IRB#: 7009
Characterization of the analgesic effects of oral cannabidiol (CBD) in healthy, normal volunteers

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I. Purpose

Cannabidiol (CBD) is a chemical constituent found in cannabis that does not have intoxicating effects; it is thought to curtail the psychoactive effects of delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis (see Mechoulam et al., 2002; Fusar-Poli et al., 2009). While studies have established the analgesic effects of THC and similar cannabinoid type-1 (CB1) receptor agonists across species (e.g., Cooper et al., 2013; Craft et al., 2013; Maguire et al., 2013), the psychoactive effects and abuse potential of these drugs decrease enthusiasm for their potential clinical utility.

Preclinical studies have demonstrated that CBD alone is effective in producing analgesia in models of neuropathic pain (Costa et al., 2007; Toth et al., 2010; Ward et al., 2011 & 2014) and non-neuropathic pain (Maione et al., 2010). Importantly, CBD does not elicit the behavioral effects indicative of abuse potential (Ward et al., 2014). Recent clinical studies have suggested that the 1:1 combination of THC:CBD in an oromucosal spray administered as an adjuvant therapy with concomitant analgesics produces analgesia in patient populations with intractable pain (i.e., Langford et al., 2013; Portenoy et al., 2012). However, to date, there have been no controlled studies investigating the analgesic effects of CBD alone. Thus, CBD's analgesic effects in humans cannot be distinguished from those of THC. Establishing the analgesic effects of CBD alone will fill a critical gap in our knowledge about the potential therapeutic effects of this drug.

II. Introductory Statement

Recent clinical studies have suggested that the combination of THC and cannabidiol (CBD), the primary chemicals in cannabis, produces pain-relieving effects in patient populations (i.e., Langford et al., 2013; Portenoy et al., 2012). However, to date, there have been no controlled studies investigating the pain-relieving effects of CBD administered alone. For this study, the pain-relieving effects of CBD will be assessed in healthy, non-substance-using adults between 21-50 years old over 4 outpatient laboratory sessions. The physiological and subjective effects of CBD will also be measured. This study, designed to establish the analgesic effects of CBD alone, will fill a critical gap in our knowledge about the potential therapeutic effects of this drug.

III. General Investigational Plan

This within-subject, double-blind, placebo-controlled study will assess the analgesic effects of a range of cannabidiol (CBD) doses (0, 200, 400, or 800 mg, po). Normal, healthy volunteers with no current pain or substance use will participate in 4 outpatient laboratory sessions over the course of 4 weeks during which the analgesic effects of CBD will be assessed using the Cold-Pressor Test (CPT), a laboratory model of pain which has predictive validity for the clinical use of analgesics. The order of CBD dose will be counter-balanced across participants; **Table 1** illustrates a representative dosing schedule. Secondary measures will include subjective and physiologic effects of CBD, and the CPT, subjective mood and drug effects, and vital signs will be measured before and at specified time points after CBD administration. Determining the efficacy of CBD in an experimental model of pain will provide important endpoints (i.e., dose, time course) of this effect to further investigate the potential role for clinical use of CBD as an analgesic.

Table 1. Representative Dosing Schedule

Day	**M**	**T**	**W**	**Th**	**F**
Week 1	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Session	1	1	1	1	1
CBD (mg)	0	200	400	800	0
Week 2	S1	S2	S3	S4	S5
Session	2	2	2	2	2
CBD (mg)	200	400	800	0	200
Week 3	S1	S2	S3	S4	S5
Session	3	3	3	3	3
CBD (mg)	400	800	0	200	400
Week 4	S1	S2	S3	S4	S5
Session	4	4	4	4	4
CBD (mg)	800	0	200	400	800

The primary outcome measures for this study will be the dose-dependent analgesic and subjective effects of CBD. There will be 4 dose conditions under which these endpoints will be measured (0, 200, 400, and 800 mg CBD). A priori planned comparisons will be performed to determine dose-dependent effects of CBD relative to placebo. We hypothesize that CBD will elicit dose-dependent increases in analgesia. We also hypothesize that CBD will fail to produce subjective effects of intoxication ('Solution liking,' 'Good solution effect,' etc.).

