UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN
10/10/2016

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

A Randomized Controlled Trial of Dronabinol and Vaporized Cannabis in Chronic Low Back Pain

2. PRINCIPAL INVESTIGATOR

Thomas D. Marcotte, PhD., Professor, Department of Psychiatry

3. FACILITIES

We plan on conducting the study at the following locations:

1. HIV Neurobehavioral Research Center/Center for Medicinal Cannabis Research (CMCR), 220 Dickinson Street, Suite B, MC8231
   San Diego, CA 92103-8231

4. ESTIMATED DURATION OF THE STUDY

We estimate that the study will take 4 years.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

This study will involve treating low back pain associated with nerve injury with two types of medicinal cannabis for eight weeks. Research subjects will consume either oral Δ9-THC (dronabinol), vaporized 4.0% Δ9-THC/6.5% CBD (estimated percentages), or placebo. An analysis will then be performed to assess the risk-benefit ratio of dronabinol and vaporized 4.0% Δ9-THC/6.5%. In addition, subjects will undergo driving simulation to determine how long it takes for them to recover from these medications.

6. SPECIFIC AIMS

AIM #1 To assess whether treatment with vaporized whole plant cannabis or oral ∆9-THC reduces spontaneous and evoked pain more than placebo, and whether there are differences between the two active treatments.
AIM #2 To examine the effects of vaporized whole plant cannabis and oral Δ9-THC (dronabinol) on mood, neuropsychological function, and psychomimetic side-effects (high, stoned, etc.) compared to placebo and to each other.
AIM #3 To examine the acute effects (after receiving stable treatment for 4 weeks) of vaporized whole plant cannabis and oral Δ9-THC compared to placebo and each other on driving skills.

7. BACKGROUND AND SIGNIFICANCE

The present proposal builds upon previous work funded by the University of California Center for Medicinal Cannabis Research (CMCR) [1]. In our first study, thirty-eight patients with a heterogeneous collection of neuropathic pain conditions (e.g., spinal cord injury pain, central post-stroke pain, peripheral neuropathy, post-herpetic neuralgia, and complex regional pain syndrome) resistant to standard pharmacologic treatments were recruited.[2] Subjects underwent a standardized procedure for smoking high dose (7% Δ9-THC), medium dose (3.5% Δ9-THC), or placebo Δ9-THC while continuing to use their regularly prescribed treatments. [2] A mixed linear model demonstrated an equivalent analgesic response to smoking cannabis with both the high and medium doses. Psychoactive effects were minimal and well-tolerated, with some acute cognitive effects, particularly with memory, at the high dose (7% Δ9-THC).

Our second study involved subjects with similar neuropathic pain diagnoses.[3] Smoking was discarded as a delivery technique in favor of vaporization to reduce exposure to harmful pyrolytic compounds.[4, 5] In addition, low dose (1.3%) Δ9-THC was substituted for high dose (7%) Δ9-THC. We did this to evaluate a further reduction of the concentration of this psychoactive constituent of

cannabis on cognitive and psychoactive side-effects. In this second study, both the low (1.3%) and medium dose (3.5%) Δ9-THC proved to be equivalent analgesics. In general, the effect sizes on cognitive testing were consistent with the minimal doses of Δ9-THC employed; the effect of the low dose (1.3%) was often less than that of the medium dose (3.5%) Δ9-THC.

Both of the above studies were 6-hour human laboratory experiments. The present study is designed to evaluate whether or not the medium dose of cannabis (3.5%) can maintain an analgesic response over an eight-week period. In addition, a direct comparison of this vaporized preparation will be made with dronabinol and placebo. The medium dose of cannabis (3.5%) has been selected as it was utilized in a human experimental laboratory experiment that compared inhaled Δ9-THC and dronabinol.[6] Using the cold-pressor test, participants immersed their hand in cold water (4 degrees C), and the time to report pain (pain sensitivity) and withdraw the hand from the water (pain tolerance) was recorded. Compared with placebo, marijuana and dronabinol decreased pain sensitivity, increased pain tolerance, and decreased subjective ratings of pain intensity. The magnitude of peak change in pain sensitivity and tolerance did not differ between marijuana and dronabinol, although dronabinol produced analgesia that was of a longer duration. Marijuana and dronabinol also increased abuse-related subjective ratings relative to placebo; these ratings were greater with marijuana. These data indicate that under controlled conditions, marijuana and dronabinol decreased pain, with dronabinol producing longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than marijuana.

A direct comparison of cannabis and dronabinol has not been performed in a clinical population. The present study will fill this void by performing a randomized, double-blind placebo controlled 8-week trial comparing the effectiveness of oral versus vaporized cannabis in patients with chronic low back pain. In addition to studying efficacy, we will also perform a driving simulation study to determine the real-world impact of cannabinoid treatments.

9. RESEARCH DESIGN AND METHODS

All procedures will be experimental, investigational and/or are carried out solely for research purposes. There will be no standard treatment or therapy (i.e., procedures that participants would receive even if not participating in research) performed in the two arms of this study that are described below:

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ARM #1. Eight-Week Randomized Controlled Study Of 4% THC/6.5% CBD Cannabis Versus Oral Δ9-THC:

An 8 week randomized, controlled phase 2/3 clinical trial of cannabinoid preparations will be performed utilizing three treatment regimens:

(1) vaporized Δ9-THC (4.0% Δ9-THC/6.5% CBD) plus placebo oral pills
(2) vaporized Δ9-THC (placebo) plus dronabinol
(3) vaporized Δ9-THC (placebo) plus placebo oral pills

Screening Potential Research Subjects:

Subjects will be recruited through letters provided patients by practitioners in the UCSD Center for Pain Medicine, Perlman Medical Office, 9350 Campus Point Drive, Suite 2C
La Jolla, CA (Appendix 1), newspaper advertisements (Appendix 2), and Research Match, a volunteer online registry funded by the National Institutes of Health (Appendix 3). In addition, ICD-9 code 724.2 will be used to identify pertinent potential subjects. The following PHI will be requested: patient name, mailing address, date of birth. A request (along with documentation of UCSD IRB approval) will be forwarded to database managers at the Clinical Data Warehouse for Research (CDWR) who will be asked to pull a subset of the data from the Electronic Health Record system to query patient information in a HIPAA-compliant manner. Volunteers will be screened via telephone

interview and, as appropriate, via face-to-face assessment. Telephone screening (respondents blind to selection criteria) will assure volunteers meet general age and medical criteria.

If already using cannabis, participants will be asked to slowly taper cannabis use over a one-week period (Baseline Week - Figure 1) so that they are only using study medications during the remaining 10 weeks of the clinical trial. If unable to abide by this, subjects will not be allowed to participate in the study. Participants will be asked to abstain from cannabis 7 days prior to study entry. In order to ensure abstinence, we will use the Draeger 5000 saliva screening test for tetrahydrocannabinol at their first experimental visit to ensure that they have adhered to this period of abstinence before the study. A level above 5 ng/ml will indicate recent use and the appointment will be rescheduled.

Baseline Period:
If eligibility criteria (see below) are met, subjects will be instructed on completing a paper diary (Appendix 4). Provided their VAS pain intensity remains above 3/10 during the Baseline Week, they will be given oral and herbal study medication (and a Volcano Vaporizer) at the next study visit one week later.

At the baseline visit, participants will be given the Beck Depression Inventory (BDI-II) in order to screen for depression and suicidality. They will also be given the AUDIT and DAST to screen for substance use problems. The PSQ and Mood Disorder Questionnaire will also be administered to screen for Schizophrenia and Bipolar Type I, respectively. The painDETECT Questionnaire will be administered to distinguish neuropathic low back pain from non-neuropathic low back pain. The Survey of Cannabis Use will be administered during this period to obtain information on the cannabis use habits of the participant.

