms (IDAS). The IDAS is a 64-item self-report measure of depression and anxiety (Watson et al.,2007). Factor analytic research indicates that the IDAS has strong convergent and discriminate validity, as well as criterion validity (Watson et al., 2008). Additionally, factor analytic research indicates that the general depression and anxiety subscales of the IDAS differentiate anxiety and depression (Watson et al., 2007; 2008). Thus, the IDAS will be used to measure anxiety symptoms and depression symptoms at all time points.

Negative Affectivity: The negative affect subscale of the 20-item Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) will be utilized to measure negative affectivity. This instrument has shown good internal consistency as well as discriminate and convergent validity (Watson et al., 1988). The PANAS will be administered at all time points to obtain levels of negative affect.

Other Substance Use: In addition to cannabis, Timeline Follow-Back (TLFB; Sobell & Sobell, 1992) will also be used to assess past 3 month use of caffeine, alcohol, tobacco, and illicit drug use during the baseline assessment, and use during weekly assessments and during the 2-week, 4-week, and 6-month post-cessation follow-ups.

Pharmacotherapy Use: The use of pharmacotherapy will be assessed using the prescription medication index (PMI). This measure assesses *class of medication (SSRI/SNRI, benzo, non-benzo hypnotic, trazodone, prazosin, atypical anti-psychotic), dosage, and use since the previous assessment. It is reasonable to expect that the distribution of these prescriptions will not differ across treatment arms after randomization. For classes that do differ, dummy codes will be generated and used in exploratory analyses to evaluate the moderating role of pharmacotherapy on outcomes.*

Table 1. Overview of assessment to be administered at each time point.

		Time Points of Administration

Construct	Assessment	Baseline	*Weekly During Group*	Post-group	2-weeks post-quit	4-weeks post-quit	6-month post-quit
Descriptive Characteristics of the Sample							
Demographics	Demographics	X					
Psychiatric Diagnoses	SCID-I	X					X
Inclusionary/Exclusionary Criteria							
Insomnia Disorder	SCID-I*	X					X
Suicide	SCID-I	X					
Cannabis Use Disorder	SCID-I*	X					X
Motivation to Quit	CL	X					
Sleep apnea	Berlin/PSG	X					
Outcomes: Sleep							
Insomnia Symptoms	CSD	X	X	X	X	X	X
	ACT	X		X	X	X	X
Outcomes: Cannabis Use							
Cannabis Use Frequency	TLFB	X	X	X	X	X	X
Relapse Status	TLFB				X	X	X
Potential Confounding Factors							
Age	Demographics	X					
Era of Service	Demographics	X					
Psychological Diagnosis	*SCID-I**	X					
Anxiety Symptoms	IDAS	X		X	X	X	X
Depression Symptoms	IDAS	X		X	X	X	X
Negative Affect	PANAS	X		X	X	X	X
Other Substance Use	TLFB	X	X	X	X	X	X
Pharmacotherapy	PMI	X	X	X	X	X	X

Note: * = modified to be consistent with DSM-5 criteria. The post-group assessment corresponds to completion of the treatment/placebo groups.

2a.3.j. Planned Data Analysis.

Generalized Linear Mixed Modeling (GLMM) will be used as the primary data analytic approach for Aims 1 and 2. We believe this approach will provide the most parsimonious test of our hypotheses based on the following considerations. First, we considered only evaluating outcomes at the 6-month follow-up. While this approach would provide information regarding long-term outcomes, it has significant limitations including: (a) increased potential for attrition and missing data, and (b) loss of knowledge regarding outcomes immediately after the quit attempt (i.e., 2-weeks, 4-weeks). For these reasons an analysis focusing solely on the 6-month follow-up would not provide the most reliable and powerful test of the hypotheses. *Second, GLMM allows for modeling slope and change over time. This approach will allow us to model change in substance use and sleep over the course of short-term (2-weeks, 4-weeks) and long-term (6-months) follow-up, while also allowing us to model any unpredicted change in substance use (e.g., cannabis) during the treatment/placebo phase.* Based on these considerations we opted to conduct the primary analysis for Aims 1 and 2 by evaluating change over time through the use of GLMM. This analytic approach is favorable for a number of reasons including its ability to include all available data, not just data from patients who complete assessments. In addition, we will conduct secondary analyses for each hypothesis to evaluate group differences at each time point.

To account for family wise error, alpha will be adjusted in all secondary analyses. *Importantly, over the course of group CBT-I (or placebo group), we will track participants' substance use, including cannabis, and sleep. We will model all outcome data from the start of the intervention. This approach will allow for modeling any unpredicted changes in cannabis use (i.e., increase or decrease in use) during the intervention portion of the study.* Below we provide a detailed overview of how GLMM will be employed for Aims 1 and 2.