IV. Protocol

PARTICIPANTS:

All research volunteers (N=18) will be between 21 and 50 years old, male or non-pregnant female, and healthy (according to medical and psychiatric examinations). It is expected that 50% of applicants will be female and that 40-50% of applicants will be non-Hispanic Caucasian, 25-30% will be Hispanic, 15-20% will be non-Hispanic Black or African American, 5-10% will be Asian or Pacific Islanders, and less than 1% will be Native Americas, Eskimos, or Aleuts. We will not accept volunteers who are substance-users, on parole or probation, nor those previously convicted of a crime of violence. The extensive medical screening assures that only healthy volunteers will be used. Any subject with abnormal medical findings will be offered referral for treatment. Likewise, if an individual is dependent on any drugs, with the exception of nicotine or caffeine, he/she will be offered referral to an appropriate treatment program.

STUDY INCLUSION AND EXCLUSION CRITERIA (list in outline form):

INCLUSION CRITERION	**METHOD OF ASCERTAINMENT**
1. Adults between the ages of 21 and 50	Clinical interview and verification with identification
2. Able to perform study procedures	Practice sessions
3. Women practicing an effective form of birth control (condoms, diaphragm, birth control pill, IUD)*	Self-report during interview
EXCLUSION CRITERION	**METHOD OF ASCERTAINMENT**
1. Female subjects who are currently pregnant or breastfeeding	Clinical interview, physical examination, serum HCG
2. Current illicit drug use	Urine drug toxicology, clinical interview
3. Presence of significant medical illness (e.g., diabetes, cardiovascular disease, hypertension, hepatitis, clinically significant laboratory abnormalities, abnormal LFTs, blood pressure > 140/90)	Medical history, physical examination, laboratory tests, 12-lead ECG
4. Current parole or probation	Self-report during interview
5. History of heart disease	Clinical interview, abnormal ECG
6. Recent history of significant violent behavior	Self-report during interview

7. Major current Axis I psychopathology (e.g., major depressive disorder, bipolar disorder, suicide risk, schizophrenia)	Psychiatric interview
8. Current use of any prescription or over-the-counter medication	Medical history
9. Current chronic pain	Self-report during interview

* For females of child-bearing age: The serum pregnancy test is performed during the screening procedure, and urine pregnancy tests are repeated on each visit. Since this test cannot detect the very early stage of pregnancy (10 day period between fertilization and implantation), an effective birth control method or sexual abstinence is required throughout study participation.

SCREENING PROCEDURES:

1) Initial telephone interviews will be carried out by research assistants and volunteers who have been trained by Dr. Cooper, during which time potential participants will be asked about their current and past drug use and general health. Individuals who are interviewed by telephone will be considered eligible for screening at the Substance Use Research Center if they are between ages 21-50, are not regular users of drugs, and self-disclose as medically and psychiatrically healthy, without chronic pain.

2) After initial determinations of eligibility, volunteers will come into the laboratory for their first screening visit. They will be asked to sign our study-specific screening consent form, allowing us to collect questionnaire data, conduct interviews, and obtain medical information. We will do an ECG test. Participants will be told that they will be taking part in a study investigating the effects of cannabidiol, an experimental oral medication taken by mouth in solution form.

3) Psychologists (e.g., the primary investigator and co-investigators) will conduct interviews and will provide a detailed explanation of the procedures outlined in the study consent form. The psychologist will also sign the screening consent form.

4) Laboratory tests will be performed that include urinalysis, urine drug toxicology, 12-lead electrocardiogram, and blood tests (complete blood count with differential, chemistry profile). A serum pregnancy test will be performed on all women during screening. All medical information will be evaluated by the study physicians.

