Protocol Title:
Effects of Nabilone on Trauma Related Cue Reactivity in Cannabis Users with PTSD

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6971

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10/15/2015

Clinic:
Marijuana Research Laboratory

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Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
Division on Substance Use Disorders

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

N/A

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
We've had one participant complete the study this year.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
60
Total number of participants enrolled to date

2
Number of participants who have completed the study to date
2
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
Yes
Describe actions taken or planned to address these problems.
In order to address recruitment challenges, we changed the inclusion/exclusion criteria in October 2017, as follows:
1) Changed the maximum age from 45 to 55
2) Minimum frequency of MJ use decreased from 4x/week to 2x/week
3) Changing the PTSD assessment from the MPSS-SR to the PCL-5
4) Other medication use criterion changed from excluding all medication use to allowing for use of stable psychotropic medications not otherwise contraindicated, and excluded use of beta-blocker medications
5) Changed laboratory test limit maximums from 2x ULN to 3x ULN
Comments / additional information

Sample Demographics

Specify population
non-treatment seeking cannabis users with PTSD
Total number of participants enrolled from this population to date
2
Gender, Racial and Ethnic Breakdown
2 male, African America, non-Hispanic, 38 and 39 years of age.

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
1
Number of participants currently enrolled
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Medication Trial

✓ Use of Placebo or Sham Treatment
✓ Administration of Substance of Abuse
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research
✓ Adults
✓ Adults over 50
✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
No
Who is the PI of the grant/contract?
Levin, Frances, MD
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
Shared pharmacotherapeutic strategies for cannabinoid & opioid use disorders
Grant Number
U54 DA037842
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Cannabis is the most commonly used illicit drug worldwide (United Nations Office on Drugs and Crime, 2013) and a subset of cannabis users develop a cannabis-use disorder (CUD). These problems may be exacerbated by the presence of comorbid psychiatric disorders. One population at high risk for CUD is individuals exposed to trauma and diagnosed with post-traumatic stress disorder (PTSD; Cougle et al., 2011). In fact, severity of problematic cannabis use, including withdrawal symptoms, is positively associated with severity of PTSD symptoms, with patients reporting cannabis use to help cope with PTSD symptoms (Boden et al., 2013). Thus, in individuals with PTSD, cannabis may serve to alleviate aspects of trauma-related symptomatology. Despite the prevalence of cannabis use among the PTSD population and self-reports that it is used to help cope with PTSD symptoms, the direct effects of cannabis on PTSD symptomology are unknown. The purpose of this placebo-controlled, within-subject study is to assess the effects of smoked cannabis and orally administered nabilone, a synthetic analog of THC, the primary psychoactive component of cannabis on multiple dimensions of PTSD symptomatology in cannabis smokers with PTSD.

This study will compare the effects of smoked cannabis and nabilone on attentional bias toward trauma-related stimuli, subjective and emotional processing to a range of trauma-and non-trauma-related images and physiological reactivity to these stimuli in individuals with CUD and PTSD. Importantly, this study will also probe the abuse related potential of nabilone compared to smoked cannabis in this population, a critical aspect in determining the potential feasibility for its use clinically to treat CUD in PTSD populations. The effects of nabilone will be compared to propranolol as a positive control. Propranolol, a beta-adrenergic antagonist, is used to treat anxiety and currently being investigated in 7 clinical trials for the treatment of PTSD (clinicaltrials.gov).

Background, Significance and Rationale

Background, Significance and Rationale
Cannabis is the most commonly used illicit drug worldwide (United Nations Office on Drugs and Crime, 2013) and a subset of cannabis users develop a cannabis-use disorder (CUD) characterized by withdrawal symptoms and difficulty maintaining abstinence. These problems may be exacerbated by the presence of comorbid psychiatric disorders. One population at high risk for CUD is individuals exposed to trauma and diagnosed with posttraumatic stress disorder (PTSD; Cougle et al., 2011). In fact, severity of problematic cannabis use, including withdrawal symptoms, is positively associated with

