NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

January 10, 2017

TO: Dr. Jermaine Jones

FROM: Dr. Edward Nunes, Co-Chair
Dr. Laurence Greenhill, Co-Chair

SUBJECT: **APPROVAL NOTICE**

Your protocol # **7347** entitled **USING PHARMACOGENETICS TO BETTER EVALUATE NALTREXONE FOR TREATING STIMULANT ABUSE** (version date 01-10-17) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **January 10, 2017 to November 6, 2017.** (Reviewed by the Full Board on 11-07-16.)

Consent requirements:

□ Not applicable:

√ 45CFR46.116(d) waiver or alteration of consent (phone screen 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 (R21 DA040225-01A1)

ENC: CFs (2), Advertisements, HIPAA forms (2)

EN/LG/Scr

Protocol Title:
Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

Version Date:
01/10/2017

Protocol Number:
7347

First Approval:
01/10/2017

Clinic:
Opioid Research Laboratory

Expiration Date:
11/06/2017

Contact Principal Investigator:
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Email: jonesje@pi.cpmc.columbia.edu
Telephone: 646 774-6113

Co-Investigator(s):
Sandra Comer, PHD
Verena Metz, PHD

Research Chief:
Frances Levin, MD

Cover Sheet

Choose from the following that is applicable to your study
I am submitting a new protocol

Division & Personnel

Division

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

Unaffiliated Personnel

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

Procedures

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

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Studies of DNA
✓ Administration of Substance of Abuse
✓ Use of Investigational Drug or Device

Population

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

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ 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
Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse
Grant Number
R21 DA040225-01A1
Select one of the following
Single Site
Business Office

RFMH
Does the grant/contract involve a subcontract?
No

Study Location

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

Lay Summary of Proposed Research

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Several preclinical and clinical studies have provided data suggesting that naltrexone (NTX) may have potential to block the abuse potential of stimulant drugs like amphetamines and cocaine. However, there are conflicting findings from the several studies investigating this question. Studies have shown that a variation in the mu opioid receptor gene (A118G) significantly affects the ability of NTX to block the effects of alcohol. The goal of this study is to investigate if this genotype may also affect the interaction between NTX and psychostimulant drugs. We propose to investigate the interaction between NTX and intranasal (IN) methamphetamine (30mg/70kg). **White** participants who meet DSM 5 criteria for mild-to-severe stimulant use disorder **and have a history of intravenous, intranasal or smoked use of amphetamine drugs,** will complete testing sessions where drug effects are examined following administration of NTX (0, 50 mg). The effects of NTX on the the abuse potential of IN methamphetamine will be assessed using self-report measurements of positive drug effects and drug self-administration. NTX's effects will then be compared between *A118G* A allele (AA) and G-allele (AG/GG) groups, in order to assess genetic influence. Participants will submit blood samples for genetic analysis upon screening. DNA samples will be batched and genotyped every few weeks, depending on the rate of recruitment. The investigators will periodically assess the genotype count of study completers to attempt to obtain equal numbers in each group.

Background, Significance and Rationale

Background, Significance and Rationale
It is estimated that worldwide there are over 75 million abusers of amphetamines and cocaine. Despite the public health significance of psychostimulant abuse, there remains no FDA-approved medication to facilitate treatment. Preclinical and clinical studies have provided data suggesting that naltrexone (NTX) may have potential for this indication (Jimenez-Gomez et al., 2010; Kim et al.,2001; 2009; Ray et al., 2012; Schad et al., 1995). However, a review of the literature reveals conflicting findings that require resolution. The introduction to genetic techniques to the study of drug abuse has helped to identify a number of genomic loci and variants that may moderate variability in treatment response (Anton et al., 2006; Arias et