5) Medical and psychiatric interviews will be conducted by a study physician in the Division on Substance Abuse and will include a physical examination and review of all medical results and study inclusion/exclusion criteria. All of the psychiatrists have completed at least 4 years of psychiatric training and most are Board Certified (those not Board Certified are in the process of obtaining certification). Based on the results of clinical interviews, physicians will confirm

whether volunteers have major current Axis I psychopathology (e.g., major depressive disorder, bipolar disorder, suicide risk, schizophrenia) requiring medical intervention.

6) During or after the physical examination, the study physician will discuss this study protocol with the volunteers and document their consent to the research study. The physician will then sign the study consent form. Study procedures will begin after the study physician verifies that participant meets inclusion/exclusion criteria, understands the medical risks of participation, and is capable of providing informed consent. The senior study physician will settle any disagreements among the study team as to a volunteer's eligibility, and will make the final decision as to study participation. All procedures are consistent with the Division of Substance Abuse Guidelines for Investigators (9/8/08).

7) Because there is a proportion of the population that is unable or unwilling to tolerate pain induced by the Cold-Pressor Test, all potential participants will undergo a practice session prior to admission into the study. Participants also will practice completing the computerized questionnaires and performance tasks under supervision of laboratory staff to allow them to become familiar with these aspects of the protocol. This training day reduces variability in the data and provides both participants and researchers with important information about how an individual will respond to the test conditions.

MEDICATION:

Cannabidiol (CBD): Placebo or active CBD (0, 200, 400, or 800 mg), provided by Insys Therapeutics, Inc., will be administered orally in liquid solution form. For study session administration, both the active and placebo drug solutions will be masked in taste and smell by peppermint oil (Insys manufactures the matching placebo, which is then re-packaged by the NYSPI pharmacy and masked by a drop of peppermint oil).

Table 1. Representative Dosing Schedule

Day	M	T	W	Th	F
Week 1	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
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CBD (mg)	0	200	400	800	0
Week 2	S1	S2	S3	S4	S5
Session	2	2	2	2	2
CBD (mg)	200	400	800	0	200
Week 3	S1	S2	S3	S4	S5
Session	3	3	3	3	3
CBD (mg)	400	800	0	200	400
Week 4	S1	S2	S3	S4	S5
Session	4	4	4	4	4
CBD (mg)	800	0	200	400	800

Based on CBD's long half-life (21-33 hrs) (Consroe et al., 1998), sessions will be separated by at least 5 days to allow for CBD clearance and prevent carryover effects. Physiological effects (heart rate and blood pressure) and side effects will be monitored throughout the session.

Laboratory Sessions and Cold Pressor Test (CPT):

In the current study, there will be four laboratory sessions to assess the effects of a range of cannabidiol doses on analgesia. During the CPT test sessions, which will start and end at approximately 0900 and 1630hr, the analgesic, subjective, and physiological effects of cannabidiol will be determined repeatedly following a pretreatment of cannabidiol or placebo (see **Table 3**). Administration of cannabidiol will occur at 1000 hr. Baseline assessments will include measurements of analgesia (CPT), mood, blood pressure and heart rate. A breathalyzer test will be done before each session and urine samples will be tested for illicit drug use and, for women, pregnancy (prior to all sessions). Participants testing positive for drugs will be excluded from further participation. A light breakfast will be provided before CBD administration (e.g., bagel, juice, coffee).

The CPT, a well-established model for producing pain in humans (e.g., Chen et al., 1989; Conley et al., 1997; Zacny et al., 1996), will be performed once before and six times after drug administration and will last approximately 15 minutes. Our laboratory and others have shown that multiple CPTs can be carried out within the same day with little or no carryover effects between tests (e.g., Conley et al., 1997; Zacny et al., 1996), and it can be used to detect the analgesic effects of cannabinoids (Cooper et al., 2013). In this assay, the two dependent measures are latency to feel pain and latency to withdraw the hand from the cold water. Because previous research has shown that experimenters of the opposite sex influence responding to painful stimuli (Clark and Goodman, 1974; Clark and Mehl, 1971; Levine and De Simone, 1991), the sex of the experimenter will always be of the same sex as the research participant.