severity of PTSD symptoms, with patients reporting cannabis use to help cope with PTSD symptoms (Boden et al., 2013). These findings correspond to preclinical evidence identifying the endocannabinoid system as a neurobiological substrate integral to the stress response associated with the development and expression of PTSD-like behaviors in laboratory animals (de Bitencourt et al., 2013), and the ability of cannabinoid receptor subtype 1 (CB1) agonists to attenuate the PTSD phenotype (Varvel et al., 2007). Similarly, oral Δ9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis (Mechoulam et al., 1970), facilitates the suppression of inappropriate fear responses in healthy volunteers (Rabinek et al., 2013), a core deficit associated with PTSD. Thus, in individuals with PTSD, cannabis may serve to alleviate aspects of trauma-related symptomatology. This may compound the difficulties abstaining from cannabis, potentially rendering individuals with comorbid PTSD and CUD a particularly intractable population to treat.

Despite the prevalence of cannabis use among the PTSD population and self-reports that it is used to help cope with PTSD symptoms, the direct effects of cannabis on PTSD symptomology are unknown. The purpose of this placebo-controlled, within-subject study is to assess the effects of smoked cannabis and orally administered nabilone on multiple dimensions of PTSD symptomatology in cannabis smokers with PTSD. Nabilone is FDA approved for nausea and vomiting associated with chemotherapy**.** We have shown (Haney et al., 2013) that nabilone, a synthetic analog of THC with better bioavailability than dronabinol (oral synthetic THC), decreases cannabis withdrawal symptoms and cannabis use in a laboratory model of relapse in healthy cannabis users and thus is a potential pharmacotherapy for CUD. This pilot study will compare the effects of smoked cannabis and nabilone on attentional bias toward trauma-related stimuli, subjective and emotional processing to a range of trauma-and non-trauma-related images and physiological reactivity to these stimuli in individuals with CUD and PTSD. The effects of nabilone will be compared to propranolol as a positive control. Propranolol, a beta-adrenergic antagonist, is used to treat anxiety and currently being investigated in 7 clinical trials for the treatment of PTSD (clinicaltrials.gov). It is FDA approved for the following indications: angina pectoris, cardia dysrhythmia, essential tremor, hypertension, migraine, postmyocardial infarction syndrome, and pheochromocytoma. This study will also probe the abuse related potential of nabilone compared to smoked cannabis in this population, a critical aspect in determining the potential feasibility for its use clinically to treat CUD in PTSD populations.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Aim 1. Compare the effects of nabilone (0.0 and 4.0 mg), propranolol (0.0 and 40.0 mg; [Schwabe et al., 2012; Hurlemann et al., 2010; Alexander et al., 2007; Grillon et al., 2004; Cahill et al., 1994; Hartley et al., 1983; Currie et al., 1988]), and smoked cannabis (0.0 and 5.6% THC) on subjective processing and emotional and physiological reactivity to trauma-related stimuli using the Emotional Stroop Task (EST; McNally et al., 1990) and to trauma-related images selected from the International Affective Picture System (IAPS; Lang et al., 1997) in non-treatment seeking cannabis smokers with PTSD. We hypothesize that under placebo conditions trauma-related stimuli will increase reactivity in both tasks relative to neutral and positive cues. We expect nabilone, propranolol, and cannabis to decrease this reactivity.

Aim 2. Compare the abuse potential of cannabis, nabilone, and propranolol in cannabis-using individuals with PTSD. Subjective drug effects associated with abuse potential, positive and negative drug effects will be measured throughout the session. Based upon earlier findings (Bedi et al., 2012; Haney et al., 2013)in healthy non-treatment seeking cannabis smokers, nabilone is hypothesized to elicit lower subjective ratings associated with drug-abuse liability and intoxication relative to cannabis, supporting its use in treatment for this population. We do not expect that propranolol will engender positive subjective effects associated with abuse liability.

Exploratory Analysis:
Sex Dependent Effects: We will investigate sex-dependent effects of smoked cannabis, propranolol, and nabilone on reactivity to trauma-related stimuli. Women are reported to be twice as likely as men to develop PTSD, with women exhibiting enhanced acquisition of conditioned fear relative to men, accompanied by a higher conditioned skin conductance response to the conditioned cue (Inslicht et al., 2013). We hypothesize that under placebo conditions, women will demonstrate heightened sensitivity to trauma-related cues relative to men. We will be prospectively tracking menstrual cycle phase in our female participants. If we have a sufficient number of women tested under the same drug condition and menstrual cycle phase, we will assess if drug effects vary as a function of menstrual cycle phase. We have found that women are more sensitive to drug effects during the follicular phase relative to the luteal phase, a time when progesterone levels are elevated (see reviews by Evans, 2007; Evans and Foltin, 2010). Therefore, we hypothesize that drug effects will be elevated when women are tested during the follicular phase relative to the luteal phase.

