Protocol Title:
Facilitating the Behavioral Treatment of Cannabis Use Disorders

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7355

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08/30/2016

Clinic:
BSU Clinical Service

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Frances Levin, MD

Research Chief:
Frances Levin, MD

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 proposing an amendment only to an existing protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Substance Abuse
Within the division/department, what Center or group are you affiliated with, if any?
Biological Studies Unit

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.
No co-investigators

Amendment

Describe the change(s) being made
To add Craigslist to the recruitment options.
Provide the rationale for the change(s)
We are seeking an alternative to print or radio ads.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
It doesn't.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
It doesn't.

Procedures

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

✓ Medication Trial
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50

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
K24
Grant Number
DA029647
Select one of the following
Single Site
Business Office
CU
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

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This project will evaluate the effect of one or two sub-anesthetic infusions of ketamine (0.11 mg/kg 2-min bolus followed by 0.6 mg/kg over 50 minutes or 1.3 mg/kg over 90 minutes) in 15 treatment-seeking cannabis-dependent individuals receiving motivational enhancement therapy (MET) and mindfulness-based relapse prevention (MBRP) therapy, using a 6-week single-blind, open label trial.

During the first two weeks of study, the participants will receive MET. In Week 2, Day 2, the participants will asked to initiate abstinence, and receive a single infusion of ketamine on the day of abstinence initiation. In weeks 3-6, the participants will receive MBRP. If the participants are not doing well, they will receive a second infusion of ketamine in Week 4, Day 2.

In addition to measures of mindfulness and impulsivity, stress sensitivity tests are incorporated into the design in order to elucidate mechanisms of action.

Background, Significance and Rationale

Background, Significance and Rationale

This proposal will focus on treating cannabis use disorders with a one or two sub-anesthetic infusions of ketamine (0.11 mg/kg 2-min bolus followed by 0.6 mg/kg over 50 minutes or 1.3 mg/kg over 90 minutes), a high-affinity non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist. Our preliminary research suggests that ketamine improves dependence-related vulnerabilities common to a variety of substances. We have shown that a single infusion improves motivation to quit, reduces cue-induced craving, improves non-reactivity, and reduces cocaine self-administration among non-treatment cocaine dependent individuals. We have also shown that ketamine infusions can be integrated into outpatient behavioral treatment, such as motivational enhancement therapy (MET) and mindfulness-based relapse prevention (MBRP), to address cocaine use disorder and alcohol use disorder. This includes a protocol with cocaine users that provides up to 2 ketamine infusions. In these protocols, some individuals who had been using cannabis problematically in addition to the substance for which they sought treatment stopped using cannabis.

In this single blind, open label trial, we extend the treatment model we have developed to treat cocaine use disorder to the treatment of cannabis use disorder, with the expectation that we will observe similar feasibility. This protocol includes a manualized sequence of MET and MBRP in conjunction with up to 2 infusions of ketamine. The primary outcome is tolerability of study medications.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
The primary purpose of this study is to assess whether giving one or two sub-anesthetic dose of ketamine to cannabis users will be feasible.

Description of Subject Population

Sample #1

Specify subject population
Cannabis dependent individuals
Number of completers required to accomplish study aims
15
Projected number of subjects who will be enrolled to obtain required number of completers
20
Age range of subject population

21-60

Gender, Racial and Ethnic Breakdown

Based on the demographic distribution of cannabis dependent individuals, we expect that our sample will be 45% Caucasian, 25% Hispanic, 25% African American, and 5% other racial groups. Approximately 30% of the sample will be female. This profile is also representative of clinical trials at our institution and elsewhere targeting cannabis dependent treatment-seeking individuals. This study does not exclude participants on the basis of race and gender, and it seeks to include women and minorities

Description of subject population
Patients will be considered eligible if they are medically healthy, cannabis dependent individuals who meet minimum use criteria, who are between the ages of 21 and 60, and who do not have a history of abuse of or adverse reaction to ketamine or benzodiazepines. Individuals with physiological dependence on certain other substances, with a history of psychotic or dissociative symptoms, with a first-degree family history of psychosis, with obesity (BMI > 32), or with cardiovascular or pulmonary disease will be excluded.
Pregnant women, women who plan to get pregnant, and lactating women will be excluded.

