NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

December 23, 2019

TO: Dr. Sandra D. Comer

FROM: Dr. Edward Nunes, Co-Chair, IRB
Dr. Agnes Whitaker, Co-Chair, IRB

SUBJECT: **APPROVAL NOTICE: CONTINUATION**
Expedited per 45CFR46.110(b)(1)(f)(8)(c)

Your protocol # **7547** entitled **DOXAZOSIN: EVALUATION OF ITS ABILITY TO ALTER THE ABUSE LIABILITY OF OXYCODONE IN HUMANS** (version date 12-23-19) and Consent Forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **January 8, 2020** to **January 7, 2021.**

Consent requirements:

X Not applicable: (RECRUITMENT COMPLETED. DATA BEING ANALYZED)

☐ 45CFR46.117 (c)(2) waiver of documentation of consent for the telephone interview.

☐ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special:

√ **Only copies of consent documents that are currently approved and stamped by the IRB may be used to obtain consent for participation in this study.**

√ **A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.**

√ **Changes to this research may be not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.**

√ **All serious and/or unanticipated problems involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.**

CC: RFMH Business Office (U54DA037842; PI: Levin)

EN/AW/Scr

Signed copy on file at IRB

Protocol Title:
Doxazosin: Evaluation of Its Ability to Alter the Abuse Liability of Oxycodone in Humans

Version Date:
12/23/2019

Protocol Number:
7547

Clinic:
Opioid Research Laboratory

First Approval:
01/11/2018

Expiration Date:
01/07/2021

Contact Principal Investigator:
Sandra Comer, PHD
Email: sdc10@cumc.columbia.edu
Telephone: 646-774-6146

Co-Investigator(s):
Jeanne Manubay, MD
Jermaine Jones, PHD
Shanthi Mogali, 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 submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Division on Substance Use Disorders
Within the division/department, what Center or group are you affiliated with, if any?
Opioid 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.
Tanya Ramey, MD - Scientific Project Officer, NIDA

Application for Continuation of Research

Status

Current Status of Study:
Study only involves secondary data analysis or chart record review of data.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Funding for this study has ended, and we have thus ended enrollment and the running of participants. We are filing for a continuation of the study in order to review participant records and assess and report the causes behind the rate of participant discontinuation.

Funding

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

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
No
Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
12/15/2020

Approved Sample and Progress

Approved sample size
27
Total number of subjects studied since first approval
13
Have there been any significant deviations from the anticipated study completion estimates?
Yes
Describe actions taken or planned to address these problems.
A higher than anticipated dropout rate occurred because participants did not meet our blood pressure criteria for continuation in the trial. We made minor modifications to our blood pressure criteria but funding for this grant ended so we are no longer enrolling participants into this study.
Comments / additional information

Procedures

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

✓ Medication Trial
✓ Administration of Substance of Abuse
✓ Off-label Use of Drug or Device

Population

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

✓ Adults
✓ Adults over 50
✓ Substance Users

Research Support/Funding

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

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?

No
Who is the PI of the grant/contract?
Levin, Frances, MD
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
Shared Pharmacotherapeutic Strategies for Cannabinoid and Opioid Use Disorders
Grant Number
U54DA037842
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

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
Healthy, adult men and women, aged 21 to 59 years, who abuse opioids and are physically dependent on them will be recruited to participate in a study to examine the ability of doxazosin, an epinephrine receptor blocker, to alter the abuse potential of oxycodone. After participants complete the screening process, they will be scheduled for inpatient admission onto our clinical inpatient where they will reside during the 8-week study (Table 1). During Weeks 1-2, participants will be transitioned from their normal opioid use regime onto oral morphine until withdrawal dissipates. At this time participants will also be stabilized on the first dose of doxazosin (0 or 16 mg/day; active doxazosin will be started at 4 mg and increased by 4 mg every 3 days). During Weeks 3-4, either active or placebo oxycodone will be available (in random order). Monday-Friday

each these drugs will be tested using our sample and choice drug vs money ($20) self-administration procedure. On Friday, participants will also complete a cue exposure session during which they will be presented drug cues to determine whether the study medication affects how participants react to them. To summarize, Weeks 1-2 and 5-6 will be stabilization weeks (0 or 16 mg doses of doxazosin administered in random order) and Weeks 3-4 and 7-8 will be test weeks under each of the doxazosin maintenance doses. At the conclusion of the study, participants will be given an exit interview, warnings about re-initiation of opioid use, and couseling about the different treatment options for Opioid Use Disorder. Within 1 week after discharge, we will assess adverse events using the a number of clinical assessments. Participants also will return weekly for their study payments for several weeks after study completion. At each of these weekly visits, we will assess participants' interest in treatment and drug use patterns.