Description of Subject Population

Sample #1

Specify subject population
Non-treatment seeking cannabis smokers diagnosed with PTSD
Number of completers required to accomplish study aims
14
Projected number of subjects who will be enrolled to obtain required number of completers
18
Age range of subject population
21-55

Gender, Racial and Ethnic Breakdown

Based upon our previous outpatient studies with non-treatment seeking cannabis smokers (Cooper and Haney, 2010; Cooper et al., 2013; Bedi et al., 2013), we expect that the racial breakdown of applications will be: 65-70% Black, and 15-20% White, and 10-15% Native American/Asian/Pacific Islanders/Mixed combined. The ethnic breakdown of the applicants is expected to be 25% Hispanic.

Because an aim of this study is to assess sex-dependent effects, we will enroll equal numbers of male and female participants (50% men and 50% women), as we have done in earlier studies in our laboratory (Cooper et al., 2013).

Description of subject population

We will recruit 18 (9 men and 9 non-pregnant women**)** non-treatment seeking, weekly cannabis smokers (21-**55** years of age), competent to provide informed consent, not currently dependent on any other drug other than cannabis, nicotine, and caffeine, who are also diagnosed with **equal to or greater than subthreshold** PTSD, in order to obtain 14 completers. Volunteers will undergo extensive medical and psychological screening to ensure eligibility. Females will be normally cycling, practicing an effective form of non-hormonal birth control other than hormonal contraceptives (i.e., barrier method). Any participants with a history of asthma or bronchospasm will be excluded.

All participants will have consistent positive urine toxicology tests for cannabinoid metabolites prior to enrollment. None will have current Axis I psychopathology except for PTSD, and / or anxiety or depression, psychopathologies that co-occur at high rates with PTSD. **Those who are on prescribed psychotropic medications (excluding tricyclic antidepressants), and have been on a stable dose for at least 3 months, will be eligible for study participation.**

Recruitment Procedures

Describe settings where recruitment will occur
Recruitment will occur in the Substance Use Research Center on the 3rd floor of NYSPI.
How and by whom will subjects be approached and/or recruited?
The first phase of recruitment is a structured telephone interview in response to an advertisement or referral (e.g., newspaper, subway, radio, internet, referral).
Telephone interviews will be carried out by the research assistants (Mr. Kamilar Britt, Ms. Corcoran, Ms. Erakky) who have been trained by Drs. Cooper and Haney, during which time potential participants will be asked about their current and past drug use, general health, and trauma. Complete psychological and trauma history will be assessed by either a clinical psychologist (Ph.D. level) or licensed mental health clinician (Master's level) using the Mini International Neuropsychiatric Interview and a study-specific trauma interview.
How will the study be advertised/publicized?

Advertisements will be placed in periodicals across the NYC area including The Daily News, and AM New York. The below text will be posted:
RESEARCH VOLUNTEERS: Healthy male and female MARIJUANA SMOKERS (age 21-**55**) who have experienced traumatic events needed to evaluate the effects of marijuana and medications on mood and behavior. Compensation for time: $406-468. Call (646) 774-7777 for information.

Also, Dr. Denise Hien of City College of New York of CUNY whose research focuses on trauma-related disorders with substance-use comorbidities will assist in recruitment for this protocol by referring non-treatment seeking cannabis-using individuals with mild to moderate PTSD who are not eligible for her studies.

Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
No

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

6929R (genetic screening for marijuana smokers)
7091R)general screening for marijuana studies)

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Non-treatment seeking cannabis users with PTSD
Create or insert table to describe the inclusion criteria and methods to ascertain them
Criteria: Method of Ascertainment

1. *21 - **55** years of age:* Demographic evaluation

2. *Male or non-pregnant female*: Demographic evaluation

3. *Current use cannabis in amounts and / or frequencies that meet or exceed those used in the proposed study, and meet criteria for CUD*: Participants must smoke one cannabis cigarette per occasion at least **2x**/week for the past month verified through self-report and THC positive urine toxicology. Psychological evaluation using the cannabis use disorder module from the MINI (Mini International Neuropsychiatric Interview form for DSM-5) will determine CUD

4. *Meet DSM-V criteria for **equal to or greater than subthreshold** PTSD:* Volunteers will undergo extensive psychological screening to ensure eligibility according to the Mini International Neuropsychiatric Interview (MINI). Participants will be judged by the clinical psychologist/mental health clinician and the study physician to be healthy enough for research, and to be at low risk for any clinically-meaningful exacerbation of PTSD symptoms via exposure to the trauma-related cues used in the study. **PTSD severity will be**

assessed using the PTSD Checklist for DSM-5 (PCL-5). Eligible participants will meet criteria for at least subthreshold PTSD, defined as meeting criterion A, endorsing at least one symptom from each of criteria B-E, and lasting for at least one month (criterion F)
5. Individuals who are currently stable on a psychotropic medication other than tricyclic antidepressants for at least 3 months, if in the study physician's opinion, the psychotropic medication the patient is taking is compatible with the study medications, does not entail risk or adverse effects from drug interactions, and is not contraindicated for study participation: **Physician's evaluation and clinical interview**

6. *Able to give informed consent and comply with study procedures:* Physician's evaluation and mental status examination

7. *Women who are normally cycling and practicing an effective form of birth control other than hormonal contraceptives (i.e., barrier methods)*: Self-report during interview
Create or insert table to describe the exclusion criteria and methods to ascertain them

Criteria: Method of Ascertainment

1. *In treatment or treatment seeking for Cannabis Use Disorder, PTSD, Anxiety or Depressive Disorders*: Clinical interview

2. *Use disorder for any drug other than cannabis. nicotine, and caffeine:* Self-report, psychological evaluation, urine toxicology

3. *Meeting criteria for current psychiatric disorders other than PTSD, Depressive , Anxiety, or Cannabis use disorder.* Mini International Neuropsychiatric Interview (MINI) will be used to assess psychiatric disorders including schizophrenia spectrum and other psychotic disorders, Bipolar and related disorders, and obsessive-compulsive and related disorders.

4. *Use of beta blocker or Coumadin medications:* **Physician's evaluation and clinical interview**

5. *Color-blind*: Clinical interview, physical exam

6. *Clinical laboratory tests outside normal limits that are clinically unacceptable to the study physician (BP > 140/90; BUN, creatinine, LFTs >* ***3x ULN as long as underlying cause is known and stable****; hematocrit < 34 for women, < 36 for men)* : Medical history, physical exam and laboratory exam (Chem panel, CBC, urinalysis, ECG)

7. *History of myocardial infarction or ischemia, clinically significant left ventricular hypertrophy, angina, clinically significant arrhythmia, or mitral valve prolapse, a heart rate* ***<****55 beats per minute, or hypotension or orthostatic hypotension (seated and/or standing blood pressure* ***<****90/60 mmHg)*: Medical history, physical exam, ECG

8. A history of asthma or bronchospasm: Medical history, physical exam

9. *Current parole or probation:* Self-report

10. *Female participants who are currently pregnant or breastfeeding*: Clinical interview, physical examination. serum HCG

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6095
Describe Study Consent Procedures
1) After initial determinations of eligibility (e.g., current drug use patterns, attitude about treatment) obtained via the telephone interview, volunteers will come into the laboratory for their first screening visit. They will be asked to sign our screening and evaluation consent form (#6095), allowing us to collect questionnaire data, conduct interviews, and obtain medical information. We will do an ECG and laboratory tests.

2) Psychologists (Drs. Haney, Cooper, Arout, Evans), will conduct interviews regarding drug use and psychiatric symptoms and will provide a detailed explanation of the procedures outlined in the consent form. The volunteer and the psychologist will then both sign the consent form. Note that this typically occurs before the physician meets with the volunteer, but no study procedures will begin until the physician obtains consent as described below.

3) Trained Clinical Intereviewers will administer the Mini Neuropsychiatric Interview (i.e., Patrick Roebke, Payal Pandya) and a trauma interview when the participant will describe his / her trauma history in detail.