al., 2014; Dahl et al,. 2006; David et al., 2007; Schacht et al, 2013). A recent meta-analysis concluded that the OPRM1 A118G SNP (rs1799971) significantly moderates the treatment efficacy of NTX for alcohol abuse, increasing effectiveness by over 2 fold among G-allele carriers (AG/GG). The current study would be the first to investigate the moderating effect of this genotype in the efficacy of NTX to treat stimulant abuse. More specifically, we propose to investigate the interaction between NTX and intranasal (IN) methamphetamine (M-AMPH; 30mg/70kg), a commonly prescribed and abused amphetamine-type stimulant. In an exploratory endeavor, data from all participants will be used to concurrently assess the ability of 5 functionally relevant genetic variants to predict NTX's treatment efficacy [ANKK1 (rs1800497); DβH (rs1611115); OPRM1 (rs1799971); OPRM1 (rs6912029) (Haggkvist et al., 2009; Hendershot et al., 2014) . This study therefore utilizes a focused approach to assess the influence of a genetic polymorphism whose influence has been substantiated by other investigations, and an exploratory approach to assess the individual and combined influence of several likely genetic moderators (Jayaram-Lindström et al. 2005; 2008) . These data may significantly advance individualized assessment and treatment of stimulant use disorder.

Specific Aims and Hypotheses

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This investigation will seek to address the following specific aims:
• Primary Aim: Compare the ability of NTX to alter the subjective and reinforcing effects of IN M-AMPH between groups of OPRM1 A118G SNP carriers (AA vs AG/GG).

We hypothesize that G-allele carriers will report significant reductions in positive subjective and reinforcing effects following active NTX pretreatment. In comparison, AA homozygous participants will report significantly less of an effect of NTX on these measures.

• Exploratory Aim: Assess the association between various functionally relevant candidate genes and NTX treatment response.

The presence or absence of one or more of the target genetic variants will be significantly associated with (and predict) change in the positive subjective and reinforcing effects of M-AMPH following 0 mg NTX and 50 mg NTX pretreatment.

Description of Subject Population

Sample #1

Specify subject population
Stimulant Users
Number of completers required to accomplish study aims
34
Projected number of subjects who will be enrolled to obtain required number of completers

70
Age range of subject population
21-50

Gender, Racial and Ethnic Breakdown
Because the minor allele of the study's primary target variant (A118G) is significantly less common among African-Americans (7%) than non-Hispanic Caucasians (28.7%) or Hispanics (27.8%)(Hastie et al., 2012), it will not be feasible to recruit an adequate number of participants of African ancestry to test the study's primary hypothesis. Further, it is not feasible to combine African-ancestry and European-ancestry participants in the same analysis because to do so would result in confounding due to population genetic differences. Thus, we will enroll only participants who self-identify as White/Caucasian or as being of European ancestry. Of this sample, we anticipate that approximately 30% will self-identify as Hispanic/Latino. Based on previous experiences with recruiting stimulant abusers in the NYC area, we anticipate that 15% of our sample will be female. **The investigators feel the anticipated ethnicity and sex enrollment figures reflect the population of amphetamine-type stimulant (ATS) users in New York City (NYC). The higher proportion of males reflects the nature of ATS abuse in this region, being primarily among gay males. The higher proportion of Hispanics is due to their higher representation within the NYC area.**
Description of subject population

- Participants will be individuals with mild-to-severe stimulant use disorder [**specifically, amphetamine-type stimulants (ATS), including ecstasy**] of Caucasian or of European descent, not seeking treatment for their drug abuse.
- Participants will be between the ages of 21 and 50, meeting the physical and mental health standards outlined in the Inclusion/Exclusion Criteria.
- Participants must have some experience with intranasal drug use.

Recruitment Procedures

Describe settings where recruitment will occur
Recruitment will primarily occur via print and online mediums. Potential participants who respond to ads will complete a brief phone screen and then are scheduled for complete screening at the New York State Psychiatric Institute (NYSPI).
How and by whom will subjects be approached and/or recruited?
We will recruit non-treatment seeking stimulant users. Initial contact is made by the study's research assistants or volunteers who receive calls from potential participants who respond to the study's various advertising methods.
How will the study be advertised/publicized?
Recruitment will be primarily through advertisements in local newspapers and online formats such as ResearchMatch and Study KiKs, along with app-based advertising.
Do you have ads/recruitment material requiring review at this time?
Yes

Does this study involve a clinical trial?
No

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Potential participants may also be recruited from protocol# 7060 (PILOT STUDY: DYNAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING TO MEASURE BLOOD-BRAIN BARRIER PERMEABILITY, PI: Dr. Sandra Comer). This 9-day inpatient study also recruits recreational stimulant users to complete laboratory testing sessions where intranasal methamphetamine is administered. Potential participants' screening information may be shared between the two protocols. For example, if a participant originally screens for study 7060, but their schedule does not accommodate the inpatient stay, they may be allowed to enroll in the current protocol, should they meet criteria. Completers from either study may also be transitioned directly into the other study, if their screening materials are still valid and show that they meet all criteria.