The cold pressor apparatus will consist of two coolers filled with either warm (37°C) or cold (4°C) water with an aquarium pump that will circulate the water. The CPT will be performed seven times throughout the session. At the beginning of each CPT trial, the experimenter will read a standardized script describing the procedures to the participant. The participant will begin the test by placing the left hand into the warm water for three minutes. During the warm water immersion, the State Anxiety Inventory will be completed; blood pressure and heart rate will be measured. The participant will be instructed to remove his or her hand from the water after three minutes and skin temperature of the thumb pad will be measured. Another scripted statement will be read describing the CPT procedure to the participant, before the participant immerses his or her hand in the cold water. Participants will be instructed to report the first painful sensation, and to remove the hand when the stimulus can no longer be tolerated. Immediately after removing the hand from the cold water, blood pressure, heart rate, and skin temperature will then be measured. Upon withdrawal of the hand, participants will be asked to rate the pain and bothersomeness of the cold-water stimulus on a scale from 0 to 10, 0 being "not painful/bothersome at all' and 10 being "most painful/ bothersome feeling imaginable." They will additionally complete a shortened Cold Pressor Test-Visual Analog Scale (CPT-VAS) and report the sensory and affective dimensions of the pain experience with the Short Form-McGill Pain Questionnaire (SF-MPQ). The CPT-VAS

questionnaire will consist of 11 items presented one at a time. Participants will be instructed to mark on a 100 mm line labeled "not at all" on one end and "extremely" at the other end indicating how they feel at that moment. The following questions will be included in the CPT-VAS: "I feel…" "Like I am coasting," "Confused," "Dizzy," "Drunk," "Elated," "Like I am floating," "Light-Headed," "Nauseated," "Sedated," "Sleepy," "Stimulated." Participants will again complete the State Anxiety Inventory. Pain dissipates rapidly after removal of the extremity from the cold water. Except for the acute stress associated with the pain test, there have been no known long-term consequences of this procedure.

Laboratory Facility: All experimental sessions will be conducted in the Substance Use Research Center (SURC) located on the 3rd floor of the NYS Psychiatric Institute. Participants will sit in a comfortable task chair in front of a Macintosh computer. A response manipulandum ("mouse") will be used for completion of pain rating scales and subjective-effects questionnaires.

Table 2. Session Schedule

Time (hr)	**TIME (min)**	**EVENT**
0900	-60	Urine, breathalyzer, breakfast
0930	-30	Baseline assessments: Mood scales, CPT
1000	0	Solution administration
1030	30	BP/HR, SRF, Mood scales
1100	60	SRF, Mood scales, CPT
1130	90	BP/HR, SRF, Mood scales
1200	120	SRF, Mood scales, CPT
1230	150	BP/HR, SRF, Mood scales
1300	180	SRF, Mood scales, CPT
1330	210	BP/HR, SRF, Mood scales, Lunch
1400	240	SRF, Mood scales, CPT
1430	270	BP/HR, SRF, Mood scales
1500	300	SRF, Mood scales, CPT
1530	330	BP/HR, SRF, Mood scales
1600	360	SRF, Mood scales, CPT
1615	375	BP/HR, SRF, Mood scales
1630	390	BP/HR, Field Sobriety Test, participant discharge

Table 3. Events Occurring During the Cold-Pressor Test

TIME (sec)	EVENT
-190	ST, Warm tank immersion, State
-10	ST, Vital Signs
0	**Cold water immersion**
180 or When hand is withdrawn	ST, Vital Signs, Pain Intensity/Bothersomeness Scales, CPT-VAS, SF-MPQ, State

ST=skin temperature Vital signs=blood pressure and heart rate CPT-VAS=Visual Analog Scales State=State Anxiety Inventory SF-MPQ=Short-Form McGill Pain Questionnaire*

**See descriptions of questionnaires above.*

SAFETY MEASURES:

The medical director of the cannabis laboratory will oversee any medical components to the study. During the sessions, a Registered Nurse and Medical Doctor will be available in the case of an emergency. During laboratory sessions, vital signs (heart rate and blood pressure) will be monitored.

