NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

March 6, 2020

TO: Dr. Sandra Comer

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

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

Your protocol **#7476** entitled **Medication Development for Opioid and Alcohol Abuse: Laboratory Study in Humans** (version date 03-06-2020) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from April 3, 2020 to April 2, 2021.

Consent requirements:

√ Not applicable: Data Analysis Only

□ 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 (DA039169)
CU Grants & Contracts (subcontract)

EN/AW/Scr
Signed copy on file at IRB

Protocol Title:
Medication Development for Opioid and Alcohol Abuse: Laboratory Study in Humans

Version Date:
03/06/2020

Protocol Number:
7476

Clinic:
Opioid Research Laboratory

First Approval:
05/31/2017

Expiration Date:
04/02/2021

Contact Principal Investigator:
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Co-Investigator(s):
Suzette Evans, PHD
Richard Foltin, PHD
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Jermaine Jones, PHD
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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.
Not applicable

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
A total of 13 participants completed the study procedures, which were generally well tolerated with the exception of hypertension experienced by 2 participants as reported previously. Preliminary analyses of our data suggest that gabapentin increases subjective ratings of Drug Liking, High, Sedated, Would Pay, Potent, and High Quality. However, it did not significantly alter the respiratory effects of oxycodone, alcohol, or the combination. We are working on the manuscript for publication.

Funding

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

Summary

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

Yes
Certificate expiration date (mm/dd/yyyy)
06/15/2023

Overall Progress

Approved sample size
24
Total number of participants enrolled to date
17
Number of participants who have completed the study to date
13
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Participants meeting criteria for OUD and AUD
Total number of participants enrolled from this population to date
17
Gender, Racial and Ethnic Breakdown

1 Female, 16 Male
2 Hispanic, 15 Non-Hispanic
5 White, 12 Black

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
4
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

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

✓ 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?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
Medication Development for Opioid and Alcohol Abuse: Laboratory Studies in Humans
Grant Number
DA039169
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 Department of Psychiatry

Please note that as per NIDA's request, Depomed, the company that markets Gralise (sustained-release gabapentin), has agreed to supply us with study medication and supplemental funding for advertising and to support a research assistant.

Study Location

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

Lay Summary of Proposed Research

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Currently, the abuse of prescription opioid medications is a pervasive problem in the U.S. In addition, co-abuse of opioids and alcohol represents a significant problem from the perspective of increased toxicity and decreased success in treatment. Surprisingly few studies have examined the effects of combined administration of opioids and alcohol in humans, and no clinical studies have examined the reinforcing effects of this combination. The current 8-9-week inpatient study will systematically evaluate gabapentin because it shows promise for treating both opioid and alcohol use disorders (OUD and AUD). The guiding principle is that a medication's effects on positive subjective responses and reinforcing effects are the best laboratory procedures to date in predicting its clinical efficacy. We will examine the ability of gabapentin to alter opioid-, alcohol-, and combined opioid/alcohol-mediated responses. Participants will meet DSM-5 criteria for moderate-severe OUD and be physically dependent on opioids. In addition, participants will meet DSM-5 criteria for moderate-severe AUD, but they will not be physically dependent on alcohol. All of the participants will be maintained on oral morphine throughout the study and different doses of gabapentin will be evaluated. Overall, the proposed study will provide a great deal of information about the safety and clinical utility of gabapentin for treating co-abuse of opioids and alcohol.

Background, Significance and Rationale

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Anticonvulsant medications, such as gabapentin, pregabalin, and topiramate, have been evaluated for the treatment of drug and alcohol dependence. Gabapentin is a particularly interesting medication because it has a good safety and tolerability profile, minimal abuse liability, and is already in widespread clinical use for other disorders, such as chronic pain, anxiety, and sleep disorders. Gabapentin inhibits neurotransmitter release by blocking presynaptic voltage-gated Na^+ and Ca^{2+} channels. Specifically, it is

thought to inhibit the alpha-2-delta subunit of presynaptic Ca^{2+} channels, which may indirectly modulate gamma-aminobutyric acid (GABA) and perhaps glutamate neurotransmission (Sills, 2006). Dr. Evans, who is a co-Investigator on this proposal, showed that pretreatment with an acute dose of gabapentin (0, 1000, or 2000 mg) did not alter the subjective effects of alcohol (0.75 g/kg) or alcohol craving in heavy drinkers (Bisaga and Evans, 2006). However, a recent clinical trial demonstrated that maintenance on gabapentin (0, 900, and 1800 mg/day) produced dose-related increases in rates of complete abstinence from alcohol in alcohol-dependent patients, as well as improvements in mood, sleep, and craving (Mason et al., 2014). Other studies have shown that gabapentin is useful in treating symptoms associated with alcohol withdrawal (Malcolm et al., 2007; Mason et al., 2009). Few studies have examined the effects of gabapentin on the abuse liability of opioids, however. A study conducted in rats demonstrated that gabapentin prevented the development of morphine-induced CPP, and blocked morphine-induced dopamine release in the nucleus accumbens (Andrews et al., 2001). Although gabapentin does not appear to be useful for treating opioid withdrawal in clinical settings (Kheirabadi et al., 2008; Sanders et al., 2013), opioid-positive urine samples were significantly lower in patients who received gabapentin compared to placebo during outpatient detoxification from opioids (Sanders et al., 2013). Thus, these preliminary studies suggest that gabapentin might be useful in treating OUD, and more substantial evidence suggests that it is useful in treating AUD. A major goal of the present proposal is to evaluate the ability of gabapentin maintenance to reduce the abuse liability of alcohol, oxycodone, and alcohol in combination with oxycodone in participants with both OUD and AUD.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

We will examine different doses of gabapentin (0 and 1800 mg) in combination with different doses of oxycodone, alcohol, and the oxycodone/alcohol combination in order to establish safety (e.g., respiratory depression), tolerability (e.g., side effects), and preliminary efficacy (e.g., subjective and reinforcing effects).

HYPOTHESIS 1: Active medication will be superior to placebo medication in reducing alcohol and/or oxycodone-induced positive subjective and reinforcing effects.

Two primary measures will be considered in each study: positive subjective responses, measured by visual analog scales and reinforcing effects measured by the crossover point on the Multiple Choice Procedure. These data will be analyzed using repeated-measures ANOVAs with planned contrasts with medication dose (2 levels) as the first factor and oxycodone and/or alcohol dose as the second factor (9 levels: placebo and active oxycodone in combination with placebo and active alcohol). Differences in subjective ratings and crossover point as a function of oxycodone and/or alcohol dose will be evaluated under each medication dose. We will conduct two sequences of planned comparisons: 1) effects of peak measures averaged across participants, and 2) time course of drug effects (all time points compared). Both sets of analyses will be accomplished by repeated measures ANOVA's.

HYPOTHESIS 2: Active medication will be superior to placebo medication in reducing alcohol and/or oxycodone craving and physiological responses (as a measure of safety).

The secondary measures of interest for this study are for craving, specifically, ratings of "I want opioids" and "I want alcohol," as well as scores on the Opioid Craving Questionnaire and Alcohol Craving Scale. Physiological responses, particularly as related to respiratory function (e.g., respiratory rate, arterial oxygen

saturation, end tidal carbon dioxide, heart rate, blood pressure) also will be evaluated. As above, these measures will be analyzed using repeated-measures ANOVAs with planned contrasts using medication dose (2 levels) and oxycodone and/or alcohol dose (9 levels: placebo and active oxycodone in combination with placebo and active alcohol) as factors. Other dependent measures (cognitive effects, sleep measures, number of cigarettes smoked, and other physiological effects) will be analyzed in a manner similar to the subjective ratings. That is, peak (or trough) and time course analyses will be conducted on these measures.