Inclusion/Exclusion Criteria

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

1) Male or female age 21 to 50 years (self-report with ID verification).

2) DSM-5 criteria for mild-to-severe stimulant use disorder, along with intravenous, intranasal or smoked use of amphetamine-type stimulants in amounts equal to or greater than administered in the current study (Psychiatric Exam, MINI SCID).

3) Able to give written informed consent to participate (Physician's assessment).

4) Females must be either post-menopausal, surgically sterilized, or using an acceptable method of contraception (double-barrier method like a condom with a spermicidal lubricant) to participate in this study (Clinical Interview, blood/urine pregnancy tests).

5) Racially Caucasian or of European descent. (Self-Report /Investigator Assessment).

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

1) Currently seeking treatment for a substance use disorder (Clinical Interview).

2) DSM-5 criteria for moderate-to-severe substance use disorders (except those involving cocaine, amphetamines and nicotine) (Psychiatric Exam).

3) Psychiatric condition that may affect the participants' ability to provide informed consent (e.g., psychotic disorder), or make participation hazardous for the participant or study staff (e.g., severe depression/suicidality, or risk of violence) (Psychiatric Exam).

4) Uncontrolled neurological, cardiovascular, and hepatic diseases, active tuberculosis, or any other disorder that might make administration of study medications hazardous (Medical History/Physical Exam).

5) Gastrointestinal or renal disease that would significantly impair absorption, metabolism or excretion of study drug, or require medication or medical treatment (Medical History/ Physical Exam).

6) Current treatment with a psychotropic medication that in the physician's judgement would interfere with the study endpoints (Clinical Interview, Psychiatric Exam).

7) History of allergy, adverse reaction, or sensitivity to amphetamines (Clinical Interview).

8) Medical conditions that may make study participation hazardous [(Medical History, Physical Examination, Vital Signs, ECG, and laboratory tests (hematology, blood chemistry, urinalysis)].

- History of seizures or cardiac risk conditions (unstable angina, cardiac arrhythmias, chest pain, strong palpitations (subjectively defined as the feeling that the heart is beating too hard, too fast, skipping a beat, or fluttering).
- Elevated liver function tests (i.e., AST and ALT > 3 times the upper limit of normal).
- Impaired renal function (creatinine > 1.2).
- Hypertension (>140/90).
- Pseudocholinesterase deficiency.
- Asthmatic symptoms within the past 3 years.

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
The participant's verbal consent is first obtained to complete the telephone screen (Research Assistant or Volunteer). Upon their first visit to NYSPI the participant is informed of the various screening procedures that determine eligibility for the study and sign a screening consent form (Study Nurse or Research Psychologist). Participants agree to provide a blood sample for genetic testing, as a part of the screening procedures. Upon this first visit, the study consent form is extensively reviewed with the participant, however, the study consent form is only signed by the participant and physician once screening procedures are completed.
Describe Study Consent Procedures

We utilize a two-step consenting processing wherein the participant first signs the screening consent with a research psychologist or nurse. Once eligibility is determined, participants sign a study consent with a physician. The physician reviews the participant's screening chart, comparing it to the study's inclusion/exclusion criteria to ensure they are met. The physician assesses whether or not the participant is fully aware of the study procedures, risks and benefits, and then signs the consent form with the participant.