Background, Significance and Rationale

Background, Significance and Rationale

In addition to modulating opioid withdrawal effects, research suggests that noradrenergic circuits may be involved in opioid reinforcement (Ventura et al., 2005). Doxazosin, an α1-adrenergic receptor antagonist, is a safe, FDA-approved medication currently used to treat hypertension. Few studies have examined the effects of doxazosin in preclinical behavioral models, but numerous studies have evaluated the effects of prazosin, another α1-adrenergic receptor antagonist, on opioid-mediated responses. In preclinical models, prazosin reduced the acquisition and expression of morphine-induced conditioned place preference (Sahraei et al., 2004; Zarrindast et al., 2002) and heroin self-administration (Greenwell et al., 2009). It also blocked morphine-induced dopamine release in the ventral striatum (Auclair et al., 2004), suppressed the development of tolerance to morphine (Kihara and Kaneto, 1986), and prevented naloxone-induced weight loss in morphine-dependent rats (Ozdogan et al., 2003). Prazosin did not share discriminative stimulus effects with morphine, and it did not alter morphine's discriminative stimulus effects (Hughes et al., 1996). It had no analgesic effects of its own in rodents and either had no effect on (Kihara and Kaneto, 1986) or potentiated morphine-induced analgesia (Ozdogan et al., 2003). In addition to its effects on opioid self-administration, prazosin also reduced self-administration of cocaine (Wee et al., 2008), nicotine (Forget et al., 2010), and alcohol (Froehlich et al., 2013a; Rasmussen et al., 2009; Verplaetse et al., 2012; Walker et al., 2008). And a low dose of prazosin given in combination with a low dose of naltrexone reduced alcohol drinking in rats at doses that were ineffective when given alone (Froehlich et al., 2013b). In humans, prazosin reduced alcohol craving, anxiety, and negative emotion following stress exposure (Fox et al., 2012), and in a small (N=17 men), randomized, placebo-controlled treatment trial, prazosin reduced the number of drinking days per week, and number of drinks per week during the last 3 weeks of the study relative to placebo (Simpson et al., 2009). Like prazosin, doxazosin produced dose-related decreases in self-administration of alcohol in rats (O'Neil et al., 2013). And when doxazosin was given in combination with the β receptor antagonist propranolol, it reduced cue-induced reinstatement of responding for cocaine (Smith and Aston-Jones, 2011). In cocaine-dependent
humans, doxazosin decreased cocaine-induced ratings of liking and desire to use cocaine (Newton et al., 2012) and improved treatment outcomes in a placebo-controlled trial for cocaine

dependence (Shorter et al., 2013). To date, no clinical studies have examined the effects of either prazosin or doxazosin on opioid self-administration or withdrawal. Although substantially more research has been conducted with prazosin, we decided to evaluate doxazosin instead because while both medications produce a similar side-effects profile (Torvik and Madsbu, 1987), doxazosin has a longer half-life and thus can be given once daily rather than 2-3 times each day, which may increase adherence in clinical outpatient settings.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

- Specific Aim 1: Assess the ability of doxazosin to alter oxycodone self-administration behavior (measured by average progressive-ratio breakpoint values) and positive subjective responses (measured by visual analog scales).

- Hypothesis 1: Doxazosin will be superior to placebo in reducing oxycodone's reinforcing and positive subjective effects.

- Specific Aim 2: Assess the ability of doxazosin to affect opioid craving (measured by ratings of "I Want Heroin") and physiological response (galvanic skin response, skin temperature, and heart rate) to drug cues.

- Hypothesis 2: Doxazosin will be superior to placebo in reducing drug craving, as well as physiological and subjective reactivity to drug cues.

- Exploratory Aim: Assess the ability of doxazosin to alter withdrawal symptoms, as measured by the SOWS, that may occur during Weeks 3, 4, 7, and 8.

Description of Subject Population

Sample #1

Specify subject population
Non-treatment-seeking participants with moderate-severe opioid use disorder
Number of completers required to accomplish study aims
27
Projected number of subjects who will be enrolled to obtain required number of completers
56
Age range of subject population

21-59

Gender, Racial and Ethnic Breakdown
The proposed study seeks to include women and minorities; the study does not exclude any potential participants on the basis of race or gender. Both males and females will be recruited. Based on previous studies, it is estimated that the sample will be 70% male, 50% Caucasian, 25% Black or African-American, 20-25% Hispanic or Latino, 0-5% Asian and Pacific Islander and less than 1% Native American. All efforts will be made to ensure that representation of women and ethnic minorities are in proportion to the population of the city of New York.
Description of subject population
Participants meeting DSM-5 criteria for moderate-severe OUD and physical dependence on opioids will be enrolled.

Recruitment Procedures

Describe settings where recruitment will occur
All in-person screening and assessments (drug interview, psychiatric evaluation, 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?
Initial telephone interviews will be carried out by research assistants and nurses; 2) drug interview and general assessment related to study issues will be conducted by a psychologist;
3) Psychiatric Examinations will be performed by a psychiatrist or psychiatric nurse practitioner, clinical psychologist. 4) SCIDs will be performed by a nurse or psychologist. Telephone screens will be recorded either electronically or on paper forms.
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, as well as electronic media (e.g., Facebook, Google, StudyKik, and websites that drug users frequent such as Bluelight and Erowid). The study will also be advertising and publicized on the New Jersey Transit Bus stops. The study will be advertising on the New York MTA Subway Train system. We will also be advertising in the New Jersey Journal's online platform. The study will be using RecruitMe as a platform for recruitment.
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
NCT03415581

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes

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

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Participants with OUD
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criterion	**Method of Ascertainment**
1. 21-59 years of age	Self-reported age and/or verification with legal identification
2. Diagnostic criteria for Opioid Use Disorder moderate-severe (304.00) as per DSM-V	Clinical interviews (telephone, psychologist, nurse, physician), naloxone challenge test/visual evidence of opioid withdrawal
3. No current or past diagnosis of schizophrenia, schizoaffective disorder, or other psychotic disorder; bipolar I or bipolar II disorder, other major mood, psychotic, or anxiety disorder that might interfere with the study	Clinical interview with physician or nurse
4. Physically healthy	Clinical interview with physician, laboratory tests (urinalysis, blood chemistry, 12-lead ECG), physical examination, self-reported medical history
5. Able to perform study procedures	Practice session or Clinical Judgement (Psychologist or Physician)
6. Normal body weight	Body mass index < 30
7. Current or history of intranasal opioid use	Clinical interviews (telephone, psychologist, physician, or Psychiatric NP)
8. Current intranasal or intravenous use of opioids in amounts and/or	Clinical interviews (telephone, psychologist, Psychiatric NP, or

frequencies that meet or exceed those used in the proposed study (e.g., 3-4 tablets of a prescription opioid medication per day or 1-2 bags of heroin per day)	physician)
9. If female and using oral contraceptives, must use alternative forms of contraception as well (e.g. condoms in combination with spermicide)	Clinical interview (psychologist, nurse, physician), physical examination
10. Has not participated in another opioid laboratory study within the past 3 months	Clinical interview (psychologist, physician,or Psychiatric NP), review of laboratory records

