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1. Title: Nabilone for Cannabis Dependence: A Pilot Study

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2.b. Medical Monitor Emergency Coverage: Dr. Kevin Hill (BPRL)

3.Facilities: Alcohol and Drug Abuse Treatment Program (ADATP), Proctor House, and the BPRL—NeuroImaging Center, McLean Hospital.

4.Estimated Duration of the Study: February 2010- June 2017. The estimated duration changed after Dr. Hill was awarded NIDA grant 1K99DA029115-01, "Nabilone for Cannabis Dependence: Imaging and Neuropsychological Performance." This pilot study will be conducted out during the K99 period of the award in preparation for a larger clinical trial to be conducted during the R00 period.

5.Specific Aims:

Aim 1: Assess the impact of treatment with either nabilone or placebo on cannabis use patterns.

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Aim 2: Assess the impact of treatment with either nabilone or placebo on performance on neuropsychological testing.

6.Progress Report and Preliminary Studies: Not applicable.

7.Background and Significance:

Despite the alarming prevalence of cannabis dependence and the corresponding impact upon public health, no consistent pharmacological treatments exist for this disorder. Nabilone (Cesamet®) is a synthetic cannabinoid FDA-approved for cancer chemotherapy with behavioral and physiological effects that overlap with Δ^9-THC (Stark and Dews 1980, Mendelson and Mello 1984). Nabilone is safe and well-tolerated, with side effects that diminish with repeated administration (Lemberger et al. 1982). Nabilone's properties make it an attractive option for study as an agonist treatment, and it may be a better choice than dronabinol for agonist treatment because nabilone is not cross-reactive with urine assays used to detect recent cannabis use (Fraser and Meatherall 1989).

8.Research and Design Methods:

8.1. Overview

We will conduct a Stage 1 pilot feasibility study at McLean Hospital to develop a medication to treat cannabis dependence. (FIGURE 1) In a randomized, double-blind, placebo-controlled trial, 60 cannabis-dependent subjects ages 18-45 will receive medical management (MM) over a 10-week period, with half receiving nabilone treatment and half receiving placebo. Participants will receive either 6 mg nabilone or placebo in addition to medical management (MM) over a 10-week treatment period.

Following treatment completion, participants will have a follow-up visits at 11, 12, 13, and 14 weeks. Primary outcomes will include self-report of cannabis smoking and results of quantitative urine drug screens for cannabis. We also will assess craving and other marijuana withdrawal symptoms as secondary measures. Mixed models ANOVA will be used to analyze the data.

The protocol described in this document has been approved by the FDA under IND 107862 to Dr. Hill.

8.2. Participants

Male and female participants (ages 18-45) will be recruited from the Boston metropolitan area via websites, newspaper advertisements, flyers, and word-of-mouth. In order to meet our target sample of 60 study completers- (participants who complete all study procedures), we expect to recruit about 120 participants and have 90 sign the informed consent form . (Our target sample size is 60 completers with 30 per group: 30 Placebo and 30 Nabilone). From ongoing studies of cannabis smokers at McLean, we expect to recruit at least 3 participants a month for our study.

8.2.1. Study Procedure

8.2.1.a. Recruitment and Intake.

Interested individuals will respond to advertisements by leaving a message (first name and call back number only) in the BPRL recruiting voice mailbox. Research assistants will call them back with 24 to 48 hours and conduct an initial phone screen that takes about 15 minutes. It will cover basic inclusion and exclusion criteria, as well as a brief description of the study to determine if the person is interested in participating. If the volunteer is appropriate and agrees to participate, they will be invited to come to the BPRL for a physical and psychiatric evaluation (SCID). Treatment alternatives will also be offered to the prospective participant if they decide not to participate or are not eligible for participation.

The initial assessment interview will be done by a research assistant and the study physician and take about 3 hours. Volunteers will first be asked to sign the informed consent (see *8.2.1.b*). Once they have agreed to participate, they will undergo a comprehensive evaluation that will include medical, psychiatric, and drug use histories as well as physical, psychiatric, and laboratory examinations. The study will be explained and an intake package, including all Drug and Alcohol and Mood and Impulsivity Assessments (see Table 8.1), will be administered. More specifically, the participants will undergo the following screening procedures:a) Detailed history of cannabis use; b) Review of DSM-IV criteria for cannabis dependence; c) Medical history and concomitant medication record; d) Physical examination; e) Laboratory screen that includes CBC, electrolytes, and BUN/creatinine; f) Urine measurement of THC; g) Urinalysis and urine pregnancy test for women; h) 12-lead electrocardiograph (EKG) i) urine toxicology screen; j) blood alcohol testing; k) Columbia Suicide Severity Rating Scale (C-SSRS). Suicide risk will be assessed by the physician at each MM visit.