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

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
We are only requesting the Waiver of Documentation of Consent for the initial telephone interview during which verbal consent to answer questions is obtained. All other consent procedures are documented with the participant and staff signatures. Verbal consent to complete the telephone interview is first obtained the research assistant (for which the waiver of documentation authorization is requested). If the participant roughly meets study criteria, he or she is scheduled for an in-person screening. Once they arrive at NYSPI, participants sign a screening consent form which is explained to them by a research nurse, study investigator or division physician.
Explain why your research can not be practicably carried out without the waiver or alteration
The waiver will allow us to better rule out significant numbers of individuals who are not eligible without wasting the time of critical staff like physicians and nurses
Describe whether and how subjects will be provided with additional pertinent information after participation
During the phone screen and upon the participants' first visit to NYSPI, the study procedures are described in detail.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Brezing, Christina, MD
Comer, Sandra, PHD
Dakwar, Elias, MD
Evans, Elizabeth, MD
Jones, Jermaine, PHD
Luo, Sean, MD
Manubay, Jeanne, MD
Marino, Leslie, MD
Mogali, Shanthi, MD
MURRAY, JANET
Shulman, Matisyahu
Tindall, Claudia
Urban, Nina, MD
Vaezazizi, Leila
Williams, Arthur
Woolfolk, Vincent
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Stimulant users will call the screening telephone number posted on newspaper ads, online ads, etc. and complete the telephone interview (by study volunteers or research assistants) if they are interested in participating in the study. If the participant roughly meets study inclusion/exclusion criteria, he or she will be scheduled for an in-person screening. Once they arrive at NYSPI, participants will sign a screening consent form that will be explained to them by a research nurse or study investigator.

Screening procedures will include: Self-reported medical history and depression inventory, measurements of height/weight and vital signs by a nurse or bachelors-level research assistant, basic clinical labs (hematology, chemistry and urinalysis), an electrocardiogram (ECG), and a clinical interview and Mini-SCID by a PhD-Level research psychologist or Clinical Psychology PhD student. A physical and psychiatric examination will be conducted by a physician. Medical oversight will be provided by Dr. Jeanne Manubay (Medical Director) and Shanthi Mogali, Division physician fellows will also be employed to be on call during lab sessions.

Study consent will be obtained from participants who pass the extensive medical and psychological screening, and testing sessions will be scheduled. Participants complete **four** lab sessions assessing the effects of pretreatment with 2 doses of NTX (0 and 50 mg; in random order) in combination with IN M-AMPH (30mg/70 kg).

Sessions will be completed on an outpatient basis. The morning of the sample session (Day 1), participants will first complete a standard 11-panel urine drug screen and pregnancy tests. Both tests must be negative to proceed with the session. Exceptions may be made for marijuana positive urine tests at discretion of the investigators, if they feel the positive result is not due to recent (within 24 hrs) use.

At 60 minutes prior to each session vital signs [blood pressure (BP), heart rate (HR), electrocardiogram (ECG)] will be assessed and participants will receive oral naltrexone or placebo. ECG, HR, oxygen saturation, respiration rate and ETCO2 will be continuously monitored (Research Assistant). An automated Criticare System will measure BP every 5 minutes. All vitals will be recorded every 5 minutes.

At -30 minutes participants will complete the pre-methamphetamine performance and subjective effects batteries, which will be subsequently assessed every 30 and 15 minutes after drug administration, respectively. Intranasal methamphetamine (M-AMPH) is administered at time 0 (by Physician), with sample session assessments continuing for 3 hours post drug administration (See Schedule of Events). Drug subjective effects will be assessed using a computerized 26-item visual analog questionnaire (VAS) and the Drug-Effect Questionnaire (DEQ), along with the Sexual Probability Discounting Task/Sex Value Assessment Task (assessment of delay discounting of condom-protected sex, only at screening and 1 hour after M-AMPH administration). Performance tasks include the digit-symbol substitution task (DSST), designed to assess changes in visuospatial processing; and the divided attention task (DAT), designed to assess changes in vigilance and inhibitory control. Following successful completion of a field sobriety test, participants are sent to their home address in a taxi or car service.

Participants will return the next day to complete the choice or self-administration session (Day 2). Participants complete a 60-minute, 10-trial self-administration procedure where at each trial they are given the option to choose between 1/10th of the sample drug or 1/10th of the alternative monetary reinforcer $15. The response requirements to choose drug or money increases independently as follows: 50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, and 2800 responses. In order to receive 100% of either reinforcer, a participant will have to select that reinforcer on all 10 trials and make a total of 11,550 responses. Following completion of the task, participants received the chosen amount of drug and/or money. Participants' vitals will be monitored for 3 hours post drug administration. Following successful completion of a field sobriety test, participants are sent to their home address in a taxi or car service. The effects of NTX pretreatment on the rewarding and reinforcing effects of M-AMPH (% shift between active and placebo) will be compared between the two A118G genotypes (AA vs AG/GG) to address the study's primary aim.

