Date: December 15, 2015

Principal Investigator: Ryan Vandrey, Ph.D.

Application Number: NA_00068969

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Title: The Role of Sleep in the Treatment of Cannabis Use Disorders

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1. Abstract

Admissions to U.S. treatment programs for cannabis-related problems have more than doubled since the mid 1990's and now number approximately 1.2 million per year. Clinical trials indicate that a majority of those who enter treatment for cannabis problems relapse. Disturbed sleep is one of the most prominent symptoms of the cannabis withdrawal syndrome, and recent laboratory research has demonstrated that heavy cannabis users experience clinically significant sleep problems following abrupt cessation of use. Similar abstinence induced effects on sleep and sleep-related risk of relapse are known to occur during withdrawal from other drugs of abuse, and, importantly, research has shown that adding sleep improvement interventions to alcohol treatment programs results in significantly improved clinical outcomes. This suggests that interventions targeting sleep disturbance among cannabis users trying to quit could help initiate initial periods of abstinence and reduce relapse. Treatment-seeking cannabis users who report an effect of cannabis on sleep quality will be randomized to one of two treatment interventions: 1) a computerized psychosocial therapy for cannabis use (cMET/CBT), Contingency Management (CM), plus nightly administration of extended-release zolpidem, or 2) cMET/CBT, CM, plus nightly placebo administration. The treatment intervention will last for 12 weeks and follow-up assessments will be conducted at 3 and 6 months after the completion of treatment. Participants will complete cMET/CBT therapy modules once weekly, complete assessments and provide observed urine specimens for toxicological testing twice weekly (e.g. Mon/Thurs, Tues/Fri), and self-administer study medication nightly during treatment. The mechanism by which we believe extended-release zolpidem will benefit study participants is an improvement in sleep. To ascertain the relationship between sleep continuity and cannabis use outcomes, objective sleep assessments (PSG) will be conducted 4 times during the study (weeks 1, 10, and 12 during treatment, and at 3 month follow-up). Sleep diaries and objective, automated sleep monitoring with EEG headband and actigraphy assessments will also be collected to provide secondary, and more frequent, measures of sleep. The proposed clinical trial will be the first controlled examination of sleep quality and the effects of a clinical intervention designed to improve sleep among heavy cannabis users during a quit attempt.

2. Objectives

Objective 1: Prospectively examine objective and subjective measures of sleep quality in a sample of heavy cannabis users receiving psychosocial treatment to quit use of cannabis.

Objective 2: Determine whether administration of extended-release zolpidem, compared with placebo, will increase abstinence rates (number of negative urines submitted) among cannabis users.

Objective 3: Determine whether sleep continuity mediates the relationship between zolpidem treatment and cannabis abstinence rates as indicated by urine toxicology results.

3. Background

More individuals in the U.S. meet criteria for current and lifetime cannabis use disorders than meet criteria for any other illicit drug use disorder. In 2009 an estimated 4.3 million Americans were dependent on or abused cannabis, which represents 1.7% of the total population aged 12 or older, and 61% of all cases of illicit drug dependence or abuse. Uncontrolled use of cannabis is associated with all the fundamental features of drug addiction including tolerance to the drug, withdrawal upon cessation, negative psychosocial and health consequences, and the inability to cut down or stop use despite the desire to do so and/or the recognition that use of the drug is causing problems. Treatment admissions for cannabis-use disorders have more than doubled since 1992 and the number of drug abuse treatment admissions where cannabis is the primary problem drug is now 1.2 million, which exceeds the number of treatment admissions for any other drug except alcohol. As is common with other abused substances, the majority of adults and adolescents seeking treatment for cannabis-related disorders have great difficulty achieving periods of sustained cannabis abstinence.

The current research base for effective interventions in the treatment of cannabis use disorders is limited to psychosocial/behavioral treatments. Even with the most highly effective psychosocial treatment, only about half of those who enroll in treatment achieve a period of sustained abstinence, and among those, approximately half return to use within a year. Based on clinical research of other abused drugs, the most promising strategy for improving drug use outcomes in the treatment of cannabis use disorders would be to identify pharmacological interventions that could be combined with existing psychosocial treatments. One pharmacological approach shown to be effective for treating drug use disorders is to reduce drug withdrawal effects. Clinical trials conducted for the treatment of opioid and nicotine dependence clearly demonstrate that administration of medications known to reduce withdrawal, in combination with psychosocial therapies, can significantly improve treatment outcomes relative to psychosocial treatments alone. Evidence from structured survey studies with cannabis users suggests that cannabis withdrawal contributes to failed quit attempts and relapse, but prospective research demonstrating this association is lacking, as is controlled clinical evaluation of pharmacological interventions known to attenuate cannabis withdrawal.

A valid, reliable, and pharmacologically specific cannabis withdrawal syndrome has been demonstrated in nonhuman and human studies. Withdrawal symptoms may include: anger and aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, decreased appetite and weight loss, headaches, physical tension, sweating, stomach pain, nausea/vomiting, and general physical discomfort. Most symptoms onset within the first 24 hours of cessation, peak within the first week, and last approximately 1-2 weeks. However, sleep-related symptoms of cannabis withdrawal have been shown to persist up to 45-days, and may last even longer.

Among the cannabis withdrawal symptoms that are reliable and frequently observed, disturbed sleep is a particularly attractive target for clinical intervention. In recent survey studies, sleep difficulty during prior cannabis quit attempts was endorsed by 67-73% of adults**.** In one survey, 65% of people who had tried to quit use of cannabis indicated that sleep difficulty during abstinence had contributed to relapse on at least one previous quit attempt. A survey of non-treatment seekers indicated that 32% had experienced sleep problems during past periods of abstinence (not necessarily quit attempts), of which 48% reported having taken a tranquilizer/sedative, used alcohol, or returned to use of cannabis specifically to improve sleep. These studies highlight the fact that sleep difficulty is common, is perceived as a barrier to cessation, and also that there may be a disparity in the frequency or severity of abstinence-induced sleep problems among cannabis users trying to quit versus those not trying to quit.

Because recall bias could skew accounts in retrospective reporting, sleep disturbance during cannabis abstinence and its relationship to relapse has been evaluated in prospective laboratory studies in order to

corroborate the clinical survey studies just described. Inpatient studies using polysomnography (PSG) assessments of sleep indicate that, indeed, abrupt abstinence from daily cannabis use negatively impacts the quantity and quality of sleep. In a recent study conducted in our lab (NA_00017909), observed alterations of sleep continuity (sleep latency, sleep efficiency) and sleep architecture (REM) induced by abrupt cannabis abstinence met criteria commonly used in the diagnosis of sleep disorders. During a second phase of this study, administration of extended-release zolpidem attenuated these abstinence-induced sleep disturbances suggesting the potential clinical utility of administering hypnotic medication to help induce abstinence and prevent relapse among those in treatment for cannabis use disorders.