Aim 1:

Hypothesis 1.1. Veterans who receive either *CBT-I-MA or CBT-I* prior to a cannabis cessation attempt will evidence a greater reduction in cannabis use frequency over the three post-quit attempt assessments (2-weeks, 4-weeks, and 6-months post-quit day) as compared to those who receive *PC*. In order to test this hypothesis a mixed-effects regression will be used to model changes in the dependent variable (frequency of cannabis use) across time as a function of group membership and baseline values (fixed effects) with a random effect for person to account for repeated measurements; frequency of cannabis use (obtained from TLFB; See 'measures' section for details).

As a secondary analysis, we will conduct an *analysis of covariance (ANCOVA; alpha set to .01)* to examine group differences in cannabis use frequency at each time point (2-weeks, 4-weeks, and 6-months post-cessation).

Hypothesis 1.2. Veterans receiving either *CBT-I-MA or CBT-I* will have greater point prevalence abstinence (PPA) over the three post-quit attempt assessments (2-weeks, 4-weeks, and 6-months post-quit day) compared to those receiving *PC*. In order to test this aim we will evaluate the differences in PPA between *CBT-I-MA and both CBT-I and PC groups, and CBT-I and PC groups* across the three follow-up assessments (2-weeks, 4-weeks, and 6-months post-cessation). This will be conducted through the use of a mixed-effects logistic regression.

As a secondary analysis, we will conduct three chi-square analyses to examine group differences in rates of PPA at each of the three time points (2-weeks, 4-weeks, 6-months post-cessation).

Exploratory Hypothesis. In terms of the above cannabis outcomes, those who receive CBT-I-MA will evidence better outcomes (reduced frequency and greater PPA) as compared to those who receive CBT-I. Results related to this hypothesis will be determined through analyses conducted for the primary hypotheses (Hypothesis 1.1 and 1.2).

Secondarily, we will conduct exploratory analyses to examine factors (e.g., adherence, dose) that account for differences observed between the CBT-I-MA and CBT-I groups in relation to cannabis outcomes through the use of mediation models. Mediators of interest will include adherence (measured by session attendance), and dose.

Aim 2:

Hypothesis 2.1. Veterans who receive either *CBT-I-MA or CBT-I* prior to a cannabis cessation attempt will evidence improved sleep quality, as indicated by self-report and objective measures, over the three post-quit attempt assessments (2-weeks, 4-weeks, and 6-months post-quit day) as compared to those who receive *PC*. In order to test this hypothesis, two mixed-effects regressions will be conducted, one for self-report sleep (see '*measures'* section for details) and another for objective indices of sleep (see '*measures'* section for details). First, we will model changes in the dependent variable (self-report or objective sleep) across time as a function of group membership and baseline values (fixed effects) with a random effect for person to account for repeated measurements (random effects).

As a secondary analysis, four ANCOVAs will be conducted to examine differences in self-reported sleep quality between groups at each time point (following 6-week treatment/placebo group, 2-weeks, 4-weeks, 6-months post-cessation attempt). *A series of four additional ANCOVAs* will then be conducted to examine group-based differences in objective sleep at each time point (following 6-week treatment/placebo group, 2-weeks, 4-weeks, 6-months post-cessation attempt). *All ANCOVAs will adjust alpha to account for family wise error rate.*

Hypothesis 2.2. Group based differences in cannabis outcomes averaged across the three post-quit attempt assessments (2-weeks, 4-weeks, and 6-months post-quit day) will be explained

by average sleep quality (self-report and objective) averaged across the three post-quit attempt assessments. To address the second hypothesis of aim 1, GLMM will be used to evaluate the mediating role of (a) self-report sleep quality averaged over time (b) objective sleep quality over time (2-week, 4-week, and 6-month post-cessation follow-ups). The MacArthur model of mediation will be used as this model, compared to Baron and Kenny's approach, is not based on a linear model. In addition the longitudinal design allows for determination of the temporal precedent of our mediator to the predictor variable, thereby meeting criteria for the MacArthur approach (Kraemer et al., 2008). Specifically, two independent models will be conducted. First, we will evaluate self-report sleep quality over time on the relation between group and average cannabis use frequency over time. Three steps will be conducted using mixed models. First, we will examine the relation between group and cannabis use frequency over time (path C). Second, we will examine the relation between group and self-reported sleep quality over time (path A). Finally, we will enter both group and self-reported sleep quality over time within the same model to predict frequency of cannabis use over time. Confidence intervals will be used to assess for significant partial mediation. Within the mediation model, the same series of steps will be conducted to evaluate the mediating role of objective sleep over time on the relation between group and cannabis use frequency over time.

Exploratory Hypothesis. In terms of the above sleep outcomes, those who receive CBT-I-MA will evidence better outcomes (improved sleep quality) as compared to those who receive CBT-I. Results related to this hypothesis will be determined through analyses conducted for the primary hypothesis of Aim 2 (Hypothesis 2.1).

Secondarily, we will conduct exploratory analyses to examine factors (e.g., adherence, dose) that account for differences observed between the CBT-I-MA and CBT-I groups in terms of sleep outcomes through the use of mediation models. Mediators of interest will include adherence (measured by session attendance), and dose.