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

Exclusion Criterion	**Method of Ascertainment**
1. Meeting DSM-V criteria for substance use disorder (moderate-severe) on drugs other than opioids, nicotine or caffeine (must be less than 500 mg caffeine daily)	Clinical interview with physician or Psychiatric NP, urine screen, observation
2. Participants requesting treatment	Self-report during interview
3. Treatment with any investigational drug during the last 30 days	Self-report during interview
4. Participants on parole or probation	Self-report during interview, criminal background check upon admission.
5. Currently pregnant or trying to conceive, or currently lactating	Blood pregnancy testing at screening, on admission and (beta-hCG), and self-report during interview and study visits
6. Current or recent history of significant violent or suicidal behavior and/or suicidal/homicidal risk	Clinical interview with a psychiatrist or Psychiatric NP, & C-SSRS, MINI, and Beck Depression Inventory
7. Cannot read or understand the self-report assessment forms unaided, or cannot comply with the requirements of the study	Clinical interview (psychologist, physician, or Psychiatric NP), or practice session

8. Elevated liver function tests (i.e., AST and ALT ≥ 3 times the upper limit of normal (ULN); bilirubin ≥ 2x ULN; hepatitis B or chronic hepatitis C)	Laboratory tests
9. Physical disorders that might make participation hazardous such as AIDS, cancer, baseline hypotension, orthostatic hypotension or syncope, hypertension (blood pressure > 140/90), uncontrolled diabetes, pulmonary hypertension or heart disease (please note that participants will be asked about previous visits to a cardiologist, chest pain, or strong palpitations; if these exist, they will be referred to a cardiologist and excluded unless cleared for participation by a cardiologist)	Clinical interview (psychologist, physician,or Psychiatric NP) physical examination, 12-lead ECG
10. Current major Axis I psychopathology other than opioid use disorder (e.g., mood disorder with functional impairment or suicide risk, schizophrenia), that might interfere with ability to participate in the study	Clinical interviews (psychologist, physician,or Psychiatric NP)
11. Sensitivity, allergy, or contraindication to opioids, doxazosin, adrenergic antagonists or agonists, or similar compounds	Clinical interview (psychologist, physician,or Psychiatric NP)
12. Planning to conceive within 6 months of study participation	Clinical interviews (psychologist, physician,or Psychiatric NP)
13. The use of prescription or over-the- counter medication that can affect CYP3A4 activity, 7 days prior to the anticipated study start date; or the use of phosphodiesterase inhibitors and MAOIs 14 days prior to the study.	Medical History, Clinical Interview (psychologist, physician,or Psychiatric NP)

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
Upon the participant's first visit to NYSPI, the general study procedures are described by a research assistant. If the participant is still interesting in screening for the study, (s)he is given a screening consent for to review. After giving the participant time to review the screening consent form, (s)he meets with a research nurse, psychologist or physician to sign the screening consent for to initiate screening procedures detailed in the document.
Describe Study Consent Procedures

A physician or psychiatric NP conducts the physical and psychiatric examinations, reviews the inclusion/exclusion criteria, and obtains consent to study participation. As a result of our ongoing consent procedures throughout screening with various personnel, the date that the participant signs the study consent form sometimes will differ from the date that the physician or psychiatric NP signs the study consent form.

Blevins, Derek MD
Brezing, Christina, MD
Comer, Sandra, PhD
Jones, Jermaine, PhD
Kidd, Jeremy MD
Manubay, Jeanne, MD
Mogali, Shanthi, MD
Murray, Janet RN
Shulman, Matisyahu, MD
Tindall, Claudia NP
Wai, Jonathan MD
Williams, Arthur MD
Woolfolk, Vincent MA
Suky Martinez MA
Muhammad Iqbal MD

Ben Srivastava MD
Ida Holt RN

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

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
As per 45CRF46.116(d) of the Code of Federal Regulations, we are requesting a waiver of consent for our telephone screen.
Explain why your research can not be practicably carried out without the waiver or alteration
Participants first respond to study advertisements via telephone.
Describe whether and how subjects will be provided with additional pertinent information after participation
If participants meet the initial inclusion/exclusion criteria based on the telephone interview, they will be invited to the laboratory for in-person screening visits where the study procedures will be explained again in detail by multiple staff members.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Blevins, Derek
Brezing, Christina, MD
Evans, Suzette, PHD
holt, ida
Iqbal, Muhammad
Jones, Jermaine, PHD
Kidd, Jeremy
Levin, Frances, MD
Manubay, Jeanne, MD
Mogali, Shanthi, MD
MURRAY, JANET
Shulman, Matisyahu, MD
Srivastava, A Benjamin
Tindall, Claudia
Wai, Jonathan, MD
Williams, Arthur
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Healthy, adult men and women, aged 21 to 59 years, who abuse opioids and are physically dependent on them will be recruited to participate in a study to examine the ability of doxazosin, an alpha-1 adrenergic receptor antagonist, to alter the abuse liability of oxycodone. After participants complete the screening process, they will be scheduled for admission onto the General Clinical Research Unit on 5-South where they will reside during an 8-week study (Table 1).