Because studies in which sleep continuity and architecture were objectively measured so far have been conducted with non-treatment seekers in residential settings, confirmatory data obtained prospectively from cannabis users trying to quit is warranted. In the proposed study we will obtain comprehensive measures of cannabis use and sleep from participants receiving outpatient treatment for cannabis use disorders. This will allow us to assess whether or not cannabis abstinence induced changes in sleep quality and/or architecture obtained from treatment-seekers maintained in their home environment are comparable to those observed in prior laboratory studies, and to determine whether changes in sleep mediate drug use outcomes during a quit attempt. This type of study is needed to confirm whether sleep is indeed a clinically important withdrawal symptom, and also to determine the external validity of the inpatient laboratory research methods being used to characterize and assess the clinical importance of cannabis withdrawal.

The primary aim of this project is to test the efficacy of extended-release zolpidem (Ambien CR®) to reduce sleep problems and relapse in treatment-seeking cannabis users. As described above, there is a clear need for improving cannabis use treatment interventions. Pharmacotherapies that reduce withdrawal and interventions that improve sleep quality have enhanced clinical outcomes in the treatment of other drug use disorders. We hypothesize that use of extended-release zolpidem as an adjunct therapy to psychosocial therapy will attenuate abstinence-induced sleep dysfunction, and that this improvement in sleep will mediate improvements in cannabis abstinence rates compared with study participants who receive placebo medication. Extended-release zolpidem was selected over other potential pharmacotherapy candidates because it is approved by the FDA and widely used as an effective treatment for insomnia, has a good safety, side effect, and abuse liability profile relative to other FDA-approved hypnotic medications. Demonstrating a positive effect of extended-release zolpidem on cannabis use outcomes in the proposed study would provide an additional clinical tool for treating cannabis use disorders that could be immediately and widely disseminated. The medication is widely available, relatively inexpensive (generic formulations are now commercially available), and would be of little added burden to patients or treatment providers. These characteristics should help adoption into regular clinical practice. Because sleep disturbance appears to be so prevalent among heavy cannabis users, particularly those seeking treatment, there is potential for this simple adjunct intervention to have a relatively broad clinical impact.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

The proposed study will be a double blind outpatient clinical trial in which eligible participants will be randomized to one of two treatment interventions: 1) a computerized psychosocial therapy that incorporates Motivational Enhancement Therapy and Cognitive-Behavioral Therapy (cMET/CBT), Contingency Management (CM, incentives for achieving abstinence), plus nightly administration of extended-release zolpidem, or 2) cMET/CBT, CM, plus nightly administration of matching placebo. The treatment intervention will last for 12 weeks and follow-up assessments will be conducted at 3, 6, and 12 months after the completion of treatment. Participants will complete cMET/CBT therapy modules once

weekly, complete assessments and provide observed urine specimens for toxicological testing twice weekly (e.g. Mon/Thurs, Tues/Fri), and self-administer study medication nightly during treatment. Participants will receive monetary rewards for achieving abstinence using an escalating schedule of reinforcement based on the results of the twice weekly urine drug tests. Objective sleep assessments (PSG) will be conducted at baseline to screen for sleep disorders, and 6 times during the study (weeks 1, 6, 10, and 12 during treatment, and at 3 and 12 month follow-ups). Sleep diaries and objective, automated sleep monitoring with EEG headband and actigraphy assessments will also be collected to provide secondary, and more frequent, measures of sleep.

Study Setting. Study procedures will be conducted at the Behavioral Pharmacology Research Unit (BPRU) and at the Behavioral Sleep Medicine Program (BSMP). The BPRU outpatient research unit contains dedicated areas for conducting confidential interviews and assessments, computer workstations with internet capability that are maintained on a secure network, a laboratory for collecting observed urine specimens, on site pregnancy testing capability, resources for shipping specimens for additional testing, a research pharmacy, and office space for research staff. The BSMP has 2 private interview rooms and two fully equipped psychophysical testing rooms for use in this study. The exception to the BPRU and BSMP serving as the research setting is that some measures of sleep will be collected in the participants' home environment.

Participants. We propose to enroll up to 200 cannabis smokers who are seeking treatment for cannabis-related problems and report associations between cannabis use and sleep quality. Enrollment will be limited to those who report effects of cannabis use on sleep because they are most likely to benefit from this intervention. This will also maximize the likelihood that a clinical effect of the study medication will be observed. Based on clinical surveys, we expect this to represent approximately 70% of those seeking treatment. We will exclude study volunteers with intrinsic sleep disorders other than insomnia and circadian rhythm disorders (e.g, sleep apnea, periodic limb movement disorders) prior to randomization. Based on our prior research studies, we estimate that 10-15% of participants will meet exclusion criteria for sleep apnea or periodic limb movement disorder during the screening PSG assessment. Those participants will be referred to treatment in the community for their sleep and cannabis use problems.

Participant Recruitment. Participants will be recruited into the study via media advertising, word-of-mouth communication, and referrals from medical and clinical care units within the Johns Hopkins Medical Institution. Advertisements will seek cannabis users who are interested in treatment for problems related to cannabis use.

Screening and Intake. Volunteers will receive a brief screening over the telephone and will be scheduled for an intake appointment if they meet initial eligibility criteria. Upon arrival for the intake assessment, written informed consent to participate will be obtained. The intake interview will include face-to-face diagnostic interviews and computerized assessment components that will take approximately 4 hours to complete. These will include a comprehensive assessment of health status including physical and mental health history, sleep history, and recreational drug use history. A urine sample will undergo toxicology screening for evidence of recent use of commonly abused drugs and urine pregnancy testing will be conducted for female volunteers. Ineligible study volunteers will be referred to treatment services provided by other community clinics near the volunteer's residence.

At intake, a locally constructed Medical History Interview and Physical examination will be conducted that collects information on health, drug use, and sleep including relationship between cannabis use and sleep quality. The DSM-IV Checklist will be used to determine participant eligibility and will characterize the sample in terms of lifetime and current Axis I psychiatric disorders. In cases where a diagnosis of psychiatric disorder is apparent, participants will be referred for treatment at community mental health facilities. The Time-line Follow-Back (TLFB) procedure will be used to obtain a detailed account of the amount and frequency of recent substance use during the prior 3 months. A 20-item Self-efficacy Inventory will be used to assess ability to avoid use of cannabis in situations involving negative affect, social discomfort, and presence of others using cannabis. The Marijuana Problems Scale will be used to