Recruitment Procedures

Describe settings where recruitment will occur
Adult male and non-pregnant female patients will be recruited in the New York City metropolitan area.
How and by whom will subjects be approached and/or recruited?
The advertisements that will be used to recruit participants will be submitted to the IRB prior to the initiation of recruitment procedures. Additionally, prospective participants are recruited by word of mouth and through liaison with other collaborating clinical services, and through ongoing inpatient studies of cannabis self-administration conducted at the Substance Use Research Center (SURC) in our division. All patients are seen by one of our psychiatrists or staff for a screening evaluation and mental status examination as part of routine admission procedures at the BSU. Patients who are cannabis dependent and appear to meet criteria are told about the study and offered further evaluation. Final informed consent is obtained after full psychiatric and medical workup is complete.
How will the study be advertised/publicized?
The study will be advertised by newspaper, radio, television, **Craigslist**, and subway advertisements, as well as on a lab-specific website.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02946489

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
No

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Marijuana dependent individuals
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criterion
1. Meets DSM-IV criteria for cannabis dependence, with at least 5 days of use per week over the past 30 days and displaying at least one positive utox during screening
Method of Ascertainment: MINI, psychiatry interview, self-report, utox

2. Physically healthy
Method of Ascertainment: Laboratory tests (urinalysis, blood chemistry, 12-lead ECG within normal limits, TB test), physical examination, self-reported medical history

3. No adverse reactions to study medications
Method of Ascertainment: Subjects will be asked about previous exposure to ketamine and midazolam

4. 21-60 years of age
Method of Ascertainment: Self-reported age, verification with legal identification

5.Capacity to consent and comply with study procedures
Method of Ascertainment: A short written test about study procedures, MINI, psychiatric interview

6. Seeking treatment
Method of Ascertainment: Psychiatric interview, self-report
Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criterion

1. Meets DSM IV criteria for current major depression, bipolar disorder, schizophrenia, any psychotic illness, including substance-induced psychosis, and current substance-induced mood disorder with HAMD > 12.
Method of Ascertainment: Psychiatric Interview, MINI, HAMD

2. Physiological dependence on another substance requiring medical management, such as alcohol, opioids, or benzodiazepines, excluding caffeine, and nicotine

3. Pregnant, interested in becoming pregnant, or lactating
Method of Ascertainment: Blood and urine pregnancy testing, self-report

4. Delirium, Dementia, Amnesia, Cognitive Disorders, or dissociative disorders
Method of Ascertainment: MINI, Psychiatric Interview

5. Current suicide risk or a history of suicide attempt within the past 2 years
Method of Ascertainment: MINI, Psychiatric Interview

6. On psychotropic or other medication whose effect could be disrupted by participation in the study
Method of Ascertainment: Psychiatric Interview, self-reported medical history

7. Recent history of significant violence (past 2 years).
Method of Ascertainment: MINI, Psychiatric Interview

8. Heart disease as indicated by history, abnormal ECG, previous cardiac surgery.
Method of Ascertainment: Laboratory tests (12-lead ECG in normal limits), physical examination, self-reported medical history

9. Unstable physical disorders which might make participation hazardous such as end-stage AIDS, hypertension (>140/90), anemia, pulmonary disease, active hepatitis or other liver disease (transaminase levels < 2-3 X the upper limit of normal will be considered acceptable), or untreated diabetes
Method of Ascertainment: Laboratory tests (urinalysis, blood chemistry, 12-lead ECG in normal limits, TB test), physical examination, self-reported medical history

10. Previous history of ketamine or benzodiazepine abuse, and/or a history of adverse reaction/experience wtih prior exposure to ketamine or benzodiazepines
Method of Ascertainment: MINI, Psychiatric Interview

11. BMI > 35, or a history of undocumented obstructive sleep apnea
Method of Ascertainment: Physical exam, self-reported medical history

12. First degree relative with a psychotic disorder (bipolar disorder with psychotic features, schizophrenia, schizoaffective disorder, or psychosis NOS)
Method of Ascertainment: MINI, Psychiatric Interview