Description of Subject Population

Sample #1

Specify subject population
Non-treatment-seeking subjects with moderate-severe opioid and alcohol use disorder
Number of completers required to accomplish study aims
24
Projected number of subjects who will be enrolled to obtain required number of completers
36
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 approximately 75% male, 55% Caucasian, 30% Black or African-American, 15% 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. Participants also will meet DSM-5 criteria for moderate-severe AUD (men and women will consume at least 15 and 8 alcohol drinks per week, respectively), but will not be physically dependent on alcohol. Participants will report simultaneous use of opioids and alcohol and will not be seeking treatment for OUD or AUD. None of the participants will be physically dependent on alcohol or any other drugs with the exception of opioids, nicotine and caffeine.

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/psychiatric nurse practitioner; 3) psychiatric interviews and oral dose administrations will be conducted by a nurse; 4) SCIDs will be performed by a trained nurse or clinical 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 AM New York, as well as electronic media (e.g., **RecruitMe**, Facebook, Google, StudyKik, and websites that drug users frequent such as Bluelight and Erowid). There will be recruitment through advertisements on MTA bus interiors.
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
NCT03205423

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
Subjects with OUD and AUD
Create or insert table to describe the inclusion criteria and methods to ascertain them

1) DSM-5 criteria for moderate-severe opioid use disorder with physical dependence. Ascertained By: Clinical interviews (telephone, psychologist, nurse, physician), naloxone challenge test/visual evidence of opioid withdrawal.

2) DSM-5 criteria for moderate-severe alcohol use disorder without physical dependence. Ascertained By: Clinical interviews (telephone, psychologist, nurse, physician) and visual evidence of alcohol withdrawal.

3) No current major mood, psychotic, or anxiety disorder. Ascertained By: Clinical interview with physician or nurse.

4) Physically healthy. Ascertained By: Clinical interview with physician, laboratory tests (urinalysis, blood chemistry, 12-lead ECG), physical examination, self-reported medical history, chest x-ray or ppd skin test.

5) Able to perform study procedures. Ascertained By: Practice session.

6) 21-59 years of age. Ascertained By: Self-reported age and/or verification with legal identification.

7) Normal body weight/Within 20% of body weight (for appropriate frame) according to 1983 Metropolitan Weight tables.

8) Current or history of illicit opioid use. Ascertained By: Clinical interviews (telephone, psychologist, psychiatric nurse practitioner and psychiatrist)

9) Current use of opioids in amounts and/or frequencies that meet or exceed those used in the proposed study (e.g., 3-4 tablets of a Rx opioid medication per day or 1-2 bags of heroin per day). Not seeking treatment for opioid use disorder (neutral attitude or not wanting treatment only). Ascertained By: Clinical interviews (telephone, psychologist, psychiatric nurse practitioner and psychiatrist).

10) Participants will consume alcohol at least 3 times per week (15 drinks per week for men and 8 drinks per week for women). In addition, they will drink alcohol and use opioids simultaneously.

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

1) DSM-5 criteria for substance use disorder (moderate to severe) on drugs other than opioids, alcohol, nicotine or caffeine (must be less than 500 mg caffeine daily). Ascertained By: Clinical interview with psychiatrist, psychiatric nurse practitioner, urine screen, observation.

2) Participants requesting treatment. Ascertained By: Self-report during interview.

3) Pregnancy or lactation. Ascertained By: Blood pregnancy testing, self-report during interview.

4) Current or recent history of significant violent or suicidal behavior and/or suicidal/homicidal risk. Ascertained By: Clinical interview (based on current state and history).

5) Cannot read or understand the self-report assessment forms unaided, or are so severely disabled that they cannot comply with the requirements of the study. Ascertained By: Clinical interview, practice session.

6) Elevated liver function tests (i.e., AST and ALT > 3 times the upper limit of normal) or impaired renal function (creatinine must be within normal limits). Ascertained By: Laboratory tests.

7) Physical disorders that might make participation hazardous such as AIDS, cancer, 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). Ascertained By: Clinical interview, ECG.

8) Current major Axis I psychopathology, other than OUD and AUD (e.g., mood disorder with functional impairment, schizophrenia), that might interfere with ability to participate in the study. Ascertained By: Clinical interviews.

9) Sensitivity, allergy, or contraindication to opioids, alcohol, gabapentin or similar medications. Ascertained By: Clinical interview.

10) Taken an investigational drug within the past 30 days. Ascertained By: Clinical interview.

11) Current or history of chronic pain within the past 3 months. Ascertained By: Clinical interview.

12) Taking prescription psychotropic medications that would potentially interfere with study procedures. Ascertained By: Clinical interview.

Waiver of Consent/Authorization

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

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
Upon the participants' first visit to NYSPI, the general study procedures are described by a

research assistant. If the participant is still interested in screening for the study, (s)he is given a screening consent 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 to initiate screening procedures detailed in the document.

Describe Study Consent Procedures

The physician conducts the physical examination; the physician or psychiatric nurse practitioner conducts psychiatric examination, 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 signs the study consent form.

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

✓ Consent Form
✓ Information Sheet

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

Bisaga, Adam, MD
Blevins, Derek
Brezing, Christina, MD
Comer, Sandra, PHD
Evans, Suzette, PHD
Foltin, Richard, PHD
holt, ida
Iqbal, Muhammad
Jones, Jermaine, PHD
Kidd, Jeremy
Luo, Sean, MD
Manubay, Jeanne, MD
Mogali, Shanthi, MD
MURRAY, JANET

Shulman, Matisyahu, MD
Srivastava, A Benjamin
Tindall, Claudia
Vorel, Stanislav, MD
Wai, Jonathan, MD
Williams, Arthur
Woolfolk, Vincent
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

The ability of gabapentin (Gralise; 0, 1800 mg/day) to alter the effects of a range of doses of oxycodone (0, 15, and 30mg/70kg per os (PO)) and alcohol (0, low dose, high dose PO) alone and in combination will be tested. Immediately after admission, participants will be stabilized on immediate-release oral morphine (30 mg, q.i.d. at 8am, 4pm, 8pm, and 11pm). In addition, they will be randomized to receive 0 mg or 1800 mg/day gabapentin once daily at 8am. When participants are maintained on active gabapentin, the dose will be titrated up to 1800 mg over the course of 1 week. Specifically, participants will receive 600 mg on Day 1, 1200 mg on Day 2, and 1800 mg on Days 3-7. If uncomfortable side effects emerge after initiation of gabapentin administration, the titration schedule will be adjusted until the side effects dissipate. After the approximately 1-week stabilization period on the first dose of gabapentin, they will initiate a 3-week testing period. At the end of the first 3-week testing period, participants will be transferred to the other dose of gabapentin using the same 1-week stabilization period and then they will again complete 3 weeks of testing. Participants will be tapered off of the medication on an inpatient basis at the end of the study.