*8.2.1.b.Informed consent.*Eligible participants will complete standard consent documentation. Prior to the volunteer being asked any question about his/her health, the volunteer will be given a consent form to read. The research assistant will go over it in detail with the volunteer. After a physician investigator answers any questions the volunteer may have concerning the study, he/she will be asked to provide their informed consent to the licensed physician investigator. If enrolled in the study, consent to communicate with their other clinicians will be obtained. Clinicians will be notified of their patients' enrollment in the study, thus allowing them to carefully monitor for changes in mood while they are undergoing treatment to stop use of cannabis.

8.2.1.c.Randomization. Participants will be stratified according to their self-reported frequency of cannabis use in the past 30 days: 1) daily use; and 2) non-daily use. The stratification procedure will guard against the possibility that one of the experimental conditions (i.e., nabilone or placebo) will be overrepresented by daily users, while non-daily users will predominantly be randomized into the other condition.

8.2.1.d.Availability and Flow of Subjects into Treatment. We plan to screen 120 participants in the course of 20 months to achieve our desired sample size.

8.2.1.e.Study Visits. Participants will come to the clinic twice a week. One visit will include a medical visit (dispensing of pills and Medical Management; see Sections 8.3.1.b, 8.3.2) and research assessments, including a urine screen (see Section 8.5.2.a and **Table 8.2**). The other visit will consist only of a urine screen (see Section 8.5.2.a). After the 10-week treatment period, participants will have 1 follow-up assessment visit at 14 weeks. During weeks 11, 12, and 13 participants will have 1 weekly Diary/Actiwatch visit to hand in their daily diaries, have their Actiwatch data downloaded, and provide a urine sample.

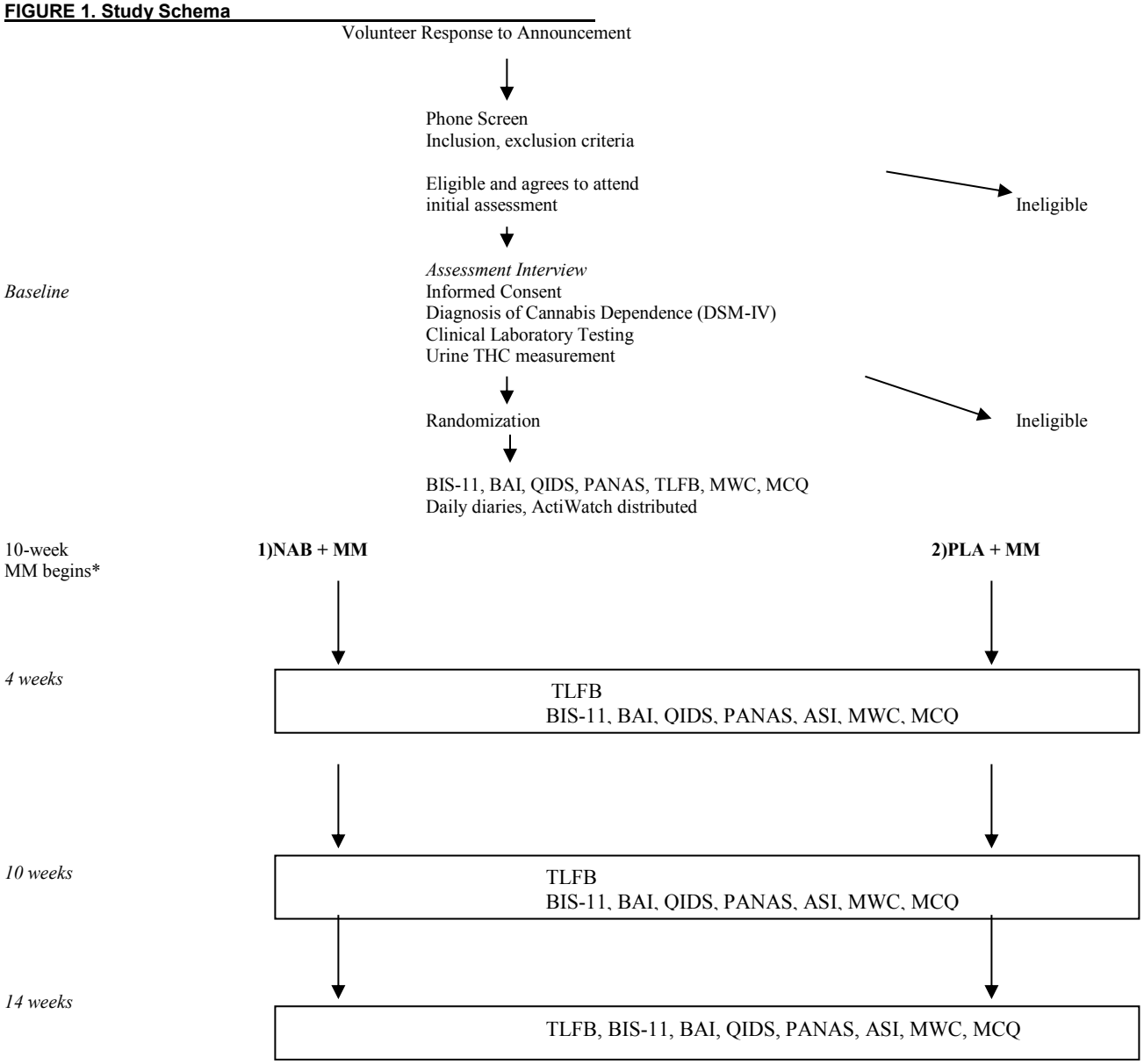
8.2.1.f.Clinical Emergencies. If a participant is intoxicated, the participant will be evaluated medically, sent home in a taxi when safe, and the appointment re-scheduled. If a participant experiences a problem that requires clinical intervention during the course of the study (e.g., mania, suicidal ideation, or dangerous intoxication), we will evaluate the situation medically, make an appropriate recommendation, and help the participant to implement this plan. This could involve hospitalization at McLean, referral to the hospital's outpatient program, or other medical or psychiatric treatment, as clinically appropriate.

