Protocol Title:
The Ability of Vaped Marijuana to Reduce the Severity of Naloxone-Precipitated Withdrawal

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Research Area:
Substance Use Disorders

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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 proposing an amendment only to an existing protocol

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
Psychiatry
Within the department, what Center or group are you affiliated with, if any?
Opioid Research Laboratory

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.
None

Procedures

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

✓ Administration of Substance of Abuse
✓ Collection of Biological Specimens
✓ Internet-based Data Collection or Transmission
✓ Medication Trial
✓ Psychiatric Assessment
✓ Use of Investigational Drug or Device

Population

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

✓ Medically and Psychiatrically Healthy Subjects
✓ 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?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
National Institute on Drug Abuse
Grant Name
The Ability of Inhaled Dronabinol to Reduce the Severity of Naloxone-Precipitated Withdrawal.
Grant Number
R21 DA049076-01A1
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

To address the opioid epidemic, there has been an increased focus on the development of novel medications to treat opioid use disorder (OUD). However, a pharmacological approach more specific to overdose harm reduction (i.e., minimizing the harmful effect of drugs among active users) may be to increase the tolerability of the overdose reversal agent, naloxone (NLX). In emergency settings, NLX administration (in suspected cases of opioid overdose) often results in violent patient behavior, as individuals who are opioid dependent awaken in a state of opioid withdrawal (Gaddis and Watson, 1992; Osterwalder, 1996). Naloxone-induced withdrawal is also common in out-of-hospital settings in which non-medical persons are asked to administer naloxone to save the lives of their peers. Analysis of the Opioid Lab's overdose reports from the individual who administered NLX found that 98% of overdose victims presented notable opioid withdrawal-related adverse events (AEs) including: nausea, abdominal pain, vomiting, joint/muscle pain, and tremor. Concerns of the adverse effects of NLX administration may prevent or delay the use of this life-saving intervention.

The goal of the proposed, proof-of-concept study is to test the combined effects of vaporized marijuana [Delta-9-tetrahydracannabinol (THC)] with NLX as a proof of concept towards the possible development of a combined overdose reversal agent with improved tolerability. Marijuana will not actually be vaped per se, but a “vaporizer” will be used to produce an aerosol from marijuana plant material, which the participant will inhale. Marijuana plant material will be obtained from the National Institutes on Drug Abuse (NIDA). In clinical studies, oral synthetic THC (Bisaga et al., 2015; Lofwall et al., 2016) reduced the severity of opioid withdrawal during opioid detoxification (Scavone et al., 2013). Clinically, cannabinoid drugs like Marinol® (oral synthetic THC), Sativex ® (nabixomols), and Cesamet® (nabilone) are used to treat nausea and vomiting, common symptoms of opioid withdrawal. This study will investigate the ability of vaporized marijuana (V-MJ) (0.00, 12.5, and 25 mg: concentration= 11.7% THC + 0.04% CBD.) to reduce the severity of opioid withdrawal precipitated by intranasal (IN) NLX (0.0 and 4.0 mg). The final dose of marijuana will be achieved in 10 puffs/vapes, in 10-12 minutes (at a temperature of 210°C).

This trial will recruit healthy participants with opioid use disorder (N=16, completers).

Testing will begin following stabilization on oral morphine (120 mg/day), which will continue throughout the trial. During each testing session, a single V-MJ + naloxone dose combination will be assessed (in randomized order), with **24 hours** between testing sessions. Laboratory testing sessions will consist of a modified naloxone challenge procedure, which quantifies the severity of naloxone-precipitated opioid withdrawal (Jones et al., 2019).

The slow rate of onset for oral cannabinoid administration would not have utility in an emergency. Therefore, the rapid pharmacodynamics of vaporized marijuana will allow the investigators the opportunity to investigate the potential utility of an ecologically valid combined cannabinoid + NLX opioid overdose emergency intervention. The investigators hypothesize that the combined administration (V-MJ + NLX) will produce significantly less withdrawal than NLX alone.

Background, Significance and Rationale

Background, Significance and Rationale
Why is naloxone-precipitated withdrawal a problem? Although there are studies that suggest that the distribution of naloxone (NLX) has a measurable effect on overall opioid overdose death rates, deaths nation-wide remain high (Centers for Disease Control (CDC), 2018; Doe-Simkins et al., 2012; Walley et al., 2013). More needs to be done to address the fatalities associated with opioid overdose. All 50 states currently allow medical providers to prescribe the opioid receptor antagonist NLX to persons most likely to witness or experience an opioid overdose. In our study team's investigation into the utility of overdose education and naloxone distribution (OEND) programs, an important barrier has emerged (Jones et al., 2014; Neale et al., 2020). Experienced opioid users have a notable baseline knowledge of opioid overdose and are keenly aware of the ability of NLX to elicit severe opioid withdrawal (Jones et al., 2014; Green et al., 2008). These individuals are also likely to have experienced NLX-precipitated withdrawal during a previous non-fatal overdose (Darke et al., 2014; Mars et al., 2015; Wagner et al., 2015). Additionally, many OEND programs inform individuals that precipitated withdrawal is a likely consequence of administering NLX (Clarke et al., 2014). Thus, the fear of inducing withdrawal is a significant barrier to NLX use, even in emergency situations (Wright et al., 2006). This fear is not unwarranted. In emergency settings, NLX administration often results in violent patient behavior (Gaddis and Watson, 1992; Osterwalder, 1996). Concerns of the adverse effects of NLX administration may prevent or delay the use of this life-saving intervention. Precipitated opioid withdrawal is also a concern for the overdose victim. Once revived, the adverse symptoms such as: joint and muscle pain, nausea, vomiting, and stomach cramps, may lead the individual to use additional opioids for relief, putting them at risk of a recurrence of severe respiratory depression (Buajordet et al., 2004).

How cannabinoids may help? The endocannabinoid system is a potential novel target for reducing opioid withdrawal severity. Studies show that opioid and cannabinoid receptors are co-localized in multiple brain regions. Both receptors also have cross-modulatory pharmacological effects including: cross-agonism, -antagonism, -sensitization, and -tolerance (Robledo et al., 2008). Preclinical studies have demonstrated that tetrahydrocannabinol (THC) decreases signs of opioid withdrawal in morphine-dependent rodents (Bhargava, 1976; Cichewicz and Welch, 2003; Gamage et al., 2015; Hine et al., 1975). In clinical studies, oral dronabinol (synthetic THC: Bisaga et al., 2015; Lofwall et al., 2016) and smoked cannabis have been shown to reduce the severity of abstinence-induced opioid withdrawal during opioid detoxification or

stabilization (Scavone et al., 2013). Clinically, cannabinoid receptor type-1 agonists such as, Marinol® (oral synthetic THC), Sativex ® (nabixomols), and Cesamet® (nabilone) are used to treat nausea and vomiting, common symptoms of opioid withdrawal. Joint and muscle pain are also common AEs associated with NLX-precipitated withdrawal. In clinical laboratory investigations of their analgesic effects, cannabinoids have shown promise in treating muscle pain (Cooper et al., 2013 & 2018).