During Weeks 1-2, participants will be stabilized on morphine and the first dose of doxazosin (0 or up to 16 mg/day; active doxazosin will be started at 4 mg and increased by 4 mg every 3 days if tolerated based on blood pressure assessments up to a maximum dose of 16 mg/day; dosing will occur at 8pm each evening). Doxazosin maintenance may be delayed until after morphine stabilization based on the judgement of the medical director. During the stabilization periods, participants will be treated for emergent withdrawal symptoms with supplemental medications (e.g., clonazepam, compazine, ketorolac tromethamine, ondansetron, ibuprofen or acetaminophen, trazodone, and/or zolpidem) until withdrawal symptoms have dissipated, based on physician or Nurse Practitioner judgment and using SOWS scores as a guide. Because numerous participants in previous studies have reported insomnia during similar procedures, oral doses of trazodone or zolpidem will be available on request at bedtime throughout the proposed study to alleviate the insomnia that may occur. We will offer a standing dose of trazodone only (100 mg), and a prn dose of 5 mg Ambien if participants continue to have problems with insomnia. If a participant has a history of non-response to trazodone, he or she will be offered 10 mg Ambien each night at bedtime. When withdrawal symptoms have dissipated, based on self-report and observer ratings, supplemental medications, with the exception of trazodone or zolpidem, will no longer be available and experimental sessions will begin. If participants are still experiencing side effects from doxazosin, additional days may be required to achieve stability; a previous study demonstrated that participants can become stable, with few adverse effects, after 2 weeks (Rodgman et al., 2016). Colace will be given to all participants as a standing order, in order to treat constipation, which is a common side effect of opioid administration. Liver function tests will be performed upon admission, every other week throughout the study, and at 1-week follow-up. Because of the effects of opoid withdrawal on orthostatic hypotension, daily orthostatic assessments will not begin until after morphine stabilization.

During Weeks 3-4, either active or placebo oxycodone will be available (order of testing active or placebo oxycodone will be randomized). During active oxycodone weeks, participants will receive $20 and a sample dose of intransasal (IN) oxycodone (0, 12.5, 25, 50, or 100 mg/70kg) during morning sessions on Monday-Friday (Table 2). The sampled dose/$ will be available during afternoon choice sessions using a modified progressive ratio self-administration procedure. During placebo oxycodone weeks, participants will receive $20 and a sample dose of placebo oxycodone (0 mg/70kg) during morning sessions on Monday-Thursday followed by afternoon choice sessions. On Friday, participants will receive $20 and 25 mg IN oxycodone during a sample session (the oxycodone dose on Fri morning will always be active). When self-administering

oxycodone, participants will be instructed to insufflate the entire dose through one or both nostrils within 5-10 seconds. Following the sample session on Fri, participants will complete a cue exposure session during which they will be presented with neutral cues followed by drug cues. This procedure will allow the investigators to determine whether the study medication affects reactivity to drug-related cues after a period of no oxycodone availability. After the cue exposure session on Fri, participants will be given the opportunity to self-administer oxycodone and/or money.

To summarize, Weeks 1-2 and 5-6 will be stabilization weeks (0 or up to 16 mg doxazosin administered in random order) and Weeks 3-4 and 7-8 will be test weeks under each of the doxazosin maintenance doses. At the conclusion of the study, participants will be given an exit interview during which the study will be described. Those who are interested in treatment for their drug use at the end of the study will be offered referrals to studies at our Substance Treatment and Research Service or other treatment providers. Participants will return weekly for their study payments for several weeks after study completion. At each of these weekly visits, we will assess participants' interest in treatment and drug use patterns (via self-report and urine drug toxicology). Within 1 week after discharge, we will assess adverse events, pregnancy (using a urine pregnancy test), general health (complete blood count, blood chemistry, urinalysis, blood pressure, heart rate, body weight, EKG), and suicide (Columbia Suicide Severity Rating Scale).

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Participants will be withdrawn from the study if they 1) do not comply with unit policies or study procedures, 2) are deemed medically at risk for further study participation, or 3) express a strong desire to receive treatment for their drug use. All participants who are withdrawn from the study will be offered referrals to treatment facilities and our Substance Treatment and Research Service. Those participants who are discontinued from study participation because of sensitivity to the respiratory effects of the opioids administered during the study will receive a special de-briefing by the study physician or Psychiatric NP prior to discharge. Specifically, participants will be warned of the risks, namely overdose and death, associated with continued opioid use.

Potential Cases of Drug-Induced Liver Injury
Liver function tests will be performed upon admission and every other week throughout the study. Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and will be considered important medical events. The threshold of laboratory abnormalities for a potential case of drug-induced liver injury will depend on the subject's individual baseline values and underlying conditions. Subjects who present with the

following laboratory abnormalities will be evaluated further to definitively determine the etiology of the abnormal laboratory values:
· Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values >3 times the upper limit of normal (3X ULN) concurrent with a total bilirubin value >2X ULN with no evidence of hemolysis and an alkaline phosphatase value >2X ULN;
· For subjects with preexisting ALT or AST or total bilirubin values above the ULN, the following threshold values will be used in the definition mentioned above:
· For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values >2X the baseline values and >3X ULN, or >8X ULN (whichever is smaller).

Concurrent with
· For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1X ULN or if the value reaches >3X ULN (whichever is smaller). The subject will be evaluated again, within 48 hours from awareness of the abnormal results. This evaluation will include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests will include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, will be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) will be performed as warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, will be considered potential Hy's law cases irrespective of availability of all of the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases will be reported as SAEs and discontinued from the study.

Hypotension
Vital signs are monitored daily on the inpatient unit in seated, supine, and standing position and during laboratory sessions, and if a consistent pattern of clinically significant hypotension is observed, in the opinion of the clinical physicians on 5-South and the study's medical director, the participant will be discontinued from the study.