assess negative social, occupational, physical, and personal consequences associated with cannabis use in reference to the prior 90 days. The Readiness to Change Questionnaire will assess current stages of change (e.g. pre-contemplation, contemplation, and action) with regards to cannabis use. The Marijuana Goals Questionnaire will assess treatment goals of abstinence versus reduced use. Information from intake assessments will be entered into the cMET/CBT system, which will automatically generate personalized feedback reports for use during treatment. Smith's Measure of Morningness and Eveningness will be conducted as a circadian rhythm assessment. The Dysfunctional Beliefs and Attitudes about Sleep (DBAS) questionnaire will be administered as a predictive tool regarding sleep difficulty later in treatment, and the Insomnia Severity Index (ISI) will be used to assess insomnia characteristics. We will use an adapted questionnaire that combines section of the Posttraumatic Diagnostic Scale (PDS) and Posttraumatic Checklist – Stressor (PCL-S) questionnaire to assess for symptoms of PTSD. Lastly, we will conduct 2 measures of Delay Discounting, which measure the degree with which participants devalue larger greater rewards for smaller immediate rewards. One is a hypothetical task in which participants make a series of choices between receiving a $1,000 delayed hypothetical reward and a smaller immediate reward (e.g., $500). The magnitude of the smaller immediate option is adjusted across trials until an indifference point is determined, i.e., until the smaller immediate and larger later rewards are considered equivalent in subjective value. The second task, called the Quick Discounting Operant Task (QDOT), assesses the degree to which delaying a real monetary reward decreases its present value for the participant. Participants make a series of choices between receive a real 80-cent reward and an adjusting smaller immediate reward (e.g., 40 cents). Upon selection of one of the options, a coin machine attached to the computer automatically dispenses the selected reward amount in coins either immediately or after the specified delay has elapsed. The magnitude of the smaller immediate option is adjusted across trials until an indifference point is determined, i.e., until the smaller immediate and larger later rewards are considered equivalent in subjective value. Participants can earn a maximum of $16 based on their responses on this task that they are allowed to keep. Delay Discounting measures have been shown to predict treatment outcomes in prior research, but there has not been a comparison of these two different approaches (hypothetical vs. actual reinforcer delivery) in the same clinical trial.

Those eligible for the study based on the initial intake assessment will then be scheduled for an outpatient overnight sleep assessment to be conducted as soon as possible, targeting completion within 5 business days. The purpose of this sleep assessment is to screen participants for evidence of pre-morbid intrinsic sleep disorders (sleep apnea, periodic limb movement disorder) and to acclimate participants to sleeping while connected to PSG equipment. Participants will come to the Johns Hopkins BSMP where they will be wired for the outpatient sleep assessment and will then be transported via taxi home (a more detailed description of PSG assessment procedures is provided below under the heading "Polysomnography (PSG)". Participants eligible for study participation following the PSG assessment will then be scheduled to begin treatment. Study volunteers will be instructed that they will be expected to initiate an attempt to completely abstain from cannabis at the start of treatment. Thus, treatment will begin on a "quit day" designated by the study volunteer in coordination with the research staff.

Randomization. Participants will be assigned to one of two treatment conditions: 1) cMET/CBT/CM + extended-release zolpidem or 2) cMET/CBT/CM + placebo (detailed descriptions provided below). Treatment assignment will be conducted using a balanced minimization procedure in which we will stratify study participants based on abstinence (> 24 hours) at the time of intake, tobacco smoking status (daily vs. non-daily, and gender. Data from prior cannabis treatment trials suggest that non-smokers and those reporting > 24 hours of abstinence prior to intake have better outcomes compared with smokers and those reporting no abstinence at intake. Gender will be balanced as a practical safeguard against unknown influences on outcome. Participants will be scheduled for their first session within 7 days of the intake assessment.

Psychosocial Therapy (cMET/CBT). A computer program will be used to deliver an intervention that combines aspects of Motivational Enhancement Therapy (MET) and Cognitive Behavioral Therapy (CBT).

The intervention is based on content from empirically tested treatment manuals, and was recently developed and validated by Budney and colleagues for outpatient treatment of cannabis use disorders in adults. cMET/CBT consists of 13 distinct modules. The first two modules use principles of MET to facilitate initial behavior change and enhance motivation to quit use of cannabis. Modules 3-12 incorporate established CBT methodology and include modules on coping with other life problems, understanding cannabis use patterns, coping with craving, managing thoughts about using drugs, problem solving, drug refusal skills, coping with lapses, managing negative moods, and assertiveness skills. Module 13 is a post-treatment module designed to enhance maintenance of abstinence and review skills used to cope with lapse or relapse episodes. During the first 8 weeks, participants complete the two MET modules and six core CBT modules (1 module/week). During weeks 9-12, they complete one elective CBT module each week and during week 12 will also complete the post-treatment module. Within each module, cMET/CBT employs interactive exercises and worksheets to enhance learning and personalize content. cMET/CBT replicates many of the key features of therapist-delivered treatment, but does so in a systematic and replicable fashion.

Participants will access cMET/CBT primarily via the Internet using private computer workstations located in the BPRU clinic. They will use a unique password to log into their customized cMET/CBT program. Audio accompaniment is provided throughout the program for those who have reading difficulties or prefer audio, and each computer workstation will be equipped with headphones for listening to audio portions of the program. The first module incorporates training for participants in use of the program. cMET/CBT has an electronic reporting system that allows staff to view password-protected, browser-based reports that summarize patient activity on the cMET/CBT and provide summary information about interactive exercises completed on the computer (e.g., reports of recent drug use, circumstances of use). In this study, a therapist will receive electronic reports for each participant to be reviewed during two scheduled face-to-face check-in sessions. Participants will be able to access their cMET/CBT program via the Internet, which will enable practice or review of elements of their program between weekly sessions during treatment, and for up to 6 months after treatment. The cMET/CBT system enables secure access from any computer with high-speed Internet access.

Case Management. In order to monitor progress on cMET/CBT and address any crises or service needs that arise during the study, participants will be assigned a case management therapist. They will have an initial 30-minute meeting with the therapist immediately prior to the first computerized session. This meeting will orient participants to the treatment intervention, with particular emphasis on explaining how cMET/CBT works and discussing the purpose and plan for therapist contact throughout treatment. In weeks 4 and 12, additional 30-minute meetings will be held where the therapist will ask questions about progress, discuss any issues with the computer intervention, and encourage use of cMET/CBT programming between sessions and during follow-up to assist with cannabis-related clinical issues. During the Week 12 session, the therapist will assess and discuss the participant's need for more treatment services and will make appropriate referrals. The meetings will explicitly not involve MET, CBT, or other therapy-oriented forms of counseling.

Participants will meet with a research assistant twice per week during treatment to gain access to the computer workstation, address cMET/CBT problems or other study questions, and to provide urine specimens. At each visit, the research assistant will ask participant about medical events/care they have received, changes in concomitant medications, and will conduct a brief interview to check for clinical crises including suicidal ideation and will make referrals to the case management therapist or staff psychiatrist as needed. The research assistant will also review any adverse events (AEs) reported at each visit, asking follow up questions with participants as appropriate to help the study staff to determine whether each AE is study related.

Contingency Management (CM). An abstinence incentive program will be administered, which provides monetary incentives to study participants for cannabis abstinence verified by urine toxicology testing. Prior research has clearly demonstrated that use of abstinence-contingent incentives is an effective

means of increasing abstinence from cannabis and other drugs compared with MET/CBT alone. Maximizing overall study abstinence rates in the present study is desirable because it will increase the number of participants in which we will be able to evaluate the effect of abstinence on sleep, thus increasing statistical power for aims related to the effect of the medication on sleep during abstinence and the effect of sleep on relapse. Use of CM is also a motivational tool for study participants to conform to the instruction to initiate abstinence right at the start of treatment, rather than to delay their quit attempt. Conformity in the onset of abstinence in the present study is important for optimizing sleep-related data collection and analysis in relation to cannabis use and abstinence. This will greatly enhance our ability to interpret findings with confidence.

The CM intervention will be implemented according to the following schedule and procedures.