Emergency medical equipment is available in our laboratory, which is located in a hospital where a full medical emergency back-up team is constantly available. We anticipate that careful participant selection, CBD dose selection and monitoring will obviate the need for such emergency care. We have been conducting inpatient and outpatient clinical pharmacology research for over 15 years and have encountered no serious adverse incidents.

STATSTICAL ANALYSIS PLAN

Repeated measures analysis of variance (ANOVA) with planned comparisons were used to assess cannabidiol's dose-related effects on measures of pain and subjective drug effects associated with abuse liability. For each participant under each dose condition, pain threshold and tolerance were calculated as the difference from baseline CPT (pre-drug administration) values. Subjective pain ratings (Pain Intensity and Bothersomeness Scales) were also measured as a function of change from the baseline response. Changes scores from each of the three active cannabidiol dose strengths were compared to placebo (i. e., 0 mg vs 200 mg; 0 mg vs 400 mg; 0 mg vs 800 mg) for each of the measures specified above. Results were considered statistically significant when p values were equal to or less than 0.01 using Huynh-Feldt corrections (SuperANOVA, Abacus Concepts, Inc., Berkley, CA).

Criteria for Early Discontinuation:

Throughout participation, we will carefully monitor participants for medication tolerability. The research team will continually assess the participant's health throughout the testing sessions and will remove participants from the study if physical or mental deterioration is observed.

The CPT has been associated with cardiovascular effects that include increases in heart rate and blood pressure. The participants will be monitored before, during, and after the CPT. Blood pressure and heart rate will be measured both before and after the test. In the past, we have found the CPT to produce about a 10-point increase in systolic and diastolic pressure (Kowalczyk et al., 2006). Participants will be informed of the cardiovascular risks associated with the test, and medical personnel will be on staff during the test in the case of an emergency. Participants may experience transient elevations in systolic and diastolic blood pressure as well as heart rate in response to cold-water immersion. A systolic blood pressure of greater than 180 or a diastolic blood pressure greater than 110 (each measure confirmed by manual reading), in which either is sustained for more than 120 sec., will result in suspending the cold pressor test for that participant for that given day. In addition, a single reading of systolic blood pressure greater than 200, or a single reading of diastolic pressure greater than 120 (each measures confirmed by manual reading), or a confirmed heart rate of greater than 160, will result in suspending the cold pressor test for that participant for that given day. If any of these parameters is exceeded, we will immediately confer with a staff internist to determine whether the episode of hypertension or tachycardia is resolving and can be followed up on an outpatient basis, or whether acute medical intervention is indicated. Under these conditions, the cold pressor test will not be administered again until consultation is sought and the IRB is alerted and approval is obtained for continuation of testing with that participant. If these changes are observed on a second occasion, the CPT will not be administered again to that participant.

Additionally, immediate removal from the study will result if significant adverse reaction to the study drug or assessment procedure is noted. Upon removal of a participant from the study, he or she will be provided with the appropriate follow-up treatment by a study physician or a research nurse. We anticipate, however, that careful screening, informed consent, dose selection, and participant monitoring, will obviate the need for such emergency care. We have been conducting inpatient and outpatient clinical pharmacology research for over 15 years and have encountered no serious adverse incidents.

MAJOR RISKS:

1) Cannabidiol: Participants are informed of possible side effects following CBD administration. The medication has few psychoactive effects (e.g., Leweke et al., 2000; Fusar-Poli et al., 2009), although there is a report of decreased anxiety and increased sedation (400 mg; Crippa et al., 2004). One placebo-controlled study administered CBD (approximately 700 mg/day) to patients with Huntington's disease for 6 weeks and reported no significant adverse effect from the medication relative to placebo (Consroe et al., 1991). CBD doses up to 1500 mg/day have been given for several weeks to schizophrenic patients with no side effects reported (Zuardi et al., 1995, 2006). Cannabidiol exposure may have a harmful effect on a fetus or a newborn, thus individuals will not be allowed to participate in the study if they are pregnant or breastfeeding, or if they cannot use an appropriate contraception method.