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
Yes
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?
No
Describe procedures used to obtain consent during the screening process
At the first contact, a standardized telephone interview will be conducted, and patients who preliminarily meet entry criteria will be scheduled for a first screening visit, during which the patient will give informed consent to provide a urine sample for toxicology and urinalysis, and to undergo a Mini International Neuropsychiatric Interview (MINI), with a psychiatrist for a medical and psychiatric evaluation, as well as completion of the Hamilton Depression Scale (HAM-D) and Dissociative Experiences Scale (DES), and if still eligible, with a research assistant for serum collection (CBC, thyroid panel, Chem 20 panel including liver function tests, serum cortisol) and other diagnostic tests (EKG). We are requesting a waiver of documentation of consent (45 CFR 46.117 (c) (1)) for the phone screen only, given that a consent form for a phone screen would be the only record linking the subject and the research.
Describe Study Consent Procedures
Eligible participants will undergo an interview with one of the consenting physicians, during which information about the study will be provided. Participants will then be asked to read the consent form on their own, after which they complete a quiz and have an opportunity to ask questions. Participants will be considered eligible if they are medically healthy, cannabis dependent individuals who meet minimum use criteria, who are between the ages of 21 and 60, and who do not have a history of abuse of or adverse reaction to ketamine or benzodiazepines. Individuals with physiological dependence on certain other substances, with a history of psychotic or dissociative symptoms, with a first-degree family history of psychosis, with obesity (BMI > 32), or with cardiovascular or pulmonary disease will be excluded. Please consult the full table of inclusion/exclusion criteria in the Human Subjects section for more details.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
A waiver of consent has been requested because the first interaction with prospective participants takes place over the phone.
Explain why your research can not be practicably carried out without the waiver or alteration
Initial screenings are conducted over the phone, and therefore in-person consent at that point is impossible. If a participant is deemed likely to be eligible, he/she is invited into the office for an in-person screening, at the start of which formal, in-person consent is obtained.
Describe whether and how subjects will be provided with additional pertinent information after participation
Subjects are provided with additional pertinent information after participation by the physician.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Dakwar, Elias, MD
Levin, Frances, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Design:15 patients meeting study criteria and providing informed consent will be entered into the 6-week trial, provided behavioral treatment, and given ketamine.

At each visit, patients will provide a urine sample that will be tested semi-quantitatively for cannabis and other drugs; complete various questionnaires; and undergo a brief evaluation during which vital signs, other safety parameters, and side effects are assessed. Two visits a week will be devoted to receiving behavioral treatment, lasting approximately 50 minutes. The other regular visit will be with a psychiatrist who will review progress, document self-reported substance use, and review side effects or other adverse events to treatment; additionally, the psychiatrist is responsible for the medical care of the patient and for decisions pertaining to study discontinuation.

There are two phases:

Phase 1 (Week 1-2)

During the first two weeks, patients will receive outpatient motivational enhancement therapy (MET) and meet with a psychiatrist twice a week. The psychotherapy sessions be taped for supervision and research purposes.

On Week 2, Day 2, patients will be asked to initiate abstinence 24 hours prior to the medication administration. On the day of abstinence initiation, they will receive an intravenous dose of ketamine (see "Infusion Procedures"). Before the scheduled outpatient infusion, an MET session will revisit goals and address ambivalence.

Phase 2 (Week 3-6)

During the last 4 weeks, patients will begin a standardized course of mindfulness based relapse prevention (MBRP); this training will occur twice a week, and take approximately one hour a session. Alongside MBRP training, patients will meet with a psychiatrist, who will continue monitoring their drug use and side effects.

In week 3 or 4, the patients will receive a second intravenous dose of ketamine (see "Infusion Procedures") if they have been unable to attain abstinence. Before the scheduled infusion, an MET session will revisit goals and address ambivalence.