Should the participant choose to participate the in the driving simulation portion of the study, the Driving History and Habits Questionnaire will be administered to obtain information on participant driving history, should they decide to participate in the driving simulation study portion.

Telephone Interview:
To determine eligibility, each prospective participant will be asked the following questions from the NIH Chronic Low Back Pain Definition:

1. Do you have low back pain?

No ……STOP…….....	0
Yes …….....	1

2. How long has low back pain been an ongoing problem for you?

Less than 1 month ……	0
1-3 months ……	1
3-6 months ……	2
6 months -1 year ……	3
1-5 years ……	4
More than 5 years ……	5

3. How often has low back pain been an ongoing problem for you over the past 6 months?

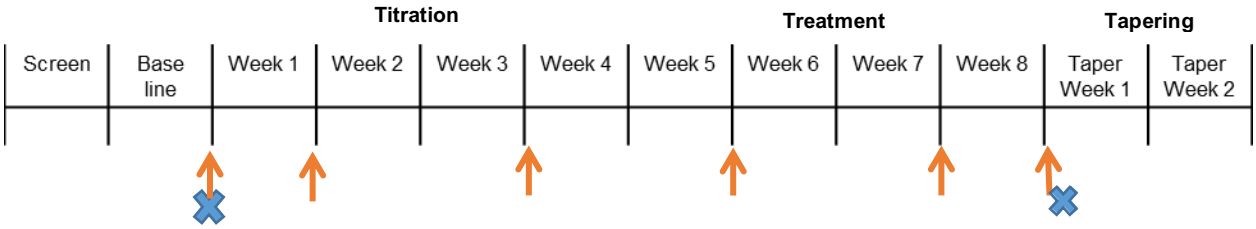
Every day or nearly every day in the past 6 months	.....	0
At least half the days in the past 6 months	.....	1
Less than half the days in the past 6 months	.....	2

4. In the past 7 days, how would you rate your low back pain on average?" (with an accompanying description of the following numerical pain intensity scale:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst imaginable pain

Titration, Treatment and Tapering Periods Beginning with Week 1, patients will receive study medication for eight weeks after which they will be tapered off of investigational treatments (Figure 1). Study visits will take place at the UCSD Center for Medicinal Cannabis Research.

Figure 1 Study Visits



Outcome measures will be collected during the six study visits, represented above as red vertical arrows. Driving simulation will be performed on the Hillcrest Campus at times denoted by the blue X's

Subjects will be randomly assigned to receive either one active study medication (e.g., medium-strength vaporized cannabis, or dronabinol) plus one placebo study medication, or double-placebo. Within the limits of safety and tolerability, patients will undergo titration of both vaporized and oral study medication during Weeks 1-4. The oral medication will be titrated from a minimum of 5 mg qd up to a maximum of 10 mg tid. The vaporized cannabis will be titrated from a minimum of 4 puffs to a maximum of 18 puffs per day. The aforementioned falls within the parameters of consumption of cannabis as depicted in a survey of medicinal cannabis patients. [8] The dosing, in terms of the maximum number of puffs at each vaporization session, will also be consistent with the amount utilized in our previous human laboratory experiment. [3] Subjects not able to tolerate the minimum amounts described above by the end of Week 4 will be dropped from the study and replaced by another volunteer. Subjects will be informed that concurrent medications should be administered on a continuing basis during the study at a constant amount and frequency.

During treatment at home, patients will maintain a paper daily diary to record their intake of vaporized cannabis (i.e., number of vaporization sessions, puffs), oral study medications, and breakthrough pain medications, as well as pain relief measurements. In order that an effect from study medication will be evident, subjects will be asked to enter data into paper diary within a one-to-two hour window following dosing of study and breakthrough medications. In between visits, patients

will be contacted by telephone every 7 days so that the investigative team can discuss compliance and answer any questions (Appendix 5).

Study Visits:

Subjects will come in for 2-hour study visits at the intervals designated by the vertical arrows in Figure 1. A review of the paper daily diary, and, after the baseline week, the completion of the assessments described below under Outcome Measures will also be reviewed.

Study Δ9-THC will be packaged in separate prescription vials for each vaporization session to be performed at the subject's residence. The vial will be marked with the date, directions for timing of vaporization session(s), and the maximum number of puffs from that vial. The collection vial will also be labeled for return of vaporized cannabis. All study medication will be packaged in a security container for purposes of preventing diversion with instructions to keep the locked strong box in a secure location. At the time of the subsequent visit, the vaporized and unused cannabis will be weighed by the research pharmacist who will report any suspected lapse of safekeeping of cannabis to the PI. Table 1 below outlines the amount of vaporized and oral study medication participants will be administered throughout the study.

Table 1 Schedule of Administration of Vaporized and Oral Study Medication

week	maximum dronabinol 5 mg or placebo tablets	maximum dronabinol 5 mg or placebo tablets per week	number of vaporization sessions per day	maximum number of puffs per day	number of 400 mg vials per week (8 puffs per vial)
Screening					
Baseline					
1	1 po qd	7	1	4	4
2	1 po bid	14	2	8	7
3	1-2 po tid	28	3	12	11
4	2 po tid	42	3	18	16
5	2 po tid	42	3	18	16
6	2 po tid	42	3	18	16
7	2 po tid	42	3	18	16
8	2 po tid	42	3	18	16
Taper Week 1	1 po tid	21	2 (average)	9	10
Taper Week 2	1 po qd	7	1 (average)	4	4

Subjects will be instructed on the use of a vaporizer at the visit prior to Week 1. The manufacturer's instructional brochure (Appendix 6) will be reviewed. In order to ensure consistency of dosing throughout the study, they will also be instructed on the use of the Foltin puff procedure at the visit prior to Week 1 (Appendix 7). A copy of both of these documents will be provided for review at home.

On completion of eight weeks of treatment or at the time of withdrawal from the study, patients will completely taper their cannabis over a period of one to two weeks to avoid withdrawal symptoms. Cannabis withdrawal symptoms will be measured via a phone call after Taper weeks 1 and 2 (Appendix 8). Questions (Appendix 26) will be added to access subject's beliefs of what they received (e.g., THC or placebo) after the first week and again after the eighth week. This will enable us to assess the effectiveness of blinding and thus report on the assay sensitivity of the study. The optimal

timing and frequency of blinding assessments has not been established. Thus, we will use a strategy to collect blinding data two times from participants: shortly after randomization and at the end of the trial. This will permit a comparison of blinding at the two stages.

If a subject does not participate in the driving simulation or the microbiome substudy, we will test their oral fluid for the presence of THC using the Draeger 5000. This will be done to exclude participants who use their own cannabis seeking pain relief because they were given placebo.

An online questionnaire will be deployed (Appendix 27). Potential participants will complete this using HIPAA compliant software, the Platinum Edition of Survey Monkey. Please see https://www.surveymonkey.com/pricing/details/ for verification of the HIPAA compliance of this survey.

Outcome Measures:

DAILY TESTING IN SUBJECT'S RESIDENCE USING PAPER DIARY

Medication intake: The timing and number of puffs of vaporized cannabis or placebo THC), oral medication (dronabinol or placebo), and breakthrough pain medication will be chronicled. (5 minutes)

REPEATED TESTING AT STUDY VISITS

Center for Medicinal Cannabis Research Forms

- Neurobehavioral Medical Screen: The clinician will fill this out to record any events that may have occurred between visits to confound results from the Neuropsychological testing such as an any trauma to the head or any open head wounds.
- Behavior Notes Instrument: The clinician will fill this out during Neuropsychological testing to note confound variables associated with participant during the appointment.
- Adverse Events Form: A form to be filled out by the clinician that records any adverse events that have occurred since the last appointment due to study medication.