Rationale: This study will investigate the ability of vaporized marijuana (V-MJ) (0.00, 12.5, and 25 mg: concentration= 11.7% THC) to reduce the severity of opioid withdrawal precipitated by intranasal (IN) NLX (0.0 and 4.0 mg). If our hypotheses are supported, this study may suggest that the combination of an intranasal opioid receptor antagonist with a cannabinoid receptor agonist may have clinical utility as an overdose reversal medication that is more tolerable than naloxone alone. Reducing the adverse effects of naloxone administration may increase its utilization while minimizing risks for the administrator and recipient.

Specific Aims and Hypotheses

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Primary Aim: Assess the ability of vaped marijuana to alter the severity of naloxone-precipitated withdrawal. We hypothesize that there will be a dose-dependent effect of vaped marijuana to attenuate the severity of naloxone-precipitated withdrawal.

Secondary Aim: Assess the safety of vaped marijuana in combination with naloxone. We hypothesize that vaped marijuana, in combination with naloxone, will produce more AEs than placebo but less than naloxone alone.

Secondary Aim: Assess the impact of vaped marijuana on naloxone's effects on pupil diameter (i.e., μ-opioid receptor blockage). We hypothesize that vaped marijuana will not significantly alter naloxone's effects on pupil diameter (in comparison to placebo).

Description of Subject Population

Sample #1

Specify subject population
Opioid-Dependent Participants with Opioid Use Disorder
Number of completers required to accomplish study aims
16

Projected number of subjects who will be enrolled to obtain required number of completers
32
Age range of subject population
18-55

Gender, Racial and Ethnic Breakdown
All efforts will be made to ensure that the representation of women and of ethnic minorities are in proportion to the individuals with Opioid Use Disorder (OUD) in New York City. It is estimated that the sample will be 70% male, 50-40% Caucasian, 45%-40% Black or African American, 0-5% Asian, Pacific Islander and Native American, and 15% will self-identify as multi-racial. We anticipate that ≈ 30% of our sample will be of Latino/Hispanic ethnicity. These estimates are based upon data from non-crisis heroin treatment admissions, reported by the New York City Department of Health and Mental Hygiene. https://ndews.umd.edu/sites/ndews.umd.edu/files/SCS-Report-2018-New-York-City-FINAL.pdf.
Description of subject population
Healthy participants meeting DSM-5 OUD criteria and physical dependence on opioids will be enrolled.

Recruitment Procedures

Describe settings where recruitment will occur
Potential applicants will first complete a telephone/videoconferencing assessments during which we will obtain information on demographics, medical, psychological and personal history, as well as details on their use of various prescription and illicit drugs. Participants who pass the initial virtual screening will be scheduled for additional in-person screening procedures at NYSPI. All in-person screening and assessments (medical examination, and naloxone challenge) will occur within the facilities of the Substance Use Research Center (SURC), located on the 3rd floor of the NYSPI. How and by whom will subjects be approached and/or recruited?

Interested participants who respond to study advertisements by call the Opioid Research Lab screening line. A research assistant or volunteer will conduct a general telephone interview to see if they meet criteria for any active studies. These telephone screens are reviewed by a senior member of the research team to determine if further in-person screening is warranted.
How will the study be advertised/publicized?
Recruitment is primarily through word-of-mouth and advertisements in local newspapers such as the Village Voice and AM New York, New York and New Jersey transportation (e.g., Subway and Bus),as well as electronic media (e.g., Facebook, Google, StudyKik) and websites that drug users frequent such as Bluelight and Erowid).The study will be using RecruitMe as a platform for recruitment. This study will be using Moshemu, which specifically targets difficult to reach, stigmatized populations (specifically substance abusers). NIDA is funding the creation of this recruitment platform and the first researchers to sign up will be able to use the platform for free. The Moshemu staff will work to use online recruitment methods to attract potential research participants to the Moshemu platform and guide them through an initial screening process. Next, researchers will be connected with these participants in order to enroll them into their studies.
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
NCT05114460

Concurrent Research Studies

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

7680: Assessing the Effects of Heroin Use on Epigenetic Aging (PI: Jermaine Jones PhD)

6723: Risks and Benefits of Overdose Education and Naloxone Prescribing to Heroin Users (PI: Sandra Comer, Ph.D.)

7712: Clinical Trials of Multivalent Opioid Vaccine Components.(PI: Sandra Comer, Ph.D.)

7788: Isolation of opioid-specific B cell lymphocytes and development of human opioid-specific monoclonal antibodies(PI: Sandra Comer, Ph.D.) A Randomized, Double-Blind, Placebo- and Active-Controlled, Crossover Study to Evaluate the Abuse Potential of Oxymorphone Compared to Other Mu-Opioid Agonists in Physically Dependent Opioid Users with Moderate-to-Severe Opioid Use Disorder (PI: Sandra Comer, Ph.D.)

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Opioid Users
Create or insert table to describe the inclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. 18-55 years of age.	Self-reported age and verification with legal identification.
2. Diagnostic criteria for Opioid Use verification with legal identification. Disorder (OUD) moderate-severe (304.00) as per DSM-V, including physiological dependence and not currently seeking treatment for OUD.	MINI Substance Use Module, naloxone challenge/visual evidence of opioid withdrawal.
3. Self-reported opioid use for non- therapeutic purposes; and positive urine drug screen for opioids.	Urine drug toxicology and clinical interviews
4. Physically healthy.	Laboratory tests (urinalysis, blood chemistry & hematology, 12-

	lead ECG), physical examination, and medical history.
5. Body mass index (BMI) ≥ 18 and ≤ 35 kg/m2 and weight ≥ 50 kg (110 pounds).	Weight and BMI calculations.
6. Able to perform study procedures.	Practice Session
7. Females must be either: a. Post-menopausal (amenorrhea for at least 12 consecutive months), surgically sterile -or b. Women of childbearing potential must agree to use an acceptable double-barrier method of contraception during screening and study participation.	Urine (Screening) and Serum (Admission Day) pregnancy tests, Nurse's assessment.
8. **Must use cannabis products on less than three occasions (occasion= a single administration period of <30 minutes) per week for the four weeks before screening.**	Clinical Interviews

Create or insert table to describe the exclusion criteria and methods to ascertain them