8.2.1.g.Participant Payments

Volunteers will receive a $50 remuneration for attending the initial assessment interview and an additional $50 for the baseline visit. They may earn $25 for each urine sample given on a non-MM day in the first 5 weeks of treatment and then $30 for each urine sample given on a non-MM day in the last 5 weeks of treatment, and they may earn $50 for attending the follow-up assessment at 14 weeks. They may earn $30.00 for each of three Actiwatch /Diary visits at weeks 11, 12, and 13 as well as $50 for the final follow-up visit. Additionally they may receive a $40 bonus for attending all follow-up visits and returning the Actiwatch. They may also receive a bonus of up to $100 for successful

completion of their diaries. They may earn a total of $705 for their participation in the study. Medication will be free. In special circumstances, a subject may receive up to $50 in public transportation cards.

FIGURE 1. Study Schema



8.3. Treatment.

8.3.1Nabilone.

*8.3.1.a.Rationale for Dose.*Nabilone (Cesamet®, Meda Pharmaceuticals, Somerset, NJ) is a potent synthetic cannabinoid receptor type 1 (CB1) agonist that received FDA approval in 2006 for the treatment of nausea and vomiting associated with cancer chemotherapy (Cesamet® product information). Nabilone will be titrated to 6 mg daily in the nabilone group. Nabilone 2 mg was well-tolerated in the pilot study we recently completed and doses up to 8 mg have been well-tolerated in other patient populations. Recent studies have demonstrated safety of nabilone at doses greater than the 2 mg maximum dose previously covered in IND 107862. Dr. Haney's group used up to 8 mg

daily without incident (Haney et al. 2013, Bedi et al. 2013) in cannabis-dependent participants and another group have used up to 3 mg daily in a participants with peripheral neuropathy (Toth et al. 2012, Bestad and Toth 2011). As a result, the FDA has permitted a maximum dose of nabilone 6 mg daily under Dr. Hill's IND 107862.

8.3.1.b.Procedures for Dispensing Medication.

Subjects will be randomized to receive either placebo or nabilone. Dr. Hill or the research assistants will present 7 day prescriptions to the McLean pharmacy and the subject will receive blister packs containing 1 week of medication or placebo, separated into daily doses. Subjects will be asked to return unused pills at each weekly medical visit; study staff will then perform a pill count for the study record. All groups will receive capsules following the same schedule: 4 capsules twice daily for 10 weeks. Each capsule will contain either nabilone or placebo, and riboflavin 25 mg (to help assess compliance). Subjects in the nabilone group will take 1 mg of nabilone at bedtime for 1 week, then increase to 1 mg of nabilone twice daily (between 7:00-9:00 a.m. and 9:00-11:00 p.m.) for 1 week, then 2 mg nabilone twice daily for 1 week, then 3 mg nabilone twice daily for 6 weeks before tapering the medication over the final 1 week by taking 2 mg nabilone twice daily for 2 days, then 1 mg twice daily for 2 days, then 1 mg at bedtime for 3 days before stopping. This schedule is designed to maximize the time spent at the maximum dose. Subjects will be assessed for side effects prior to each dosing increase and the study physician will decide if increasing the dose as scheduled is appropriate.