2) Pain procedure (Cold Pressor Test): During the CPT there may be significant discomfort associated with the stimuli. However, pain dissipates rapidly after removal of the extremity from the cold water. Except for the acute stress associated with the pain test, there have been no known

long-term consequences of these procedures. Participants who are unable to tolerate the procedures during the training session will not be enrolled in the study.

Participants will be monitored continuously throughout the experimental procedure. Emergency medical equipment is available in our laboratory, which is located in a hospital where a full medical emergency back-up team is constantly available. As stated above, (page 10), the CPT is associated with cardiovascular changes that include elevations on heart rate and blood pressure. If systolic blood pressure of greater than 180 or a diastolic blood pressure greater than 110 (each measure confirmed by manual reading), in which either is sustained for more than 120 sec. is observed the CPT for that participant will be suspended for that given day. In addition, a single reading of systolic blood pressure greater than 200, or a single reading of diastolic pressure greater than 120 (each measures confirmed by manual reading), or a confirmed heart rate of greater than 160, will result in suspending the CPT for that participant for that given day. If any of these parameters is exceeded, we will immediately confer with a staff internist to determine whether the episode of hypertension or tachycardia is resolving and can be followed up on an outpatient basis, or whether acute medical intervention is indicated. If these changes are observed on a second occasion, the CPT will not be administered again to that participant.

3) Blood drawing: Blood drawing during the screening process may cause mild discomfort at the site where the needle is inserted, and it poses a small risk of bruising at the site as well as an extremely low risk of infection. A total of 15 ml of blood will be drawn throughout the 4-session study; we will do complete blood chemistry and a plasma pregnancy test during screening (15 ml).

INSTRUMENTS USED:
Prescreening and Screening Assessments: Measures used to initially characterize participants include personal questionnaires, medical history, physical examination, laboratory assessments of blood and urine, and body weight. In addition, females will be administered a serum pregnancy test (beta HCG). A detailed list of screening measures is shown below:

Telephone Interview: 10 min. (Appendix 3)
Intake and Drug History Questionnaire: 10 min. (Appendix 4)
General Health Questionnaire: 5 min. (Appendix 5)
Medical History Questionnaire: 10 min. (Appendix 6)
Michigan Alcoholism Screening Test: 5 min. (Appendix 7)
Beck Depression Inventory: 5 min. (Appendix 8)
Race and Ethnicity Questionnaire: 1 min. (Appendix 9)
Trauma Assessment for Adults – Self-Report: 5 min. (Appendix 10)
Yale PRIME Screening Test: 5 min. (Appendix 11)
Vocabulary Assessment: 5 min. (Appendix 12)
Fagerstrom Test of Nicotine Dependence: 5 min. (Appendix 13)
Personal and Drug History Interview: 30 min. (Appendix 14)
Mini-SCID Assessment: 30 min. (Appendix 15)
Physical and Psychiatric Examination: 30 min. (Appendix 17-18)
Laboratory and Hospital Tests: 1 hr.

Study Session and CPT

A. Solution Rating Form (Appendix 19)

B. Visual Analog Scale – WAS (Appendix 21)

C. State Anxiety Questionnaire (Appendix 20)

D. 11-point Lichert pain intensity scale (Appendix 23)

E. Cold Pressor Test-Visual Analog Scale (CPT-VAS) (Appendix 22)

F. Short Form-McGill Pain Questionnaire (SF-MPQ) (Appendix 24)

Safety Measures

A. Vital signs including heart rate, systolic and diastolic blood pressure, oral body temperature, respiratory rate (10 minutes)

B. Physical Examination (30 minutes)

C. Laboratory Chemistries (15 minutes)

D. ECG (20 minutes)

E. Urine Toxicology (for drugs of abuse) (5 minutes)

F. Adverse Events Assessment (5 minutes)