In the event that groups differ in terms of potential confounding factors (e.g., psychological conditions, pharmacotherapy) exploratory analyses will be conducted to investigate these factors as moderators of the outcomes. Should moderation be demonstrated (i.e., significant effect size), we will use this information to formally power the next study to specifically test for these factors (Kraemer et al., 2002).

Power Analysis.

For this study, our primary aims are to investigate the impact of *CBT-I-MA and CBT-I (compared to PC)* on (a) frequency of cannabis use and PPA, and (b) self-reported and objective indices of sleep. We expect that group based differences in cannabis outcomes will be partially attributable to sleep. *In addition, we expect that CBT-I-MA will evidence better outcomes compared to CBT-I. Exploratory analyses will examine factors that may account for these differences.*

Existing empirical work has established medium to large effect sizes for the effect of therapist administered CBT-I on sleep outcomes among individuals with psychiatric comorbidities (Cohen's d's range from 0.56 – 2.20; Smith et al., 2005). *While no research has examined the effect size of CBT-I with an adjunctive mobile app, previous research has demonstrated a small/medium sized effect (Cohen's d's = 0.42) to observe differences in outcomes between treatment as usual for substance use disorders and treatment as usual with a technology-based adjunctive component (McKay et al., 2010).* In addition, no research has examined the impact of CBT-I on cannabis use outcomes. However, previous work has demonstrated that sleep disturbances resulting from withdrawal from cannabis use are attenuated through sleep interventions (Cohen's d's range from 1.4-2.4; Vandrey et al., 2011).

Based on these established effects, we conducted a power analysis to determine the necessary sample size to detect the hypothesized effects. To begin, power calculations were based on the hypothesis related to tests of mediation on the relation between group and sleep outcomes, as this would require the greatest sample size to detect the established effect size given the required analyses. Based on established methods to calculate power for mediation, *a sample of 168 Veterans would be required to detect a small/medium mediation effect with a power of .80 and alpha of .05.* This sample size would allow for the ability to detect the additional expected effects for Aims 1 and 2.

In terms of the primary hypothesis of Aim 1 (Hypothesis 1.1), *the impact of CBT-I-MA and CBT-I on frequency of cannabis use post-cessation, we based our power calculations on an ANCOVA with the inclusion of 3 covariates as this would provide an overestimation of the sample size required for the GLMM analysis. A sample of 168 individuals would allow for a detection of a significantly smaller effect in terms of the primary aim (d = .42), providing confidence in our ability to detect the hypothesized effect of d = 1.4. This sample size will also allow for adequate power to detect group differences between CBT-I-MA and CBT-I (d = .42; Aim 1 Exploratory Hypothesis).*

In terms of the secondary hypothesis of Aim 1 (Hypothesis 1.2), *the impact of CBT-I-MA and CBT-I on PPA,* we used power calculation software to calculate the effect size based on a test of independent proportions. With an estimated abstinence rate of 20% within the placebo condition (PC; based on previous research; Marijuana treatment project research group, 2004), and alpha of .05, *168 Veterans (56 per group) will allow for power of .80 to detect a 30% difference in the prevalence of abstinence in the CBT-I group. As we conservatively estimate a 50% abstinence rate in the CBT-I condition, we will have enough power to detect the expected effect.*

In terms of Aim 2, investigating the role *of CBT-I-MA and CBT-I* on subjective and objective sleep quality, *we based our power analysis on an ANCOVA with the inclusion of 3 covariates and 3 groups as this would overestimate the required sample size needed within GLMM models. A sample of 168 individuals would allow for a detection of a smaller effect in terms of the primary aim (d = .42), providing confidence in our ability to detect the hypothesized conservative effect of d = .56. This will also allow for adequate power to detect group differences between CBT-I-MA and CBT-I (d = .42; Aim 2 Exploratory Hypothesis).*

Therefore a total sample of 168 will be adequate to detect all expected effects. An intent-to-treat approach will also be used. Therefore, all individuals randomized will be included in analyses. In the event that a set of individuals do not receive a minimum intervention dose (i.e., attend 70% of group sessions; Litt et al., 2007; Project Match Research Group, 1997), we will conduct analyses with and without these individuals. This sample size is feasible over the course of 4 years as evidenced in previous work conducted among outpatient substance use research protocols (Heinz et al., 2013).

Missing Data. Based on our protocol to limit participant attrition, we expect relatively little missing data over the 6 months of this study. We will limit the effect of missing data both methodologically and statistically. *First, we will account for 10% loss prior to randomization. Therefore, we will aim to recruit 187 individuals, with the goal of randomizing 168 individuals for the intent-to-treat analyses.* Second, we chose to model our data using a GLMM approach as this method allows for multiple missing data points within longitudinal designs making this a robust analytic method for handling missing data. *Additionally, as it is likely that not all participants will be included in analyses due to missing data, we will examine the reliability of the results by re-conducting analyses on complete data sets obtained through multiple imputation procedures and pooling*

results (Graham, 2012). Sensitivity analysis will then be conducted to examine the impact of missing data on outcomes (Carpenter et al., 2007).