NIH Task Force on CLBP Impact Score

The impact score is a novel combination of 3 constructs; pain intensity, interference, and function. It is assembled in the Repeated Measures Recommended Minimal Dataset (Appendix 9).[9]

Pain Relief

Neuropathic Pain Scale: This instrument has an ordinal scoring of one to ten for several characteristics of neuropathic pain.[10, 11] Specifically, the responses measure pain characteristics such as intensity, sharpness ("like a knife"), burning ("on fire"), aching ("like a bruise"), cold ("freezing"), sensitivity ("like raw skin"), itching ("like poison oak"), unpleasantness ("intolerable"), and the amount of deep versus superficial pain. (5 minutes)

Mood Evaluation

Profile of Mood States (POMS): The POMS measures six identifiable mood or affective states: 1) Tension-Anxiety 2) Vigor-Activity 3) Depression-Dejection 4) Fatigue-Inertia 5) Anger-Hostility 6) Confusion-Bewilderment. The POMS can be re-administered on a weekly basis, which is long enough to detect the respondent's mood responses to his or her current life situation, but short enough to assess acute treatment effects. Sixty five items rated from 0 to 4 and scored in terms of total mood disturbance. [12] (10 minutes)

Beck Depression Inventory-II (BDI-II): The BDI-II is a twenty-one item depression scale in which participants can rate depressive symptoms and attitudes from 0 to 3 in terms of intensity.[13] We will measure clinical depression using the BDI-II and will include this measurement in analyses to provide an adjusted view of analgesia and side-effects. (3 minutes)

Neuropsychological Testing

WAIS-III Digit Symbol test: a test of concentration, psychomotor speed, and graphomotor abilities. This pen and paper test involves having subjects substitute a series of symbols with numbers as quickly and accurately as possible during a 120 second period. The results are expressed as the number of correct substitutions.[14] (10 minutes).

Hopkins Verbal Learning Test (HVLT): The HVLT provides information on the ability to learn and immediately recall verbal information across trials, as well at the ability to retain, reproduce, and recognize this information after a delay.[15] A list of 12 words (four words from each of three semantic categories) is presented to the subject over three trials. After each trial, the subject is to recall as many items as possible from the list in any desired order. A 20-minute delay follows the administration of the three trials, after which the subject is asked to recall the list. Subjects are then read a list of 24 words, one at a time, and are asked if the word appeared in the original list. The items presented during the recognition phase contain the originally presented words, words in the same semantic class, and unrelated words. In order to minimize practice effects that may result from repeated administrations, six alternate forms of the test are available. (10 minutes)

Grooved Pegboard Test: This is a test of fine motor coordination and speed.[16] In this test, subjects are required to place 25 small metal pegs into holes on a 3" x 3" metal board. All pegs are alike and have a ridge on one side, which corresponds to a notch in each hole on the board. First the dominant hand is tested, and subjects are asked to place the pegs in the holes as fast as they can. This is then repeated with the non-dominant hand, and the total time for each hand is recorded. (5 minutes)

Psychomimetic Effects of Cannabis

Marijuana subscale (M-scale) of the Addiction Research Center Inventory: The M-scale consists of 12 true or false questions corresponding to symptoms of cannabis intoxication; the maximum possible score is 12.[21] The questions will be rephrased to evaluate the experience from the past week rather than an acute response to cannabis. (3 minutes)

Sensory Testing

Cold-Pressor Test (CPT): The cold-pressor apparatus will consist of two water coolers, fitted with a wire cradle and an aquarium pump for water circulation. One cooler will be filled with warm water (37 °C) and the other with cold water (4 °C). Participants will remove jewelry from the hand and forearm at the beginning of the session; during the test, participants will be instructed to rest a hand with fingers spread apart on the wire cradle. Each CPT will begin with an immersion of the left hand into the warm water bath for 3 min. During this time, blood pressure and heart rate will be measured. After removal of the hand from the warm water, skin temperature of the thumbpad will be recorded and participants will listen to a standardized script describing the procedures (Appendix 11). Participants will then immerse the left hand into the cold water bath and will be instructed to report the first painful sensation after immersion. They will then be asked to tolerate the stimulus as long as possible, but will be permitted to withdraw their hand from the cold water at any point. Maximum immersion time will be 2 min. Latency to first feel pain (pain sensitivity) and latency to withdraw the hand from the water (pain tolerance) will be recorded. Blood pressure and heart rate will be measured before and after each immersion using the arm that was not immersed in the water bath.

Microbiome Assays:

Stool Sample: Participants will be asked to provide a stool sample, a saliva sample, and a blood sample at their first, second, and sixth experimental visit. Participants will provide up to 20 milliliters of blood and 10 milliliters of saliva per sample. The overall objective of collecting the blood sample is to investigate inflammatory markers or other biomarkers that relate to changes in the microbiome. The overall objective of collecting the saliva and stool samples is to assess the effects of oral administration vs. inhalation of exogenous cannabinoids on the gut microbiota, as well as downstream effects on gut and systemic inflammation and neurocognition. CB_1 and CB_2 ligands that increase gut barrier function ("gatekeepers") are expected to result in reduced inflammation. Programmed death 1 (PD-1) and its ligand PD-L1 are expressed in inflammatory environments such as the intestinal epithelium in inflammatory bowel disease Untargeted metabolomics applied to stool samples and blood is a powerful approach to identify compounds produced by gut microbes that gain access to the host bloodstream where it may exert systemic and CNS effects. We hypothesize that the composition of the gut microbiota may be altered (measured by 16S rDNA profiling) by cannabinoids, in turn influencing inflammatory states, or alternatively, reduced inflammatory states may result in an alteration of the gut microbiota. This will be a longitudinal substudy of an ongoing randomized clinical trial. Stool, saliva, and blood samples for microbiome analysis will be collected before participants receive study treatment 1 week after participants receive study treatment, and 8 weeks after participants receive study treatment (dronabinol, vaporized cannabis, or placebo). Pre- and post-neurocognitive assessments will be done in all participants. The gut microbiota and relevant microbial metabolome will be assessed using a metabolite extraction and reconstitution protocol followed by untargeted HILIC/MS profiling in ESI negative mode. We will measure markers of gut inflammation (PBMC PD-1/PDL-1), systemic inflammation (IL-6), microbial translocation (sCD14) and neurocognitive function. Oral THC is expected to have the greatest impact on the gut microbiota due to higher local concentrations with this route of administration compared to vaporized cannabis.

TESTING VIA TELEPHONE CALL AFTER TAPER PERIOD

Cannabis Withdrawal Scale: The Cannabis Withdrawal Scale can be used as a diagnostic instrument in clinical and research settings where monitoring of withdrawal symptoms is required.[22] This will be performed after the 2-week tapering period has concluded. (10 minutes) If there was a previous adverse event or events (AE(s)), the Cannabis Solicited Adverse Events instrument will again be administered to ensure that the AE(s) have resolved. Participants will continue to be followed until there is resolution of the AE(s).

ARM #2. Driving Simulation:

Subjects with drivers' licenses will be scheduled for two experimental visits; one before they begin the randomized controlled trial, and a second visit after finishing their 8th week treatment. The initial visit will involve a 20-minute session to garner baseline values for driving skills. This visit will coincide temporally with the first session for the randomized controlled trial prior to Week 1 (Appendix 12).

At the time of the second driving simulation visit, subjects will be assigned the same medication that they have been using during the randomized controlled trial. Using a Volcano Vaporizer, subjects will inhale the average number of puffs they had consumed per session throughout the four previous weeks of the randomized controlled trial. They will use the Vaporizer before Hour 2 and again before Hour 6 (Table 3). They will also take the same oral medication that was provided during the randomized controlled trial. In addition to examining the effects on driving simulation, acute effects of study medications on spontaneous pain and vital signs will be determined (Appendix 13). We will administer the simulator sickness assessment during the first 2 hours of the appointment to ensure that the participant is physically able to perform the driving simulation tasks.