Weeks 1-2
A $5 voucher will be earned for each urine specimen provided regardless of the test results. The reason for this is that it typically takes at least 2 weeks for urine drug screens to test negative for cannabis among frequent users.

Weeks 3-12
Cannabis-free samples/reports. During weeks 3-12, participants will earn monetary bonuses when urine specimens test negative for cannabis, and self-report having abstained from using cannabis. During weeks 3-12, the first cannabis-free sample/report will earn $1.50; with each consecutive cannabis-free sample/report collected thereafter earning an increment of $1.50 above the previously earned amount. An additional $10 bonus will be added for each week during which both samples/reports are cannabis-negative. Monetary bonuses will be delivered to participants during scheduled clinic visits once urine test results are available. It is possible that test results will not be available the same day as the specimens are obtained.

Cannabis-positive samples/reports. No monetary bonuses are earned for a cannabis-positive urine sample or "self-report" of use. Following a positive sample, the bonus for the next cannabis-free sample/report will be reset to the $1.50 value, with subsequent cannabis-free samples/reports handled based on the DELIVERY SCHEDULE below. In order to encourage participants to get back on track with abstinence after a positive sample/report, if they provide 3 consecutive negative samples then bonus earnings will return to what they had been prior to the positive sample/report. Clients who provide cannabis-positive samples/reports during weeks 3-12 will not earn the maximum amount of abstinence bonuses listed below.

DELIVERY SCHEDULE ($/DAY)

WEEK	SAMPLE 1	SAMPLE 2	BONUSES	$/WEEK	TOTAL
1	$5.00 (noncontingent)	$5.00 (noncontingent)	----------	$10.00	$10.00
2	$5.00 (noncontingent)	$5.00 (noncontingent)	----------	$10.00	$20.00
3	$1.50	$3.00	$10.00	$14.50	$34.50
4	$4.50	$6.00	$10.00	$20.50	$55.00
5	$7.50	$9.00	$10.00	$26.50	$81.50
6	$10.50	$12.00	$10.00	$32.50	$114.00
7	$13.50	$15.00	$10.00	$38.50	$152.50
8	$16.50	$18.00	$10.00	$44.50	$197.00
9	$19.50	$21.00	$10.00	$50.50	$247.50
10	$22.50	$24.00	$10.00	$56.50	$304.00

11	$25.50	$27.00	$10.00	$62.50	$366.50
12	$28.50	$30.00	$10.00	$68.50	$435.00

TOTAL POSSIBLE DOLLARS EARNED = $435.00

Medication. Study participants will receive medication for daily administration throughout the 12-week treatment intervention period. Medication will be dispensed for outpatient use with instructions to take a single dose each night 30 minutes prior to when they plan to go to sleep. Participants will initially receive a 4-day supply of medication (time to next appointment plus 1 day). After this they will receive additional doses at scheduled visits such that they maintain at least a one-week medication supply. This will ensure that medication administration can continue in the event of a missed clinic visit, adverse weather, holidays, or planned vacations. Doses will be packaged and labeled with a quality assurance code, and the phone number for contacting BPRU medical staff 24 hours/day. In the event of an emergency, BPRU medical staff will be able to break the blind using the QA code.

Study medications (active and placebo) will be prepared by our research pharmacy using an encapsulation method. The outer capsule will be packed with an inert substance and contain a pill, either commercial zolpidem or a placebo pill of similar size and color, but unfortunately lacking the appropriate branding stamp. Participants randomized to receive active medication will receive a single target dose containing 12.5 mg extended-release zolpidem each day for the first 10 weeks of the treatment intervention. The 12.5mg dose was selected because it is the recommended dose for healthy adults under age 65 based on clinical trials for treating insomnia. It has been shown to be safe and effective for daily use in the treatment of insomnia in healthy individuals for up to 1 year with no evidence of tolerance or rebound insomnia. Because heavy cannabis users may react differently to extended use of the medication, a drug taper will be conducted during Weeks 11 and 12 so that we can detect disordered sleep patterns or other effects that may occur following discontinuation of the medication, whether due to rebound effects of the medication or the emergence of pre-morbid sleep disorders that may have been masked by chronic cannabis use and medication during the first 10 weeks. During the 14-day taper, 12.5 mg extended-release zolpidem will be administered on days 1, 3, 6, 10, and 14, and placebo will be administered on remaining days. Participants will not be informed about the taper, but all participants will be told that they could receive placebo medication during the study.

While the 12.5 mg dose is commonplace for use in the treatment of insomnia, dose adjustments may be required to maximize therapeutic benefit in this study. Participants will complete assessments about medication side effects and sleep during each clinic visit. Based on weekly reviews of these reports, if there is an indication that the current dose is not being tolerated, daily dose will be reduced by 6.25 mg. Contrarily, if evidence of clinically important sleep disturbance is present, the investigators will issue a recommendation for study dose to increase by 6.25 mg. All recommended dose changes will be submitted to the BPRU pharmacy, who will manage blind medication conditions. Those participants assigned to the active medication condition, will receive appropriate dose adjustments. However, to ensure the safety of participants and minimize the likelihood of medication abuse/dependence, the daily dose of zolpidem administered will never exceed double the daily recommended dose (25 mg/night).

During the study, we will assess medication adherence in 2 ways. First, the BPRU pharmacy will add 15mg acetazolamide (a sub-clinical “micro” dose) to each medication capsule (active and placebo doses) to allow for urine toxicology testing of medication usage. For comparison, clinical use of acetazolamide for altitude sickness, epilepsy, glaucoma, or edema is typically in the range of 250-750mg/day. Acetazolamide is excreted unchanged in urine and a recent trial supported by NIDA suggests that it is a good biomarker of medication adherence for up to 96 hours (Hampson et al, under review; documentation provided in IRB application supplementary materials). The first urine specimen obtained each week during treatment will be split and a portion of the specimen submitted to an external toxicology laboratory for analysis to detect the presence of acetazolamide. Participants will be compensated $6 per week that

acetazolamide testing confirms self-report of medication adherence (whether positive for those who report taking the medication, or negative for those who report not taking the medication). Thus, we want to incentivize accurate self-reports and not overly incentivize taking the medication among individuals who may take it and not report side effects in order to earn more money. At the end of the study, a bonus of $50 will be paid to participants who have positive urine acetazolamide tests on 7-8 weeks, a bonus of $75 will be paid to participants who have positive urine acetazolamide tests on 9-10 weeks, and a bonus of $150 will be paid to participants who have positive urine acetazolamide tests on 11-12 weeks. In addition, we will use electronic medication packaging (e.g. MEMS cap) to monitor when study participants access medication. This will be used to validate self-report and provide immediate reinforcement for medication adherence since there will likely be a delay of 2-4 weeks for getting urine toxicology results. Participants will earn compensation on an escalating schedule based on the electronic medication monitors during the study to encourage continuous adherence. Participants will be paid $0.50 the first day they self-report taking the medication at bedtime as instructed AND the electronic monitor indicates the medication container was opened at an appropriate time. The amount of compensation will then increase by $0.25 each day to a maximum of $2 per day. If a day of medication use is missed, or the time stamp on the opening of the container does not match sleep time, compensation for taking the medication is reset back to $0.50 and participants must again work their way up to $2/day. The total possible compensation for full medication adherence is $384.75 (maximum of $222 for urine toxicology; $162.75 for self-report confirmed by electronic monitoring).