Criteria for Testing Sessions:

a. Do not administer study drug if: Heart Rate <60 or >130 bpm, Systolic Pressure <90 or >165 mm Hg, Diastolic Pressure < 60 or >100 mm Hg, or if a subject has orthostatic vital signs as follows: a supine BP of 85/55 or less, a **seated BP of 85/55** or less, or an orthostatic decrease of >20 systolic and >15 diastolic upon standing.

b. Discontinue a session if a single reading is: Heart Rate <50 or > 175 bpm, Systolic Pressure <90 or >180 mm Hg, Diastolic Pressure or < 55 or >120 mm Hg.

c. Notify the study MD if Heart Rate < 50 bpm, Systolic Pressure < 90 mm Hg, Diastolic Pressure < 55 mm Hg.

d. We will perform orthostatic assessments prior to oxycodone administration and 1 hour after. If a subject has a HR < 55, a supine BP of 85/55 or less, a **seated BP of 85/55** or less, or an orthostatic decrease of >20 systolic or >15 diastolic upon standing, or a HR > 35 bpm upon standing, oxycodone will not be administered, and the laboratory session will be postponed a day. We will not continue lab sessions until orthostatic vital signs are normal. If orthostatic hypotension occurs, the subject will be offered water or Gatorade, and asked to remain seated. Orthostatic vital signs will then be checked hourly, and the study MD will be notified for further management.

Criteria for Discontinuing Enrollment
If at any time hypotension or orthostatic hypotention occurs with clinical symptomology such as: dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, or headache, an adverse event will be recorded. If at any time, hypotension or orthostatic hypotension occurs with clinical symptomology such as: dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, or headache, an adverse event will be recorded. If > 3 AE's from orthostasis occurs, the subject will be stabilized on a lower dose of doxazosin. If symptomatic orthostatic hypotension occurs on the lowest active doxazosin dose (4 mg), the participant will be discontinued from the study and treated based on the study MD's assessment. If the subject's vital signs decrease by >30 systolic or >15 diastolic from BP recorded on admission, and if a subject develops orthostatic symptoms, the subject will be discontinued.

Blood and other Biological Samples

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

During the screening process and within 1 week following discharge, blood will be drawn for laboratory testing and, for women, pregnancy testing. Liver function tests will be performed upon admission and every other week throughout the study. Approximately 40 cc (3 tablespoons) blood will be drawn for these purposes.

Urine drug testing will be performed at each screening visit, thrice weekly while participants are inpatient, and during each post-study visit. Urine pregnancy tests will be performed upon admission and monthly during the inpatient period.

Assessment Instruments

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

See Table 3 for a summary of events.

Screening Instruments
Telephone Interview: 10 min
General Health Questionnaire: 5 min
Medical History Questionnaire: 10 min
Drug History Questionnaire: 10 min
Short Michigan Alcohol Screening Test: 5 min
Beck Depression Inventory: 15 min
Clinical Drug/History Interview: 30 min
Demographic Information (e.g., age, race, ethnicity, gender, marital status, family income, occupation, etc.): 45 min
Self-reported Trauma Assessments (e.g., Life Events Checklist, Modified Sexual Experiences Survey, Trauma Symptom Inventory, Distress Tolerance Scale): 30 min
Physical and Psychiatric Examination including a Mental Status Evaluation: 1 hr
Laboratory Hospital Tests: 2-3 hr
Columbia-Suicide Severity Rating Scale (C-SSRS): 5 min
MINI: 30 min
36-Item Short Form Survey Instrument (SF-36) Health Survey: 5 min
Lifestyle Profile: 2 min
Sleep Quality Assessment: 5 min
Insomnia Severity Index: 2 min
Locally developed Sleep Questionnaire: 2 min
Quality of Life Enjoyment and Satisfaction Questionnaire: 5 min

Subjective and Performance Tasks and Sleep Assessments
Digit-Symbol Substitution Task: 3 min
Divided Attention Task: 10 min
Subjective Effects Measures*: 5 min
*Four questionnaires will be used to assess subjective effects during laboratory sessions (see Comer et al., 1999 for details). The first questionnaire is a 26-item visual analog scale designed to assess subjective and physiological effects. The first 18 lines are labeled with adjectives describing mood states ("I feel...alert, anxious, a bad drug effect, depressed, energetic, a good drug effect, gooseflesh, high, irritable, mellow, muscle pain, nauseated, restless, sedated, sleepy, social, stimulated, talkative") and 4 additional lines are labeled with questions about the dose just received ("The dose was potent," "The dose was of high quality," "I liked the dose," "For this dose I would pay..."). Participants also indicate, by making a mark along a 100 mm line, how much they want each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rate each item on the visual analog scale from "Not at all" (0 mm) to "Extremely" (100 mm), except for the "For this dose, I would pay" question, which ranges between $0 (0 mm) and $20 (100 mm). The second questionnaire is a 12-item opioid symptom checklist consisting of true/false questions

designed to measure opioid effects ("I feel normal," "My skin is itchy," "I feel relaxed," "I feel like I am coasting," "I feel like I am nodding," "I feel high," "I feel sleepy," "I feel drunken," "I feel nervous," "I have a lot of drive," "I feel like I am 'on a soapbox' (need to talk)," "My stomach is turning," and "I am feeling a pleasant sick"). The visual analog scale and opioid symptom checklist together constitute the subjective-effects battery. The third questionnaire is the 16-item Subjective Opiate Withdrawal Scales. Participants rate each item on a scale from 0 to 4, with 0 being "Not at all" and 4 being "Extremely" ("I feel anxious," "I feel like yawning," "I'm perspiring," "My eyes are tearing," "My nose is running," "I have gooseflesh," "I am shaking," "I have hot flashes," "I have cold flashes," "My bones and muscles ache," "I feel restless," "I feel nauseous," "I feel like vomiting," "My muscles twitch," "I have cramps in my stomach," "I feel like shooting up now"). The fourth questionnaire is a 6-item Drug Effects Questionnaire. Specific items on the Drug Effects Questionnaire are: "How strong a drug effect are you feeling right now?" "Do you feel any good effects from the drug?" "Do you feel any bad effects from the drug?" "Which one of the drugs listed below is the drug most like?" "Rate the degree to which you would be willing to take today's drug again." "Do you like the way the drug makes you feel right now?" Participants describe drug effects by selecting among a series of possible answers ranging from 0 ("No (good, bad, etc.) effects at all") to 4 ("Very strong effects"). Ratings of drug type are: "Placebo (No drug), Stimulant, Sedative or Tranquilizer." Ratings of drug liking range between -4 ("Dislike very much") and 4 ("Like very much"). In addition to the above items, an Opioid Craving Questionnaire (OCQ) will be administered each evening throughout the study. Each question on the OCQ will be rated on a 7-point scale with "Strongly Disagree" at one end and "Strongly Agree" at the other end. Total scores can range between 0 and 70.