At each gabapentin dose administration, participants will receive 6 capsules in order to maintain the dosing blind. Based on our previous studies, we will test placebo, 0.50 g/kg, 0.75 g/kg alcohol (Evans & Levin 2003, 2004, 2011; Reed et al., 2012). Alcohol dose will be calculated based on the estimated total body water (TBW) of each participant to eliminate differences in alcohol pharmacokinetics (Watson et al., 1980), using different regression equations for males and females. The beverage volume will be 350 ml for females and 500 ml for males. Participants can select their preferred mixer from among a selection of equicaloric, non-caffeinated beverages and the investigators will prepare a SINGLE drink each session with 100 proof vodka added to achieve the correct volume for each individualized alcohol dose. Lime or peppermint drops will be added to the top of the beverage and food color will be mixed in to mask its flavor and color. Participants will consume the entire beverage within 5-7 min (5 for women, 7 for men) under staff supervision. The placebo beverage will consist of the mixer alone. For oxycodone/alcohol combination doses, oxycodone (~ 0.75 or 1.5 ml of a 20 mg/ml concentrated solution) will be added to the beverage.

The active medication doses were chosen based on estimated effectiveness in reducing alcohol-mediated effects and/or maximum estimated tolerability. An 1800 mg maximum daily dose of

gabapentin was chosen because it was well tolerated and effective in treating alcohol dependence (Mason et al., 2014). A 1-week titration/stabilization period will be used because we have found in previous studies that this schedule is well tolerated by both alcohol and cocaine abusers (Hart et al., 2007; Mariani et al., 2006).

During test weeks, participants will receive 9 dose combinations of oxycodone (0, 15, and 30 mg/70kg) and alcohol (0, low, and high doses). Oxycodone and alcohol will be administered at the same time because most abusers report simultaneous use (McCabe et al., 2006), and previous studies have reported that the peak effects of oxycodone and alcohol occur at similar time points (see Comer et al., 2010; Kirkpatrick and de Wit, 2013; Rush et al., 2001; Walsh et al., 2008). Each dose combination will be administered on separate days (Table 1) and the time course of acute effects will be assessed prior to and for 6 hours after dose administration (Table 2). The first two participants in each study will receive the active oxycodone and alcohol combinations (15mg/70kg oxycodone + low-dose alcohol; 30mg/70kg oxycodone + high-dose alcohol) in ascending order under each maintenance condition to ensure safety. Thereafter, if the dose combinations are safely tolerated, all doses will be administered in random order. Sessions will be separated by at least 48 hours and session events will be identical on each test day (Table 2).

During the laboratory sessions, the subjective effects battery will consist of a Drug Effects Questionnaire (Evans et al., 1995), Visual Analog Scales (e.g., “I feel high,” “I feel sociable”), the Biphasic Alcohol Effects Scale (Martin et al., 1993), an Alcohol Craving Scale (adapted from Tiffany and Drobes, 1991; Tiffany et al., 1993), the Opioid Symptom Checklist (Derogatis et al., 1974; Fraser et al., 1961; Martin and Fraser, 1961), an Opioid Craving Questionnaire (adapted from Tiffany and Drobes, 1991; Tiffany et al., 1993) and a short form of the State-Trait Anxiety Inventory (Marteau and Bekker, 1992). The Subjective Opiate Withdrawal Scale (SOWS; Handelsman et al., 1987) and the Clinical Opiate Withdrawal Scale (COWS; Wesson and Ling, 2003) will assess opioid withdrawal, and the revised Clinical Institute Withdrawal for Alcohol Scale (CIWA-Ar; Sullivan et al., 1989) will assess alcohol withdrawal.

Although our laboratory typically uses operant self-administration procedures, the Multiple Choice Procedure (Griffiths et al., 1993; Mumford, Evans et al., 1995) will be used in the proposed studies because it is an efficient method of assessing drug reinforcement. At the end of each laboratory session, participants will make 9 discrete drug versus money choices (dose received that day versus $0.25, $0.50, $1.00, $2.00, $4.00, $8.00, $16.00, $32.00, and $64.00). For each dose combination, the primary dependent variable in this task is the “crossover point,” which is the maximum dollar value at which participants choose the dose over money. Over the course of the study, participants will make 243 individual choices between the dose and money (9 choices per session x 27 sessions = 243 choices). They will be informed at the beginning of the study that one of their 243 choices will be reinforced randomly during a final session at the end of the study (physiological responses will be monitored for safety, but no data will be collected during this last session).

Two cognitive tasks also will be used in the proposed study. The Digit Symbol Substitution Task (DSST; McLeod et al., 1982) assesses psychomotor ability and the Divided Attention Task assesses attention (DAT; Miller, 1987). In our experience, these tasks can sensitively detect the

effects of drugs and drug withdrawal on cognitive functioning. They can also be used to screen for potential adverse effects of study medications on cognition. The DSST and DAT will be completed before and repeatedly after drug administration.

Breath alcohol levels will be determined before and repeatedly after each dose administration during laboratory sessions using breathalyzers (Alco-Sensor III, Intoximeters, Inc., St. Louis, MO). In addition, hart rate (HR) and blood pressure (BP) will be measured using a Criticare Poet Plus 8100 vital signs monitor (Critical Systems, Inc., Waukesha, WI), and recorded at 10-min intervals. Arterial oxygen saturation, respiratory rate (RR), and end tidal CO_2 also will be measured using the Criticare monitor. A soft sensor will be placed over the fingertip on the non-dominant hand. Respiration will be monitored continuously throughout the laboratory session and recorded every 10 min. Pupil photographs will be taken before and after drug administration using a digital pupilometer (Neuroptics), which captures a downloadable image of the eye and reports pupil diameter.

A Sleep Questionnaire will provide subjective ratings of sleep (quality, hours of sleep, etc.). In addition, objective sleep measures will be assessed using a wrist-worn ActiWatch Activity Monitoring System (Respironics Co., Bend, OR).

Adverse events, urine drug toxicologies, cognitive and physical functioning will be assessed repeatedly during the inpatient stay (Table 3).

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. Vital signs prior to oxycodone administration must be within acceptable ranges (%SpO2 > 92) for drug administration to occur. Careful attention will be paid to oxygen saturation since respiratory depression is a clear sign that no further doses should be administered. We will ask participants to take a deep breath if their oxygen saturation falls below 90%. In the unlikely event that prompted breaths do not bring the oxygen saturation above 90% within 3 min, we will provide supplemental oxygen through a nasal cannula. We will administer naloxone if the above measures are unsuccessful in restoring normal oxygen saturation. A participant will be withdrawn from the study if he/she experiences an overdose (over-intoxication requiring medical intervention: e.g. naloxone administration), develops a psychiatric or medical problem for which it is deemed that further study participation would endanger his/her health, or requests exit or referral to treatment.

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 prior to discharge. Specifically, participants will be warned of the risks, namely overdose and death, associated with continued opioid use. A standard script will be reviewed with all subjects prior to discharge to discuss the increased risk of overdose and how the prevalence of fentanyl/carfentanil in street heroin compounds this risk. Buprenorphine or naltrexone will be offered to subjects. Buprenorphine or naltrexone will be initiated prior to discharge for those who wish to initiate treatment with these medications. As part of research safety measures for discharge, the research volunteers are bridged with buprenorphine/naloxone films for up to 2 weeks, if they decide to pursue buprenorphine/naloxone treatment. Staff on 5-South and in the Opioid Lab will facilitate engagement in a methadone program for participants who wish to be maintained on it.