Sleep Assessment. Sleep will be assessed via polysomnography (PSG), EEG headband, actigraphy, DBAS, ISI, and sleep diaries.

Polysomnography (PSG). PSG will conducted while participants sleep at home during weeks 1, 10, and 12 during treatment, and at the 3 and 12 month follow-ups. On PSG nights, participants will come to the laboratory 2-3 hours before their habitual bedtime. Certified PSG technicians will wire participants for sleep recording using standardized procedures for ambulatory PSG recording with demonstrated reliability. Recommended placement for EEG, EOG, and EMG according to the American Academy of Sleep Medicine (AASM) will be used. We will acquire 6 EEGs (F4-A1, F3-A2, C4-A1, C3-A2, O1-A2, O2-A1), right and left electro-oculograms (EOGs) linked to a single mastoid, submental EMGs, bilateral anterior tibialis muscles, and ECG (single modified ECG lead II). Respiratory function and effort will be measured via oronasal thermistor, nasal air pressure transducer, pulse oximetry, and abdominal and thoracic inductance plethysmographic belts. All EEG and EMG signals will be acquired at a base sampling rate of 500Hz using a Compumedics, Safiro polygraph. This device is strapped to the body, permitting full range of motion and mobility within the home. Once sensor placement is finished and tested, the technician will provide instruction regarding the placement of respiratory sensors at bedtime and how to initiate and terminate recording using an event marker on the device. Prior to lights out, participants will call the technician to ensure the device and sensors are functioning properly. The sampling rates and montage used in this protocol meet or exceed AASM scoring and data acquisition procedures. PSG data will be stored on DVDs and a secure server that is backed up daily. Certified PSG technicians will score each record according to AASM criteria. All clinical indices will be calculated and a report generated by Somnologica software. Dr. Smith will review all scored records using a rigorous quality assurance program to ensure the reliability and validity of the reports.

EEG Headband. Portable, wireless EEG monitors will be used to obtain additional objective sleep data during the 12-week intervention. EEG headbands use EEG leads placed on the forehead via elastic headband to provide objective measures of sleep continuity and basic sleep architecture (light sleep, deep sleep, REM sleep, and awake). We will use commercially available EEG headband units (e.g. Zeo, Sleep Profiler) that meet or exceeds US safety standards. Validation studies have been conducted showing that data from EEG headbands correlate highly with PSG. EEG headbands will be used in order to capture valid data at least once per week during the study. On the occasion that there is a malfunction in data capture (battery not fully charged, corrupt file), participants will be asked to repeat use of the EEG headband until data from one sleep night is captured for the week.

Actigraphy. On the first day of treatment, participants will be provided with a small, inexpensive actigraphy monitor to wear continuously during the 12-week intervention. Actigraphy monitors use an accelerometer to measure movement and is equipped with an event marker so that participants can indicate lights out each night. Algorithms from actigraphy data provide objective estimates of circadian rhythm and sleep continuity and have been shown to be sensitive to treatment changes. These specific devices and their algorithms will be validated against the PSG assessments obtained in this study. For the purpose of this study, actigraphy measures of sleep latency, wake after sleep onset time, sleep efficiency and total sleep time will be derived as secondary measures of sleep continuity.

Self-report assessments. Participants will call in to the lab to record their time to sleep and time awake each day. They will also complete a sleep diary assessment in which they will record time to bed and final awakening, sleep latency, number of awakenings, subjective sleep quality, level of arousal upon awakening, and sleep continuity parameters each day they come to the laboratory. Sleep diaries are widely used in sleep/insomnia research and have demonstrated sound psychometric properties, significant correlations with PSG, and sensitivity to treatment. In addition, the ISI will be administered weekly and the DBAS will be administered monthly during treatment to assess for changes in clinically important sleep patterns and beliefs.

Circadian Rhythm Assessment. We will assess circadian rhythm using a self-report questionnaire (Smith's Measure of Morningness/Eveningness) and via analysis of urinary melatonin over 24 hours. Both measures will be conducted during Week 1 and Week 12 to investigate any changes over time related to changes in cannabis use. For urine collection, participants will be provided with collection bottles to take home with them during the clinic visit prior to a scheduled PSG. They will be instructed to obtain samples from each urine void beginning after the first void on the prior day up to and including the first void of that day in accordance with standard procedures. Each specimen will be labeled with the time of collection. Urine toxicology testing will be conducted by a certified external toxicology laboratory for quantitative creatinine and the primary metabolite of melatonin, 6-sulpha- toxymelatonin (aMT6s).

Cannabis Use Assessment. The primary study outcome measure will be rates of cannabis abstinence. Cannabis use will be assessed via urine toxicology testing and self-report using the TLFB. Consent to participate in the study will include agreement to provide urine specimens under direct staff observation twice weekly (Mon–Thurs or Tues–Fri) during treatment and at each follow-up assessment. All specimens will be tested for 11-nor-delta-9-THC-9-carboxylic acid (THCCOOH), the primary marijuana metabolite using a THCCOOH cutoff level of 50 ng/mL. We will also address adulteration and inadvertent dilution of urine specimens. In prior studies, diluted urine specimens caused by use of diuretics and/or consumption of large quantities of liquid represent the vast majority of threats to validity. We will test for creatinine (using the standard cutoff of 20 ng/mL per SAMSHA testing guidelines), and 4 other indicators of adulteration (pH level, glutaraldehyde, nitrites, and oxidants). When urine specimens are deemed invalid, participants will be asked to provide another specimen within 4–24 hours. Urine specimens obtained at intake and the first specimen collected on Weeks 2, 4, 6, 8, 10 and 12 will be sent to a certified external toxicology laboratory for quantitative GC-MS analysis. This will allow for an assessment of outcomes by intake urine cannbinoid concentration, and for assessment of sleep measures by cannabinoid concentration, as well as change in quantitative concentration over time by group. Urine specimens collected during Week 1 and Week 12 will also be tested for evidence of synthetic cannabinoid use to assess whether participants shift from using cannabis to more readily available and more difficult to detect cannabinoid products such as Spice and K2.

Additional Assessments. At each clinic visit, participants will complete the TLFB in which they will report daily use of cannabis, alcohol and other drugs. They will also complete a Medication Side-Effects Questionnaire and Marijuana Withdrawal Checklist. For each of these measures, participants will rate adjectives on a 4-point scale (none, mild, moderate, severe) based on their experience of potential medication side effects (obtained from clinical trials and described on the package insert) and cannabis

withdrawal symptoms since their last clinic visit. Vital signs will also be obtained via automated monitor. During Weeks 6 and 12 we will re-administer the PCL-S to assess for changes in PTSD symptoms, and at Week 12 the two Delay Discounting tasks will be repeated.