Subjects who finish both arms of the study will complete a total of 4 lab sessions Sample (Day 1) and Choice (Day 2): 0 mg NTX + M-AMPH & Sample (Day 1) and Choice (Day 2): 50 mg NTX + M+AMPH . Each of the 4 lab sessions will take approximately 4 hours to complete (See Testing Schedule).

The two arms of the study will be completed at least 72 hrs apart. The time between the two arms should allow for the clearance of the study drug from the urine. However, participants who are amphetamine positive the day of the second set of lab sessions may proceed with the session, if after meeting with the investigator, (s)he feels that no other acute amphetamine use is responsible for the positive result.

One month after the discharge, participants will be asked to return to the laboratory for a follow-up evaluation. At this time, participants will be asked about drug use since discharge and will provide a urine sample to test for drugs of abuse.

You can upload charts or diagrams if any
Schedule of events.pdf
Testing schedule.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Participants will be withdrawn from the study if they: 1) do not comply with division policies or study procedures, 2) are deemed medically at risk for further study participation based upon Criteria for Terminating a Session (detailed below), 3) express a desire to receive treatment for their drug use. All participants who are withdrawn from the study will be offered referrals for appropriate medical treatment with their primary care physician and/or treatment for substance use. Treatment studies ongoing at Substance Use Treatment and Research Service (STARS) will be described and the participant will be given a list of inpatient and outpatient treatment services in the New York City area.

Criteria for Terminating a Session: The occurrence of any of the following abnormalities in a participant's vital signs will result in the immediate ending of a laboratory session: (a) Systolic blood pressure > 180 mm Hg, sustained for longer than 6 minutes (> 3 consecutive readings), (b) diastolic blood pressure > **100** mm Hg, sustained for longer than 6 minutes (> 3 consecutive readings), (c) heart rate > (220 – subject age x 0.85) bpm, sustained for longer than 6 minutes (> 3 consecutive readings), and **(d) significant ECG abnormality (e.g., >10 PVC's/hr, or multifocal PVS's, or significant ST changes, chest pain), or seizure are observed.**

Blood and other Biological Samples

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

During screening a 30cc venous blood sample will be collected for medical evaluation. Another 30cc sample will be used to obtain DNA for genetic testing (60 cc in total).

As an NIH-funded genetics study, whole blood samples may be used to make a cell line to create a source of DNA for storage in a repository for future research. If participants consent to their sample being used in future research, their DNA may be available to researchers indefinitely. For the purposes of the current study, DNA information will be kept for a maximum of 5 years.

Assessment Instruments

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

Screening:
Medical History Questionnaire
Clinical Interview/Substance Use Inventory (Research Psychologist)
MINI SCID (Research Psychologist)
Physical/Psychiatric Exam (Physician)
Beck's Depression Inventory
Basic Clinical Labs (Hematology, Chemistry and Urinalysis)
Electrocardiogram (ECG)
CD-RISC-25 (Resilience Scale)
Sexual Probability Discounting Task/Sex Value Assessment Task

Lab Session:
Visual Analog Scale (VAS) assessment of drug effects
Drug Effects Questionnaire (DEQ)
Progressive Ratio drug self-administration
Sexual Probability Discounting Task/Sex Value Assessment Task
Digit Symbol Substitution Task (DSST)
Divided Attention Task (DAT)

Please attach copies, unless standard instruments are used
Substance Use Inventory.pdf
MEDICAL HISTORY QUESTIONNAIRE.pdf
BDI.pdf
SCID.pdf

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
2

Drug #1

Name of the drug
methamphetamine
Manufacturer and other information

Methamphetamine for human use will be obtained from NIDA via the Research Triangle Institute.
Approval Status
IND is approved
IND#
133276
Who holds the IND/IND sponsor?
Other
Enter Name
Jermaine Jones

Drug #2

Name of the drug
Naltrexone Hydrochloride
Manufacturer and other information
Commercially available naltrexone will be purchased from Cardinal Health.
Approval Status
IND is approved
IND#
133276
Who holds the IND/IND sponsor?
Other
Enter Name
Jermaine Jones

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
Although this study will only recruit individuals not seeking treatment, on the last day of the study participants will receive information about different treatment options for drug abuse including: medication trials at STARS, along with inpatient and outpatient behavioral therapy.