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, approximately 30 cc blood will be drawn for laboratory testing. Urinalysis will be performed at each screening visit, 1 random sample analyzed weekly while participants are inpatient and on each follow-up visit.

Several studies have demonstrated that responses to opioids, alcohol, and medications for treating OUD and AUD may vary depending on genetic polymorphisms (Anton et al., 2008; Kranzler et al., 2013; Oslin et al., 2003). An ongoing study in our laboratory (Dr. Jermaine Jones, co-Investigator on the present proposal) is designed to examine the relationship between oxycodone-mediated effects and genetic variability. We will pool the data from the current studies with that database, although it is beyond the scope of the present proposal to examine the influence of genetic variation on our measures of interest because of our small sample sizes. A recent study attempting to carefully replicate previous candidate gene studies for amphetamine-mediated effects reported that their original findings were likely false positives and the investigators expressed caution in conducting these types of studies (Hart et al., 2013). However, we will collect samples for genetic analyses (e.g., 118G, 511C (or 31T), and CYP2D6 (*3,*4,*5,*6,*7, or *8)) to conduct exploratory analyses of the relationship between the candidate genes and our study endpoints. Approximately 30cc blood will be drawn for this purpose.

Phamacokinetic samples for gabapentin and morphine are drawn twice during in-patient stay; A total of approximately 40cc's of blood will be drawn for this purpose.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Screening Instruments
Telephone Interview: 10 min
Drug History Questionnaire: 10 min
General Health Questionnaire: 5 min
Short Michigan Alcohol Screening Test: 5 min
Medical History Questionnaire: 10 min
Mental Status Evaluation: 10 min
Beck Depression Inventory: 15 min
Clinical/Drug History Interview: 30 min
36-Item Short Form Survey Instrument (SF-36) Health Survey: 5 min
Lifestyle Profile II: 2 min
Sleep Quality Assessment (PSQI): 5 min
Insomnia Severity Index: 2 min
Locally developed Sleep Questionnaire: 2 min
Quality of Life Enjoyment and Satisfaction Questionnaire: 5 min
Test of Premorbid Functioning: 10 minutes.
Flanker Inhibitory Control and Attention Test: 3 minutes
Picture Sequence Memory Test: 7 minutes
List Sorting Working Memory Test: 7 minutes
Picture Vocabulary Test: 4 minutes
Oral Reading Recognition Test: 3 minutes
Dimensional Change Card Sort Test: 4 minutes
Pattern Comparison Processing Speed Test: 3 minutes
Auditory Verbal Learning Test (Rey):3 minutes
Oral Symbol Digit Test: 3 minutes

Physical and Psychiatric Examination including a Speech Task: 1 hr Laboratory
Hospital Tests: 2-3 hr
Subjective and Performance Tasks
Digit-Symbol Substitution Task: 3 min
Divided Attention Task: 10 min

*Several questionnaires will be used to assess subjective effects during the study. The first questionnaire is a 26-item visual analog scale designed to assess subjective and physiological effects. The first eighteen lines are labeled with adjectives describing mood states (“I feel…alert, anxious, a bad effect, depressed, energetic, a good effect, gooseflesh, high, irritable, mellow, muscle pain, nauseated, restless, sedated, sleepy, social, stimulated, talkative”) and four 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 al 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 13-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 Opioid 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 could range between 0 and 70. In addition, the Biphasic Alcohol Effects Scale (Martin et al., 1993), an Alcohol Craving Scale (adapted from Tiffany and Drobes, 1991; Tiffany et al., 1993), and a short form of the State-Trait Anxiety Inventory (Marteau and Bekker, 1992) will be administered. A 14-item sleep questionnaire (St. Mary’s Hospital Sleep Questionnaire) asking about the quantity and quality of the previous night’s sleep will also be administered each evening.

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
Gabapentin (Gralise)
Manufacturer and other information

Depomed markets Gralise, a once a day formulation of gabapentin.
Approval Status
IND is approved
IND#
135,131
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
During the last week of the study and/or prior to discharge, participants will receive counseling about different treatment options. For those participants requesting outpatient treatment, appropriate arrangements will be made during the last week, including placement in an outpatient treatment study at our Substance Treatment and Research Service (STARS), if they are eligible, or participation in group therapy 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 they decide to pursue treatment with buprenorphine/naloxone, they must come in every 3-5 days to pick up the films to bridge them. If they do not want medication assisted treatment for opiate dependence with buprenorphine/naloxone, we will still provide them with 3-4 buprenorphine 8mg/naloxone 2mg sublingual films for harm reduction purposes. We and the social workers on 5-South will make arrangements with a provider for those requesting medication-assisted treatment.

Clinical Treatment Alternatives

Clinical treatment alternatives
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.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

DRUG ADMINISTRATION:

The major risk of research participation is clearly related to drug administration. These risks include the possibilities of deleterious behavioral effects due to drug intoxication. However, we have had experience thus far with a number of different drugs of abuse, including alprazolam, alcohol and numerous opioids, including oxycodone. We have administered alcohol to approximately 230 individuals and we have administered oxycodone (oral or intravenous) to over 100 individuals, with no serious adverse consequences. Our careful procedures and monitoring will minimize any risks. We carry out follow-up interviews of participants at 3 months after study termination. At that time, in addition to assessing general health and well being, we obtain information about each participant's level of drug use. In our experience over the many years that we have carried out this kind of research, participation in these studies appears to neither increase nor decrease drug use in the long term, and in the short term, drug use declines after study participation (Roux et al., 2012).

We are following the National Advisory Council on Drug Abuse Recommendations for the Administration of Drugs to Human Subjects and the NIAAA council guidelines for Ethyl Alcohol Administration in Human Experimentation. The doses of alcohol (low and high: ~0.5 and 0.75 g/kg) being administered are within the psychoactive range and the dose of alcohol will not exceed the equivalent of 3 drinks. Thus, the risk of drug toxicity appears minimal when the drugs are administered as proposed – under careful medical supervision. The investigators and the staff are well trained in behavioral observation, and participants will be monitored throughout the session, thereby allowing us to detect untoward reactions to the dosing regimen. In addition, vital signs will be monitored and performance tasks indicative of drug intoxication will be measured. Because the drugs administered are expected to produce some sedation and performance impairment, participants will be observed for several hours after drug/alcohol administration both in the laboratory and on the inpatient unit. A physician and/or a psychiatric nurse practitioner will be present in the laboratory during the time of expected peak drug effects. A physician will be on call in the event of an emergency. A physician* and/or a psychiatric nurse practitioner will be present for long enough after dose administration to ensure stability of vital signs. [*The attending study physicians who cover the majority of our laboratory sessions are Drs. Manubay and Mogali (both have been working in our lab for several years). C. Tindall, NP has been working in our lab for 10 years as an research nurse].

Oxycodone. 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, dry mouth, headache, sweating, weakness, seizures, and pruritis have also been reported. More rarely, arrhythmias, bradycardia, and tremors have been reported.

Alcohol. The most common side effects of alcohol include: dizziness, faintness, irritability, confusion, drowsiness, sleepiness, sleep disturbance, lightheadedness, loss of coordination and clumsiness, gait disturbance, lack of concentration, tremor, restlessness, gastrointestinal upset, vomiting, headache, pallor, flushing, sweating, dry mouth, slurred speech and fatigue. Rare side effects that could be more serious include: depression, itching, fever, palpitation (heart pounding), arrhythmia (irregular heart beats), nausea, increased or decreased blood pressure, blurred vision, rash, or possibly an allergic reaction.