In-person, 90-minute assessment interviews will be conducted 3, 6 and 12 months after completion of treatment. At each follow-up, the measures administered at intake will be repeated. Data on cannabis use and other treatment participation/change efforts will be collected for the full 3-6 month window to create a seamless database regarding drug use and treatment participation both within and external to the study. Urine drug testing will be conducted using the protocol employed during treatment. Treatment satisfaction questionnaires will be collected to provide additional information on participant perceptions of the treatment they received and whether perceptions change over time. A home-based PSG assessment will be conducted at the 3 and 12-month follow-up assessments to screen for evidence of emergent sleep disorders. Provisions will be made to collect some follow-up data by phone or by mail for those unable or unwilling to come to the clinic.

b. Study duration and number of study visits required of research participants.

The treatment period of the study will last for 12 weeks. Participants will have 30-60-minute appointments twice per week at the BPRU during the 12 weeks of treatment. Additional visits, approximately 90-minutes in duration, are required to wire participants for the home-based sleep assessments during Weeks 1, 6, 10, and 12. Participants will have follow-up appointments 3 months (interview and sleep assessment; 180 minutes), 6 months (interview only; 90-minutes), and 12 months (interview and sleep assessment; 180 minutes) after treatment ends.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Administration of capsules containing zolpidem or placebo during the study will be double blind. Blinding of the medication during the study is required to reduce expectancy bias and is standard scientific practice for this type of research.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Routine medical care for any illness will not be affected during this study.

e. Justification for inclusion of a placebo or non-treatment group.

All study participants will receive an active treatment (cMET/CBT + CM) for treating problems related to cannabis use. Placebo medication is included for some participants in this trial for scientific integrity in the evaluation of the effectiveness of zolpidem as an adjunct therapy for improving abstinence and reducing withdrawal in heavy cannabis users. The consequences of cannabis withdrawal are not life threatening and we do not anticipate any serious adverse events related to the study procedures to occur.

f. Definition of treatment failure or participant removal criteria.

We intend to use an intent-to-treat approach for participant inclusion in the proposed study. Thus, our intent is to retain and include all participants in the study once randomized. Exceptions to this may include immediate study discharge of participants who exhibit unacceptable behavior in the clinic, attempt to steal of purposefully damage study equipment, or who have a serious

adverse event related to the study medication/procedures. The study investigators may discharge participants for other reasons not known at this time.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants will be offered referrals to community treatment clinics when the study ends or if their participation ends prematurely.

5. Inclusion/Exclusion Criteria

Inclusion criteria:

1) Age 18-55 years. Those older than 55 will be excluded due to significant changes in sleep and poor tolerability of 12.5 mg dose of extended-release zolpidem that can occur with increased age.
2) Use of cannabis on ≥ 50 of prior 90 days and seeking treatment for cannabis-related problems
3) Report difficulty sleeping without use of cannabis, or using cannabis to get better sleep
4) Able and willing to give informed consent to participate

Exclusion criteria:

1) Currently meets DSM criteria for dependence on a drug other than cannabis or nicotine, history of dependence on sedative/hypnotic drugs, or current Axis I psychiatric disorder associated with significant effects on sleep (e.g. major depression)
2) Moderate sleep apnea (apnea/hypopnea index > 15) or periodic limb movement disorder (arousal index > 15) during intake PSG assessment
3) Pregnant, breast feeding, or planning to become pregnant within the next 3 months
4) Current psychosis, dementia, suicidal ideation, or other conditions associated with severe cognitive/social impairment
5) Allergy to any ingredient in extended-release zolpidem or prior adverse reaction to zolpidem
6) Current use of drugs that are strong inhibitors or inducers (e.g. ritonavir, nefazodone, carbamazapine) of metabolism via cytochrome P450 3A4 enzymes (primary system for metabolism of zolpidem), or current illness resulting in severe hepatic impairment
7) Use of hypnotic medications to resolve sleep difficulties more than 4 times in the prior month
8) Currently meets DSM criteria for alcohol abuse, dependence, or self-reports use of 20 or more standard drinks of alcohol per week in the prior month
9) History of or current evidence of significant medical or psychiatric illness judged by the principal investigator or medical monitor to put the participant at greater risk of experiencing an adverse event or that could otherwise negatively impact the integrity of the trial, including, but not limited to: CNS disorders, COPD; cardiac disease (e.g. CHF, arrhythmias, CAD and valvular heart diseases); or pulmonary disease
10) Sa02 by Pulse Oximetry of < 95% for 5min or greater while awake and seated

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Zolpidem extended-release (Ambien CR®) was selected for use in this study because it is a short-acting nonbenzodiazepine hypnotic approved by the FDA for the treatment of insomnia. Zolpidem acts as a selective agonist at the alpha-1 subunit of the $GABA_A$ receptor. The recommended dose of the extended-release formulation of zolpidem for a healthy adult under 65 is 12.5 mg. At that dose, mean peak plasma levels are reached after 1.5 hours, and the elimination half-life is approximately 2.8 hours. Clinical trials

have demonstrated that zolpidem, in both its rapid and extended-release formulations, significantly reduces latency to persistent sleep, reduces nocturnal awakenings, and increases total sleep time. Other studies have shown zolpidem to reliably increase slow-wave sleep. Under acute drug effect conditions, zolpidem likely impairs memory and psychomotor functioning, but controlled studies suggest that these effects do not perisit past waking the day after taking the medication. The most frequently reported side effects reported during clinical trials were headache (19% versus 15% receiving placebo), somnolence (15% versus 2% receiving placebo), dizziness (12% versus 5% receiving placebo), and nausea (7% versus 4% receiving placebo).

A sub-clinical "micro" dose (15mg; versus clinical doses of 250-750mg) of acetazolamide powder will be added to all medication capsules to be used as a biomarker of medication adherence. Acetazolamide will be obtained from a clinical manufacturing company (Letco Medical) and added to study capsules unchanged. Acetazolamide was selected because it is rapidly absorbed and excreted without metabolism in urine, where it can be non-invasively sampled. In a recent study conducted by NIDA and investigators at the University of Kentucky, acetazolamide was added to 30mg oxycodone in a blind clinical laboratory study and the pharmacokinetic profile was evaluated. The rate of urinary elimination decreased steadily following cessation of dosing (half-life =16.1±3.8h, n=10) with low inter-subject variability. For each of four consecutive mornings after dosing cessation, the rates of urinary acetazolamide elimination remained quantifiable and significantly declined in a predictable manner. There was no effect of acetazolamide on oxycodone pharmacodynamics, Cmax, Tmax or elimination half-life, and no adverse events associated with acetazolamide dosing.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Our prior research has shown that abrupt cessation of heavy cannabis use results in sleep disturbances that resemble insomnia. Although the medication has not been approved by the FDA for use in the treatment in cannabis use disorders per se, it has been approved by the FDA for use in the treatment of insomnia. We have obtained an IND (103,211) from the FDA to conduct research to investigate the effects of extended-release zolpidem in the treatment of cannabis use disorders.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Not applicable to this protocol.

7. Study Statistics

a. Primary outcome variable.

Primary outcome variable is the number of urine samples negative for cannabis use.

b. Secondary outcome variables.