3) Medical and / or psychiatric interviews will be conducted by a physician in the Division on Substance Abuse (e.g., Drs. Manubay, Bisaga, Levin, Williams, Brezing, Luo, Dakwar, Mogali, Evans, Marino, Shulman, Vaezazizi, Blevins, Wei, or Kidd), and will include a physical examination, and review of

medical results and study inclusion/exclusion criteria. All of our 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). Physicians will determine whether volunteers meet for PTSD and do not have any other current Axis I psychopathology excluding mild to moderate depressive or anxiety disorder. The physicians discuss this protocol with the volunteers and document their consent to the research study. Study procedures will begin after the physician verifies that participant meets inclusion/exclusion criteria, understands the medical risks of participation, and is capable of providing informed consent. If needed, Dr. Bisaga 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).

Thus, several interviews in which drug use is probed will be conducted with volunteers prior to telling them the nature of the study. In this way, we minimize the probability that they will misrepresent their drug use in order to gain entry into the research. Volunteers expressing interest in treatment at any point during participation will be given an immediate treatment referral. Note that participants will smoke more marijuana outside the laboratory than they will receive in the
study.

Following the physical and consent, volunteers will report to the laboratory again, and re-read the study consent form with study personnel.

We find that this multi-consent process provides participants with more information at each decision point. Such a procedure provides fully informed consent.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Arout, Caroline
Blevins, Derek
Brezing, Christina, MD
Cooper, Ziva, PHD
Dakwar, Elias, MD
Evans, Elizabeth, MD
Evans, Suzette, PHD
Haney, Margaret, PHD
Hien, Denise, PHD
Kidd, Jeremy
Levin, Frances, MD
Manubay, Jeanne, MD
Marino, Leslie, MD
Mogali, Shanthi, MD

Shulman, Matisyahu, MD
Smith, Kathryn
Vaezazizi, Leila
Type in the name(s) not found in the above list
Jonathan Wei, MD

Study Procedures

Describe the procedures required for this study

Participants: Over 2 years we will recruit 18 (9 men and 9 women; to obtain 14 completers) non-treatment seeking cannabis smokers (21-45 years of age) who are also diagnosed with DSM-V criteria for **at least subthreshold** PTSD. Volunteers will undergo extensive medical and psychological screening to ensure eligibility.

Design: This is a double-blind, placebo controlled, within-subject study. Participants will be trained in study procedures and complete four, 8- hour outpatient laboratory sessions, with at least 72-hours between sessions for medication clearance (Table 1). As per our usual procedures, we will track the menstrual cycle and collect blood samples for estradiol and progesterone to verify menstrual cycle phase for a exploratory analysis. Blood will be drawn before baseline measurements of each session for both men and women. Blood from men will not be analyzed. We will also test for pregnancy every session with urine tests.

Drugs: Nabilone capsules (4 mg) will be obtained from Meda Pharmaceuticals, Inc., propranolol capsules (40 mg) will be obtained from Teva Pharmaceuticals, and cannabis cigarettes (0.0 and 5.6% .THC) will be provided by NIDA. Nabilone pills (4) and propranolol capsules (1) will be over-encapsulated in size 00 capsules using white, opaque lactose filler. For the placebo condition, 4 size 00 capsules containing lactose filler for nabilone and 1 size 00 capsule containing lactose filler for propranolol will be administered. The active (5.6% THC) and inactive (0.0% THC) cannabis cigarettes will also be visually identical. Drug administration will be randomized, double-blind, and double dummy.

Procedure: Participants will be instructed not to smoke cigarettes or cannabis after midnight the evening before sessions; compliance will be verified by assessing carbon monoxide exhalation. Tobacco smokers will be allowed to smoke cigarettes at consistent times during each session to prevent nicotine withdrawal (Parrott, 1995). Before each session, alcohol use will be measured using a breathalyzer test and illicit drug use will be measured using urine drug toxicology. If individuals are positive for any drugs other than cannabinoids, the session will be rescheduled. Women will have a urine pregnancy test and blood drawn to measure estradiol and progesterone to assess menstrual cycle phase. A standardized light breakfast will be served and baseline assessments completed. Baseline assessments will include monitoring of resting heart rate, as well as seated and standing blood pressure. If heart rate is less that 55 beats per minute, and/or seated or standing blood pressure is less than 90/60 mmHg, study drugs will not be administered and the session will be rescheduled. During each session, Nabilone (0 mg or 4 mg) and propranolol (0 mg or 40 mg) will be administered followed by cannabis smoking (0.0 or 5.6% THC) according to our cued-smoking procedure (Foltin et al. 1987) (Table 2). To examine attentional bias toward trauma-related stimuli and subjective and emotional processing to a range of trauma-and non-trauma-related images, the Emotional