In order to monitor potential side effects from the initial dose of nabilone or dose increases, participants will be observed at the laboratory facility for 3 hours following the following the second dose of the day in weeks 1, 2, 3, and 4. Participants will come into the Behavioral Psychopharmacology Research Laboratory in the evenings for monitoring by a research assistant and a study physician. This observation period is follows the SAMHSA guidelines for induction of buprenorphine, another agonist pharmacotherapy (CSAT 2004). Participants will remain in the natural settings laboratory for 3 hours while having vital signs taken every 30 minutes. Participants will be allowed to leave the facility after being cleared by a study physician. Participants will be allowed to leave the facility if they have 1) pulse rate less than 120 beats per minute; 2) blood pressure less than 140/90.

*8.3.1.c.Dose Adjustment***.**

Subjects who cannot tolerate dose increases either subjectively or by monitoring of vital signs (hypotension, for example), will remain at the dose they were taking prior to the increase (4 mg daily, 2 mg daily, or 1 mg daily). Subjects who experience uncomfortable side effects (e.g., drowsiness or vertigo) may have their dose lowered from 6 capsules a day to 4 or from 4 capsules a day to 2; a subject receiving active nabilone, for example, could then have a dose reduction from 6 mg of nabilone daily to 4 mg daily (or lower). None of the subjects in Study 1 required a dose reduction. If this leads to fewer side effects, the study physician will ask if the subject is willing to try the full dose again. If not, or if the subject tries the full dose again and is unable to tolerate

it, the subject will be maintained on the lower dose. If a subject cannot tolerate 2 capsules per day, the medication will be discontinued, but the subject will continue to be followed for research visits.

8.3.2. Medical Management Visits.

8.3.2.a.Weekly Visits with the Study Physician. Participants will be seen weekly during treatment by the study physician for medical visits. In addition to dispensing the study medication, the physician will utilize Medical Management (MM) (Pettinati et al 2004), a manualized treatment that was used in the NIAAA COMBINE Study. MM was derived from empirically-tested manualized therapies (Carroll and O'Malley 1996, Mason and Goodman 1997) that were originally designed to approximate a primary care approach to the treatment of alcohol dependence. The treatment is delivered by a medical professional who monitors medication side effects, provides strategies to increase medication adherence (Volpicelli et al. 1997), and supports abstinence. The initial 40-60 minute session includes reviewing the cannabis dependence diagnosis and negative consequences from smoking marijuana, recommending abstinence, providing medication information, and offering strategies to enhance medication adherence. In subsequent 15-25 minute visits, recent substance use, overall functioning, medication adherence, and side effects are discussed. Session structure varies according to drug use status and medication adherence. If a participant is not adherent to the medication regimen, the clinician evaluates the reasons and helps the subject devise plans to enhance medication adherence. Participants who use cannabis are given common-sense behavioral recommendations, such as avoiding parties where marijuana will be present. Presence and severity of side effects will be obtained through a standard Adverse Events Checklist as well as the "Frequency and Intensity of Side Effects Rating/Global Report of Side Effects Burden" (Wisniewski et al. 1997), a 2-minute questionnaire that assesses the frequency, intensity, and level of burden of side effects. Medication adherence will be assessed in several ways, as outlined below in Section 8.6.These sessions will be audiotaped and a sample will be rated by a senior clinician in order to ensure fidelity to the MM process.

*8.4. Safety Monitoring.*Nabilone has been shown to have a favorable safety profile; it has been well-tolerated in several clinical trials and no adverse events have been reported (Ware et al. 2008, Frank et al. 2008, Skrabek et al. 2008). Drug-drug interactions are not a major concern with nabilone because it does not induce cytochrome P450 3A4 isoenzymes and lacks significant 3A4 inhibitory effect (Nahas et al. 2002). Nonetheless, we will monitor safety through the standardized methods described above in the MM visits. We will have a low threshold for obtaining additional medical workup during the study if the subject reports medical symptoms. If a participant has a clinically significant laboratory or other medical abnormality that cannot be attributed to another cause, the participant's medication will be discontinued and the participant will be followed for research visits.

As discussed above in Section 8.2.i.a, the study physician will perform a physical examination and obtain an ECG at baseline and at 14 weeks. Laboratory data (urinalysis, blood chemistries, complete blood count, electrolytes, and liver function tests) will be done at baseline and at 14 weeks as well. Given that according to its labeling, nabilone should not be taken with alcohol, sedatives, hypnotics, or other psychoactive substances because they could potentiate the central nervous system effects of nabilone, urine toxicology and blood alcohol testing will be done weekly along with the twice weekly quantitative THC urine screens during treatment. Women of childbearing potential will have urine pregnancy tests weekly each time a urine sample is given in addition to pregnancy tests at weeks at 4, 10, and 14 weeks during treatment; women who become pregnant will have their medication discontinued and will be referred to an obstetrician; like all participants, they will still be followed for research visits.