Cannabis use indices including duration of continuous cannabis abstinence, self-reported frequency and amount of cannabis use obtained from the TLFB, and quantitative urine toxicology results. Sleep PSG indices including latency to persistent sleep, sleep efficiency, total sleep time, % REM, % SWS. Headband EEG, actigraphy and sleep diary indices including sleep continuity, sleep efficiency, sleep architecture and sleep quality.

c. Statistical plan including sample size justification and interim data analysis.

Sample Size: A sample size of 100 is needed to have 80% power to detect differences in the number of urine samples negative for cannabis use, assuming 23% negative urines in the placebo group (average abstinence rate in prior clinical trials of MET/CBT), and 40% or greater negative urines (40% increase from placebo estimate) in the extended-release zolpidem group. A sample size of 77 is needed to have 80% power to detect differences in sleep efficiency based on the effect size of 0.90 obtained for the effect of zolpidem vs. placebo on sleep efficiency in our prior inpatient study. For the relationship between zolpidem and sleep efficiency, with a sample size of 100 we would have 80% power to detect effects of size 0.82 or greater. Power to detect an effect of sleep efficiency after controlling for treatment assignment was calculated via simulation. With 100 participants and a 40% increase in negative urines we would have 80% power to detect odds ratios of 1.54 or greater. Note that we have requested to increase the total sample size to exceed 100 because the CM condition was added after we had run an initial cohort of 18 study participants. Because this is expected to significantly alter abstinence rates, which could impact study outcomes, the participants enrolled to date will be considered pilot subjects and will not be included in the primary study analyses. Further, due to lower than expected medication adherence rates and higher than expected rates of study drop out, we plan to randomize up to 200 participants in order to achieve a target of 100 participants who are retained in treatment and are compliant with the medication. Our primary analyses will still be conducted as an intent-to-treat as detailed below, but we wish to have adequate power to detect differences in sub-group analyses as well.

Preliminary Analyses: We will examine whether study completers differed from those who failed to complete the study with regard to demographic or cannabis use variables or response to abstinence (withdrawal, craving). This will inform the generality of study results.

We will examine the data for missing values. When applicable, we will impute scores by averaging the closest pre and post values; otherwise our statistical approach will accommodate missing data.

Initial descriptive statistics on main outcome variables will be calculated including frequency tables, histograms, and measures of central tendency and variation. Unusual data values will be identified and the associated records will be double checked for accuracy. Continuous variables not meeting assumptions required for parametric analyses will be either transformed or analyzed by the nonparametric counterpart of the parametric approach typically employed to ensure proper inferences.

Outcome Analyses: Longitudinal logistic regression will examine the effect of treatment group and time on the number of negative urine samples, controlling for variables used in the stratified randomization, where log odds(-urine$_{ij}$) = β_o+ β_1Zolpidem+ β_2Time$_j$+ $\beta_{3\text{-}p}x_{3\text{-}p}$+$\varepsilon_{ij}$. This statistical approach will also be used for outcomes from PSG and subjective sleep ratings.

To test the relationship between improvement in sleep and reduction in cannabis use, mediation will be established in 3 steps using the following longitudinal regression models and PSG data from weeks 1, 6, and 10 (prior to dose taper):

1) Medication accounts for variations in sleep efficiency, Efficiency$_{ij}$ = β_o+ β_1Zolpidem+ β_2Time$_j$+ $\beta_{3\text{-}p}x_{3\text{-}p}$+$\varepsilon_{ij}$.
2) Variations in sleep efficiency account for variations in probability of a negative urine, log odds(-urine$_{ij}$) = β_o+ β_1Efficiency+ β_2Time$_j$+ $\beta_{3\text{-}p}x_{3\text{-}p}$+$\varepsilon_{ij}$.
3) The relationship between extended-release zolpidem and probability of negative urine is attenuated after controlling for sleep efficiency, log odds(-urine$_{ij}$) = β_o+ β_1^*Zolpidem+

$\beta_2 Time_j + \beta_{3\text{-}p} x_{3\text{-}p} + \varepsilon_{ij}$ and log odds(-urine$_{ij}$) = $\beta_o + \beta_1 Zolpidem + \beta_2 Time_j + \beta_3 Efficiency + \beta_{4\text{-}p} x_{4\text{-}p} + \varepsilon_{ij}$, from which we can calculate proportion of treatment effect explained (PTE). Testing the null hypothesis that $\beta_1^* = \beta_1$ is equivalent to testing $\beta_3 = 0$ in the full model, provided that step 1 is successful (e.g., the correlation is nonzero).

d. Early stopping rules.

A DSMB has been formed to assess the progress and safety of this study every 6 months following study initiation. The study may be stopped based on the recommendation of the board for any concerns related to feasibility, safety, or efficacy at any time.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Participants may experience cannabis withdrawal symptoms while trying to quit cannabis use during the study. Cannabis withdrawal symptoms may include anger and aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, decreased appetite, weight loss, headaches, physical tension, sweating, stomach pain, nausea, vomiting, increased blood pressure, and general physical discomfort. These symptoms have been observed in prior studies when participants abruptly stop using cannabis. There are no reports in the current literature of severe physiological or psychiatric consequences resulting from cannabis withdrawal. Some cannabis withdrawal symptoms may be attenuated in participants who are assigned to the extended-release zolpidem drug condition.

Other potential risks relate to administration of extended-release zolpidem. Under acute drug effect conditions, zolpidem likely impairs memory and psychomotor functioning, but controlled studies suggest that these effects do not persist past waking the day after taking the medication. The most frequently reported side effects reported during clinical trials were headache, somnolence, dizziness, and nausea. Though rare in incidence, there have been reports of suicidal ideation and “sleep-driving” among patients taking zolpidem. Zolpidem is classified as a Schedule IV narcotic along with most other hypnotics. Zolpidem has a moderate abuse liability relative to other hypnotics. A history of illicit substance use is reported as a risk factor for zolpidem abuse, but we are not aware of any reports that specifically indicate that past or present cannabis use was associated with an increased risk for zolpidem abuse or dependence.

Breech of confidentiality about self-reported drug use and biological tests indicating recent drug use is also a risk.

b. Steps taken to minimize the risks.

Recruiting and Informed Consent. Participants are not a "vulnerable population" as defined by human subjects protection guidelines; that is, they are not minors, pregnant women, under legal coercion or restriction, or mentally impaired. They are competent adults who provide their voluntary written informed consent. Participants will be recruited via media advertisements that clearly state the nature and intent of the study or referrals from other health service providers aware of the nature of the research. The consent process will inform the participant in detail of the procedures, time involvement, compensation, risk, and treatment options other than participation in our study. The staff member obtaining written informed consent will have completed training specific to obtaining informed consent in the conduct of human research. Particular emphasis will be given to providing information regarding the potential risks involved with taking the study medication. Volunteers will also be instructed that they may withdrawal from

participation at any time without losing any of the compensation that they have earned to that point. Participants will be provided with a research card to be kept on their person while participating in the study. The card will indicate that the person is actively participating in a study in which they could receive zolpidem or placebo, and will list contact information for the study team. Participants will be encouraged to share this information with medical providers they come in contact with during the study.