Infusion Procedures: One or two ketamine infusions will take place at the BSU within the Division on Substance Abuse. Further, studies with depression have suggested that a single dose has (antidepressant) efficacy. Thus, for the purposes of this study, a single infusion may suffice to affect the outcome measures. If it does not suffice, patients will undergo a second infusion. Patients will be abstinent from intoxicants and will have not eaten since midnight prior to the infusion so as to reduce the risk of nausea, adverse interactions, and aspiration. Participants will be informed throughout the study that they may receive any of a number of substances at the infusion, including buspirone, d-cycloserine, ketamine, midazolam, memantine, saline, or any combination of these. This will serve to further disguise the administration of ketamine, and thereby further minimize the risk that patients will subsequently seek out ketamine. Ketamine hydrochloride (0.11 mg/kg 2-min bolus followed by 0.6 mg/kg over 50 minutes **for the first infusion** and 1.3 mg/kg over 90 minutes **for the second infusion**), will be prepared and packaged for slow-drip infusion by the pharmacy at NYSPI, and will be administered at 12 pm by a physician. The dose of ketamine was selected on the basis of published reports suggesting that it was sub-anesthetic and well-tolerated; it is also comparable to the dose used in the depression studies. Infusions will take place in the presence of an ACLS and BLS certified psychiatrist (Dr. Dakwar) who will remain available for up to two hours after the infusion is terminated and who will provide a brief safety and psychiatric evaluation at the end of the monitoring period. Blood pressure and heart rate will be monitored every five minutes beginning five minutes before the infusion and continuing after the infusion until vital signs normalize; SBP elevation > 60 mm and DBP > 40, or absolute SBP>200 and DBP>115 and HR > (220 – age) X 0.85, will result in infusion discontinuation (please see "Risks" for more information about managing BP or HR). The physician will also be responsible for decisions pertaining to the discontinuation of the infusion in the case of an adverse event. The physician will also be guiding mindfulness-based exercises for the duration of the infusion. A Clinician Administered Dissociative States Scale (CADSS) will be administered following the infusion by the physician or the staff. Ketamine and norketamine (an active metabolite) levels will be obtained at 30 minutes into the infusion and at 60 minutes (20 minutes after the infusion is terminated), the results of which will remain unavailable to all staff for each participant until all assessments are complete. The infusion will be preceded by a urine toxicology to ensure the absence of illicit substance use to minimize the risk of adverse interactions. Female participants will also be tested for pregnancy. Following the infusion, participants will undergo close monitoring, and prior to discharge (occurring at least 3 hrs post-infusion) psychiatric/medical clearance and a field sobriety test.

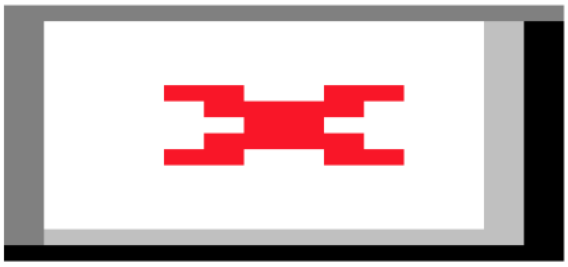
Motivational Enhancement Therapy (MET):

All patients will receive five MET sessions with a therapist over the first two weeks. Staff involved in MET will receive a 3-hour training in MET prior to providing therapy to participants, and a psychiatrist is available during all sessions for support or consultation in case it is needed. The psychiatrist will also see participants briefly following the therapy session before they go home. Staff will receive weekly supervision from the PI for the duration of the trial.

Mindfulness-Based Relapse Prevention (MBRP):

All patients will have eight MBRP sessions with therapists using a structured MBRP manual adapted for the purposes of this study to the individual setting, in collaboration with one of its lead authors, who will also be guiding efforts to ensure manual fidelity. Staff involved in mindfulness training receive a 3-hour training in MBRP prior to providing training to participants, and a psychiatrist is available during all sessions for support or consultation in case it is needed. The psychiatrist will also see participants briefly following the mindfulness training session before they go home. Staff will receive weekly supervision from the PI for the duration of the trial.

	Procedures (by week)	1	2 A	2 B	2 C	3 A	3 B	3 C	4	5	6	E
ACTIVITY	Infusion*			X			X					
	MET	X	X	X		X	X					
	Abstinence			X			X					
	MD meet	X	X	X	X	X	X	X	X	X	X	X
	MBRP				X			X	X	X	X	
ASSESSMENT	TLFB	X	X	X	X	X	X	X	X	X	X	X
	VAS, CCQ	X	X	X	X	X	X	X	X	X	X	X
	FFMQ	X			X			X		X	X	X
	U-tox	X	X	X	X	X	X	X	X	X	X	X
	BPRS(+)			X			X					
	Battery			X			X					
	CADSS			X			X					
	(Nor)Ket			X			X					
	PSS	X			X			X	X	X	X	X
	DCQ	X			X			X	X	X	X	X
	BIS	X			X			X	X	X	X	X
	DES				X			X				
	Hood			X			X					
	CGI			X	X	X	X	X	X	X	X	X
	Safety			X	X	X	X	X	X	X	X	X