Criterion	Method of Ascertainment
1. Seeking treatment for Opioid Use Disorder.	Clinical Interview
2. Current or history of a psychiatric condition that would affect participants' ability to provide informed consent (e.g., mood disorder with functional impairment or schizophrenia) or make participant hazardous for the participant (e.g., recent suicidal ideation) or staff (e.g., significant history of violence).	Beck's Depression Inventory, CSSRS Screener, Psychiatric Examination (with psychiatrist or clinical psychologist)
3. Current DSM-V diagnosis of substance use disorders requiring medically managed detoxification, other than OUD (e.g., alcohol or benzodiazepine dependence).	MINI: Substance Use Module & Clinical Interviews
4. Medical condition resulting in chronic pain (>3 months).	Clinical Interviews, Medical History, Physical Examination.
5. Clinically significant abnormality on physical examination, vital signs, screening laboratory tests, or 12- lead ECG.	Physical examination, vital signs, screening laboratory tests, or 12-lead ECG.
6. Significant cardiovascular, hepatic, renal, respiratory, gastrointestinal, endocrine, immunologic, dermatologic, hematologic, or	Medical History, Physical Exam

neurologic disorder.	
7. Any surgical, or medical condition that may interfere with the absorption, distribution, metabolism, or excretion of the study drugs.	Medical History, Physical Exam
8. Baseline hypotension, orthostatic hypotension or syncope, hypertension (blood pressure > 140/90), pulmonary hypertension or heart disease.	Medical History, Physical Exam, Nurse's Assessment
9. Any of the following values for laboratory tests: a. positive pregnancy test, b. hemoglobin < 12 g/dL in males and < 11 g/dL in females, c. neutrophil count < 1.0 × 109/L, d. platelet count < 75 × 109/L, e. creatinine clearance < 50 ml/min per modified Cockcroft-Gault equation, f. aspartate aminotransferase or alanine aminotransferase > 3.0 × upper limit of	Laboratory Testing
10. Hypersensitivity to opioids, history of significant adverse reactions to cannabinoids, and allergy or contraindication to any other drugs administered as a part of this investigation.	Clinical Interviews, Medical History
11. Use of an investigational agent within 30 days.	Clinical Interviews

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
Yes
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

General Telephone Screening: Participants who respond to study advertisements will complete a general Opioid Reserach Laboratory Telephone Screener. Verbal consent to complete the telephone screen is noted on the screener form by a volunteer or research assistant. Telephone screens are reviewed by a senior member of the research team to determine if further, study-specific screening procedures are warranted.

Remote Study-Specific Screening: Participants who pass the telephone screen will receive a copy of the **8061** screening consent form via an encrypted email (if the participant has email access), to review while the research assistant reviews it with them over the phone. A research assistant, volunteer, nurse, or psychologist will note on a physical copy of the consent form, that verbal consent was obtained to initiate study-specific remote screening procedures. Following screening consent, participants to begin remote screening procedures to minimize the number of in-person visits to NYSPI. During remote screening, the participant will complete various screening assessments (e.g., CSSRS, BDI, PhD Interview Nurses assessment) with the research assistant, nurse, or psychologist through HIPAA-compliant platforms such as Zoom or Facetime, or telephone. The investigators will address any concerns the patient may have regarding confidentiality during this process such as access to a private space in which to take calls. These remote assessments are primarily collected in Qualtrics (e.g., PhD Interview, NIDA Assist BDI, and CSSR-S), while some medical history forms are completed on paper by the assessor).

In-Person Screening: Prior to their first in-person visit, participants will be informed of the risk of COVID-19 exposure while traveling to, and while at NYSPI. This information is included in the screening consent form. During the in-person visit, the participant will sign a physical copy of the HIPAA form. Participants will be given the option of having the signed copy of the consent form sent to them via email, instead of receiving a physical copy.

Describe Study Consent Procedures
The study consent will have been reviewed with the participant extensively over the phone, during the screening phase of the study. A research assistant (BA/BS) will read the consent form verbatim. The participants will be offered the opportunity to ask questions of an investigator or physician during each of the in-person screening visit(s), and again when they meet with the MD or NP, who will conduct the consenting process. A physical copy of the study consent will be signed with a physician or NP on the day of admission (or the final day of screening).The physician or NP will review the inclusion/exclusion criteria, comparing it to the participant's screening data, prior to obtaining study consent. Participants will be given the option of having the signed copy of the consent form sent to them via encrypted email, instead of receiving a physical copy.

List of Consenters:
Castillo, Felipe MD
Comer, Sandra, PhD
Jones, Jermaine, PhD
Manubay, Jeanne, MD
Parmon, Eric, MD
Greiner, Miranda, MD
Luba, Rachel PhD
Franco-Corso, Silvia, MD
Tindall, Claudia, NP
Perez, Freymon, BA
Allwood, Nicholas BA
Martinez, Suky PhD
Gopaldas, Manesh MD
Jimenez, Herman RN

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data?
No
Is breach of confidentiality the main study risk?
No
Is consent for this research procedure ordinarily not required outside of the research context? Explain
We would like to request a waiver of documentation of consent via 45CRF46.117(c), for the study-specific Remote Screening Procedures. Following a brief general telephone screener, some of the study-specific screening procedures will be conducted remotely, potential participants will review the approved screening consent form, but we will not be obtaining their signature. Instead, the staff member who reviews the consent form with the participants and obtains their verbal consent, will document and attest that verbal consent was obtained on the screening consent form. Study Consent will be documented with the participant and physician's (or Nurse Practitioner's) signature.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Allwood, Nicholas
Arout, Caroline
Castillo, Felipe, MD
Comer, Sandra, PHD
Franco, Silvia, MD
Gopaldas, Manesh
Greiner, Miranda, MD
Jimenez, Herman
Jones, Jermaine, PHD
Luba, Rachel, PHD
Manubay, Jeanne, MD
Martinez, Suky
Parmon, Eric
Tindall, Claudia
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Screening: Healthy adults with Opioid Use Disorder will be recruited for this study in accordance with the Inclusion/Exclusion criteria, using the measures outlined in the "Assessment Instruments" section of the PSF. After reviewing screening results, a physician and the study PI will make the final decision as to whether the participant is eligible for the study.

To minimize the number of visits to NYSPI (minimizing the risk of COVID-19 exposure for participants and staff), some screening measures will be conducted via telephone, Zoom, or Facetime (only HIPAA-compliant, CUIMC accounts will be used). Study staff (research assistant, nurse, or psychologist) will simultaneously complete paper copies, based on the subjects' responses, or enter data directly into the appropriate electronic data capture system (e.g., Qualtrics- which will contain no PHI).

This study requires that some screening procedures occur on-site (e.g., physical, psychiatric evaluation, ECG, bloodwork). One of the final screening assessments will be the naloxone challenges (to verify opioid dependence). This test will only be performed after the other screening assessments have verified that the participant is sufficiently healthy to minimize the risk of this procedure. The day prior to their in-person visit(s), a research assistant or nurse will complete a COVID-19 symptom screener. Additionally, a test for the presence of COVID-19 and/or its antibodies will be performed prior to admission. As with any significant lab results, a member of the medical team will disclose and discuss a positive COVID-19 test result, and provide appropriate treatment referrals.