Cannabis Withdrawal and Medication Side Effects. It is unlikely that any adverse event should arise that requires medical or psychiatric treatment. Volunteers for this study with current depression, the major risk factor for development of suicidal ideation, will be excluded from the study and referred to community treatment programs. Study volunteers who have blood pressure that exceeds 140 mmHg systolic or 90 mmHg diastolic during the intake assessment will receive a brief consultation from a medical staff member and provided a written letter encouraging them to see their primary care doctor to discuss methods of getting blood pressure under control. Because cannabis abstinence has been shown to increase blood pressure in some cases, study volunteers with a high initial blood pressure must return to the laboratory with blood pressure below 140/90 mmHg before being allowed to begin study participation. Vitals will be tracked and observed at each visit during the study when blood pressure assessments >140/90 mmHg will continue to be monitored with medical review and referrals as needed. At any time, SBP >180 mmHg or DBP >110 mmHg will prompt immediate evaluation by the study physician and referral to the emergency room if deemed necessary. These participants are also reviewed to determine if it is safe for them to remain in the clinical trial. Participants with a history of abusing sedative/hypnotic drugs will also be excluded to minimize the likelihood that the study medication gets used outside of the intended dosing regimen. We will also limit access to study medication to a maximum of 7 doses at a time, except under special circumstances when additional doses may be dispensed to account for holidays, expected inclement weather, or planned vacations. Participants will be informed of the risk of “sleep driving” or occurrences in which they might engage in behaviors during the night, but have no memory the following day. We will recommend to participants that they inform others they live with to help monitor their behavior during the night and take any other necessary precautions against driving or operating dangerous machinery during nighttime hours. All participants will be instructed prior to initiating the study that they should call the study PI, medical monitor, and/or 911 in the event of suicidal ideation onset or the occurrence of any other significant adverse event during participation in the study. Should an adverse event or injury occur at the research facility, the medical, nursing, and several research staff at BPRU are trained in CPR, and mobile emergency crash carts are available at multiple locations in the building. If appropriate, participants would be taken to the Johns Hopkins Bayview Medical Center Emergency Department, located across the street from the research facility. Blood pressure and heart rates will be monitored at each clinic visit, and any PSG assessments that exhibit evidence of an abnormal ECG will be referred to study medical staff for review and consultation. The Principal Investigator will be immediately notified of any serious adverse events that arise. These include reports of severe side effects from study medication, accidents, or hospitalization episodes that occur while individuals are participating in the study. In any instance of a serious adverse event, the Principal Investigator will immediately provide a detailed report to the IRB, FDA, NIH, and DSMB.

Ongoing review of eligibility. A review of all current study participants is conducted during weekly lab meetings, where staff review patient progress as well as any medical events or changes in patient concomitant medication. In any case where an ongoing study participant has a change in health status or medication that meets a study exclusion criterion, the medical and scientific team will meet and discuss the safety and scientific risk/benefit of retaining versus withdrawing the study participant.

Confidentiality. Participants’ names will be recorded only on the informed consent and necessary medical and payment forms. Anonymous participant identification numbers will be used on all other forms and labeling of biological fluids and test results. All information gathered will be kept in locked research staff offices or file cabinets located within a secure building protected with security guards and video surveillance 24-hours per day. All medical information obtained will be handled in accordance with HIPAA

regulations. Only research staff will have access to participant records. The limits of confidentiality (e.g. suspected child abuse or neglect, or harm to self or others) will be discussed in detail with the participants during the informed consent process. To reduce the likelihood of patient records disclosure we intend to apply for a Certificate of Confidentiality. These methods have been successful in prior research studies.

c. Plan for reporting unanticipated problems or study deviations.

In any case in which a participant ceases study participation due to medication/cannabis side effects or cannabis withdrawal, the Principal Investigator will make a detailed report to the IRB and will disclose the medication condition to the volunteer in attempt to help the volunteer avoid the medication and a similar reaction in the future. No serious adverse events are anticipated.

A Data and Safety Monitoring Board (DSMB) has been established to provide oversight on this project during its execution. David Neubauer, MD will serve as the chair of the DSMB. The DSMB will convene every 6 months to review cumulative summaries of adverse events, results of quantitative urine toxicology testing for biomarkers of zolpidem use among those in the active treatment condition, and participant accrual and retention rates over the course of the 5-year trial. Safety reviews and interim analyses will all be conducted with drug conditions remaining blind (e.g., conditions A and B). The medication blind will be broken at the request of the DSMB if there is a safety concern or question about efficacy that they think may warrant stopping the study early.

Adverse Events (AEs) will be defined on the basis of the NIH Guidelines on Data and Safety Monitoring for Intervention Trials. These guidelines define an AE as any reaction, side effect or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the study interventions. A new illness, symptom, unfavorable or unintended sign, or worsening of a pre-existing condition or abnormality will be considered an AE. Stable chronic conditions such as diabetes that are present prior to study entry and do not worsen will not be considered AEs.

Dr. Vandrey will make immediate reports for serious adverse events (SAEs), defined as any event that is fatal, near fatal, produces substantial disability, or requires hospitalization, to study co-investigators, the DSMB, the IRB, the Johns Hopkins Risk Management Office, the Department of Psychiatry Chair, Program Officer at NIDA, and the FDA.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

With confidentiality procedures in place, the legal risks of this study are minimal.

e. Financial risks to the participants.

The financial risk to study participants is minimal. Costs related to this research will be supported by NIDA grant U01-DA031784. Participants will be compensated for their participation to offset the costs associated with travel to and from the clinic and for their time involvement.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Study volunteers may directly benefit by receiving treatment for cannabis use problems at no cost. All study participants will receive evidence-based psychosocial treatment tailored for adult cannabis users. Half of the study participants will also receive extended-release zolpidem, a medication hypothesized to provide additional clinical benefit resulting in improved abstinence outcomes. If effective, use of extended-

release zolpidem could quickly and easily be adopted in clinical interventions for cannabis use disorders on a broad scale. Approximately 1.2 million Americans enroll in treatment for cannabis use disorders each year, so it could be argued that many others would benefit from the conduct of this study if it indeed results in the identification and adoption of a medication that significantly improves abstinence rates when combined with traditional psychosocial treatments for cannabis use disorders. Because we anticipate only relatively minor risks (cannabis withdrawal; zolpidem side effects) to study participants, we feel that the proposed research has a positive risk benefit ratio.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will receive compensation according to the schedule below.

Completing the intake assessment:	$20
PSG assessment:	$50/each (6 assessments for $300 total)
Headband EEG assessment	$10/week (12 weeks for $120 total)
24-hour urine collection	$10/collection (2 collections for $20 total)
Follow-up Visits (3, 6, & 12 month):	$50/each (3 assessments for $150 total)
Complete 2 clinic visits/week	$10/week (12 weeks for $120 total)
Compliant with sleep diary calls	$10/week (12 weeks for $120 total)
Abstinence contingent incentives	$435 (maximum amount)
Medication adherence incentives	$384.75 (maximum amount)
Quick Discounting Operant Task	$32 (maximum amount)
Equipment Return	$30

The total possible amount of remuneration is $1731.75.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The only direct costs to the participants will be their transportation to and from Bayview for all study appointments. That cost has been factored into the compensation for participating. All other study-related costs will be paid for by NIDA grant U01-DA031784.