You can upload charts or diagrams if

any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Patients may elect to drop out at any time, and they may be removed by the treating clinicians for clinical reasons, including 1) clinically significant worsening leading to an acute psychiatric emergency (e.g., suicidality, psychosis, mania), or **2 or more weeks of moderately significant worsening (ascertained by a clinical evaluation following 2 weeks of a score of at least 6 or 7 on the CGI improvement scale. A score of 6 or 7 would lead to a clinical evaluation and then clinical judgment as to whether the patient should be discontinued); 2) inability to comply with study procedures prior to to the 1st infusion**; or 3) medical complications of treatment. Patients who terminate due to medical or psychiatric problems will be offered the necessary level of care (e.g., psychiatric hospitalization for psychosis, inpatient detoxification and rehabilitation for worsening drug use). **Due to the risks to pregnant women and their unborn children associated with these medications, becoming pregnant would result in a participant's early discontinuation from the study.**

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Two vials of blood will be drawn during the screening process amounting to 10 cc (¾ tbsp). This is to determine if there are abnormalities that preclude enrollment into the study. The tests to be run are CBC, chem.-20 with LFTs, and b-HCG (for females). During the study, ketamine and norketamine levels will be obtained ½ hour into the infusion and 20 minutes after it is terminated; samples are frozen at -20 C and packaged in dry ice before being sent to the Nathan Kline lab. These samples will require about 10 cc (1 tbsp).

Assessment Instruments

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

Interviews: Mini International Neuropsychiatric Interview (MINI): A semi-structured diagnostic interview designed to assist researchers in making reliable DSM-IV psychiatric diagnoses (45 min); Clinician Administered Dissociative States Scale (CADSS): A 23 item clinician administered instrument used to measure current dissociative symptoms (5 min); Dissociative Experiences Scale (DES): A 28 item questionnaire for assessing the extent of daily dissociative experience, modified to be administered by a clinician (5 min); Brief Psychiatric Rating Scale (BPRS) for positive symptoms: A 4 item subscale for assessing psychosis (1 min); Hood Mysticism Scale (HMS): a 32 item scale for assessing infusion-dependent mystical experience, modified to be administered by study staff (5 min); Five Facet Mindfulness Questionnaire (FFMQ): A 39 item instrument modified to be clinician administered that assesses five mindfulness domains: observing, describing, acting with awareness, non-judging of inner experience, and

non-reactivity (5 min); Timeline Follow-Back (TLFB): a retrospective method of quantifying daily consumption of alcohol and other drugs, assisted by the maintenance of a weekly use diary (5 min); Barratt Impulsiveness Scale (BIS): a 30 item questionnaire used to assess impulsivity, modified to be administered by a clinician (5 min); Adverse Symptom Report (ASR): At each visit, the presence, date of onset, or resolution of adverse effects will be queried and recorded; Clinical Global Impression Scale (CGI): The CGI severity and improvement scales measure the overall clinical status of the subjects and change from baseline; Hamilton Depression Scale (HAM-D): A 21 item instrument used to measure current depressive symptoms; Treatment Service Review (TSR): A 8 item questionnaire that assesses the recent exposure of participants to treatment obtained in the community in excess of what is provided in this protocol; Childhood Traumatic Events Scale (CTES): A 6 item semi-structured interview that assesses childhood trauma prior to age 17.

Self-Reports: Psychiatric Epidemiology Research Interview Life Events Scale (PERI): A 102 item self-report that evaluates possible traumas that a participant may have experienced in his/her life in the past 6 months; Drug-Taking Confidence Questionnaire (DCQ): A validated assessment of self-efficacy; Alcohol Abstinence Self-Efficacy Scale: a 40-item assessment that assesses confidence to stop using alcohol in various situations (5 min); Perceived Stress Scale (PSS): A 9 item scale that measures levels of subjective stress, modified from a monthly assessment to one that evaluates stress between visits (5 min); VAS for alcohol craving (VAS-A): A 10 cm long line from "not at all" to "extremely" to assess craving intensity and frequency (1 min). Temperament and Character Inventory (TCI): 240 item questionnaire evaluating 4 temperament and 3 character dimensions.

Physiological Measures: Blood pressure and temperature.