Admission and Morphine Stabilization: Once eligibility is determined, participants will be admitted into the secure NYSPI inpatient unit for the duration of the study (approximately 4 weeks). Following admission, participants will begin 5-14 days of stabilization on oral morphine (30 mg, QID: 700, 1300, 1800, 2200 hrs). Additionally, 10-20mg PO hydromorphone doses will be available PRN to address withdrawal symptoms insufficiently managed by oral morphine and supplemental medications alone (to a maximum of 80 mg per day). Hydromorphone will be available in addition to QID oral morphine when deemed clinically appropriate by the study physician. **The participant must exhibit at least "mild" opioid withdrawal according to the COWS (score >8).** Once stabilized, participants will receive oral morphine daily (30 mg) at 700, 1300, 1800, and 2200 hrs. **Prior to the initiation of testing sessions, stability on morphine will be established. Stability will be defined as participants exhibiting a mean COWS score not exceeding 5, with no hydromorphone administration.** Vitals and Respiratory Rate will be assessed immediately before and for one hour (in 15-minute intervals) following the additional dose to ensure against oversedation.

Common clinically used medications such as, clonidine, zolpidem, and Compazine will be available, along with methocarbamol (750-1500 mg, every 6 hours, not exceeding 6000mg in 24 hours). The use of these medications will be suspended by 6 PM the day before a lab session. Participants who cannot stabilize and will be discharged and offered the same end-of-study treatment options described below.

Safety Session: Testing will not begin until withdrawal symptoms are no longer present, based upon the Clinical Opioid Withdrawal Scale (COWS: Handelsman et al., 1987). Prior to testing vaped marijuana in combination with intranasal (IN) naloxone, participants will complete a Safety Session. During the safety session, they will receive a test dose of vaped marijuana (25 mg). If a participant's vital signs exceed any of the following benchmarks outlined in the Criteria for Early Discontinuation, they will be discontinued from the trial (Table 1).

Table 1: Study Design

	Week 1						Week 2							
	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun
	Admission	Stabilization	Stabilization	Stabilization	Stabilization	Stabilization	Stabilization	Stabilization	Stabilization	Stabilization	NLX 0mg + V-MJ 0mg	NLX 4mg + V-MJ 25mg		
	Week 3						Week 4							
	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Sun
	NLX 0mg + V-MJ 12.5mg	NLX 0mg + V-MJ 25mg	NLX 4mg + V-MJ 12.5mg	NLX 4mg + V-MJ 0 mg			Discharge							

Laboratory Testing: Laboratory testing sessions will consist of a modified naloxone challenge procedure (A.K.A. Wang Test: Wang et al., 1974). The challenge begins with baseline assessments. Ten common symptoms of opioid withdrawal (gooseflesh, vomiting, tremor, sweating, restlessness, lacrimation/nasal congestion, yawning, warming/cooling sensations, stomach pain, and muscle ache) will be assessed by a research assistant trained in administering the SOWS/COWS. For safety, the physician or nurse who is providing medical oversight will directly observe its administration.

Each symptom is coded as either "absent" or "present," with between 1 and 6 points added when a symptom is observed (Table 2). Following pre-test assessments, a physician or nurse practitioner will administer the study drug combination (1000-1100 hrs). Assessments of withdrawal are made at 10-minute intervals for 50 minutes. The total withdrawal score is calculated at the end of the session. To minimize carry-over effects, sessions will be conducted at least 48 hours apart (>5 half-lives of both medications). See Table 1 for an example dosing schedule. The following dose combinations of vaped marijuana (V-MJ) and IN naloxone will be tested in random order:

- Naloxone 0 mg + V-MJ 0.0 mg
- Naloxone 0 mg + V-MJ 12.5 mg
- Naloxone 0 mg + V-MJ 25 mg
- Naloxone 4 mg + V-MJ 0.0 mg
- Naloxone 4 mg + V-MJ 12.5 mg
- Naloxone 4 mg + V-MJ 25 mg

	Table2:Rating Scale for Opioid Withdrawal											
	(Pre-test)		Time after first naloxone dose									
	0 min		10 min		20 min		30 min		40 min		50 min	
Signs and Symptoms	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Gooseflesh	6	0	3	0	3	0	2	0	1	0	1	0
Vomiting	6	0	3	0	3	0	2	0	1	0	1	0
Tremor	6	0	3	0	3	0	2	0	1	0	1	0
Sweating	6	0	3	0	3	0	2	0	1	0	1	0
Restlessness	4	0	2	0	2	0	1	0	1	0	1	0
Lacrimation/ Nasal Congestion	4	0	2	0	2	0	1	0	1	0	1	0
Yawning	4	0	2	0	2	0	1	0	1	0	1	0
Feeling of Change in Temperature	3	0	1	0	1	0	1	0	1	0	1	0
Stomach Pain	3	0	1	0	1	0	1	0	1	0	1	0
Muscle Ache	3	0	1	0	1	0	1	0	1	0	1	0
Actual time of observation												
Scores												
Pupil Diameter												

Vaping of cannabis provides a rapid and efficient method of drug delivery from the lungs to the brain (Abrams et al., 2007; Azofeifa et al., 2016). This investigation will use the MIGHT Vaporizer (manufactured by Stoke and Bissel), which allows for precise temperature control of hot air convection heating. The device will be set to 210°C. Co-investigators (Dr. Arout and Haney) currently use this device and are confident in its safety and biocompatibility. A clinical trial from Australia (Arkell et al., 2019), utilized the Mighty Medic device to administer 125 mg THC (11%) to healthy volunteers. Same percentage as the current trial, but a lower dose. AEs were minimal (increased self-reports of being "Sedated" and "Anxious"). Furthermore, Carra et al., (2020) characterized the delivery kinetics, efficiency, and decarboxylation yields of the Mighty Medic for delta-9-tetrahydrocannabinol and cannabidiol. Thus, the investigators are confident that the proposed doses of vaped MJ will be pharmacodynamically efficacious and well-tolerated.

Dose Rationale: The naloxone dose selection was based on the purpose-designed, overdose first-aid drug Narcan® Nasal Spray (4mg/0.1ml).

The V-MJ doses were selected based on proposed efficacy and safety. In a recent trial, Spindle et al., (2018) conducted a controlled examination of the effects of vaporized and smoked cannabis in "infrequent" cannabis users (N=17). For vaporized conditions, mean peak plasma concentrations for THC were 7.5 ng/mL at the 10-mg dose and 14.4 ng/mL at the 25-mg dose. Among these normal health volunteers, modest impairment of cognitive functioning and psychomotor agitation (e.g., significantly decreased task performance) were the most common adverse events.

Please Note A 2 mg naloxone dose condition was dropped on the recommendation of the NIDA

scientific officer.

During the Lab session, additionally, adverse events (AEs) unrelated to withdrawal will be quantified using the Systematic Assessment for Treatment Emergent Events (SAFTEE: Levine and Schooler, 1986). Pupil diameter will be measured using a Neuroptics®) digital pupilometer. Heart rate (HR) and blood pressure (BP) will be measured using a Criticare® vital signs monitor and recorded at 15-min intervals. For safety, vital signs (HR, BP, and pulse oximetry) will be monitored every 5 minutes for the first 30 minutes, then every 15 minutes for the next 1.5 hours at which point THC plasma concentrations should be negligible. Additional vital monitoring will occur every 30 minutes for the next 2 hours, for a total of 4 hours of post-dose monitoring. In the Criteria for Early Discontinuation section, we have outlined vitals parameters that will preclude a participant from completing additional sessions and discontinue their enrollment in the trial.