Gabapentin. Common side effects include dizziness, drowsiness, loss of balance, confusion, headache, nausea, vomiting, dry mouth, blurred vision, cold or flu-like symptoms, loss of balance, trembling, skin rash, loss of appetite, stomach pain, weight gain, breast swelling, changes in urination, rapid back and forth movement of eyes, and peripheral edema. Antacids containing aluminum or magnesium may interfere with the absorption of this medication. Hydrocodone (Lortab, Vicodin, and others), morphine (Kadian, MS Contin, and others), and naproxen can interact with this medication by worsening dizziness, drowsiness and confusion. Rare side effects that could be more serious are weight gain, chest pain, irregular heart

rhythm, shortness of breath, delusions, increased risk of suicidal thinking and behavior, increased risk of seizures if discontinued abruptly, easy bruising or bleeding, or possibly an allergic reaction. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has also been associated with antiepileptic drugs, including gabapentin. Participants will be stabilized on gabapentin over a period of approximately 1 week. We have used similar titration periods safely in several previous studies (Hart et al., 2004, 2007; Mariani et al., 2006). Participants maintained on active gabapentin at the end of the study will be tapered off of the medication over a period of approximately 1 week.

INCREASED SENSITIVITY TO PRESCRIPTION OPIOIDS:

Participants who were dependent on opioids upon admission to the hospital may be less tolerant to the effects of opioids at discharge. They will be counseled about the risks of decreased tolerance 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 opioids 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.

NALOXONE CHALLENGE TEST:

To determine whether or not participants are dependent on opioids prior to admission into the hospital, we will administer up to 0.8 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 to alleviate those symptoms.

STABILIZATION ON MORPHINE:

Participants may experience withdrawal discomfort during the stabilization period during the first few days after admission into the hospital including sweating, restlessness, stomach pain, headache, anxiety, nausea, vomiting, dizziness, runny nose, yawning, muscle aches, or tremors. If participants experience these symptoms, we will prescribe medications such as clonidine, clonazepam, ketorolac tromethamine, ondansetron, and ibuprofen or acetaminophen to alleviate those symptoms. Benzodiazepines will only be administered in relatively low, oral doses so the risks of adverse reactions due to the combination of opioids and benzodiazepines will be low. Clonidine and other comfort medications will only be used during the initial stabilization phase and will be discontinued prior to the laboratory sessions.

PREGNANCY:

Female participants must not be pregnant to be included in the study. Pregnancy tests will be performed during screening and every other week during study participation.

BLOOD DRAWING:

During the screening assessments, approximately 30 cc venous blood will be collected for medical evaluation. In addition, approximately 70 cc venous blood will be collected for genetic testing (DNA will be extracted and stored in our freezer) and measurements of plasma levels of morphine and gabapentin. Blood drawing may cause slight discomfort at site of needle entry and result in a small bruise.

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, family members, or made public in any way. A Certificate of Confidentiality **has been** 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. Blood samples for genetic testing will be sent only with participant code numbers, with no potentially identifying information. Only the study investigators will have access to the codes linking the participant to his or her identifying information. The agencies performing these genetic tests will not have access to the subjects' 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 is stored without names or other identifiable information. Participants will be identified only through a numerical code in all electronic databases.

Describe procedures for minimizing risks

Opioid Administration: Medications will be administered by medical staff trained in the use of opioids, and in the management of respiratory effects of opioids. Emergency doses of an opioid antagonist(naloxone), resuscitative and intubation equipment, and oxygen will be readily available. During experimental sessions, oxygen saturation and vital signs will be continuously monitored, and the participant will be observed for early signs of hypotension, apnea, upper airway obstruction and oxygen de-saturation.

Criteria for Withholding Drug: Vital signs prior to oxycodone administration must be within acceptable ranges (%SpO2 > 92) for drug administration to occur. Careful attention will be paid to oxygen saturation since respiratory depression is a clear sign that no further doses should be administered. We will ask participants to take a deep breath if their oxygen saturation falls below 90%. In the unlikely event that prompted breaths do not bring the oxygen saturation above 90% within 3 min, we will provide supplemental oxygen through a nasal cannula. We will administer naloxone if the above measures are unsuccessful in restoring normal oxygen saturation. We have safely tested a bolus dose of 50 mg intravenous oxycodone in a previous study, so we do not anticipate problems with the doses of oxycodone proposed here (Comer et al., 2008).

Sensitivity to Opioids: 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.

Study Drug: Participants will be informed about the possible side effects of gabapentin and will be told to notify a nurse or physician if begin to experience any of them. If present, medical staff will note which symptoms are present, their severity, and make a decision whether to continue the participants in the study.

Naloxone Challenge: We will monitor their participants' reactions to naloxone for up to 50 min. At the end of this period, we may prescribe oral morphine or an intramuscular injection of morphine to alleviate those symptoms.

Stabilization: If participants experience withdrawal symptoms, we will prescribe drugs such as clonidine, clonazepam, ketorolac tromethamine, ondansetron, and ibuprofen or acetaminophen to alleviate those symptoms. Trazodone or zolpidem will be available on some evenings at bedtime throughout the study to help alleviate the insomnia that participants may experience.

Inpatient Facilities: We describe the isolation, boredom and inactivity at length prior to signing the consent form. Of course, participants are free to leave the study at any time. However, participants are advised to avoid evening, night, and weekend discharge so that measures to prevent opioid overdose can be instituted.

Additional Procedures to Minimize Risk:
a) Participants are fully informed of the potential side effects of the drugs and the risks of the procedures. 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. 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. b) An extensive battery of screening tests, including psychometric evaluations, interview assessments, and a medical examination in order to provide as much information as possible upon which to base participant selection. c) The maintenance of continuous visual observation and communication with participants throughout experimental sessions in order to provide adequate information about methods and procedures, as well as to immediately detect any adverse participant reactions. d) Strict adherence to the agreement with participants to permit withdrawal from participation in the research at any time in order to minimize any adverse participant reactions. e) The location of the laboratory within the Psychiatric Institute complex to assure the continuous availability of an on-call psychiatry resident in order to provide medical treatment as needed. All participants are fully informed of the various side effects that they might experience, and since all have had extensive drug histories, these should be familiar to them. Participants are monitored 24 hr/day. 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.

During the last week of the study and/or prior to discharge, participants will receive counseling about different treatment options. For those participants requesting treatment, appropriate arrangements will be made including placement with a buprenorphine provider, enrollment in an outpatient treatment study at our Substance Treatment and Research Service (STARS), if they are eligible, or enrollment in a therapeutic community. Our research staff, as well as social workers on the inpatient unit, facilitate activation of Medicaid and treatment engagement prior to discharge. Initiation of buprenorphine or naltrexone administration will be provided on the inpatient unit. We will provide up to 2 weeks of buprenorphine/naloxone sublingual films to bridge those participants who desire treatment and need time to enter a facility. They will be expected to come here every 3-5 days to pick up the amount of films needed to bridge them to treatment. If buprenorphine maintenance is not desired, we will provide them with 3-4 sublingual films with instructions upon discharge for harm reduction purposes. Follow up treatment is also available to all participants who request it. We will provide a naloxone kit and training to all participants prior to discharge from the inpatient unit on how to recognize the symptoms of opioid overdose and how to respond to it. We will also counsel them about the risks of overdose at each visit during

screening and at each visit when they pick up their study payments. During the screening and study payment visits, we will perform urine drug screens, including screening for fentanyl use. We will discuss the results of the urine drug tests with all participants and warn them about the particular risks associated with the use of fentanyl.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
We deal with issues of confidentiality by using coded records, store signed consent forms in a locked safe, and try to the best of our ability to maintain confidentiality. Electronic data are stored on computers that are password protected. We **have obtained** a Certificate of Confidentiality for this study. We also point out to prospective participants that we cannot assure that their drug histories and other personal records might not become known. Those who are hospitalized have hospital charts and we cannot guarantee the confidentiality of these charts.
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 subjects directly.