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
1

Drug #1

Name of the drug
Ketamine Hydrochloride
Manufacturer and other information
The pharmacy at PI will be supplying the drug.
Approval Status
IND is approved

IND#
110,464
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Dakwar, Elias, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
The screening process should take about a week, after which eligible participants will be consented and provided MET, an effective psychotherapy for cannabis use disorders. Ineligible participants will be referred to appropriate treatment. Thus, the maximum duration of delay to treatment is about a week.
Maximum duration of delay to standard care or treatment of known efficacy
MET and MBRP are evidence-based behavioral treatments for cannabis use disorders that are provided to all consenting participants after they complete the screening process. The maximum delay to standard treatment is therefore about a week.
Treatment to be provided at the end of the study
All participants will be referred to appropriate evidence-based treatment for substance use disorders, including 12-step groups, further psychotherapy, addiction psychiatry, or outpatient rehabilitation, depending on the individual's needs and preferences.

Clinical Treatment Alternatives

Clinical treatment alternatives
Participants not interested in entering this trial will be referred to appropriate treatment for cannabis dependence, such as 12-step groups or outpatient/inpatient rehabilitation.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

The major risk of research participation is related to ketamine administration. Other risks include intravenous line placement.

Pregnant and lactating women are especially at risk as the medications used can be harmful to a fetus or newborn child as well as the mother herself.

Describe procedures for minimizing risks
1) Ketamine: The dose of ketamine employed in this study was specifically selected because it is equivalent

to the dose used with therapeutic effect in other settings, and comparable to doses that have been used safely in substance users (alcohol, cannabis, cocaine, opioids) in different protocols at this facility (Protocols 6162, 6176, 7014, 7051, 7057). Ketamine at the dose used in this study may be associated with a wide spectrum of psychological, perceptual and physiological effects. The psychological and perceptual effects include depersonalization, derealization, word-finding difficulties, slowed cognition, anxiety, agitation, confusion, and sensory changes. Physiological effects at the high dose include dizziness, blurred vision, and nausea. Additional side effects of ketamine that are more prominent at higher doses include tachycardia, increased blood pressure, sedation, analgesia, incoordination, jaw clenching, transient rash, increased perspiration, nystagmus, and fatigue. These effects tend to resolve immediately after the infusion is stopped. Participants are informed that they may stop the infusion and/or withdraw from the study at any time. A sitter will be present to address any distress that may emerge. In case of outpatient administration, participants will be closely monitored post-infusion to assess for persistent effects, and participants will only be discharged after 3 hrs have elapsed post-infusion and they have passed medical/psychiatric clearance and a field sobriety test.

The sitter, an ACLS certified physician, will also monitor for any side effects. Nausea and vomiting will be treated supportively and, if severe, with anti-emetic agents. So as to reduce the risk of nausea, vomiting, and aspiration, participants will be NPO after midnight prior to infusions. Anxiety and agitation will also be treated supportively and with relaxation exercises. If these side effects do not remit with such measures, and/or if the participant persists in asking that the session be stopped, the administration of ketamine will be discontinued. In other studies utilizing comparable doses of ketamine infusion, anxiety, psychosis and perceptual changes have always spontaneously resolved within 30 minutes of terminating the infusion, often within 5 minutes. Intramuscular preparations of midazolam and/or thiothixene will be kept available at the central pharmacy in order to rapidly control a ketamine-induced level of emotional distress, psychosis, or delirium should it persist. Any participant requiring pharmacotherapy to control a psychiatric complication of drug administration will be removed from the study, kept overnight for observation, and given referrals, if necessary, the next day, assuming the person can be safely discharged from hospital.
The administration of subanesthetic ketamine IV also induces a modest rise in vital signs. During the ketamine infusion, vital signs (blood pressure and heart rate) will be monitored every five minutes beginning five minutes before the infusion begins, and will be monitored after the infusion until baseline vital signs are restored. If HR > (220 – patient age) X 0.85 BPM, and if systolic blood pressure increases by > 60 mm or diastolic blood pressure increases by > 40 mm (or SBP>200 and DBP>115) during the ketamine infusion, the infusion will be permanently discontinued. The blood pressure and heart rate will be monitored and if there is no decrease after 5 minutes, then nitroglycerin, clonidine, or propranolol will be administered. If high blood pressure is symptomatic, i.e., blurred vision, headache, chest pain, the subject will be transferred to the ER.

Any medical risks from increased blood pressure will be minimized through the careful screening of potential subjects. Subjects will be excluded for baseline hypertension or any history of cardiovascular illness. In addition, an ACLS certified physician will be present during the procedure. Continuous ECG monitoring and pregnancy testing will be provided, as well.