At the beginning of driving simulation appointments, participants will be given a urine toxicology and a breathalyzer test to test for any illicit substances that is not prescribed by a physician. Should the participant screen positive for an illicit substance, they will either be asked to reschedule or be discontinued from the study at the Principal Investigator's discretion. If this happens, participants will be compensated $10 for arriving to the scheduled appointment.

During the Driving Simulation study visit, the participants will be given paper and pencil forms that measure the following:

- **Psychoactive Effects (including Drug Liking):** A total of 15 separate VAS ratings will be presented at the time of driving simulation as a 100-mm horizontal line, anchored on the left with `not at all' and on the right with `extremely' (Appendix 10). Participants will pencil in a vertical line along the horizontal line that represents their current feeling (questions usually phrased, `During the past week, did you feel ___after consuming the vaporized cannabis?'). Ratings will be: any drug effect, a good drug effect, a bad drug effect, high, drunk, impaired, stoned, as if you liked the drug effect, sedated, confused, nauseous, like you desired more of the drug, anxious, down, and very hungry. Similar VAS questions have been shown to be sensitive and reliable subjective measures of cannabis intoxication.[17-20] (5 minutes)
- **Pain Relief**: The degree of pain relief after taking the study medication will be assessed by asking the participate to rate if their pain is (1) very much improved (2) much improved (3) minimally improved (4) no change (5) minimally worse (6) much worse (7) very much worse.
- **Pain Score:** Participants will be asked to rate their pain before and after vaporizing marijuana between 0 = no pain and 10=worst possible pain.
- **Driving Simulation Self-Assessment:** This comprises of a total of two questions to be asked hourly. They ask participants to rate how well they did on a VAS scale how well they believe they performed on the driving simulator and how much they believe their ability to perform on the driving simulator was affected by study drug.
- **Driving Test Questionnaire:** This will be administered to evaluate for possible confounding variables on the day of the driving simulation. We will ask the participant how much they slept the previous night and about their experience with computer games.

Sensory Testing

The Cold Pressor Test administered at all study visits will also be administered during driving simulation 3 times at hours 1, 3, and 7 to measure acute effects of pain relief.

By conducting repeat assessments for four hours following the first vaporization, we will be able to determine at what point participants no longer exhibit acute effects for each of the study medications. Participants will then complete a second vaporization and ingestion of oral medication before hour 6. We will then assess them for three hours in order to determine whether the acute effects are similar to those seen after the first vaporization, or perhaps greater (due to cumulative/residual effects).
To minimize the novelty of the driving simulations, participants will complete a pretest training session to re-familiarize themselves with the hardware and the tasks that they are to encounter during the simulations. Four separate tasks will be embedded within the simulation.

Table 3 Assessments of Acute Effects One Day following 2 and 8 Weeks of Cannabis Treatment

Hour	1		2	3	4	5		6	7	8
Vital Signs	X	Vaporization/Oral Medication	X	X	X	X	Vaporization/Oral Medication	X	X	X
Numerical Pain Intensity Score	X		X	X	X	X		X	X	X
Cold Pressor Test	X			X					X	
Pain Relief			X	X	X	X		X	X	X
Psychoactive Effects			X	X	X	X		X	X	X
Driving Simulation	X		X	X		X		X	X	X
iPad Performance Testing	X		X	X		X		X	X	X
Blood Draw (Δ9-THC levels)	X		X	X	X	X		X	X	X

Driving simulations: Simulation hardware will consist of a 3-screen, wide field-of-view monitor setup, steering wheel, and accelerator and brake pedals. The fully interactive simulations will assess lane tracking (standard deviation of lateral position [SDLP], or "weaving"), response to divided attention stimuli (accuracy, response time), car following, and performance during scenarios simulating routine driving as well as crash avoidance situations.

Participants in the simulator study will also be assessed for far visual acuity (Snellen Visual Acuity eye chart; need to have acuity of 20/40 or better, with or without correction), color vision, and contrast sensitivity (Vistech Contrast Sensitivity (Pelli-Robson Chart)). Participants will complete an orientation and practice drive prior to the initial simulation, in order to familiarize them with the controls and roadways.

- **Task 1: Lane Tracking/Divided attention:** Participants will be instructed to maintain their lane position and speed, and respond to divided attention stimuli in the two corners of the monitor. The primary outcomes are standard deviation of lateral deviation (SDLP), latency and accuracy on the divided attention tasks, and speed deviation. SDLP is a measure of how well subjects maintain their lane position, providing an index for each subject's road tracking error and ability to control the lateral motion of the car. It is primarily controlled by automatic information processing and outside of conscious control. SDLP has been shown to be sensitive to the effects of medications in both on-road and simulator studies (23-27). It has been examined in individuals under the influence of alcohol, marijuana, and MDMA, as well as with neurologic populations (28-32). SDLP has also demonstrated good test-retest reliability over short and long-term follow-ups (33-36). (7 minutes)
- **Task 2: Car Following:** The primary outcomes are (1) coherence between the participant and lead cars (a general correlation [0–1] of the participant's ability to accurately track the speed variations of the lead car); (2) time delay (or the reaction time to changes in the lead car's speed); and 3) distance from the lead car (7 minutes)
- **Task 3: Multi-tasking (Surrogate Reference Task [SuRT]):** The primary outcomes are response latency and accuracy on the SuRT tasks. In addition, we will examine SDLP and speed deviation during this more challenging divided attention task. The SuRT is a visual

perceptual task which presents subjects with an approximately 8" touch screen filled with circles and requires participants to point to a target circle.

Figure 1. Surrogate Reference Task (SuRT)

The level of difficulty is varied by changing the ratio of the size of the distractor circles and target circles. The equipment will be to the side of the monitor. Task conditions will include no search, easy, medium and hard searches (based upon the standard SuRT protocol). The SuRT is a measure of performance under high cognitive load and controlled processing, in that participants must divide their attention among three stimuli (roadway, speedometer, and events in the periphery), and is reflective of the workload generated by a real task (e.g., a GPS system). Face valid tasks such as navigation destination entry draw attention away from the road in highly variable ways (i.e. there tend to be large differences in how people attack problems associated with complex interactions). On the other hand, surrogate or structured tasks allow us to look at changes in attention in a more controlled fashion. This will enable us to address how participants under the influence of cannabis vary allocation strategies with workload. (5 minutes).