8.5. Research Measures.

See **Table 8.2** for the schedule of assessments.

8.5.1. Diagnostic Assessment. To make the diagnosis of cannabis dependence, the Structured Clinical Interview for DSM-IV (SCID) (First 1996) will be used.

8.5.2. Drug and Alcohol Use Assessment.

8.5.2.a. Urine Screens. The primary outcome measure will be cannabis use, as measured by twice-weekly quantitative urine screens during treatment. Cannabis is a particularly challenging drug of abuse for measuring outcome because of the *false-positive* urine screens that can occur as the result of long-term accumulation of cannabis metabolites. In an attempt to avoid false-positive results, we will obtain 2 supervised urine samples weekly: 1 at the medical visit and 1 on another day, ordinarily with 3-4 days separation from the clinical visits (e.g., Monday-Thursday, Tuesday-Friday, or Monday-Friday); this should maximize the time frame covered by our urine screens. We will send the urine samples to Quest Diagnostics Laboratory (Cambridge, MA, a NIDA-certified laboratory), where the urines will be screened by immunoassay for the THC metabolite 11-nor-carboxy-Δ 9-tetrahydrocannabinol (THC-COOH) as well as other drugs of abuse. Urine creatinine concentrations will also be measured to assess urine concentration. The threshold for detection of THC-COOH will be 20 ng/ml. Samples positive for this metabolite will undergo further analysis by gas chromatography-mass spectroscopy to obtain quantitative THC-COOH concentration; we will then calculate the ratio of this metabolite to urine creatinine concentration. We will adopt the method of Heustis and Cone (1998) to differentiate new marijuana use from residual drug excretion as a result of previous use; these recommendations are based on their controlled clinical studies of urinary excretion profiles of creatinine and marijuana metabolites following marijuana administration in humans. We will label a urine negative (i.e., abstinent from cannabis) if 1) the ratio of THC-COOH to creatinine in the urine does not increase by >50% from the ratio obtained in the previous urine screen, and 2) the participant also reports using no cannabis since the previous urine test.

8.5.2.b.Self-Report. We will use 3 methods of self-report in an effort to determine the most appropriate and effective method for use in this population. An ActiWatch Score will be determined via compact, wrist-worn, battery-operated activity monitors that are excellent devices for monitoring multiple drug use, drug craving, and sleep/wake activity (Licata et al., under review). We will provide participants with a packet of 1 page, self-addressed, prepaid postage Daily Diary pages which participants will be asked to fill out between 7:00 and 9:00 a.m. each day and hand them in during their weekly visits to the lab. The diary consists of a series of questions about cannabis and other drug use as well as eating and sleeping habits. During the weekly visits, we plan to collect cannabis use data using the Timeline Follow Back(TLFB) (Sobel and Sobel 1992) protocol that was developed for alcohol.

*8.5.2.c.Other Drug and Alcohol Use Assessment.*Severity of cannabis and other substance use and its associated problems will be assessed at baseline and weeks 4,10, and 14 with the Addiction Severity Index (ASI, 5th edition) (McLellan et al. 1992), a widely-used and independently-validated interview that measures the severity of problems in 7 areas of functioning that are frequently affected in patients with SUDs: drug use, alcohol use, employment, legal status, medical condition, social functioning, and psychological status. In addition to our primary focus on cannabis use (urine screens plus days of use), we will examine other substance use (using urine screens plus days of other substance use). We will use this method to determine the number of days of cannabis use and of any substance use (and conversely, days of abstinence). We will examine ASI composite scores as secondary measures of substance use outcome. We will also use the self-administered Drug and Alcohol Use Questionnaire. This measure, administered at baseline, addresses the context of lifetime and recent drug and alcohol use, as well as sociodemographic data. At each treatment visit, patients will complete a brief Weekly Drug and Alcohol Use Inventory, indicating their number of days using marijuana, other drugs, and alcohol during the previous week. The Marijuana Goals Questionnaire (Griffin et al. 1989) is a brief questionnaire administered at baseline to assess treatment goals, specifically, whether a participant is seeking abstinence or reduction in cannabis use. A 12-item self-administered questionnaire, the Marijuana Craving Questionnaire (MCQ), will be used to assess craving at baseline and weekly during treatment and at the 14-week follow-up visit (Heishman et al. 2009). A short form of the Marijuana Withdrawal Checklist (MWC) will be used to assess withdrawal symptoms at baseline and weekly during treatment and at the 14-week follow-up visit (Budney et al. 1999). If there is a discrepancy among results obtained by these methods of substance use assessment, we will meet with the participant and have a conversation about their substance use. After the conversation, we will use our clinical judgment to determine the level of use that we believe is most accurate for that participant. A new 6-page questionnaire that we created, the Marijuana Perceptions of Risk and Experiences Questionnaire (MPRE), will be distributed at baseline, and once during weeks 4, 10 and 14 to assess each participant's perceptions of cannabis risk/harm and his or her motivations to quit/continue using cannabis throughout the course of treatment.