A 7-item sleep questionnaire (Haney et al., 2004) asking about the quantity and quality of the previous night's sleep will also be administered each morning. In addition, an objective sleep measure (sleep efficiency: percentage of time spent asleep) will be collected each night via an Actiwatch.

Drug Exposure. On Fridays during some test weeks at 10 am, participants will receive a single dose of 25 mg oxycodone and $20. The subjective, performance, and physiological effects of oxycodone will be measured repeatedly during these sessions. **Cue Exposure.** On Fri during placebo oxycodone test weeks, beginning at 1 pm, participants will be presented with neutral cues followed by drug cues. Two opaque pitchers will be placed on the participant’s desk at the beginning of the session. Hidden under one pitcher will be a glass of water. Hidden under the second pitcher will be a straw and a glycine packet filled with lactose. There will be two 3-min exposure trials separated by 5 min of relaxation. During the first exposure trial, participants will be exposed to the neutral cues. After a 5-min relaxation period, participants will be exposed to the drug cues. Immediately after each cue presentation, participants will complete an Opioid Craving Questionnaire. Physiological measures (heart rate, respiratory rate, blood pressure, skin temperature (ST), and galvanic skin response (GSR)) will be collected during cue presentation. Participants will be informed that after completion of the questionnaires, they will have the option to choose the dose of oxycodone that they received during the morning session or money. Progressive Ratio (PR) Choice. Immediately following the Cue Exposure procedure, participants will be given the opportunity to respond for up to $20 or 25 mg oxycodone after completing a 10-trial modified progressive-ratio procedure. During each trial, participants will work for $2 or 1/10th

of the dose that they received during the Drug Exposure Session. The number of responses (finger presses on a computer mouse) required to receive the first 1/10th of the dose will be 25, followed by 50, 100, 200, 400, 800, 1600, 3200, 6400, and 12800 responses. Thus, it becomes increasingly difficult for participants to receive drug each time they choose the drug option. The motivation to respond for drug will be assessed by the breakpoint value, which is the last ratio completed for drug (i.e., lower drug breakpoint value = lower propensity to relapse). After participants complete the task or stop responding, they will receive whatever fraction of the money and/or dose that they earned. Using similar procedures in previous studies in our laboratory, we have shown that Bup/Nx and SR-NTX produced dose-related reductions in heroin self-administration (Comer et al., 2002, 2005). In our ongoing trial using this procedure, breakpoint values on Fri were approximately 2000 when active heroin was available. That is, participants chose the drug option on 7-8 of the 10 choice trials during the modified progressive ratio task.

Actiwatch (Philips Respironics): ~10 hr

In addition to the above, the following questionnaire will be completed weekly throughout the study: Cognitive and Physical Functioning Questionnaire (CPFQ): 2 min
Impulsivity Assessments (to be completed after admission to 5-South)
Barratt Impulsiveness Scale: 5 min
Impulsivity Questionnaire: 5 min
Sensation-Seeking Scale: 5 min
UPPS Impulsive Behavior Scale: 5 min
Immediate Memory Task/Delayed Memory Task: 20 min
GoStop Task: 15 min
Subject Opiate withdrawal symptoms (SOWS) - 5 min

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
Doxazosin
Manufacturer and other information
Cardura XL; doxazosin mesylate extended release tablet in combination with oxycodone
Approval Status
IND is approved

IND#
137123
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Comer, Sandra, PHD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
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 can 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 participation in group therapy at STARS or Narcotics Anonymous. Induction onto Suboxone or Vivtrol treatment will also be available to all participants prior to discharge.

Clinical Treatment Alternatives

Clinical treatment alternatives
This study is not a treatment study. Participants expressing interest in treatment will be immediately referred to an appropriate treatment provider, and will not be included in the study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
1) Opioid Administration During Laboratory Sessions
In the current proposal, an intranasal dose of up to 100 mg will be used. The most frequently reported adverse experiences associated with oxycodone administration are: lightheadedness, dizziness, sedation, nausea, and vomiting. Hypotension, respiratory depression, mood changes (euphoria, dysphoria), constipation, skin rash, and pruritis have also been reported. The most

serious possible adverse effect is respiratory depression. However, our careful participant selection and selection of doses should preclude the occurrence of such an event. We have safely tested a bolus dose of 50 mg intravenous oxycodone in a previous study, so we do not anticipate significant respiratory depression to occur. During the laboratory session, vital signs (heart rate, blood pressure, and arterial oxygen saturation) will be monitored. Prior to drug administration, blood oxygen saturation must be within acceptable ranges (> 92%) for drug administration to occur. If respiratory difficulty is observed, then, with the exception of vital signs monitoring, the session will be discontinued. Careful attention will be paid to oxygen saturation and, for safety, oxygen will be available for emergency use during the experimental session. We will ask participants to take a deep breath if their oxygen saturation falls below 85%. Such requests are effective in restoring normal oxygen saturation in preoperative patients given opioids. In the unlikely event that prompted breaths do not bring the oxygen saturation above 90% within 1 min, supplemental oxygen will be administered through a nasal cannula and the flow rate adjusted as necessary. In addition, resuscitation equipment and naloxone injection will be available in the testing area if respiration was seriously depressed (i.e., if a research participant was no longer able to respond to verbal commands to take deep breaths). In such an event, naloxone (0.4 mg to 0.8 mg intravenously) would be administered, followed by subsequent doses every 1 min until an individual responds to verbal commands to breathe deeply (with the total naloxone dose not to exceed 10 mg). During the time of apnea, participants will be ventilated with an Ambu Bag by a trained research nurse. If significant respiratory depression did occur, the affected individual would be monitored for three hours for signs of recurrent respiratory depression.