- **Task 4: Crash avoidance/decision-making:** In order to assess treatment effects during routine and non-routine events we will include scenarios addressing 1) the “yellow light dilemma”, wherein individuals need to respond to a yellow light onset by abruptly braking (risking a rear-end collision), or go through the intersection (risking running a red light), and 2) crash avoidance. Participants will be instructed to drive 45mph, and will encounter 8 green traffic lights, 4 of which will switch to yellow. These will be randomized within each drive. Consistent with California law (37), the yellow light phase (time before the yellow light turns red) will be 4.3s. The time available to perceive and respond to the yellow light will be held constant for all participants by controlling initiation of the yellow light by using the vehicle’s velocity to determine the time-to-location (start of intersection). This will be set at 3.4, 3.0, 2.7 and 2.2s, settings which in previous studies have shown to elicit a range of responses (running the yellow light, stopping) (38, 39). The primary outcomes will be stop/go percent and perception-reaction time (PRT; time of yellow onset to start braking or accelerating through the intersection), although a number of additional behavioral outcomes will be of interest. The simulation will also include a crash avoidance scenario in which the participant drives down a visually complex roadway (moving cars, pedestrians) and encounters the sudden appearance of a pedestrian, or car pulling out, in the roadway. Primary outcomes are the PRT to the incursion, and whether a collision occurs. Since an important aspect of this task is the unexpected nature of the event, the incursion point and object (vehicle, pedestrian) will vary across assessments (but be consistent across all participants). (5 minutes)

Performance-based tablet assessments: The following will be performed using an iPad with software designed by Digital Artefacts LLC (119 Oakdale Campus Iowa City, IA 52242 (319) 335-4985 http://www.digitalartefacts.com):

- **Critical Tracking**: This test assesses the participant's ability to adapt to an error signal in a first-order compensatory task, and has been shown to be sensitive to the effects of Δ9-THC. Participants use their finger to overcome built-in error in horizontal deviation from a midpoint by returning the cursor to the midpoint. However, the frequency, and velocity, of the deviations increases as a function of time. The primary outcome is the average lambda-c across 5 trials. (5 minutes)
- **Time estimation.** Cannabis can affect time perception and estimation. Deficits in temporal processing could have significant implications for driving, for example in estimating the amount of time available to pass through a yellow light, or anticipating cross-traffic. We will thus administer a brief measure of time estimation. As recommended by Sewell et al., we will use an approach that minimizes the use of subvocal counting, which may artificially decrease variation that might occur during real-world multi-tasking. Five trials, with randomly generated durations ranging from 5 to 30s (e.g., 7, 11, 29, 14, 23 seconds), will be generated. During each assessment, participants will complete the five trials. The participant will sit at a computer, and once the test starts will be presented with random letters in random parts of the screen. The participant is then to count the number of "M"s that appear until a second flash on the screen, at which point he/she is to announce the number of "M"s and the amount of time that has elapsed. The primary outcome is the ratio of estimated time to actual time. (3 minutes)
- **Balance.** Individuals may exhibit increased body sway when taking cannabis. To assess balance, participants will hold the iPad to their chest with their arms crossed, and their postural sway will be assessed while: 1) standing on both feet with eyes closed and 2) on a single foot and raising the other leg with the knee bent at 45 degrees, with eyes closed. Sway will be calculated using the iPad triaxial accelerometer.
- **Visual Spatial Memory Learning Test** Cannabis can affect memory acutely. Variation in some aspects of cognitive performance has been found to be moderately and positively correlated with some individual aspects of the SFST; particularly among tasks which assess reaction time. Impairment of these cognitive processes can also contribute to the completion of complex tasks such as driving or the SFST. We will assess short term memory using a visual-spatial learning test (VSLT). This test is modeled after other tests of visuospatial memory (e.g., the Brief Visuospatial Memory Test-Revised, Visual Spatial Learning Test). The test requires the subject to a) memorize 5 designs that are difficult to verbally encode, b) recognize them among a group of 15 designs (8 foils) and c) recall the correct placement of these designs on a 6 X 4 matrix. Participants will complete one trial. The score is the number of figures correctly identified and placed. (2 minutes).

Assays for Δ9-THC in Plasma

For purposes of correlation with the above findings, serum levels of THC will be determined hourly. Blood will be collected in grey top (NaF) tubes tubes and then the tubes inverted 8-10 times to mix. EDTA plasma will be processed as soon as possible after collection. The tubes will be centrifuged at 400xg for 10 minutes to separate plasma and cells and then, using a transfer pipette,

plasma will be removed carefully to avoid disturbing the cell layer. The plasma will be transferred to 1.8 ml cryovials and stored as plasma aliquots at –70C.

Δ9-THC and metabolites will be quantified using isotope dilution ultra-performance liquid chromatography (UPLC) and tandem mass spectrometry (MS/MS) using methodologies similar to what have been published. Briefly, deuterium labeled internal standards will be added and proteins will be precipitated using acetonitrile. Δ9-THC and CBD will be isolated using solid phase extraction and analyzed using electrospray ionization. Δ9-THC will be analyzed using positive ion electrospray while negative ion ESI will be used for CBD using Waters Xevo TQS equipped with Waters Acquity UPLC. The limit of quantification (LOQ) will be 0.5 ng/mL of each of the components in whole blood. Our laboratory at UCSD has been using similar methodologies to accurately quantify small molecules for many years (39).

10. HUMAN SUBJECTS

Total number of participants to be enrolled: This will be a single site study with 120 participants enrolled at UCSD.

Age: Because of the problems inherent in the use of cannabis in children and adolescents, we will not enroll individuals below the age of nineteen. Frequent use can affect school performance and relationships with family members in younger individuals [42, 43]. Earlier and greater involvement with marijuana has also been associated with increased risk of poor mental health [44, 45].

Gender: Both male and female populations develop chronic low back pain (CLBP); however, there is a tendency towards a higher incidence in males.

Ethnic background: CLBP is ubiquitous. Global studies have shown that low back pain is one of the most common complaints that patients bring to their physicians [46, 47]. Given the diverse ethnic background of San Diego, we should be able to recruit subjects from multiple ethnic backgrounds. A neuropathic component has been found in approximately 37% of patients with CLBP [48]; given the relative frequency of the latter, we should not encounter difficulty recruiting 120 participants.

Health status: Individuals with significant cardiovascular, hepatic or renal disease, uncontrolled hypertension, and chronic pulmonary disease (eg, asthma, COPD), will be excluded. This will be operationalized using criteria from the literature on adverse effects of medicinal cannabis [49, 50].

Inclusion criteria

- Age greater than 18
- Presence of chronic low back pain (CLBP) defined as the response to two questions 1) How long has back pain been an ongoing problem for you? 2) How often has low back pain been an ongoing problem for you over the past 6 months? A response of greater than 3 months to question 1 and a response of “at least half the days in the past 6 months” to question 2 will define CLBP according to the NIH Task Force on Research Standards for Chronic Low Back Pain (Appendix 15). [9].
- Visual average numerical pain intensity greater than 3/10 during one-week observation period
- To avoid confounding by concurrent medications and/or prior cannabis exposure, participants will have had a stable analgesic regimen that they will continue throughout the study and not having used cannabis for more than 7 days prior to study entry. The latter criteria will be verified by the use of the Draeger test at the first experimental visit.

Exclusion criteria

- Presence of another painful condition of greater severity than the back pain condition which is being studied.
- History of traumatic brain injury.
- Clinically significant or unstable medical condition. Individuals with significant cardiovascular, hepatic or renal disease, uncontrolled hypertension, and chronic pulmonary disease (eg, asthma, COPD), will be excluded. With respect to cardiovascular and pulmonary status, a clinician will screen participants with a tool developed for detection of congestive heart failure, coronary artery disease, obstructive and/or restrictive lung disease (Appendix 28 Cardiopulmonary Screen). Hepatic and renal disease will be evaluated with liver and renal function laboratory tests. If warranted clinically, subjects will undergo further evaluation (urinalysis, electrocardiogram, and/or chest X-ray).
- A positive result on toxicity screening will exclude individuals from participation. A urine drug test that screens for 5 categories of drugs: marijuana (Δ9-THC), cocaine, amphetamines/methamphetamines, opiates, benzodiazepines and phencyclidine (PCP) will be employed. A positive result for opioids and/or THC will not be exclusionary if the patient is receiving a prescription for an opioid and/or THC.
- Allergy to sesame oil, lactose, or gelatin
- Vascular disease, especially Raynauld's syndrome, systolic blood pressure > 170 mm, diastolic blood pressure > 100 mm
- Recent injuries to the upper extremity
- Cognitive impairment, such as Dementia or Alzheimer's Disease
- Substance Abuse History: individuals with current substance use disorders[55] as assessed using the Drug Abus65e Screening Test (DAST-10) (a score greater than or equal to 3) and the Alcohol Use Disorders Identification Test (AUDIT) (a score greater than or equal to 8 or a score greater than or equal to 7 if over 65 years old) (Appendix 31).
- Pregnancy as ascertained by a mandatory commercial pregnancy test
- Women who are lactating
- History of schizophrenia, bipolar depression with mania, current suicidal ideation or past history of suicide attempt. Cannabis can exacerbate pre-existing schizophrenia, and has been linked to an increase in the risk of suicide in such patients.[56] In patients with bipolar disorder, cannabis use has been associated with worsening of manic and psychotic symptoms.[57] Such findings suggest that cannabis is contraindicated in individuals with serious mental health issues, a line of reasoning that will be observed in the present study by excluding patients in the bipolar/schizoaffective/schizophrenic spectrum.
- Suicidality. Exposure to cannabis does not lead to depression but it may be associated with suicidal thoughts and attempts[58]. Therefore, the BDI-II will be used to measure suicidal ideation.
- Unwillingness to abstain from dronabinol for the rest of the study if taking dronabinol before study participation.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Four methods will be used for patient recruitment. First, a UCSD clinician may ask patients directly if they are interested in the study. For example, a UCSD Center for Pain Medicine clinician can provide interested patients with an information sheet about the study, including research staff contact information (Appendix 1). Second, we will use ResearchMatch to send a recruitment message to potential participants who meet the criteria specified. (Appendix 3). Third, newspaper advertisements