8.5.3.Mood and Impulsivity Assessments. We will monitor participants' mood throughout the study using 3 assessments. The Beck Anxiety Inventory (BAI) is a 21-

item self-report measure that can be used to assess the severity of anxiety. The Quick Inventory of Depressive Symptomatology (QIDS-SR) is a short self-report questionnaire for depressive symptoms used successfully in the STAR*D project. The Positive and Negative Affect Scale(PANAS) is a 20-item self-report scale in which mood variables are rated by participants on a 1-5 scale. The Barratt Impulsiveness Scale (BIS-11) is a commonly used tool to measure impulsivity in various neuropsychological disorders as well as in substance abuse. Three dimensions can be assessed using this scale, which include Cognitive Impulsivity, Motor Impulsivity, and Non-planning Impulsivity.

Table 8.1 Schedule of Measures

Measure	Baseline	Weekly	Weeks 4 &10	Week 14
Diagnostic Assessment				
1. Structured Clinical Interview for DSM-IV[a]	X			
Drug and Alcohol Assessment				
2. Quantitative Urine Toxicological Analysis[b]	X	X[b]	X	X
3. Addiction Severity Index	X		X	X
4. Drug and Alcohol Use Questionnaire	X			
5. Weekly Drug and Alcohol Use Inventory	X	X	X	X
6. Marijuana Goals Questionnaire	X			
7. Marijuana Craving Questionnaire	X	X	X	X
8. Marijuana Withdrawal Checklist	X	X	X	X
9. Marijuana Perceptions of Risk and Experiences	X		X	X
Mood and Impulsivity Assessment				
10. Quick Inventory of Depressive Symptomatology	X		X	X
11. Beck Anxiety Inventory	X		X	X
12. Positive and Negative Affect Scale	X		X	X
13. Barratt Impulsiveness Scale	X		X	X
Medical & Safety Assessment (medical visits)				
14. Physical examination	X			X
15. ECG	X			X
16. Urine pregnancy test	X		X	X
17. Laboratory tests[c]	X			X
18. Adverse Events & Side Effects	X	X		X
19. Columbia Suicide Severity Rating Scale	X	X	X	X

[a]Full SCID at baseline
[b]Twice a week during treatment;
[c]Tests include urinalysis, liver function tests, electrolytes, complete blood count, & blood chemistries

8.6.Medication Adherence Assessment. The proposed studies involve chronic administration of medication given under double-blind conditions. Three methods of

medication adherence will be used as multiple methods are preferred (Weiss 2004): 1) pill counts will be made; 2) participants will record when they take their capsules on the ActiWatch-Score device; 3) urinary riboflavin levels (a 25 mg dose will be given with each dose of medication) will be measured using a UV spectrophotometer. If there is a discrepancy among results obtained by these methods, we will meet with the participant and have a conversation about their medication adherence. After the conversation, we will use our clinical judgment to determine the level of adherence that we believe is most accurate for that participant.

8.8. Data Management

All data collected will be de-identified with participant ID numbers and used for research purposes only. Written records will be kept in a locked file cabinet in a locked office. They will be destroyed after 5 years. Computerized data files will also be de-identified with participant ID numbers and kept in a password protected file on a password protected computer.

8.9. Statistical Analysis

The primary data analysis will be an intent-to-treat analysis, which includes all randomized participants. Of note, every attempt will be made to continue assessing participants even if they drop out of treatment. In addition, we will replicate all analyses with the completers only. The primary and secondary outcome variables are intended to explore various aspects of response to therapy and to help define a clinically meaningful response. The primary outcome measures, Actiwatch-scores, daily diaries, TLFB self-report data, in addition to quantitative urinary THC metabolites, have been chosen for their ability to indicate daily use of cannabis by relying on self-report of use.

Specifically, for assessing the effect of nabilone on cannabis use patterns, we propose to use the generalized estimating equations (GEE) approach to longitudinal analysis, appropriately accounting for the positive correlation among repeated urine screen assessments within the same individual.

Analyses of secondary substance use outcomes will focus on the number of days of cannabis use and of any substance use (and conversely, days of abstinence) during treatment and post-treatment follow-up. In addition, we will also examine the ASI Drug and Alcohol composite scores. Frequency of days of cannabis use (and any substance use and days of abstinence) will be analyzed via a log-linear (or Poisson) regression model, controlling for pre-treatment frequency of days of cannabis use. Although log-linear regression methods are considered appropriate for the analysis of count or frequency data, in many biomedical applications, count data have variability that far exceeds that predicted by the Poisson distribution; we expect that days of cannabis use (and any substance use and days of abstinence) will not be an exception. Linear mixed effects models will be used to examine the effect of treatment group on changes in the ASI Drug and Alcohol composite scores during treatment and post-treatment follow-up assessments (as determined by the group-by-time interaction in the linear mixed effects regression models). The linear mixed effects model will include random intercepts and slopes to appropriately account for correlation among repeated measures and heterogeneity of variance over time; the model will be fit using PROC MIXED in SAS.