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 using drugs.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Blood Drawing: During the screening assessments, 30 cc venous blood samples will be collected for medical evaluation. For subject who qualify for the study another 30 cc will be collected for genetic testing (**60 cc total**). Blood drawing may cause mild discomfort at the site where the needle is inserted, and it poses a small risk of bruising at the site as well as an extremely low risk of infection.

Psychological Distress: The structured interviews, rating scales, and questionnaires should add no physical risk. However, because many of the interviews and assessments are time consuming to complete and involve topics of a sensitive nature, some people have found them to be physically or emotionally tiring. Patients are informed prior to study entry that they can refuse to answer any questions and that they can request to stop at any time. If a participant becomes agitated during any of the interviews or assessments, he or she will be provided with therapeutic assistance.

Methamphetamine Administration: The major risks of intranasal M-AMPH administration are increased blood pressure and heart rate. Other side effects include excitation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, dry mouth, diarrhea, constipation, and weight loss. Less common side effects include seizures, blurred vision, increased thought disorders, psychosis, and hallucinations. Our Division has safely administered psychoactive stimulants including cocaine, amphetamine and methamphetamine via oral, smoked, intravenous and intranasal routes in numerous studies without significant medical complications (Comer et al., 1996, 2001, 2013; Collins et al., 2007; Hart et al., 2001, 2008; Foltin and Haney., 2004: Kirkpatrick et al., 2012).

Naltrexone Administration: Naltrexone may mildly impair the functioning of the liver. This effect on the liver typically resolves after naltrexone is discontinued. Naltrexone may also cause stomach upset, nausea, and vomiting. In addition, administration of naltrexone may increase blood sugar levels, which may produce symptoms such as dizziness, increased breathing, dehydration, sedation, and localized seizures. Naltrexone administration may also induce opioid withdrawal symptoms in an opioid-dependent participant. Although this risk is unlikely as regular opioid use would exclude screening subjects.

Subsequent Drug Use: The possibility of study participants increasing their drug use as a result of their participation in the proposed study is small. Previous studies have shown that administration of drugs of abuse to drug-abusing volunteers does not lead to increased drug use after study participation:
• Bigelow GE, Brooner RK, Walsh SL, Preston KL, Liebson IA. (1995) Community outcomes following research exposure to cocaine or opioids. In: IHL, editor. Problems of Drug Dependence 1994: Proceedings of the 56th Annual Scientific Meeting. Washington DC: NIH; p. 354.
• Elman I, Krause S, Karlsgodt K, Schoenfeld DA, Gollub RL, Breiter HC, et al. (2001) Clinical outcomes following cocaine infusion in nontreatment-seeking individuals with cocaine dependence. Biol Psychiatry 49: 553–555.
• Fischman MW, Schuster CR, Resnekov L, Shick JF, Krasnegor NA, Fennell W (1976) Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 33: 983–989.
• Pratt WM, Davidson D. (2005) Does participation in an alcohol administration study increase risk for excessive drinking? Alcohol 37: 135–141.

Analysis of our own 1 month follow-up data across 5 studies where opioids were administered found that participation decreases drug use and facilitates entry into treatment. More specifically, 42% of our study completers were not using heroin 1 month after study completion and 55% decreased their heroin use from 5.9 bags per day at baseline to 2.9 bags per day at the 1-month follow up visit. In addition, 21% initiated buprenorphine or methadone treatment, 6% enrolled in a detox program, and 25% were referred to treatment (Roux et al., 2012). A similar follow-up analysis of studies where cocaine was administered yielded similar results. Cocaine use significantly decreased at 1 month (-$165.13/week) and 3 months (-$118.59/week) after study participation. This decrease was not accompanied by a change in other drug use, e.g., a compensatory increase in alcohol, marijuana or nicotine use (Kalapatapu et al., 2012).

Pregnancy: Female participants must not be pregnant to be included in the study. Urine pregnancy tests are performed at each screening visit and immediately prior to each lab session.