2) Doxazosin

Doxazosin (Cardura ®XL; doxazosin mesylate extended release tablet) was approved by the U.S. Food and Drug Administration in 2005 for the treatment of benign prostatic hyperplasia (enlarged prostate gland). The most common adverse events related to treatment with doxazosin are dizziness, nausea, runny nose, headache, weight gain, and feeling tired or drowsy. Less common side effects include: floppy iris syndrome, yellowing eyes/skin, dark urine, easy bleeding/bruising, fever, and persistent sore throat. Serious side effects of doxazosin include hives or other signs of an allergic reaction, fainting, pounding heartbeat, trouble breathing, swelling in the ankles, hands, or feet, vision changes, slurred speech, and an erection that is painful or lasts 4 hours or longer. Participants will be informed about the possible side effects of doxazosin and will be told to notify a nurse or physician if they begin to experience any of them. Medical staff will note which symptoms are present, their severity, and make a decision whether to continue the participant in the study.

3) Hypotension

We will follow stringent guidelines for monitoring vital signs during titration of doxazosin dose and throughout the study. Just before the 8pm dose and 2 hours after dosing (10pm), and at 7am and 1pm, orthostatic assessments of heart rate (HR) and blood pressure (BP) will be measured. Prior to dosing, a HR < 55, a supine BP of 85/55, a **seated BP of 85/55**, or an orthostatic decrease of >20 systolic or >15 diastolic upon standing, or an increase in HR of >30 bpm upon standing, will be considered an adverse event of “hypotension” and result in holding the doxazosin dose. In order to be considered an AE these measurements must be accompanied by clinical symptoms such as: dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, or

headache. The subject will be offered water or Gatorade, and orthostatic vital signs will be checked again in one hour. The study MD will be called to provide further management. The subject will be required to have normal vital signs for 3 consecutive days on a given dose of doxazosin XL, before titrating upward. We will titrate the doxazosin XL dose gradually to a tolerated dose (but no more than 16 mg) to determine what might be an appropriate dose in this population.

4) Increased Sensitivity to Opioids
Participants who were dependent upon admission may be less tolerant to the effects of opioids at discharge. Participants will be counseled about the risks of decreased tolerance to opioids prior to discharge, and made aware that they may be more sensitive to the effects of opioids upon completion of the study. They 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.

5) Morphine Stabilization Period
The major risk of the initial stabilization period is the emergence of opioid withdrawal symptoms such as sweating, anxiety, nausea, vomiting, diarrhea, stomach upset, changes in blood pressure, weakness, restlessness, feelings of changes in temperature, sneezing, runny nose, watery eyes, gooseflesh, and insomnia. If participants experience withdrawal symptoms, we will prescribe medications to alleviate those symptoms.

6) Naloxone Challenge Test
To determine whether or not participants are dependent on opioids before admission into the study, we may administer up to 3.0 mg naloxone intramuscularly (by injection) which may produce a number of withdrawal symptoms. Participants may experience certain effects such as: sweating, restlessness, stomach pain, diarrhea, headache, anxiety, nausea, vomiting, dizziness, runny nose, yawning, muscle aches, or tremors. We will monitor their reactions to naloxone for up to 45 min. At the end of this period, we may prescribe oral morphine sulfate (up to 50 mg) to alleviate those symptoms. The doses of morphine have been carefully selected to be below dangerous levels, but participants will be informed that they may experience side effects which may include: drowsiness, itchiness, dry mouth, sweating, restlessness, constipation, headache, anxiety, slowed breathing, nausea, vomiting, dizziness, sedation, or tremors. To ensure that participants can safely undergo this procedure, it is only completed following the physical examination.

7) Confidentiality
Potential participants divulge information that is sensitive and may have adverse social consequences if released. This would include information released to insurance companies, health care agencies, or family members, or information made public in any way. We deal with issues of confidentiality by using coded records, storing signed consent forms in a locked safe, and trying to the best of our ability to maintain confidentiality.

8). Fall Risks

Fall precautions will be in place throughout the study. When subjects are on the inpatient unit, the unit staff will follow their fall precaution protocol. Staff conduct “fire rounds” every 30 minutes to check on every patient on the unit for safety purposes. The inpatient unit also has common areas that have glass windows, which ensures that subjects are easily seen. Additionally, this protocol requires subjects to wear special clothes with short pant legs, non-skid slippers or shoes, and ensures monitoring while a subject showers or is ambulating. When subjects are in lab, staff will be monitoring vital signs more frequently and will escort subjects to the bathrooms.

Describe procedures for minimizing risks

1) Study Procedures

Participants are fully informed of the potential side effects of the drugs and the risks of the procedures. Should a woman become pregnant during the experimental protocols, she will be excluded from further participation. We will perform a blood pregnancy test at screening, and urine pregnancy tests upon admission and monthly during the study, and will advise female participants to use an effective method of birth control prior to admission into all protocols. Participants are monitored by trained medical staff during experimental sessions. Emergency medical equipment is available in our laboratory and, as well, we are located in a hospital where a full medical emergency back-up team is constantly available. We anticipate, however, that careful participant selection, dose selection, and participant monitoring will eliminate the need for such emergency care. In addition, we have developed guidelines for opioid administration such that oxygen saturation dictates whether supplemental oxygen will be administered. Naloxone is available during all laboratory sessions in the event of serious respiratory depression.