In secondary analyses of mood outcomes, mood episodes will be assessed during treatment and post-treatment follow-up, using the QIDS, BAI, and PANAS; changes in risk of mood episodes during treatment and post-treatment follow-up assessments will be analyzed via a logistic regression model (similar to the logistic model above) that will be fit using the GEE approach (as implemented in PROC GENMOD in SAS) to account for correlation among repeated binary outcomes on the same individual. To examine the effect of nabilone on changes in risk for mood episodes during treatment and post-treatment follow-up, the logistic regression model will include the effects of treatment condition and the baseline measureof the outcome.

9. Human Subjects and Recruitment Strategies:

9.1. *Sample Size:* In order to meet the target sample of 60 completers, we expect to recruit 120 participants, ages 18-45, and have 90 of them sign the informed consent form.

9.2. *Advertising:* Participants will be recruited via websites, newspaper advertisements, flyers on campus, and word-of-mouth. We will not specifically recruit participants from particular patient units at McLean. Participants may not be inpatients at McLean at the time of their participation in the study.

9.3. *Inclusion criteria*

1) Age range 18-45 years; 2) DSM-IV diagnosis of cannabis dependence, based on the Structured Clinical Interview for DSM-IV (SCID); 3) express a desire to quit cannabis use within the next 30 days; 4) have used cannabis on $\geq$4 days within the past 30 days (i.e., an average of $\geq$1 day per week); 5) for women of childbearing age, a negative pregnancy test at screening with agreement to use adequate contraception to prevent pregnancy and monthly pregnancy tests; 6) consent for us to communicate with their prescribing clinician; 7) furnish the names of 2 locators, who would assist study staff in locating them during the study period; 8) live close enough to McLean Hospital to attend study visits; 9) plan to stay in the Boston area for the next 3 months; and 10) are willing and able to sign informed consent.

9.4. *Exclusion criteria*

1) Current diagnosis of other drug or alcohol dependence (excluding nicotine); 2) recent (within 3 months) significant cardiac disease; 3) current serious psychiatric illness or history of psychosis, schizophrenia, bipolar type I disorder; 4) current medical condition (including significant laboratory abnormalities, such as liver function tests >5 times the upper limit of normal range) that could prevent regular study attendance; 5) mental retardation or organic mental disorder; 6) acutely dangerous or suicidal behavior; 7) currently in a residential treatment setting in which substance use is monitored and restricted, since the restricted access to drugs could represent an important confounding variable; 8) pregnant, nursing, or, if a woman of childbearing potential, not using a form of birth control judged by the investigator to be effective; 9) concomitant daily treatment with opioid analgesics, sedative hypnotics, or other known CNS depressants; 10) known hypersensitivity to cannabinoids or sesame oil ; 11) disease of the gastrointestinal system, liver, or kidneys that may impede metabolism or

excretion of nabilone; 12) inability to read or write in English. The potential hazards of a Schedule II medication like nabilone underscore the importance of English proficiency in this medication trial; 13) a history of seizures, head trauma or other history of CNS insult that could predispose the subject to seizures .

10. Miscellaneous Information:

- If the participant wants to terminate the study, he/she may do so at any time.
- Any questions or concerns related to this study should be directed to Dr. Hill.

References

Beckmann CF, Jenkinson M, Smith S.M. (2003). General multi-level linear modeling for group analysis in FMRI.NeuroImage, 20, 1052–1063.

Bedi G, Cooper ZD, Haney M. (2013). Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. Addiction Biology 18, 872-881.

Bestad JA, Toth CC. (2011). An open-label comparison or nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Practice 11, 353-368.

Budney AJ, Novy, PL, Hughes JR. (1999) Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction 94, 1311-1322.

Carroll KM, O'Malley SS. Compliance Enhancement: A Manual for Psychopharmacology of Alcohol Dependence. 1996.

Center for Substance Abuse Treatment.*Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction.*Treatment Improvement Protocol (TIP) Series 40.DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.

Cesamet® product information.(2008) Valeant Pharmaceuticals, Aliso Viejo, CA.

First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient/Non-patient Edition, (SCID-I/P) or (SCID-I/NP). New York, Biometrics Research, New York State Psychiatric Institute, 1996.

Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. (2008). Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 336, 199-201.