will be utilized (Appendix 2). Fourth, ICD-9 code 724.2 will be used to identify pertinent potential subjects. The following PHI will be requested: patient name, mailing address, date of birth. This request (along with documentation of UCSD IRB approval) will be forwarded to database managers at the Clinical Data Warehouse for Research (CDWR) who will be asked to pull a subset of the data from the Electronic Health Record system to query patient information in a HIPAA-compliant manner. All recruitment methods will rely on potential subjects voluntarily initiating contact with study research staff.

Data Mining
HIPAA Access to personal health information (PHI) will be requested through a waiver of consent and partial waiver of HIPAA Authorization for recruitment purposes. In order for a partial waiver of HIPAA authorization to be granted, we present the following options:

1 A plan to protect identifiers from improper use and disclosure
Multiple procedures for protecting against or minimizing risks will be put in place. All research staff will complete training for HIPAA and human subjects' protections regulations and procedures. Confidentiality of participant data will be maintained through several mechanisms. All participants will be assigned identification numbers, and a list linking names and ID number will be stored separate from participant data in a locked file cabinet and electronically on a secure server. Access to this list will be restricted to the principal investigator, project manager and research assistant. Blood specimens will be stored in a -70 degree freezer using the ID number.

Paper documents will be kept in a locked cabinet in the CMCR office on Dickinson Street. Electronic information will be stored in a password-protected account.

2. Justification as to why these procedures could not a) practicably be done without the waiver, and b) be done without access to, use, or disclosure of the PHI;
The proposed study cannot be done without the specified information because PHI is required in order to contact potential participants and screen for eligibility for the study. We will only collect minimal PHI necessary to distinguish patients who have chronic lower back pain who may qualify for the study. Once they have been identified, patients who agree to participate in the study will be consented and authorization will be obtained.

3. Justification that the privacy risk to individuals whose PHI will be used or disclosed is minimal and reasonable in relation to the anticipated benefit, if any, to the individuals;
PHI acquired for the purposes of recruitment will not be disclosed to any other agency, party or individual (other than the sponsor (NIDA), FDA and UCSD research compliance personnel). Evidence of UCSD IRB approval will be required to obtain this document from NIDA.

4. What PHI will be used and who will access, use or disclose the PHI. ICD-9 code 724.2 will be used to identify pertinent potential subjects. The following PHI will be requested: patient name, mailing address, date of birth. This request (along with documentation of UCSD IRB approval) will be forwarded to database managers at the Clinical Data Warehouse for Research (CDWR) who will be asked to pull a subset of the data from the Electronic Health Record system to query patient information in a HIPAA-compliant manner.

☒ History and Physical Exam	☒ Progress Notes
☒ Operative Report(s)	☒ Discharge Summary(ies)
☒ Diagnoses	☒ Medications
☒ Radiology Images	☒ Radiology Reports
☒ Pathology Reports	☒ Laboratory Reports
☒ EKG Reports	☒ Consult Reports
☒ Alcoholism or Alcohol Use	☒ Drug Abuse Information

Only authorized members of the research team will have access to PHI, specifically the principal investigator, project manager, and research associate/assistant.

12. INFORMED CONSENT

Process To Be Followed For Obtaining Consent/Assent/Permission And HIPAA Authorization.

We request a waiver of documented consent for conducting the phone screening. This part of the research, i.e., the telephone interview, presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. If a subject qualifies for the study and decides to participate, the screening information will be kept with their research record. If they not qualify for the study, the screening information will be destroyed.

1. Potentials volunteers will be screened via telephone interview (Appendix 16) and, as appropriate, via face-to-face assessment. Telephone screening (respondents blind to selection criteria) will assure volunteers meet general age and medical criteria. For those subjects interested in proceeding to a face-to-face assessment, a consent form will be mailed with instructions to peruse the document. The intent of this is to allow sufficient time for the prospective participant to consider whether to participate; a step to be taken to minimize the possibility of coercion or undue influence.
2. The Research Associate will obtain consent /authorization. The person in this position will undergo CITI training to gain requisite knowledge to perform the consent /authorization process. S/he will have sufficient knowledge of the study to answer any questions regarding the study. S/he will explain the research activity, how it is experimental (e.g., a new drug, extra tests, separate research records, or nonstandard means of management, such as flipping a coin for random assignment or other design issues). S/he will inform the human subjects of the reasonably foreseeable harms, discomforts, inconvenience and risks that are associated with the research activity. Information communicated to the participant/parent or legally authorized representative during the consent/assent/permission process will not include exculpatory language through which the participant is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the University or its agents from liability for negligence.
3. The Investigator will retain the original consent form and HIPAA authorization in a master research file. An electronic copy of the signed informed consent and HIPAA authorization will also be inserted into the electronic Medical Record alerting other providers of the subject's participation in this research protocol.

13. ALTERNATIVES TO STUDY PARTICIPATION

The therapeutic alternatives that are reasonably available that may be of benefit to a potential participant include standard of care measures; e.g., spinal manipulation, acupuncture, biofeedback, cognitive-behavioral therapy, massage and/or a comprehensive rehabilitation programs.

In a study such as the present one where there is no prospect of direct benefit to the participant, another alternative is to note participate.

14. POTENTIAL RISKS

Likely

- ☐ difficulties with balance
- ☐ eye irritation
- ☐ throat irritation
- ☐ increased heart rate
- ☐ possible low blood pressure
- ☐ reversible problems with your appetite, lethargy

Less Likely

- ☐ some change in your mood (good or bad)
- ☐ loss of memory
- ☐ decreased ability to concentrate or think properly

Rare But Serious

- ☐ dizziness
- ☐ head and chest pressure
- ☐ disorientation
- ☐ agitation
- ☐ combativeness
- ☐ incoherence
- ☐ visual hallucinations

Physical harm: Risks of inhaled cannabis products may include psychomotor coordination difficulties, eye irritation, throat irritation, increased heart rate, possible hypotension, and reversible appetite/mood/memory/cognition effects.

There may be some discomfort when blood samples are taken, and there is a small risk of bruising, infection, or inflammation at the site at which the needle is inserted. We will be taking two tablespoons of blood for the purposes of this study.

There is virtually no risk associated with pain testing in cold water unless there is a circulatory problem. The subject will be free to withdraw their hand from the water bath at any time. However, there is always the possibility of damage despite these precautionary measures.