We will monitor subjects for depression and suicidality throughout the protocol with the BDI and C-SSRS. At discharge, participants will be offered treatment with sustained-release naltrexone or a clinically effective dose of sublingual buprenorphine/naloxone (e.g., 8-16 mg) Additional doses of buprenorphine/naloxone will be given to subjects to bridge them until they are able to meet with a treatment provider who will manage their maintenance therapy. We will not offer detoxification, unless participants wish to transition to sustained-release naltrexone. All participants will be warned of the risks of opioid overdose, particularly overdose on fentanyl. They will be offered training on how to recognize an opioid overdose and how to reverse it with naloxone. All subjects will be provided with a kit containing naloxone.

During the follow up period after discharge, subjects will complete a self-report drug use questionnaire, urine drug toxicology, BDI, and C-SSRS. Participants deemed at risk by virtue of the emergence of depressive symptoms meeting criteria for a Major Depressive Episode (as assessed by a psychiatrist), or reporting current active suicidal ideation (“Yes” to CSSRS questions 4 or 5) that was not present before and constitutes a change will be withdrawn from the study and treated for their depressive symptoms according to the clinical judgment of the study physicians or psychiatric nurse NP, including as necessary antidepressant treatment. Participants withdrawn from the study during the inpatient phase for reasons of depressed mood or suicidality will be maintained on the clinical research unit and treated clinically until a psychiatrist or Psychiatric NP determines that they no longer require inpatient treatment. They will then be discharged into outpatient treatment if required.

Participants endorsing clinically significant depressive symptoms on the BDI or suicidal ideation or behavior since the previous visit on the CSSRS to be assessed by a study psychiatrist during the follow-up session. Any participant judged to meet criteria for Major Depression, or who is experiencing significant depressive symptoms according to the psychiatrist's or Psychiatric NP's clinical judgment will be provided with referrals for treatment for their depression. Any participant judged to be at emergent risk due to suicidal thoughts or behavior will be escorted by a research staff member and security to the NY Presbyterian Hospital Emergency Room. The researcher will remain with the participant until he or she is taken for assessment.

The formal study completion day will be the last visit (there are several visits, depending on how much participants earn - they get paid a maximum of $600 per week). If participants are leaving the state (some travel following the study) and request payment by mail, we will recommend that they stay to complete the follow-up period for safety reasons. If they decline to do so, we will mail them their payment in $600 weekly increments as mail order checks (they will not receive the extra $25 for each follow-up visit). Our research group has been conducting inpatient and outpatient clinical pharmacology research for more than 20 years and our careful precautionary measures should ensure that no serious adverse events occur.

2) Recruitment and Informed Consent
Participants will be recruited via newspaper and online advertisements, as well as posting of flyers and word-of-mouth. The first phase of recruitment is a structured telephone interview. Those volunteers passing the initial interview visit the laboratory and receive a brief description of the study and are asked to consent to be screened. This screening consent form covers all interviews, questionnaires, and collection of appropriate medical information. They receive a physical exam (including blood and urine tests), ECG, medical history evaluation, and psychiatric interview. Only those judged psychiatrically and physically healthy are accepted to continue. They are given the opportunity to ask questions and discuss participation at length. Those who pass this screening will have the study described to them in detail by one of the investigators, and then will sign a study consent form. Volunteers report to the laboratory prior to admission to practice the study performance tasks used during the study. We find that this multi-consent process provides participants with substantially more information at each decision point. They always have information about the study for which they are volunteering, and have engaged in the behaviors that will be required. Such a procedure provides fully informed consent.

3) Confidentiality
A Certificate of Confidentiality will be obtained for the current study and procedures for protecting confidentiality of records will be followed. Specifically, all data records containing identifying information will be kept in locked files and on password-protected computers. Only the study investigators will have access to the codes linking the participant to their identifying information. Only the primary investigator and other core study staff will have access to identifiable information, which will be maintained on site under lock and key. All computer data are stored without names or other uncoded identification. Patients will be identified only through a numerical code in all electronic databases.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
We have obtained a Certificate of Confidentiality for this study from NIDA. The records for this study will be kept confidential and will only be accessible to study staff. Screening information, which may include the participant's name, will be kept in a locked filing cabinet. Once a participant is enrolled into the study all further documents will be identified solely by initials and an assigned number.
Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There are no direct benefits to subjects for participating in this study.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will be paid $50/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 proportionately small. In addition to the per diem payment, participants have the opportunity to earn money during the experimental sessions ($20 per sample session plus up to $20 per self-administration session). Participants will also be paid for completing the screening process ($25/visit), one training session prior to admission ($25), a naloxone challenge test ($25), and a follow-up evaluation 1 week after the completion of the experiment ($25). Payments will be in cash, separated into several installments ($600 per week) at the end of the study in order to prevent large one time payments. Total payments will be between approximately $6550 and $7350. On some occasions, it may be necessary to repeat sessions (e.g., due to catheter failure).

References

References

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Rodgman, C., Verrico, C.D., Holst, M., Thompson-Lake, D., Haile, C.N., De La Garza, R., Raskind, M.A., Newton, T.F.: Doxazosin XL reduces symptoms of posttraumatic stress disorder in veterans with PTSD: A pilot clinical trial. J Clin Psychiatry 77(5) e561-e565, 2016.

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 unbolded Consent Script(s)
Upload copy(ies) of bolded Consent Script(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Upload evidence of FDA IND approval(s)
Upload a copy of Certificate of Confidentiality
Upload copy(ies) of the HIPAA form
Upload any additional documents that may be related to this study