Fraser AD, Meatherall R. (1989). Lack of interference by nabilone in the EMIT d.a.u. cannabinoid assay, Abbott TDxcannabinoid assay, and a sensitive TLC assay for delta 9-THC-carboxylic acid. J Anal Toxicol 13, 240.

Frederick B, Rohan M, Elman I, Lukas S, Renshaw P. (2004).Improved localization of fMRI activation in the basal forebrain at high field using warped anatomic images.The College on Problems of Drug Dependence 2004 Meeting, San Juan, Puerto Rico.

Friston KJ, Frith CD, Turner R, Frackowiak RS. (1995). Characterizing evoked hemodynamics with fMRI. NeuroImage 2, 157–165.

Griffin ML, Weiss RD, Mirin SM, Lange U. (1989).A comparison of male and female cocaine abusers.Arch Gen Psych 46, 122-126.

Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin RW. (2013). Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. Neuropsychopharmacology 38, 557-565.

Heishman SJ, Evans RJ, Singleton EG, Levin KH, Copersino ML, Gorelick DA. (2009). Reliability and validity of a short form of the Marijuana Craving Questionnaire.Drug Alcohol Depend 102, 35-40.

Huestis MA, Cone EJ. (1998). Differentiating new marijuana use from residual drug excretion in occasional marijuana users. J Anal Toxicol 22, 445-454.

Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Menci WE. (2007). Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. Biol Psychiatry 61, 31-40.

Lemberger L, Rubin A, Wolen R, DeSante K, Rowe H, Forney R, Pence P. (1982). Pharmacokinetics, metabolism and drug-abuse potential of nabilone. Cancer Treat Rev 9, 17-23.

Licata SC, Penetar D, Rodolico J, Palmer C, Berko J, Geaghan T, Looby A, Peters E, Ryan E, Renshaw P, Lukas SE. Effects of daily treatment with citicoline: a small double-blind, placebo-controlled study in cocaine-dependent volunteers. Psychopharmacology, under review.

Mason BJ, Goodman AM. Brief Intervention and Medication Compliance Procedures - Therapist's Manual. 1997.

McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M (1992). The Fifth Edition of the Addiction Severity Index.J Subst Abuse Treat 9,199-213.

Mendelson JH, Mello NK. (1984). Reinforcing properties of oral delta 9 tetrahydrocannabinol, smoked marijuana and nabilone: influence of previous marijuana use. Psychopharmacology 83: 351-6.

Nahas G, Harvey DJ, Sutin K, et al. (2002). A molecular basis of the therapeutic and psychoactive properties of cannabis (D9-tetrahydrocannabinol). Prog Neuro-Psychopharmacol Biol Psychiatry 26, 721-730.

Pettinati HM, Weiss RD, Miller WR, Rounsaville BJ, Ernst D. (2004). Medical Management Treatment Manual: A Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism Monograph.

Rohan ML, Kilgore WDS, Eskesen JG, Renshaw PF, Yurgelun-Todd DA. (2001). Match-warped EPI anatomic images and the amygdala: Imaging in hard places. 2001 International Society for Magnetic Resonance in Medicine Conference, Glasgow, Scotland, Abstract #1237.

Skrabek RQ, Galimova L, Ethans K, Perry D. (2008). Nabilone for the treatment of pain in fibromyalgia.J Pain 2, 164-173.

Sobell LC, Sobell M B. (1992). Timeline Follow Back. A technique for assessing self-reported alcohol consumption. In R. Litten& J. Allen, *Measuring alcohol consumption.*pp. 41-72. Humana Press, Totowa, NJ.

Smith SM, Jenkinson M, Beckmann CF, Miller KL, Woolrich M. (2007). Meaningful design and contrast estimability in FMRI.NeuroImage 34, 127–136.

Stark P, Dews PB. (1980). Cannabinoids I. Behavioral effects. J Pharmacol Exp Ther 214, 124-30.

Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, Garven A, Bestad J, Korngut L. (2012) . An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain 153, 2073-2082.

Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. (1997). Naltrexone and alcohol dependence.Role of subject compliance.Arch Gen Psychiatry 54, 737-742.

Ware MA, Daenick P, Maida V. (2008). A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting.TherClin Risk Manag 4, 99-107.

Weiss RD (2004). Adherence to pharmacotherapy in patients with alcohol and opioid dependence.Addiction 99, 1382-1392.

Wisniewski SR, Rush AJ, Balasubramani GK, Trivedi MH, Nierenberg AA. (2006). Self-rated global measure of the frequency, intensity, and burden of side effects. J PsychiatrPract 12, 71-79.

Woolrich MW, Ripley BD, Brady JM, Smith SM. (2001). Temporal autocorrelation in univariate linear modelling of FMRI data.NeuroImage, 14, 1370–1386.