Confidentiality: Potential participants divulge information that is sensitive and may have adverse social consequences if released. This would include information released to insurance companies, health care agencies, or family members, or information made public in any way. A Certificate of Confidentiality will be obtained for the current study and procedures for protecting confidentiality of records will be followed. Specifically, all data records containing identifying information will be kept in locked files and on password-protected computers. 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 their identifying information. The contract 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 are stored without names or other uncoded identification. Patients will be identified only through a numerical code in all electronic databases.

Genomic Information: Participants will be notified that these samples will be used for an investigation into the association between drug abuse and genotype, and that these samples will be archived for future investigations. Participants will also be informed of the Genetic Information Nondiscrimination Act (GINA) that generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate based upon genetic information.

Describe procedures for minimizing risks

Screening: 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.The exclusionary criteria are designed to minimize the risks to participants. The evaluating study physician or Principal Investigator reviews all medical assessments along with medical history to determine if any would make study procedures hazardous.

Participant Education: All participants will be informed of the possible side effects and risks mentioned above, which will also be included in an informed consent document. For eligible participants, the study PI and research psychiatrist will describe the study in detail including study procedures, and possible risks and

benefits of participation. Participants may sign the consent form only after reading it, having any questions answered, and being given a copy to keep.

Consent Procedures: Participants will provide informed consent to screening and all study procedures prior to testing. Participants are instructed to call us if any untoward effects occur after the laboratory session and are given an emergency contact number.

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 will obtain a Certificate of Confidentiality for this project. 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. Participants in other studies have understood these procedures and have agreed to participate under these conditions.
Will the study be conducted under a certificate of confidentiality?
Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There are no direct benefits to the participants.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will receive $50 for each screening visit, for up to 4 visits. This money will be paid at the end of each day.

Participants will receive $125 for each of the 4 completed lab sessions. Additional money can be earned during experimental sessions.

Participants will also be compensated $25 for any unscheduled visits for repeat laboratory/screenings tests and $50 for the 30-day follow-up visit.

Total payments will be between $650-$800.

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Uploads

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RESEARCH VOLUNTEERS
Have you used Meth or Ecstasy before? Caucasian or Latino men and women, aged 21-50 yrs needed for a research study at the NY State Psychiatric Institute. Earn up to $800. Call the Substance Use Research Center at (646) 774-6243.

RESEARCH VOLUNTEERS
Have you smoked or snorted amphetamines before? Caucasian or Latino men and women, aged 21-50 yrs needed for a research study at the NY State Psychiatric Institute. Earn up to $800. Call the Substance Use Research Center at (646) 774-6243.

Do you use Crystal?
The Substance Use Research Center at the NY State Psychiatric Institute seeks healthy, Caucasian or Latino Meth or Ecstasy users, between the ages of 21-50, for a research study evaluating stimulant effects. You can earn up to $800. For more information, call (646) 774-6243.

Do you use Meth?
The Substance Use Research Center at the NY State Psychiatric Institute seeks healthy, Caucasian or Latino Meth or Ecstasy users, between the ages of 21-50, for a research study evaluating stimulant effects. You can earn up to $800. For more information, call (646) 774-6243.

Do you use Ecstasy?
The Substance Use Research Center at the NY State Psychiatric Institute seeks healthy, Caucasian or Latino Meth or Ecstasy users, between the ages of 21-50, for a research study evaluating stimulant effects. You can earn up to $800. For more information, call (646) 774-6243.

Do you Party?
The Substance Use Research Center at the NY State Psychiatric Institute seeks healthy, Caucasian or Latino Meth or Ecstasy, users between the ages of 21-50, for a research study evaluating stimulant effects. You can earn up to $800. For more information, call (646) 774-6243.

Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse Screening Consent Summary Form

Purpose of Study

The goal of this research study is to collect **information** on the effects of amphetamine-type drugs, how they interact **with the medication naltrexone,** and how genetics may alter this interaction. Genetics is the study of how genes control characteristics like your hair and eye color. Just as differences in our genetic code help explain why we all look different, these differences can also help to explain why some medications are effective for some people but not for others.

You are being asked to screen for this study as a stimulant user. By participating, you will help researchers meet the goals of the study. This study is being funded by the National Institute on Drug Abuse. Dr. Jermaine Jones is the principal investigator and the person in charge of the study. All screening and study procedures will be conducted at the New York State Psychiatric Institute (NYSPI).