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 for each visit of the screening process ($25/visit). We anticipate that screening will necessitate 3-4 visits. Participants will also be paid $25 for a follow-up visit approximately 4 weeks after study completion.

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. 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 approximately $5700. It is not possible to determine a priori the exact number of study days (e.g., accounting for holidays, admission date, staff schedules, etc.) and the consent form does not specify a number.

Assuming that the participant agrees to continue in the protocol, s/he will be paid according to the same schedule described above.

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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 Information Sheet(s)
Upload copy(ies) of bolded Information Sheet(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
hipaa op:alc feb 2019.pdf
Upload any additional documents that may be related to this study

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

Protocol Number: 7476 **Principal Investigator:** Sandra D. Comer, Ph.D.

Name of Study: Medication Development for Opioid and Alcohol Abuse: Laboratory Study in Humans

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

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

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

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

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

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

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

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

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

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

4. Please note that:

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

  Sandra Comer PhD., New York State Psychiatric Institute
  1051 Riverside Drive (Unit 120) New York, NY 10032

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

5. This Authorization does not have an end date.

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

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

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

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

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

Statistical Analyses

In order to control for Type-1 error and to be consistent with the 2017 FDA Assessment of Abuse Potential of Drugs Guidance for Industry, drug liking was considered the primary abuse liability endpoint. VAS data were analyzed using repeated-measures ANOVAs with planned contrasts with medication dose (2 levels) as the first factor, OXY dose as the second factor (3 levels), ALC dose as the third factor (3 levels), and time as the fourth factor (16 levels). Two repeated-measures ANOVAs were conducted: 1) mean time course of drug effects across the test session, and 2) mean peak ratings. P values less than 0.05 were considered statistically significant, consistent with the 2017 FDA Assessment of Abuse Potential of Drugs Guidance for Industry.

Informed Consent for Participation in Research

Study Title:	Medication Development for Opioid and Alcohol Abuse: Laboratory Study in Humans
Study #:	NYSPI IRB#7476
Principal Investigator:	Sandra D. Comer, Ph.D.
Study Doctor:	Jeanne M. Manubay, M.D.
Study Center Address:	New York State Psychiatric Institute 1051 Riverside Drive, Unit 120 New York, NY 10032

24-Hour Emergency Contact:	Dr. Sandra Comer	646-774-6146
	Mr. Vincent Woolfolk	917-873-4331

You should keep a copy of this form. If you have any questions or problems during the study, call the phone number(s) above.

The study doctor wants to know if you would like to be part of a research study.

If you have any questions about the study or do not understand something in this form, you should ask the study doctor or study staff. You should also discuss your participation with anyone you choose in order to better understand this study and your options.

Participating in a research study is not the same as getting regular medical care. The purpose of regular medical care is to improve your health. The purpose of a research study is to gather information.

Study Purpose and Overview

Summary: This page is a summary of the study in which you are being asked to participate. This outline is meant to be a guide for you to use while considering the study and reading the consent form. It is not meant to replace the consent form you will be asked to sign if you decide to participate in the study. The consent form contains much more detailed information about the study and the risks that you will be asked to consider in making your decision.

- The main purpose of this research study is to gather information on how safe and effective a medication called gabapentin is for the treatment of opioid and alcohol use disorder. Gabapentin (Gralise®) is a medication given orally (by mouth) and is currently approved by the U.S. Food and Drug Administration for the treatment of pain from nerve damage. You are confirming that you drink alcohol at least 3 times per week and you are physically dependent on heroin or prescription opioids. Also, you are confirming that you are not seeking treatment for your substance use. This study is funded by the National Institute on Drug Abuse and Depomed, the company that markets gabapentin.
- Throughout the study (about 8 weeks) you will live on 5-South, a locked inpatient psychiatric unit. After stabilization on morphine given by mouth (orally) and the study medication (gabapentin), you will begin testing.
- You will receive a drink (beverage) containing either: active oxycodone, active alcohol, a combination of active oxycodone plus active alcohol, or "placebo," a beverage containing neither oxycodone nor alcohol.
- Throughout the study there will be 18 lab sessions where the drink is administered. These sessions are about 6.5 hours long and include: behavioral testing (answering questionnaires) and physiological testing (measurements of heart rate and breathing).
- Counseling about different treatment options and referrals for treatment are available at any time, before, during, or after your participation in this study. You will be asked about your interest in treatment twice during the study, once near the beginning and once near the end of your stay.

Risks: There are several risks and discomforts associated with participation in this study. Please read the risks section of the consent form for more details and explanations of these risks. Common side effects of gabapentin include dizziness, drowsiness, loss of balance, confusion, headache, nausea, vomiting, dry mouth, blurred vision, cold or flu-like symptoms, loss of balance, trembling, skin rash, loss of appetite, stomach pain, weight gain, breast swelling, changes in urination, rapid back and forth movement of the eyes, and swelling in the hands and feet. In addition, a rare but serious adverse event has been reported in association with gabapentin called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity. Some of these events have been fatal or life-threatening, and include symptoms such as fever, rash, abnormal lymph nodes, and sometimes looks like an acute viral infection. Alcohol can make you feel dizzy, faint, confused, drowsy, and nauseated. The most serious side effects of opioids include: slowed breathing, periods where breathing stops, or death.

This is a voluntary research study and you do not have to participate if you do not want to. This research is not meant to benefit you directly**.** Please contact Dr. Sandra Comer, who is in charge of the study, with any questions at (646) 774-6146.

PURPOSE OF THIS STUDY

The main purpose of this study is to gather information on how safe and effective a medication called gabapentin is for the treatment of opioid and alcohol use disorder. Gabapentin (Gralise®), which will be used in the current study, is a medication given orally (by mouth) and is approved by the U.S. Food and Drug Administration for the treatment of pain from nerve damage. Another formulation of gabapentin (Neurontin®) is approved for treating both nerve damage pain and seizure disorders. You are confirming that you drink alcohol at least 3 days a week (15 drinks per week for men and 8 drinks per week for women), and that you are physically dependent on heroin or prescription opioids. In addition, you are confirming that you are not dependent on any other drug with the exception of opioids, nicotine, and/or caffeine, and you are not currently seeking treatment for your drug use. The National Institute on Drug Abuse and Depomed, the company that markets gabapentin, are funding this study.

The study will examine how gabapentin may affect your response to oxycodone, alcohol, and the combination. It is planned that about 24 people with a diagnosis of opioid and alcohol use disorder will complete this study.

VOLUNTARY

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Medical Center.