Stoop Task (EST) and the International Affective Picture System (IAPS; Lang, Bradley, and Cuthbert, 1997) will be used. These procedures will begin 120 minutes after nabilone administration, 60 minutes after propranolol administration, and 10 minutes after cannabis smoking. Cue reactivity using the EST and drug-related subjective effects will be assessed throughout the session in order to assess these effects before, during, and after Tmax for each drug condition. Drug administration will be randomized, double-blind, and double dummy.

Cue Reactivity Tasks: *Emotional Stroop Task (EST).* Based on the classic Stroop color-naming task (Stroop, 1935), the EST has been used to demonstrate cognitive bias towards trauma-related stimuli, a hallmark cognitive processing deficit in PTSD (McNally et al., 1990). Participants are asked to indicate the color of a word that is presented in randomized colors (yellow, green, red, and blue). The semantic content of the word varies in emotional valance to include neutral, pleasant, threatening, and trauma-related words. Participants will be asked to indicate the color of the word that appears on the computer screen as quickly and accurately as possible using corresponding buttons on the computer keyboard; the next word will then be presented (Cassiday et al., 1992). Neutral words, positive words, negative words, participant-specific trauma-related words, and a second group of neutral words that matched to participant-specific trauma-related words according to various lexical characteristics that may effect responding will appear in random order over the 5-minute task period. Latency and accuracy of color-naming as a function of word-type will be analyzed. Individuals with PTSD exhibit longer color-naming times for words specific to their trauma relative to other word types (Ashley et al., 2013; Cisler et al., 2011). Thus, we expect color-naming latency to be longer for participant-specific trauma-related words relative to neutral and positive words, and we expect cannabis and nabilone to decrease this latency.

Visual Cue Task. The International Affective Picture System (IAPS) includes 1,000 images that vary in affective valence (pleasant versus unpleasant) and arousal (Lang et al., 1997). For this, participants are presented with images varying in valence (pleasant, neutral, and unpleasant), with pleasant and unpleasant stimuli matched for arousal levels. Images are presented for 6 sec followed by a 15 sec interval during which time the participant will rate his/her personal reaction to the image according to affective dimensions of valence and arousal using self-report scales (Bradley & Lang, 1994). During each session, 40 images will be presented: 10 pleasant, 10 neutral, 10 negative, 10 participant-specific trauma-related. The participant-specific trauma-related image**s** will include images representing images that depict the type of trauma a specific participant has experienced (depicting violence, death, bodily injury, natural disasters, combat, and sexual assault). Presentation of images will be randomized and they will not be repeated across sessions.

Physiological Measures: *Skin Conductance* (SC) is an index of physiological arousal and a sympathetic nervous system response that is hypothesized to be dysregulated in PTSD (Pole, 2007) and has been shown to be a marker of reactivity to trauma-related cues in PTSD patients (Felmingham et al., 2011). SC to trauma related cues during the EST and the IAPS procedure will be measured using the BIOPIC Systems equipment and software that Dr. Bisaga has used for other studies. Under placebo conditions, trauma-related words on the EST and images are expected to elicit increases in SC; women will exhibit a more pronounced SC response to these cues. Active nabilone, cannabis, and propranolol are expected to dampen SC in response to trauma-related words and images.

Heart Rate and Blood Pressure. Heart rate will be continuously recorded using a heart rate

monitor (Polar FT60) starting 30 min before capsule administration and throughout the session. Both seated and standing blood pressure (Sentry II automated vital signs monitor; NBS Medical Services, Costa Mesa, CA) will be periodically monitored before capsule administration and until the end of the session.