Additional Assessments During Laboratory Sessions (completed at -30, +15, +30, +45, +60):

- The subjective effects battery will consist of Visual Analog Scales and the Opioid Craving Questionnaire (Tiffany et al., 1993),
- Two cognitive tasks will be used in the proposed studies. The Digit Symbol Substitution Task (McLeod et al., 1982) and the Divided Attention Task assesses attention (DAT; Miller, 1987).
- Brief Psychiatric Rating Scale (BPRS) will be performed at +45

At the end of the test testing session, the participant may receive a rescue dose of oral morphine (30 mg). If COWS scores remain >5 at the next measurement timepoint (+15 minutes) an additional 20 mg may be provided, at the discretion of a study physician. The testing session may also be terminated 20 minutes following naloxone administration (if withdrawal is too severe (COWS >20) and the rescue dose given at this time. A physician, nurse practitioner, or nurse will be notified once the COWS score goes above 9. The RA will notify the physician/nurse practitioner once the criterion for the morphine rescue has been met, who will then administer the rescue dose. If a morphine rescue is given, vital signs will continue to be monitored for the entire 4-hour period. If a participant receives a rescue dose during the testing session, the 1 pm morphine dose may be held at the discretion of the physician.

Suicidality and Pregnancy will be monitored weekly throughout the inpatient period using the CSSRS and a urine pregnancy test, respectively.

Discharge: On the day of discharge, All participants receive counseling on opioid overdose risk and prevention, and receive an overdose response kit that includes 2 doses of the overdose reversal agent naloxone. Prior to discharge, all participants (completers and dropouts) will receive education concerning the various pharmacological treatment options for opioid use disorder. We strongly encourage participants to consider buprenorphine, methadone, or naltrexone maintenance and explain the benefits of these treatments in our discharge procedure. Prior to discharge from the inpatient unit, subjects who express interest in treatment will be given the opportunity to receive sustained-release naltrexone or titration onto a modest dose of buprenorphine/naloxone (prior to leaving the unit), with referral to a local treatment provider. If they refuse both of these options, they will be given a supply of buprenorphine/naloxone for up to 7 days. Bup/naloxone may also be given if a participant needs a bridge between discharge and entering treatment.

Follow-up: Participants will be asked to return to the laboratory 1 month after study completion to assess general health and drug use. The follow-up visit may be conducted virtually.

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which include but are not limited to:

- Infection Control/PPE – Guidelines
- Research participants will only come on-site if absolutely necessary for study procedures.
- No volunteers/externs on-site during Stage 1.
- Clinical research teams will screen their participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
- COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

Dose Escalation Safety Pilot.
To help ensure the safety of the higher doses of vaped marijuana, the first three participants will receive V-MJ and naloxone in a dose-escalating order. The V-MJ 0 mg + naloxone 0 mg, and V-MJ 0 mg + naloxone 4 mg dose combinations will be inserted randomly in the sequence below.

- V-MJ 12.5 mg + 0 mg Naloxone,
- V-MJ 25 mg + 0 mg Naloxone,
- V-MJ 12.5 mg + 4 mg Naloxone,
- V-MJ 25 mg + 4 mg Naloxone.

A physician or nurse practitioner will provide close monitoring of each session from the adjacent observation room, or within the testing room itself. A summary of the findings from these first three participants will be reported to the IRB -on a case-by-case basis- before moving forward to the randomized dosing described above. Participants' plans to initiate treatment for opioid use disorder will also be included in our report to the IRB.

Suicide Risk Management Plan
The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to quantify the severity of suicidal ideation and behavior. The CSSR-S is only administered by study staff who have been trained in its administration. During screening and follow-up, the C-SSRS is used to assess for suicidal ideation. If there is expression or suspicion of suicidality outside of these two timepoints, the C-SSRS will first be administered, and action taken accordingly, as outlined below. If a participant endorses active suicidal ideation/behavior, staff will notify an Opioid Research Laboratory psychiatrist (Dr. Felipe Castillo) or clinical psychologist (Drs Rachel Luba or Suky Martinez), who will conduct a brief, standardized clinical interview that reviews the C-SSRS score and quantifies the specific suicidal plans and access to lethal means (e.g., firearms). If the Opioid Research Lab clinicians are unavailable, the RA is instructed to contact another Division clinician. The Substance Use Research Center maintains an "on-call" list of NYS licensed psychologists and psychiatrists who are "on duty" for the day to provide clinical coverage. This list is posted in the Opioid Lab research spaces, and available in our Lab's Google Drive.

For participants who are deemed at imminent risk of harm to self or others, the clinician will arrange a transfer to the closest Emergency Room (ER). The clinician will speak with the responsible ER physician to provide all relevant information and request follow-up on disposition. For participants with non-active suicidal ideation/behavior (i.e., not at imminent risk), the clinician will complete the Stanley-Brown Safety Plan [Stanley B, Brown GK. Safety Planning Intervention: A Brief Intervention to Mitigate Suicide Risk. Cognitive and Behavioral Practice. 2012;19(2):256-264].

In either above scenario, study staff will also inquire if the participant is currently receiving mental health treatment, and if so, she/he will attempt to contact the participant's mental health provider. If the participant is not currently receiving mental health care, they will be provided with referrals to a qualified mental health provider. Finally, the study staff and clinician will extensively document the safety steps that were taken, the referral process, and follow-up events, in the participant's chart.

When Opioid Lab clinicians are unavailable, clinical staff on 4-South will manage suicide risk and other clinical issues that may arise with study participants. However, 4-South staff are informed to notify an Opioid Lab clinician of any important clinical issues that arise with our participants. The inpatient unit is provided with a nights and weekends "on-call," which includes the cell phone number of the physician to be contacted in such situations.

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Do Not Administer Vaped Marijuana (T: -15 mins) if:

- Systolic BP<110 or > 150 mm Hg; Diastolic BP < 60 or>90 mm Hg, or Heart Rate< 60 or >110 BPM

Do Not Administer Naloxone (T: 0 Mins) if:

- Systolic BP<110 or > 150 mm Hg; Diastolic BP< 55 or >95 mm Hg, or Heart Rate< 60 or >110 BPM

Discontinue A Session if:

- Systolic BP<90 or > 180 mm Hg; Diastolic BP < 50 or >120 mm Hg, or Heart Rate < 50 or > (220-Subject's Age) x .85 BPM (Sustained for >10 minutes).
- BPRS score no greater than 31

In either of the above situations, vital signs will be monitored continuously until they return to pre-dose baseline, and the study physician or nurse practitioner will be notified for further management. If deemed necessary by medical staff, appropriate clinical management of abnormal vital signs will occur regardless of their severity or duration.

Criteria for Early Discontinuation from the Trial:

- If any of the readings above occur during the Safety session.
- If two Vaped Marijuana+ Naloxone testing sessions have to be discontinued based on the above criterion.