Extensive laboratory experience suggests that sub-anesthetic ketamine generally produces transient effects without any persistent changes, but there are some data suggesting that ketamine, and glutamate modulators in general, may alter the glutaminergic system in such a way as to render vulnerable subjects more likely to

develop psychotic disorders. Previous studies, therefore, have tended to exclude participants with a personal or family history of psychosis in order to reduce the psychiatric risks that ketamine may pose. Accordingly, individuals with a personal or first-degree family history of psychosis will be excluded from this study. Furthermore, the protocol involves close monitoring and an assessment of psychiatric stability prior to discharge; this both ensures that any lingering sedation is allowed to dissipate, and that participants are closely monitored for persistent side effects. Participants will be screened by a psychiatrist and cleared for continued participation following the infusion on Week 2, Day 2, and they will also be followed twice weekly during the following phase of the trial. Subjects will be provided a number to call to reach an on-call psychiatrist (24 hours/day) should unpleasant effects occur after subjects have left the testing facility.

Ketamine is also associated with some abuse liability, though this abuse liability is significantly lower than that of other drugs of abuse, such as cannabis, cocaine, nicotine, alcohol, benzodiazepines, or opioids. Ketamine is generally insufflated, ingested, or injected intramuscularly in the community, and is of ten used in combination with other substances such as gamma-hydroxy-butyrate (GHB) or 3,4-Methylenedioxymethamphetamine (ecstasy). There is a risk, therefore, that participants may seek out ketamine after becoming exposed to it, and develop problematic patterns of ketamine use during or after the study. This risk may be compounded by the fact that it is given in this study to individuals who may have an increased vulnerability to developing substance use problems in light of their dependence on cannabis. While this important risk cannot be removed entirely, various safeguards can be implemented to ensure that it is minimized, including: 1) exercising "a minor deception" and giving participants the impression that they may receive any of a number of medications during each infusion, while ensuring that the side effects and risks are clearly conveyed; this may prevent patients from identifying ketamine and subsequently seeking it out; 2) excluding participants with a history of ketamine misuse or abuse; and 3) carefully monitoring drug use to ensure that any emergent patterns of misuse or abuse of ketamine, or any other substance, is properly addressed in a timely manner. Futhermore, ketamine is administered in this study in a way that is unrepresentative of how it is commonly used in the community (slow-drip IV infusion). In addition, this slow, sustained method of administration is unlikely to lead to the acute powerful effects generally associated with heightened abuse liability.

Participants who develop a significant adverse reaction during or after the infusion (psychosis, agitation, or adverse psychological response that is persistent and/or requiring pharmacotherapy; blood pressure elevation requiring termination) will lead to the blind being broken. This will alert the participant to his or her propensity for an adverse response to the drug, thus ensuring future safety.
There is a risk of adverse interactions with the study medications if participants are actively intoxicated on illicit medications. In order to minimize this risk, participants are encouraged to remain abstinent before the infusion, and will be tested daily with urine toxicology. They will also undergo a field sobriety test on the day of the infusion, prior to administration. In addition, they will be evaluated by a clinician (Dr. Dakwar) for DSM-IV signs of any intoxication.
In conclusion, the careful evaluation of participants during the screening process for cardiovascular, psychiatric, medical, and historical vulnerabilities to ketamine infusion; the presence of a psychiatrist with ACLS certification (the PI) during and after the infusion who will monitor for side effects and adverse events; the sub-anesthetic, generally well-tolerated dose at which ketamine will be infused; the close monitoring during infusion; the psychiatric evaluation and clearance to go home; the regular outpatient visits to monitor for persistent effects; and the provision of supportive and pharmacological measures to

address any side effects all ensure that the medical and psychiatric risks involved in participation in this study will be minimal.

2. Blood drawing/Intravenous placement: Another risk in the study is that bruising or a blood clot could form at the site of the intravenous line or venipuncture. Medical staff with extensive experience with IV placement will remain available to ensure that risks are minimized.