Subjective Effects Battery: The 21-item self-report State Anxiety Questionnaire (STAI; Spielberger et al., 1971) will be used to assess anxiety. Mood and Drug Effect visual analog scales (MDE-VAS) will include subjective ratings indicative of PTSD symptomatology (e.g., 'I feel anxious,' 'I feel on guard,' ' I feel jumpy,' ' I feel emotionally numb'), abuse liability (e.g., 'I like' the capsules) and drug craving (e.g., 'I want cannabis;' Haney et al., 2004).

Cannabis and Capsule Rating Forms (Cooper & Haney, 2010) will consist of 5 VAS questions (drug strength, good effect, bad effect, drug liking, and willingness to smoke the cannabis again or take the capsule again). The subjective effects battery will be completed before capsule administration and several time-points after capsule administration and cannabis smoking. [The capsule and cannabis rating forms will only be done after capsule administration and cannabis smoking.]

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

1) *Symptom Provocation:* Before each session, participants will complete **the PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013)**, which will ask participants to rate the **incidence** of PTSD symptoms either in the past week or from the previous session. Significant increases in scores from the previous session will be flagged and a clinician will discuss the severity of symptoms with the volunteer and determine the safety of proceeding with the session and study participation. If symptom provocation suggests increased severity of PTSD from mild or moderate to "severe" the patient will be removed from the protocol. Clinical staff will undertake a risk assessment and determine the appropriate course of action.

2) Participants may be discontinued if they fail to follow the study procedures.

3) Participants may be discontinued if they request treatment during the study.

4) Individual study sessions will be rescheduled and study drugs will not be administered if participants have resting heart rate < 55 beats per minute at baseline or evidence of hypotension or orthostatic hypotension (seated and or standing blood pressure < 90/60 mmHg)

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

We will do a complete blood chemistry and a plasma pregnancy test (15 ml blood) at screening.
We will perform urine pregnancy tests before each laboratory session, in addition to doing urine drug tests.

At the beginning of each session, 10 mls of blood will be drawn from all participants. This blood sample will be used to determine plasma hormone levels for female participants. We will draw blood from all participants to control for any potential effects that the blood draw may have on behavior.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

PTSD / Trauma assessments during screening:
Trauma Interview - interview that relates to the volunteer's trauma history, current symptoms, and frequency of symptoms - 10 min
Extended self-report Life Events Checklist (Weathers et al., 2013) - 10 min
The Modified Sexual Experiences Survey, MSES; Koss & Gidycz, 1985; Messman-Moore et al., 2000) - 10 min
PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013) - 10 min
Mini International Neuropsychiatric Interview (MINI) - 20 min

Assessments during sessions
PCL-5 - 10 min
Emotional Stroop Task (Stroop, 1935; Cassiday et al., 1992; Ashley et al., 2013) - 5 min
Visual-Cue Task (Bradley and Lang, 1994; Lang et al., 1997) - 20 min
State Anxiety Questionnaire (STAI; Spielberger et al., 1971) - 3 min
Mood and Drug Effect Questionnaire (Haney et al., 2004) - 2 min
Capsule Rating Form (CRF; Cooper and Haney, 2010) - 2 min
Marijuana (Cannabis) Rating Form (MRF; Cooper and Haney, 2010) - 2 min
Physiological assessments: Skin conductance, heart rate, seated and standing blood pressure

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
3

Drug #1

Name of the drug
Cannabis
Manufacturer and other information
NIDA supplies cannabis cigarettes
Approval Status
IND is approved
IND#
36,369
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Foltin, Richard, PHD

Drug #2

Name of the drug
Nabilone
Manufacturer and other information

Meda Pharmaceuticals
Generic Name - Nabilone
Other name - Cesamet
Manufacturer - Meda Pharmaceuticals, Somerset, NJ 08873-4120

Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain

FDA conditions are met

Drug #3

Name of the drug
Proranolol

Manufacturer and other information
Generic Name - Propranolol, HCL
Other name - Inderal
Manufacturer- Teva Pharmaceuticals, North Wales, PA, 19454
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain
FDA conditions are met

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
Participants will be given a treatment referral if they are interested in treatment for cannabis use of for PTSD.