Discontinuation Criteria for Suicidality and Pregnancy

- If a participant self reports the development of suicidal ideation (with intent) throughout the inpatient phase, study procedures will be discontinued and appropriate treatment and follow-up care arranged prior to discharge.
- If a participant becomes pregnant during the inpatient period, study procedures will be discontinued and appropriate follow-up care arranged.

COVID-19
If a participant is admitted onto the inpatient unit and subsequently tests positive for COVID-19 or develop symptoms, they will discontinue study procedures and be discharged from the unit. The appropriate referral will be made (e.g. emergency department, home with outpatient follow-up via telemedicine) depending on the participants' clinical status.

Blood and other Biological Samples

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

Biological Sample	Volume
Blood Sample for comprehensive metabolic panel collected during screening.	24 ml
Urine samples for drug toxicology during each screening visit.	10-15 ml each
Expired air samples will also be taken at each screening visit to detect the presence of recent alcohol consumption.	N/A

Nasal swab will be collected to test for the presence of the COVID- N/A

19 virus or its antibodies.

Assessment Instruments

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

Screening Assessments **(**Staff Qualified to Administer or Review**)**:
● NIDA-Modified ASSIST: Adapted questionnaires designed to assist clinicians serving adult patients in screening for drug use (PhD).
● Addiction Severity Index (ASI; McLellan et al., 1992): A self-report structured instrument that evaluates the severity of functional impairment in various addiction-related areas (BA/BS).
● Drug Abuse Screening Test (DAST-10; Skinner, 1982). A 10-item, "yes" or "no" questionnaire was designed to assess the degree of problems related to drug use (BA/BS).
● Beck Depression Inventory (BDI-II; Beck et al., 1972). The BDIII is a 21-item self-report instrument that measures the severity of depression. Each item is rated on a 4-point scale ranging from 0 to 3 (PhD or MD reviews any scores above 30).
● Substance Use Inventory (i.e., Clinical Interview by PhD, Comer et al., 2008). This locally-developed questionnaire will be used to determine quantity (i.e., dollars spent per day) and frequency (i.e., days) of substance use including alcohol, amphetamines, cocaine, marijuana, opioids, phencyclidine and sedatives.
● Other screening assessments include medical history evaluation (RN or NP), physical examination (MD), ECG (MD), blood chemistry/hematology (MD), breathalyzer (BS/BA), urine pregnancy testing (BA/BS), and 11-panel urine drug toxicology (BA/BS).

Study Assessments:
● Modified Naloxone Challenge
● Systematic Assessment for Treatment Emergent Events (SAFTEE: Levine and Schooler, 1986). Adverse events (AEs) unrelated to withdrawal will be quantified using this scale.
● Pupil diameter will be measured as a proxy of μ- opioid receptor activation.
● Drug "Liking", and other subjective drug effects will be assessed using a Visual Analog Scale (VAS).
● Opioid Craving Questionnaire (adapted from Tiffany and Drobes, 1991; Tiffany et al., 1993).
●Subjective and Clinical Opiate Withdrawal Scales (Handelsman et al., 1987; Wesson and Ling, 2003). Withdrawal Scales (Handelsman et al., 1987; Wesson and Ling, 2003)
●Cognitive Tasks: Two cognitive tasks will be used: The Digit Symbol Substitution Task (DSST; McLeod et al., 1982) assesses psychomotor ability and the Divided Attention Task assesses attention (DAT; Miller, 1987).
●Brief Psychiatric Rating Scale (BPRS: Ventura et al., 1993) used to measure psychiatric symptoms such as anxiety, depression, and psychoses.
● Apple Watch or FitBit for Analysis of Sleep Quality and ECG throughout the testing session.

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
Marijuana
Manufacturer and other information
NIDA Drug Supply Program
Approval Status
IND is approved
IND#
156207
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Jones, Jermaine, PHD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment

For those participants requesting outpatient treatment, appropriate arrangements will be made, including placement in an outpatient treatment study at our Substance Treatment and Research Service (STARS), if they are eligible or Narcotics Anonymous. As part of research safety measures for discharge, we will bridge participants to treatment with buprenorphine/naloxone sublingual films for up to 2 weeks. If a participant decides to pursue treatment with buprenorphine/naloxone, s/he will come in every 3-5 days to pick up the films. A urine toxicology sample will be collected at this visit. If a participant does not want medication assisted treatment for opioid dependence, we will provide them with 3-4 buprenorphine 8mg/naloxone 2mg sublingual films for harm reduction purposes. Induction onto Vivitrol treatment will also be available to all participants prior to discharge. Induction onto Vivitrol will entail an individually tailored in-patient detoxification from opioids prior to Vivitrol.

Maximum duration of delay to standard care or treatment of known efficacy

4-**6** Weeks
Treatment to be provided at the end of the study
This is not a treatment study. However, counseling about different treatment options and referrals for treatment are available to participants at any time before, during, or after their participation in this study. Participants will also be informed that they do not have to participate in this study in order to get a referral to help stop taking drugs. Furthermore, our lab is an official New York State Dept. of Health naloxone training and distribution site, therefore, they will receive overdose education and naloxone without engaging in any study procedures. Prior to discharge, participants will receive counseling about the different treatment options for opioid use disorder (Vivitrol, buprenorphine, methadone, behavioral therapy, etc.). Additionally, our standard discharge procedure includes education about the risks of opioid overdose, how to identify opioid overdose, and how to use a naloxone kit provided to them as certified
opioid overdose responders.

For those participants requesting outpatient treatment, appropriate arrangements will be made, including placement in an outpatient treatment study at our Substance Treatment and Research Service (STARS), if they are eligible or Narcotics Anonymous. As part of research safety measures for discharge, we will bridge participants to treatment with buprenorphine/naloxone sublingual films for up to 2 weeks. If a participant decides to pursue treatment with buprenorphine/naloxone, s/he will come in every 3-5 days to pick up the films. A urine toxicology sample will be collected at this visit. If a participant does not want medication-assisted treatment for opioid dependence, we will provide them with 3-4 buprenorphine 8mg/naloxone 2mg sublingual films for harm reduction purposes. Induction onto Vivitrol treatment will also be available to all participants prior to discharge. Induction onto Vivitrol will entail an individually tailored in-patient detoxification from opioids prior to Vivitrol.

Clinical Treatment Alternatives

Clinical treatment alternatives
This is not a treatment study. Treatments for OUD include medications (naltrexone, buprenorphine, or methadone) and/or psychotherapy. Participants will be informed about these various treatment option at several points during the screening process and throughout the study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
1) Naloxone Challenge Testing Paradigm: For this study it is important that we assess physical opioid dependence during screening. The naloxone challenge will also be an important testing procedure throughout the study enrollment period. The naloxone challenge is a slightly modified version of the Wang Test [Wang et al., (1974) Rating the presence and severity of opiate dependence. Clinical Pharmacology and Therapeutics 16(4), 653-658.] This test will be performed under the supervision of a research nurse and will take approximately 50 minutes to complete. A dose of naloxone will be administered and signs and symptoms associated with opioid withdrawal (“gooseflesh,” “vomiting,” “tremor,” “uncontrollable

yawning," etc.) will be scored every 10 minutes. During the procedure, we will measure blood pressure, heart rate, and blood oxygen saturation using an automated blood pressure machine and pulse oximeter both immediately before and up to 30 min after the naloxone dose. If significant withdrawal is noted, the effects of naloxone will then be alleviated by the administration of morphine (up to 50 mg p.o.). For a recent publication, we reviewed the most recent naloxone challenges completed (N=29) by the Opioid Laboratory (Jones et al., 2020), all of which were completed without unanticipated AEs/SAEs.