ALTERNATIVES TO STUDY PARTICIPATION

This is not a treatment study. Data are being collected for research purposes. Counseling about different treatment options and referrals for treatment are available at any time before, during, or after your participation in this study. You do not have to participate in this study in order to get a referral to help stop taking drugs. If you are interested in treatment, an appropriate outpatient treatment will be arranged. Available treatments for opioid use disorder include methadone and naltrexone maintenance. Maintenance on buprenorphine and the buprenorphine/naloxone combination also are available. Available treatments for alcohol use disorder are naltrexone, disulfiram and acamprosate. We will talk to you about your interest in treatment at least twice during the study, once near the beginning and once near the end of your stay. If you are interested in treatment with a medication for your opioid and alcohol use disorder, we can start giving you the medication before you leave the hospital. If you are interested in treatment with methadone, we will arrange for you to begin treatment after you leave the hospital. We will also ask you if a friend or family member would be interested in helping you with your treatment.

STUDY PROCEDURES

You have been chosen as a potential participant in a research study. You have signed the screening consent form, and passed the medical and psychiatric screening. If you are a woman, you have been given a pregnancy test at screening and you will be given another when you move into the hospital. If you are pregnant or breastfeeding, or if you have had an abortion within the past six months, you will not be able to participate. If you think you might be pregnant, please tell the investigator. Also, since pregnant women may not participate in

this research, women must practice an effective method of birth control until the end of the study.

Practice Session: If you agree to participate, you will have a practice session before and/or after you move into the hospital to show you what happens during the laboratory sessions.

Naloxone Challenge Test: You may be given up to 0.8 mg naloxone, a drug used to reverse the effects of opioids, which will put you into a state of withdrawal. If you prefer not to receive naloxone, you can come to the laboratory at some point during the screening process to show us clear symptoms of opioid withdrawal. We will tell you if you can participate in the study when all screening procedures are completed.

General Information About 5-South: While enrolled in the study, you will live on 5-South, a locked inpatient psychiatric unit, for about 8 weeks, during which visitors are not allowed. At times when you are not required to fill out questionnaires or do tasks, you can read or do puzzles, as long as these activities do not interfere with the research study protocol. You are free to do other activities on 5-South, which has a game room and television room. You also can use the telephone, books and other reading materials on 5-South. However, you agree not to leave the unit except with staff members for any reason during the study period. Staff will be available to escort you outside the unit for "fresh air" breaks up to four times per day along with gym visits up to three times per week (for those who are physically healthy). You will be given 3 meals per day, along with a bedtime snack.

Stabilization Periods: During the first several days after admission, you will be stabilized on the first dose of gabapentin (active or placebo), given orally once a day, and oral morphine, given 4 times a day. During the stabilization period, you may experience opioid withdrawal symptoms. Therefore, extra medications will be available to you during this period to reduce any withdrawal symptoms that you may experience. About halfway through the study, you will be stabilized on the second dose of gabapentin (active or placebo).

Laboratory Sessions: Laboratory sessions will take place on the 3rd floor of the New York State Psychiatric Institute, and each will last at least 6.5 hours. You will either receive a drink containing either active oxycodone, active alcohol, active oxycodone plus active alcohol, or placebo (no oxycodone or alcohol) for 3 days in a week (Monday, Wednesday, and Friday) for 3 weeks in a row. You sometimes may be asked to take a deep breath if your breathing slows down. Laboratory sessions will include behavioral and physiological testing. You will be asked to answer questions on the computer, and we will measure your heart rate and breathing. After stabilization on the second dose of gabapentin, you will complete another 3 weeks of testing that will be identical to the first 3 test weeks. At the end of each of the two stabilization periods, approximately 2 tablespoons of blood will be collected (one sample in the morning and another in the afternoon) for drug level tests.

Debriefing Session: At the end of the study, we will have a debriefing session with you to answer any questions that you may have. In addition, we would like to meet with you one month after you leave the hospital for a follow-up study visit. During this visit, we will collect blood samples, questionnaires will be given and an electrocardiogram (ECG) will be done.

Genetic Information: As a part of this study, DNA samples are collected using 2 tablespoons of your blood. The purpose of this part of the research study is to look at differences in people's DNA in an attempt to try to understand differences in how people respond to drugs. At the end of this form you are able to decide how your genetic sample is used (check one). For the current study, samples will only be kept for a maximum of 5 years and you can tell us to remove and destroy the samples at any time during or after the study. However, if you provide consent for your DNA to be used by other researchers, once these samples are out

of our hands, you will no longer be able to withdraw consent for their use. Because these samples will have been completely de-identified, there will be no way to trace your sample back to you. In some cases, whole blood samples can be used to make a cell line (cells from participants' blood will be cultured and kept alive to further study the DNA). The purpose of establishing a cell line is to create a source of DNA for storage in a repository for future research. Once created, cell lines can be used indefinitely.

RISKS AND INCONVENIENCES

Oxycodone. The most frequently reported adverse experiences associated with oxycodone administration are: lightheadedness, dizziness, sedation, nausea, and vomiting. Decreased blood pressure, slowed breathing, mood changes (euphoria, dysphoria), constipation, skin rash, dry mouth, headache, sweating, weakness, seizures, and itchiness have also been reported. More rarely, irregular heartbeats, slowed heartbeats, and tremors have been reported.

Alcohol. The most common side effects of alcohol include: dizziness, faintness, irritability, confusion, drowsiness, sleepiness, sleep disturbance, lightheadedness, clumsiness, loss of balance, inability to concentrate, tremor, restlessness, stomach upset, vomiting, headache, pale skin, flushing, sweating, dry mouth, slurred speech and tiredness. Rare side effects that could be more serious include: depression, itching, fever, heart pounding, irregular heart beats, nausea, increased or decreased blood pressure, blurred vision, rash, or possibly an allergic reaction.

Gabapentin. Common side effects include dizziness, drowsiness, confusion, headache, nausea, vomiting, dry mouth, blurred vision, cold or flu-like symptoms, loss of balance, trembling, skin rash, loss of appetite, stomach pain, weight gain, breast swelling, changes in urination, rapid back and forth movement of eyes, and swelling in the hands and feet. Antacids containing aluminum or magnesium may interfere with the absorption of this medication. Morphine can interact with this medication by worsening dizziness, drowsiness and confusion. Rare side effects that could be more serious are weight gain, chest pain, irregular heart rhythm, shortness of breath, delusions, increased risk of suicidal thinking and behavior, increased risk of seizures if discontinued suddenly, easy bruising or bleeding, or possibly an allergic reaction. In addition, a rare but serious adverse event has been reported in association with gabapentin called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity. Some of these events have been fatal or life-threatening, and include symptoms such as fever, rash, abnormal lymph nodes, and sometimes looks like an acute viral infection. You will be stabilized on gabapentin over a period of about 1 week during the study while you are living in the hospital. You will be tapered off the study medication before discharge.

Oral Morphine During Stabilization. During stabilization on oral morphine, you are likely to experience opioid withdrawal symptoms such as anxiety, sweating, nausea, vomiting, diarrhea, stomach upset, changes in blood pressure, weakness, restlessness, feelings of changes in temperature, sneezing, runny nose, watery eyes, gooseflesh, and insomnia. In order to help with these symptoms, you will receive supplemental medications for treating the various symptoms of withdrawal: hydroxyzine or clonazepam for anxiety/restlessness, bismuth subsalicylate (Pepto Bismol®) for diarrhea, clonidine for yawning, runny nose and eyes, sweating, and temperature changes, zolpidem (Ambien®) for insomnia, acetaminophen or ibuprofen for muscle pain and discomfort, simethicone for nausea and stomach upset, and promethazine for vomiting or severe nausea.