- **Psychological harm:** Mental and/or emotional distress may result from questions asked during assessment or as a result of the time taken in the assessment process. Additionally, some neuropsychological tests may require concentrated effort and may be frustrating for the subject to complete.
- **Legal harm:** We will be asking sensitive questions about use of marijuana, and testing for illicit substance use. Access to such material for legitimate research purposes is generally acceptable, as long as the researcher protects the confidentiality of that information.
- **Social harm:** Invasions of privacy and breaches of confidentiality may result in embarrassment within one's business or social group. Every effort will be made to maintain confidentiality of the subject's participation to lessen this type of risk. Subjects may have some discomfort or feel embarrassed when they provide a stool sample.

- **Economic harm:** Eligibility for insurance, political campaigns, and standing in the community are problems may result from loss of confidentiality. Vaporizing marijuana may hinder application for future employment, if drug screening is a condition of employment. It is likely that detectable traces of marijuana will remain in the subject's hair or blood for a minimum of six weeks after vaporizing. If applicable, a letter will be written to the subject's employer explaining their participation in this research study and the dates of participation. Confidential information regarding your history, DNA information (genetic risk for certain diseases), substance use or health diagnosis may become known outside of the research setting.
- **Reproductive risks:** The procedures in this research are known to hurt a pregnancy or fetus in the following ways: poor educational attainment. A participant should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. Subjects will need to use birth control while on this study. Acceptable methods of birth control are: oral contraceptive pills, diaphragm and condom with spermicide, progestin implant, intrauterine contraceptive device.
- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let subjects know if they learn anything that might make you change your mind about participating in the study.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

At every study visit, stopping criteria will include:

Pulse: an irregular pulse or pulse rate > 110 beats per minute
Blood Pressure: systolic blood pressure > 180 mmHg or diastolic > 110 mmHg
Respirations: respiratory rate > 20 breaths per minute
Pulse: an irregular pulse or pulse rate greater than 110 beats per minute will result in cessation of participation and, if deemed advisable by a study clinician, transfer to the emergency department (across the street from our research center).

Blood Pressure: If the systolic blood pressure is ≥ 160 to < 180 mmHg or the diastolic is ≥ 100 to < 110 mmHg, a study clinician will conduct an evaluation to see if the participant has symptoms that would mandate discontinuation. Examples would include severe headache, confusion, chest pain, dyspnea, irregular heartbeat, and/or palpitations. Final determination regarding possible discontinuation will be made by a study investigator. If discontinued from the study, the participant will be asked to have their blood pressure evaluated by their primary care physician as soon as possible. If the systolic blood pressure is > 180 mmHg or the diastolic is > 110 mmHg, the participant will be discontinued from the study and either be transferred to the emergency department or be asked to visit their primary care physician as soon as possible. The end organ response to the blood pressure will guide the clinician's decision (e.g., the development of angina pectoris or hemiplegia will mandate transfer to the emergency department).

Respirations: shortness of breath will result in potential cessation of participation and possible transfer to the emergency department following evaluation by a study clinician, who will consult with the study investigator.

A locally developed self-report instrument, the Cannabis Solicited Adverse Events (Appendix 29) will be administered to assess distress from psychological effects of cannabis. This will be performed on a prn basis by the trained staff and routinely at the end of the acute

administration session. The items on this instrument ask participants about experiencing anxiety, paranoia, and hallucinations. Excess intoxication will also be assessed using this instrument which asks participants about their having dizziness, drowsiness, confusion, emotional changes, and/or cognitive changes. Positive responses to these items, if Grade 2, 3 or 4 (see below for definitions), will result in notification of a study clinician who will speak with the participant to see if discontinuation of participation in the study would be in her or his best interest.

Using the Cannabis Solicited Adverse Events instrument mentioned above, an Adverse Events Form (Appendix 30) will be completed. Adverse events will be characterized as 1 = Mild, 2 = Moderate, 3 = Severe, and 4 = Life Threatening using the following definitions (consistent with those used by the National Cancer Institute):

GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Inasmuch as the scoring of Grades 2, 3, and 4 mention that an intervention is indicated, AEs with Grades 2 or 3 will be brought to the attention of a study clinician so that s/he may interact with the participant to determine if discontinuation of study participation is warranted. This will be done in consultation with an investigator. Grade 4 AEs will be managed by reports tendered to the FDA and the IRB within the required time limits specified by each organization. There will also be a determination of whether the AE is related, possibly related or not related to the study by the investigator for Grades 1 to 4.

Furthermore, the participant will be followed by the research team to insure that the AE(s) resolve. This might include recommending that the participant see their primary care physician (e.g., for a change in blood pressure medication).

Risks will also be mitigated using the following measures:

- Preventing children and adolescents from gaining access to medicinal cannabis because of potential harm to their well-being. Subjects will be required to store cannabis in an area of their home that would prevent anyone else from discovering its location.
- Because some people cannot control their use of cannabis, we will not allow patients with recent substance abuse histories (less than 12 months) to participate.
- We will exclude patients if they are pregnant or refuse to exercise birth control if engaging in sexual activities that could result in pregnancy, have a heart disease or heart rhythm problem or have a history of serious mental illness (e.g., schizophrenia, mania, or a history of hallucinations or delusions)
- In order to avoid carcinogens, we will have subjects use a vaporizer rather than smoke joints or use a water pipe.

- We will instruct subjects not to drive a car or operate heavy machinery for 3-4 hours after use of medicinal cannabis, or longer if larger doses are used or the effects of impairment persist. They will use a designated driver for automobile transportation if they have to go out sooner than 3-4 hours after taking this medicine.
- As the response to cannabis varies widely, participants will titrate to effect and in essence use the minimum amount of medicinal cannabis needed to obtain relief from pain.
- A cannabis withdrawal syndrome will be under surveillance for two weeks; difficulty with getting to sleep and angry outbursts might require that they withdraw from the cannabis more slowly.

The UCSD Department of Psychiatry (Appendix 17) is committed to providing the resources and other supports (e.g., data management and information systems, statistical, and physical performance site) to ensure the timely implementation, conduct, and completion of this program.

Data and Safety Monitoring Board (DSMB)

A DSMB will be selected utilizing a group of experts that will advise the study investigators, with the primary responsibility to monitor human subject safety. The members will be comprised of at least 3 independent clinicians familiar with the conduct of clinical trials The DSMB will consider study-specific data as well as relevant background information about the test agents and target population under study. The DSMB will review the protocol, including the safety monitoring plan, and identify any major concerns prior to implementation. During the trial the DSMB will review:

1. Real-time and cumulative safety data for evidence of study-related adverse events, unanticipated problems
2. Factors that might affect the study outcome or compromise the trial data (such as protocol violations, losses to follow-up)
3. Staff performance for protection of privacy, confidentiality, and maintenance of secured databases
4. Progress of interventional trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention.

The DSMB should conclude each review with each member's recommendation as to whether the study should continue or be modified. Recommendations for modification of the design and conduct of the study may include corrective action when performance is unsatisfactory. Confidentiality must always be maintained during all phases of DSMB review and deliberations. The DSMB report will include the participants' demographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, a summary of all and serious adverse events, and any actions or changes with respect to the protocol.

16.PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

As stated above in Section 11, 3 methods will be used for patient recruitment. First, a clinician may ask patients directly if they are interested in the study. UCSD Center for Pain Medicine clinicians can provide interested patients with an informational sheet about the study, including research staff contact information (Appendix 1). Second, a list of patients meeting specific 'International Statistical Classification of Diseases and Related Health Problems' (ICD-9 724.2) criteria for chronic low back pain will be sent an informational letter informing them about the study and inviting them to contact research staff if interested in learning more information (Appendix 1). Third, newspaper advertisements may be used (Appendix 2). All recruitment methods will rely on potential subjects voluntarily initiating contact with study research staff, an "opt-in" approach.