To the investigator's knowledge, this will be the first clinical laboratory investigation that will co-administer naloxone and marijuana to an opioid-dependent population. Therefore, there may be novel, unanticipated adverse effects.

2) Marijuana Administration: Smoking is the principal route of cannabis use, providing a rapid and efficient method of drug delivery from the lungs to the brain. Generally, smoked THC is well tolerated even at doses similar to the proposed doses of vaped marijuana in the current study. Huestis et al. (1992) examined the disposition of THC after smoking a single cigarette (multiple inhalations) containing 1.75% THC (ca. 16 mg) or 3.55% THC (ca. 34 mg) with few AEs and no SAEs.

In studies of vaped marijuana in normal healthy volunteers, modest impairment of cognitive functioning and psychomotor agitation (e.g., significantly decreased task performance) were the most common adverse events. Increases in HR and decreases in Systolic BP have also been reported, however, these changes were not clinically significant (Farokhnia et al., 2020, Spindle et al., 2018).

Spindle et al., (2018) conducted a controlled examination of the effects of vaporized and smoked cannabis in "infrequent" cannabis users (N=17). For vaporized conditions, mean peak plasma concentrations for THC were 7.5 ng/mL at the 10-mg dose and 14.4 ng/mL at the 25-mg dose. For smoked cannabis conditions, mean peak THC concentrations were 3.8 ng/mL at the 10-mg dose and 10.2 ng/mL at the 25-mg dose. Among these normal health volunteers, modest impairment of cognitive functioning and psychomotor agitation (e.g., significantly decreased task performance) were the most common adverse events. Two participants vomited (1 after 25-mg THC vaporized inhalation, and 1 after 25-mg THC smoked inhalation) and another experienced hallucination after inhaling 25 mg of vaporized cannabis.

Concerning physiological measures, significant increases were seen in HR at the 25 mg smoked dose (mean 19.1 beats/ min) and both doses of vaporized cannabis (10mg, 23.3 beats/min, and 25mg beats/min). Systolic BP decreased after the 10 mg smoked cannabis dose (mean −10.1 [23.9] mmHg vs placebo) but did not differ across vaporized doses (mean: 10mg, −7.7; 25mg, −6.1 mmHg). Though statistically significant, these values did not meet AE/SAE criteria and no participants were prematurely terminated due to their physiological response to smoked or vaporized cannabis. See also Farokhnia and Colleagues (2020) who examined smoked, and vaporized cannabis [6.9% THC (~50.6 mg)] among occasional (45%) and frequent (55%) with few AEs and no SAEs.

Finally, a clinical trial from Australia (Arkell et al., 2019) utilized the Mighty Medic device to vape 125 mg THC (11%) in a sample of healthy volunteers. Same percentage as the current trial, and a lower dose. AEs were minimal (increased self-reports of being "Sedated" and "Anxious").

Adverse effects such as dysphoria, delirium, anxiety, and psychosis have been observed following the administration of high doses of THC and with the use of higher potency/concentrated marijuana products (Ashton 2001; Barkus 2016; Devin et al., 1987; Grotenhermen, 2003).

There are many unknowns about vaping, including what chemicals make up the vapor and how they affect health over the long term. The Centers for Disease Control and Prevention (CDC) has noted an outbreak of lung injuries and deaths associated with vaping among people who use e-cigarettes, and THC vaping devices. These cases appear to predominantly affect people who modify their vaping devices or use black market modified e-liquids. Finally, there is a small risk of electric shock or being burned while using the Mighty Medic Device. Co-Investigators Haney and Arout have administered the higher dose of marijuana (25 mg), using the MIGHTY vaporizer, to approximately 16 participants to date. They report no unanticipated AEs or SAEs.

In summary, the investigators feel that there is sufficient data on the safety and tolerability of rapid-delivery THC inhalation routes (e.g., smoked and vaporized) to justify the current design and eligibility criteria.

3) Increased Sensitivity to Opioids and Discharge: Opioid-dependent participants may be less tolerant to the effects of opioids at discharge. Participants will be told that this increased sensitivity to opiates could result in overdose and death and that extreme caution must be exercised after they leave the hospital if they choose to use any opioid again.

4) Morphine Stabilization: It is possible that during the initial morphine maintenance stabilization phase, some participants may experience mild opioid withdrawal. These symptoms include nausea, vomiting, teary eyes, runny nose, loose stool, stomach cramps, shakiness, anxiety/irritability, increased heart rate, sweating/chills, restlessness, and body aces/discomfort.

The most serious side effects of morphine administration include: respiratory depression or death. More common side effects may include allergic reaction and respiratory depression. The most frequently reported adverse experiences associated with opioid administration are: nausea, vomiting, headache, dry mouth, itchiness, drowsiness, sweating, dizziness, stimulation, sleepiness, lightheadedness, restlessness, a feeling of well-being, talkativeness, difficulty urinating and constipation.

5) COVID-19 Related Risks: Most participants will need to take public transportation to arrive at NYSPI. This will carry with it the risk of exposure to COVID-19. Exposure risk while participants are at NYSPI for screening will be minimal given the procedures the institute has in place (e.g., masks inside at all times for participants and staff, staff symptom attestation, social distancing, etc.,). In-person interaction with study staff has also been minimized through the use of virtual screening procedures when possible. The risk of COVID-19 exposure while on 5-South should be minimal as COVID-19 testing prior to admission is being implemented for both research participants and patients. We will do everything that we can, in line with NYSPI policy, to minimize risk to research participants and staff posed by COVID-19.

6) Confidentiality: Another risk to this study involves the confidentiality of private and personal information.

7) Pregnancy: Female participants must not be pregnant to be included in the study.

8) Blood Drawing. During blood drawing, there is a risk of slight discomfort and/or bruising at the site where the needle is inserted. Approximately 216 ml will be taken during the study (24 ml screening +192 ml inpatient)= (14.6 tablespoons or one cup). When someone donates blood, two cups (32 tablespoons) are taken on one occasion.

9) Nasal Swab: To test for COVID-19 a 6-inch cotton swab will be placed up both sides of the nose; participants may find this uncomfortable.

10) Inpatient Facility: The risks involved in exposure to the inpatient unit and laboratory are minimal, but participants may become bored or restless.

11) Psychological distress: The structured interviews, and questionnaires should add no physical risk. However, because many of the interviews and assessments are time-consuming to complete and involve topics of a sensitive nature, some people have found them to be physically or emotionally tiring.