Clinical Treatment Alternatives

Clinical treatment alternatives
Participants are not seeking treatment for their cannabis use. The alternative is not to participate in the study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
The major risk of research participation is related to drug administration and symptom provocation due to exposure to trauma-related cues. We have had vast experience thus far with a range of abused drugs, including cannabis, and scheduled medications, including nabilone. We have experience with administering the amount of cannabis and the dose of nabilone proposed in the current study with no adverse consequences.

Cannabis. We have safely administered the amounts of cannabis in the currently proposed experiments in single and repeated dose studies with no adverse consequence. Possible side effects of smoked cannabis include: sedation, gait disturbance, tiredness, sadness, anxiety, concentration difficulties, increased heart rate, palpitations, dizziness, sleep disturbance, changes in food intake, restlessness, confusion, sleepiness, clumsiness, gastrointestinal upset, headache, nausea, dry mouth, pallor, flushing, sweating, and slurred speech.

Nabilone. We have safely administered the dose of nabilone that will be administered in this study with no adverse consequences (Bedi et al., 2013; Haney et al., 2013). Nabilone may produce orthostatic hypotension. Other side effects include feeling intoxicated, dry mouth, headache, dizziness, drowsiness, and trouble concentrating.

Propranolol. The primary risks associated with the dose of 40 mg propranolol, which is used for the off-label indication of anxiety , include bradycardia, hypotension, and light-headedness. Other adverse effects include sleepiness, short-term memory loss, lethargy, diarrhea, insomnia, cold hand and feet, numbness and / or tingling of fingers or toes.

Symptom Provocation. Exposure to trauma-related cues may exacerbate PTSD symptoms.

Phlebotomy: Participants will provide a blood sample during screening and at the beginning of each session; they will be warned that blood drawing may cause slight discomfort at the site of needle entry and may result in a small bruise.

Describe procedures for minimizing risks
Cannabis. All participants will be carefully monitored and fully informed of the side effects that they might experience. Because all volunteers currently smoke cannabis, these effects should be familiar to them.

Nabilone. At screening, we will exclude volunteers with bradycardia (<55 beats/minute) or hypotension (systolic pressure <90 mmHg). During the study, heart rate and blood pressure will be measured prior to capsule administration. Orthostatic blood pressure will be assessed several times after nabilone administration. Participants will not leave the laboratory until blood pressure is normal.

Propranolol. At screening, we will exclude volunteers with bradycardia (<55 beats/minute) or be measured prior to capsule administration. Orthostatic blood pressure will be assessed several times after propranolol administration. Participants will not leave the laboratory until blood pressure is normal.

Symptom Provocation. Before each session participants will complete the **PCL-5 (Weathers et al., 2013)**, a scale that has been shown to reliably assess and monitor PTSD symptom **incidence** over time (Ruglass et al., under review). Increases in scores from the previous session and screening will be flagged and a clinician will discuss the severity of symptoms with the volunteer and determine the safety of proceeding with the session.

A physician from our Division listed in the "Persons designated to discuss and document consent" and the "Consent procedures" sections (i.e., Drs. Frances Levin, Adam Bisaga) will be designated to be available by phone or pager during each outpatient session and in or nearby NYSPI (on the CUMC campus) in the event that it is necessary to see the participant due to an event that requires clinical attention.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
We applied for a Certificate of Confidentiality on August 1st, 2017 for this study from the National Institute on Drug Abuse. Our records will be kept confidential and will only be accessible to study staff. Screening information, which may have the participant's name, will be kept in a locked filing cabinet. Once a participant is enrolled into the study all further documents will be identified solely by initials and an assigned number
Will the study be conducted under a certificate of confidentiality?
Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There are few direct benefits to research volunteers in the proposed study. Prior to study acceptance, all volunteers will have a medical and psychiatric work-up. Referrals will be offered to participants who are interested in treatment for PTSD or CUD any stage of their research participation. We repeat our offer for treatment referral at screening and at discharge from the study.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will be paid in cash as follows: $25/screening (up to 3 visits) and $25 for a training session prior to being accepted into the study. They will be paid $40 for session, and a bonus $40/session for completion of the study. The bonus payment encourages participants to complete all of the sessions. Additionally, participants will be given $6 in cash for transportation for screening, training, and sessions. Total study earning will range from $406-$468.

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