In order to safeguard against risks towards pregnant women, evaluation will be conducted on whether the risk of treatment is acceptable for women of childbearing potential. Staff will discuss with participants the risks associated with participation and the importance of adequate birth control practice. In addition, staff will evaluate whether the participant is willing and reliable to practice effective birth control during the study. Urine pregnancy testing will be conducted at baseline evaluation and on a weekly basis throughout the course of the study. Staff will periodically discuss with patients to review importance of not becoming pregnant, and adequacy of birth control practices (all of which will be documented). As the testing methods used have limitations, participants will be encouraged to inform the research staff if they believe they have become pregnant so that the safety of the participant can be ensured. As the risk towards pregnant women outweighs the benefits of participating in this study, if a participant becomes pregnant during the course of the study, they will be discontinued from their participation.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
A Certificate of Confidentiality will be acquired for this study from the National Institute on Drug Abuse to offer protection for the privacy of subjects by protecting identifiable research information from forced disclosure (e.g., through a subpoena or court order). The Certificate of Confidentiality allowed investigators and others with access to research records to refuse to disclose information that could identify subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. The Certificate of Confidentiality is granted for studies that collect information that, if disclosed, could damage subjects' financial, employability, insurability, or reputation, or have other adverse consequences.

We use coded records (i.e. initials and numbers), store signed consent forms in a locked room, and try, to the best of our ability to maintain confidentiality. Only coded records will be entered into the computer and the security of electronic data is ensured at the level of the server, the user, and the database. We do, however, point out to prospective patients, that we cannot assure that their drug histories and other personal records might not become known.
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
All patients will receive MET and MBRP. **MET has been found to be effective in treating Cannabis Use Disorder (Dennis et al., 2004; Nordstrom & Levin, 2007; Sellman et al., 2001), and MBRP has been shown to be effective to preventing cannabis dependence relapse (Grant et al., 2015)**

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 given $10 for each visit to cover the costs of travel, which they will receive each day that they come. Participants will also be compensated with $25 on the days of medication administration. Taking into account screening visits, participants may earn up to $195.

References

References

Dennis, M., Godley, S. H., Diamond, G., Tims, F. M., Babor, T., Donaldson, J., ... & Hamilton, N. (2004). The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. Journal of substance abuse treatment, 27(3), 197-213.

Grant, S., Hempel, S., Colaiaco, B., Motala, A., Shanman, R. M., Booth, M., ... & Sorbero, M. E. (2015). Mindfulness-Based Relapse Prevention for Substance Use Disorders.

Nordstrom, B. R., & Levin, F. R. (2007). Treatment of cannabis use disorders: a review of the literature. American Journal on Addictions, 16(5), 331-342.

Sellman, J. D., Sullivan, P. F., Dore, G. M., Adamson, S. J., & MacEwan, I. (2001). A randomized controlled trial of motivational enhancement therapy (MET) for mild to moderate alcohol dependence. Journal of Studies on Alcohol, 62(3), 389-396.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
7355 CL ad 20180521.pdf
7355 Ad.pdf
Upload evidence of FDA IND approval(s)
Upload copy(ies) of the HIPAA form
7355 HIPAA.pdf
Upload any additional documents that may be related to this study

Are you ready to stop using marijuana?

The Substance Use Research Center at the Columbia University Medical Center/New York State Psychiatric Institute is seeking marijuana users who wish to participate in a treatment study.

We are looking for healthy men and non-pregnant women between the ages of 21 and 60 years old who are seeking to reduce or stop cannabis use. Participants will receive medication and free, weekly individual psychotherapy for the duration of the 6-week study period. Twice weekly clinic visits are required at Columbia University Medical Center; travel compensation is provided for participation.

Please reply to this post with your phone number or call us at 888-497-8427.

For more information, please visit our website: newyorkaddictiontreatment.org

ARE YOU READY
TO STOP SMOKING POT?

Columbia University Medical Center
is recruiting participants
for a cannabis study

If interested, please call: **888.497.8427**

COLUMBIA UNIVERSITY MEDICAL CENTER

NEW YORK STATE | New York State Psychiatric Institute

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 7355 **Principal Investigator:** Elias Dakwar, MD

Name of Study: Glutamatergic Modulation to Facilitate the Behavioral Treatment of Cannabis

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form.

1. **The Health Information that may be used and/or disclosed for this Research includes:**

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**

☑ Researchers and their staff at the following organizations involved with this Research:
Substance Use Research Center, New York State Psychiatric Institute

☑ The Sponsor of the Research,
NIDA
and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. **Please note that:**
   - You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

     Elias Dakwar, MD, 1051 Riverside Drive, Unit 66, New York, NY 10032

   - While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. **This Authorization does not have an end date.**

6. **You will be given a copy of this form after you have signed it.**

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**