Describe procedures for minimizing risks
1 & 2) Naloxone Challenge Testing Session + Marijuana Administration: During these testing sessions, vital signs (heart rate, blood pressure, and arterial oxygen saturation) will be monitored. Before drug administration, all vitals must be within normal ranges for drug administration to occur. Testing sessions will be continuously monitored by a research assistant and nurse, with a physician observing for the first 2 hours after experimental drug administration, and on-call throughout the entire testing session. Resuscitation equipment and supplemental oxygen are available in the testing area, for emergency purposes.

The specific risks that may be associated with vaporized marijuana will be mitigated using the procedures below:

- The time that each participant will spend vaping is less than 10-12 minutes (per testing session). Thus, each participant will only have minimal exposure to the aerosolized drug product.
- All participants will be trained in the proper use of the vaporizer, prior to testing.
- Participants will be excluded from the trial if they suffering from respiratory tract or lung disease.
- Participants will be closely monitored for symptoms of respiratory irritation (e.g., cough, shortness of breath, chest pain) during or after the usage.

Our careful participant selection and selection of doses should preclude the occurrence of SAEs Drs. Manubay, Mogali, or Castillo will screen all potential volunteers to ensure they meet medical inclusion/exclusion criteria. Other physician coverage is available as a backup, and the Attending Psychiatry service will cover daily rounds on the NYSPI inpatient unit where these volunteers will reside. Nurses will provide 24-hour/7-day supervision.

3) Increased Sensitivity to Opioids and Discharge: Upon discharge, all participants (completers and non-completers) receive education on opioid overdose risk and prevention, including a New York State Department of Health Overdose Response Kit that includes 2 doses of naloxone. As this study would enroll only participants not seeking treatment for their opioid use (because an opioid is administered as a part of the study), most will return to illicit opioid use upon discharge. All participants are given a strong warning about the growing prevalence of fentanyl adulteration within the illicit drug market. We strongly encourage participants to consider buprenorphine, methadone or naltrexone maintenance and explain the benefits of these treatments in our discharge procedure. Those who are interested in treatment for their drug use at the end of the study can meet with the NYSPI Social Work department to find a treatment provider. For those who are interested, induction on buprenorphine or naltrexone will be made available to them before leaving the inpatient unit. All participants will return to NYSPI at 1-month post-discharge for a safety follow-up visit. Analysis of our participants following discharge has been conducted across a number of our previous studies (Roux et al., 2012). We have found the discharge procedures mentioned above to be effective at negating the risk of overdose, encouraging participants to engage in treatment, and lowering overall illicit opioid use.

4) Morphine Stabilization: To assist with stabilization, oral morphine dosing (30 mg, four times/day) may be extended for up to 3 days for those participants who require additional stabilization. Participants who are not able to achieve stabilization during this time and experience discomfort/withdrawal will be discharged from the protocol. Participants will also have access to commonly used medications for opioid withdrawal, throughout the stabilization period.

The study will only enroll participants whose street opioid use exceeds that of the morphine maintenance dose. The dose of morphine was selected with care to preclude those that produce clinically relevant respiratory depression and has been administered in prior studies without serious adverse events (Jones et al., 2012).

5) COVID-19 Related Risks: NYSPI is committed to minimizing risk to research participants and staff posed by coronavirus 2019 (COVID-19). Participants will be notified of the risk of COVID-19 exposure traveling to and from NYSPI and while at NYSPI. We will encourage participants to exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds. NYSPI is taking the following steps to minimize
the risk of COVID-19 to our patients and staff:

- All research at NYSPI has been modified to reduce in-person visits and procedures.
- We are monitoring research participants and staff for signs and symptoms of COVID-19.
- We are taking extra precautions at NYSPI to reduce the risk of COVID-19 infection, including but not limited to physical distancing, the requirement of face-covering for all study participants, and appropriate PPE for all staff.
- We have increased our routine cleaning and disinfection procedures.

6) Confidentiality: We will do everything we can to keep others from learning about subjects' participation in the research. Concerning virtual study procedures, to ensure confidentiality, only HIPAA-compliant videoconferencing and web-based platforms (when needed) will be

used (e.g, WebEx, Facetime). Electronic Data Capture systems will be encrypted. Any electronic communications sent to participants will be encrypted.

7) Pregnancy: Urine pregnancy tests will be performed at each screening visit and a serum pregnancy test upon the day of admission. For women of childbearing potential, a nurse evaluates the participants' methods of birth control and evaluates their willingness to, and reliability to practice effective birth control.

8/9 Blood Drawing and Nasal Swab: To minimize risks only a nurse or trained phlebotomist will perform these procedures.

10) Inpatient Facilities: The inpatient unit has procedures in place to minimize boredom on the unit. The study staff will also participants will be provided with access to tablets that contain various forms of entertainment (e.g movies, games).

11) Psychological distress: Patients are informed prior to study entry that they can refuse to answer any questions and that they can request to stop at any time. If a participant becomes agitated during any of the interviews or assessments, he or she will be provided with therapeutic assistance.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
All volunteer PHI is confidential and will be protected according to the guidelines established by HIPAA. This allows the investigators on this project to use or share health information with the U.S. Department of Health and Human Services representatives, the NYSPI IRB, the NY Office of Research Integrity, the FDA, other research collaborators, or when required by law.

Each subject will be assigned a unique identifying number to minimize the use of PHI. Data containing volunteer names are kept separately from coded data so that the two cannot be joined. All written documents, including PHI, will be stored in locked cabinets at the NYSPI. Key access will be limited to immediate laboratory personnel. Electronic information will reside on a stand-alone, password-protected computer. Electronic transmission via e-mail or fax with volunteer PHI will have a statement of confidentiality and will be encrypted. Any information or materials emailed to participants will be encrypted. Only HIPAA-compliant videoconferencing platforms will be used (e.g. CUIMC Zoom accounts). Only secure, encrypted, HIPAA-compliant electronic databases will be used (e.g., CUIMC Qualtrics accounts).

Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
This study was not designed to benefit participants directly. However, we have shown that drug use significantly declines after participation in our inpatient laboratory studies: specifically, 58% of participants reported a nearly 50% decrease in use from pre-admission levels (Roux et al., 2012).

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 are compensated (in Cash) for each visit of the screening process ($25-50/visit, depending on its duration) for approximately 3 visits plus $50 for the follow-up visit. If a participant is disqualified prior to their in-person screening, their compensation may be sent to them in the form of an Amazon gift card or will be wired to them.

Participants will be paid $25/day with a $50/day bonus for completion of the study. Use of a per diem bonus is necessary to keep participants from leaving the study during the last several days when the money remaining to be earned would otherwise be proportionally small.

Payments will be separated into several installments ($600 per week) at the end of the study in order to prevent large one-time payments. To minimize the number of visits to NYSPI to receive their study compensation, participants may request wire delivery of their $600 payments using a secure service like Western Union.

Total payments for study completers will be approximately $1,200-**1,700**.

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