Once protected health information (PHI) is obtained, measures to protect privacy and confidentiality will be implemented. This will include coding, removal of identifying information, limiting access to data, and the use of a Certificates of Confidentiality that will be applied for from the National Institute of Drug Abuse following IRB approval. Physical safeguards for research data will include storage of paper records in locked files, separation of personal identifiable demographics data from study data referenced only to a unique study ID. Electronic records will be maintained on a HIPAA Compliant server using password protection.

All laboratory specimens, evaluation forms, reports and other records will be identified only by a coded number in order to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done with coded numbers only. All stored samples are accessible only to the HNRP laboratory personnel and the appropriate study members. Samples are stored under the coded identifiers in freezers equipped with locks, behind locked doors requiring ID scan entry.

The consent process will be performed under conditions to insure privacy and confidentiality. It will take place in a private exam room in the Department of Psychiatry, 220 Dickinson St. San Diego, CA. Should interviewee disclose suicidal ideation (Appendix 18), further evaluation will take place. Important elements of the history that permit appraisal of the seriousness of suicidal ideation include the intent, plan, and means; the availability of social support; previous suicide attempts; and the presence of comorbid psychiatric illness or substance abuse. After intent has been established, outpatient management will be sought.

17. POTENTIAL BENEFITS

There is no direct benefit to subjects.

18. RISK/BENEFIT RATIO

There is a substantial disconnect between the therapeutic use of cannabis and research on the risks and benefits of this practice. Although edible marijuana merchandise has become widely available at medical dispensaries, there is little information in the literature on the medical efficacy of these products [62]. Pharmacologic oral preparations, which like the edible products, avoid deleterious effects upon the respiratory system, have had more attention from the scientific community [63-69]. However, some experts have opined that whole plant cannabis is superior to the FDA approved oral cannabinoid preparations, e.g., synthetic tetrahydrocannabinol (dronabinol, Marinol®) and/or the synthetic analog of Δ9-THC (nabilone,Cesamet®). As testament to this belief, oral cannabinoids have been on the market in the United States for many years and are not widely used [70]. Peak plasma concentrations occur 1 to 6 hours after ingestion, with a magnitude approximately 10% of that achieved with smoking [71]. As a result of the pharmacokinetics of oral preparations, it has been postulated that the preference expressed by patients for herbal cannabis is a result of the faster onset and shorter duration of action allowing titration of dose to the desired effect [72]. The present study will compare the risk benefit ratio of herbal cannabis to an oral preparation (dronabinol). We know that cannabinoids appear to have some benefit in alleviating a heterogeneous collection of neuropathic pain conditions [2, 3]. Preliminary recommendations have been issued from the College of Family Physicians in Canada to help guide clinicians in prescribing cannabis for the treatment of for chronic noncancer pain [73]. But we do not know if chronic low back pain will respond to cannabis (or dronabinol).

19. EXPENSE TO PARTICIPANT

There will no expense for participants other that the cost of travel/parking.

20. COMPENSATION FOR PARTICIPATION

Subject payments are requested in order to compensate subjects for their participation. Total compensation could equal $960.

Participants will be asked to arrange for transportation to and from the research site. For the screening appointment, participants will receive $40. For the baseline visit, participants will be given $10 for their arrival. Participants will receive $20 for each microbiome stool and saliva sample. If participants provide stool and saliva samples for the first, second, and sixth experimental visits, they will receive $60. Participants will receive $20 for each microbriome blood sample. If participants provide blood samples for the first, second, and sixth experimental visits, they will receive $60. We will budget $20 per week x10 weeks equals $200 and $65 per visit x6 visits equals $390. The total per subject payment will be $760 for visits. Compensation will be pro-rated if the subjects does not complete by weeks of participation and study visits attended.

For the baseline driving visit, participants will receive $20. In addition, we will pay subjects for one other driving session. In this driving session, we are budgeting $20 per hour for 9 hours equals $180 per subject. While the experiment will last 8 hours, the time for preparation and lunch will have the participant stay at our center for a total of 9 hours. Compensation will be pro-rated if the subject does not complete driving simulation at $20 per hour. The total compensation for both driving visits will be $200.

Inasmuch as participants will be given a vaporizer worth $600 to take home and use, they will not be compensated for their visits and weekly journals until study completion and after they return the vaporizer. Should they withdraw from the study prematurely, they will be compensated for completed visits but still be required to return the vaporizer they were given in order to be compensated.

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22. FUNDING SUPPORT FOR THIS STUDY

This study will be funded by the National Institute of Drug Abuse as 1R01DA038634-01A1 "A Randomized, Cross-Over Controlled Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain"

23. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

24. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

IND 102847 Vaporized Cannabis

This study involves an FDA-regulated investigation product for vaporized cannabis. Barth Wilsey MD is the IND holder (subsequently transferred to Dr. Marcotte). The IND Acknowledgement and Form 1572 from 2008 are attached (Appendices 20 and 21). An email from the FDA official is attached stating that the IND is may be used for the present study (Appendix 22).

The investigational drug will be handled by the UCSD Investigational Pharmacy. Accountability records will be maintained according to policies and procedures (Appendix 23). This has been discussed with the UCSD Investigational Pharmacy. Sign out logs will be kept as dictated by NIDA and DEA officials. At the end of each experimental session and/or study visit, all unused materials will be collected and stored in a sealed container that will be returned to the UCSD Investigational Pharmacy, with the exact amount noted and dated in the log (e.g., “bulk cannabis weighing x mg”). All records will be made available to the DEA and the Research Advisory Panel of California, which supervises all controlled substance research in California. At the end of the study, all unused plant

material (i.e., cannabis not vaporized or the debris from vaporization) from each subject's 8 week treatment period and, if applicable, driving simulation session will be collected and placed in a container, which will disposed at the facility used to incinerate unwanted medical or containment materials.

25. OTHER APPROVALS/REGULATED MATERIALS

No other UCSD review committees have reviewed and approved/authorized this study or are currently reviewing the study. However, we have multiple federal and state reviews that are being conducted. Marijuana is currently classified at the highest (most restrictive) level as a Schedule I drug (no accepted medical use, high potential for abuse). U.S. investigators are subject to specific Food and Drug Administration (FDA) and Drug Enforcement Agency (DEA) regulations concerning research with controlled substances. These reviews are described below:

DEA: Under the Controlled Substances Act (21 USC 822 (a)(1)) and implementing DEA regulations, persons conducting clinical research with any controlled substance must register with the DEA, keep specific types of records, provide evidence of safety precautions to prevent diversion, and periodically report to the DEA. The PI, Barth Wilsey, has maintained a Schedule I license to study marijuana for over a decade. The DEA in Washington is awaiting UCSD IRB approval and will then have the San Diego Branch inspect the UCSD Investigational Pharmacy to insure that the facility meets their guidelines for secure handling of cannabis.

FDA: Barth Wilsey, has an IND to study vaporized cannabis. A document was made to them earlier this year providing the background on the present proposal.

NIDA: The source of marijuana will be the National Institute on Drug Abuse (NIDA); they will not release the marijuana until DEA and FDA approvals are granted. As we have documentation that the FDA will allow us to proceed (Appendix 21), the only remaining regulatory approval is that from the DEA.

A Certificate of Confidentiality has been obtained from NIDA.

Research Advisory Panel of California: Some States may have their own registration requirements for Schedule I substances above and beyond the Federal requirements. California requires registration with the Regulatory Advisory Panel of California (RAPC). We have received approval from this agency (Appendices 24 and 25).

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

N/A