Increased Sensitivity to Opioids: As a result of study participation, it is possible that you will be less tolerant to the effects of opioids at discharge. You will be counseled about the risks

of decreased tolerance to opioids. You should be aware that you may be more sensitive to the effects of heroin or other opioids upon completion of this study. This increased sensitivity to opiates could result in overdose and death. Thus, doses of heroin or other opiates that you used to take before entering the hospital could be enough to cause you to stop breathing and die. It is for this reason that an evening, night or weekend discharge from the hospital is discouraged. Fentanyl and carfentanil are powerful synthetic opioids that can be added to heroin without your knowledge and these further increase your risk of overdose. Extreme caution must be exercised after you leave the hospital, if you choose to use any opioid again.

Naloxone Challenge Test. To determine whether or not you are dependent on opioids, we may administer up to 0.8 mg naloxone by injection into your arm muscle, which may produce a number of unpleasant withdrawal symptoms. You 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 your reactions to naloxone for up to 45 min. At the end of this period, we may prescribe oral morphine or an intramuscular injection of morphine to alleviate those symptoms. The doses of morphine have been carefully selected to be below dangerous levels, but you should be aware that you may experience side effects which may include: drowsiness, itchiness, dry mouth, sweating, restlessness, constipation, headache, anxiety, slowed breathing, nausea, vomiting, dizziness, sedation, or tremors.

Blood Drawing. During blood drawing, there is a risk of slight discomfort and/or bruising at the site where the needle is inserted. Approximately 100 ml (about half a cup) will be taken during the study. When someone donates blood, two cups (32 tablespoons) are taken on one occasion.

Inpatient Facility. The risks involved in exposure to the inpatient unit and laboratory are minimal, but you may become bored or restless. Additionally, cigarette smoking on 5-South is not allowed. Electronic cigarettes can be purchased and used at certain times, and nicotine gum or patch will be prescribed on the unit.

BENEFITS

This study is not designed to benefit you personally.

CONFIDENTIALITY

We will do everything we can to keep others from learning about your participation in the research. The information you give us for this study is covered by a Confidentiality Certificate from the National Institutes of Health (NIDA). With this Certificate, the investigators cannot be forced (for example, by court subpoena) to disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure, such as to report suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others, or contagious diseases; if you have consented to the disclosure, including for medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. Such information will be reported to the appropriate authorities. If we learn about serious harm to you or someone else, we will take steps to protect the person or persons endangered even if it requires telling the authorities without your permission. However, we will only disclose

information to the extent necessary to prevent harm to the person or persons believed to be endangered

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project or from Institutional regulatory personnel that is needed for auditing or program evaluation by NIDA which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note however, that if an insurer, employer or other outside party, learns of your participation, and obtains your consent to receive research information, then the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Signed consent forms and other forms containing identifying information will be kept in a locked file, and all interviews, assessments, etc. will be coded with initials and numbers. Your name and other personal identifying information will be stored in an electronically secure database at New York State Psychiatric Institute. Electronic data are also coded and are stored on computers that are password protected.

If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to all researchers to release it. Your private information will only be used for this particular study. Your biological specimens, if collected, may or may not be used by other researchers or for future studies, as indicated by your choices at the end of this consent.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

All records containing links and identifying information related to your genetic information will be kept in locked files and on password-protected computers. This information will only be available to NYSPI personnel key to this investigation. Your blood sample will be labeled with a code that will be used throughout screening and testing. The sample will not have your name, or address on it. The laboratories carrying out the DNA analysis (Columbia University, Human Genetics Resources Core, 630 W. 168th St. New York, NY 10032) and LGC Genomics (100 Cumming Center, Beverly, MA 01915) will never know your identity. If you also agree to have your DNA stored for future research, this number will be removed from your sample so there will be no way to know that it came from you, and it will not be possible to trace your identity.

The Genetic Information Nondiscrimination Act (GINA) provides additional protections for you against discrimination based upon your private genetic information. This Federal law generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance or by adoption agencies. GINA also does not protect you against discrimination based on an already diagnosed genetic condition or disease. If you would like to know more about it you can discuss this with the principal investigator of this study (Dr. Comer, 646 774-6146) or you can go to the following website http://www.genome.gov/10002328.

COMPENSATION

As a result of participating in this research, you will receive $25 for each laboratory screening visit, to a maximum of three visits, and $25 for the naloxone challenge test/visual inspection of withdrawal symptoms prior to being accepted into the study. This money will be paid at the end of each day. You will also receive $50/inpatient day, plus a bonus of $50/inpatient day for completion of the study, and $25 for a follow-up study visit about 4 weeks after you leave the hospital. Total payments will be between approximately $5,700, depending on the number of days it takes you to complete the study.

Payments will not exceed $600 per week. You will return on a weekly basis for your payments until you have received all of the money you earned while participating in the study. Failure to comply with the protocol could result in a deduction from your pay or dismissal from the study. If you withdraw early, you will not receive any of the bonus payment; you will only be paid $50 for each day that you completed.

We are required by law to report your earnings to the IRS. Therefore, your Social Security Number and amount earned will be reported, and you will receive the appropriate IRS form at the end of the year in which you have been paid. Please be aware that research participation may affect your eligibility to get or to keep entitlements such as Medicaid and other city and state support services. No information about which study you participated in will be provided to the IRS.

Research Standards and Participants' Rights

Participation in this project is voluntary, and you may refuse to participate or discontinue participation at any time without loss of benefits to which you are otherwise entitled. You will be notified of significant new findings that may impact your safety and that may relate to your willingness to participate. By signing this consent form, you are indicating willingness to join the research project described to you on this form.

In Case of Injury

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances. New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

Please be aware that:

1. The New York State Psychiatric Institute, Columbia University and New York Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital

2. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.

3. No monetary compensation for wages lost as a result of injury will be paid to you by Research Foundation for Mental Hygiene, the New York State Psychiatric Institute, Columbia University and New York Presbyterian Hospital.

4. By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

Questions

The investigators will answer to the best of his/her ability any questions that you may have now or in the future about the research procedures, or about your response to the procedures. You may contact the Principal Investigator, Dr. Sandra Comer, who can be reached at (646) 774-6146, if you have any questions. If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of participants in research studies). You may call the IRB Office at (646) 774-7155 during regular office hours.

CONSENT

Dr. Comer **may** □**, may not** □ use my genetic sample for the current study.

Dr. Comer **may** □**, may not** □ use my genetic sample for future related studies of drug abuse.

Dr. Comer **may** □**, may not** □ use my genetic sample to create cell lines from my DNA for storage at a national repository. Once the trial ends, I will not be able to request the destruction of the sample because the link of my DNA sample to my identity will have been removed.

I have read this form, and I have been able to ask questions about this study. The study doctor or study staff has talked with me about this study. They have answered all my questions. I voluntarily agree to participate in the research study described above. By signing this form, I do not give up any of my legal rights. I will be given a copy of this consent form.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion, is capable of freely consenting to participate in this research.

_____
Printed Name of Physician/Nurse Practitioner Explaining Consent

_____ _____
Signature of Physician/Nurse Practitioner Explaining Consent Date