Participation in this screening 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. This is not a treatment study. **Information is** being collected for research purposes. Referrals for treatment are available at any time. 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 treatment referral will be arranged.

Study Procedures

You have been selected as a potential research volunteer. In order to participate in the study, you must first pass medical and psychiatric screening. This will include answering a general health questionnaire and other questionnaires relating to drug use; receiving an interview by a psychologist; and a physical examination. An electrocardiogram will be done to check the functioning of your heart. Blood samples are also collected to assess your general physical health, and urine samples are collected to test for drugs of abuse as well as pregnancy. If you are a woman, you will be given a pregnancy test. If you think you might be pregnant, please tell the investigator. You will be given another pregnancy test before each testing session, and if it is positive you will not be eligible to participate. Additionally, this study has a genetic component that requires the collection of a blood sample to extract DNA (described in detail in the Study Consent form). The cells of your body contain a molecule called deoxyribonucleic acid, or DNA for short. DNA is passed down from your parents and carries a code, in the form of genes, which determines your physical characteristics, such as the color of your hair and eyes.

If you are still eligible after the screening, the study will be described to you in detail and you will be given a detailed Study Consent form outlining all aspects of the study.

Risks

During blood drawing, there is a risk of slight discomfort and/or bruising at the site where the needle is inserted. Approximately 2 tablespoons will be taken for health testing**. If** you qualify for the study, another 2 tablespoons will be collected for genetic testing (4 total tablespoons). When someone donates blood, 32 tablespoons are taken on one occasion.

The structured interviews and questionnaires are time consuming to complete and involve topics of a sensitive nature.

As in any research study, it is possible that personal information about you could become known to other people. The investigators will take precautions to prevent this from happening. Your name will not appear on any questionnaires or tests that you complete during the study. Instead, all questionnaires and tests you complete will be coded with a study code number. The results from your individual genetic analyses will be kept confidential as described above.

Benefits
You are not expected to benefit directly from participation in this study. However, research studies such as this one may help scientists investigating risk factors for drug abuse, and **in** the development of treatment medications.

Confidentiality
We have applied for a Certificate of Confidentiality issued by the National Institutes on Drug Abuse (NIDA). With this Certificate, the researchers cannot be forced to release any research data in which you are identified, even under a court order or subpoena, without your written consent. The Certificate does not prevent the researchers from reporting suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others. Such information will be reported to the appropriate authorities.

You should understand that 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. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Records will only be available to research staff and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Your name and other personal identifying information will be stored in an electronically secure database at New York Psychiatric Institute. Electronic **information is** also coded and is stored on computers that are password protected. 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.

Compensation
As a result of participating in this screening you will receive $50 per screening visit, to a maximum of four visits. If you are enrolled in the study and complete all study procedures, you will earn between $650 and $800.

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. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator at (646) 774-6113 so that you can review the matter and identify the medical resources that may be available to you

Questions
The investigators will answer to the best of his ability any questions that you may have now or in the future about the research procedures. You may contact the Principal Investigator, Dr. Jermaine Jones, who can be reached at (646) 774-6113, if you have any questions. You will be given a copy of this consent form to take home with you. 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 human subjects in research studies. You may call the IRB Main Office at (646) 774-7155 during regular office hours.

Documentation of Consent

I voluntarily agree to participate in the research study described above.

Name of Participant_____

Signature of Participant_____ Date_____

Investigator, Physician, or Nurse

Printed Name_____

Signature_____Date_____

Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

Consent Summary Form

Below 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 need to sign if you decide to participate in the study. The consent form contains much more detailed information about the study and the risks you will need to consider in making your decision.

- You are being asked to participate in a research study that is attempting to collect information on the effects of an amphetamine drug, if they can be blocked by another medication, and how your genetics plays a role. Genetics is the study of how genes control characteristics like your hair and eye color. Just as differences in our genetic code help explain why we all look different, these differences can also help to explain why some medications are effective for some people but not for others.

- You will complete 4 laboratory sessions. During 2 of these sessions an amphetamine drug will be administered intranasally, along with an oral dose of the medication naltrexone. During the other 2 sessions you will have the opportunity to work for the drug or money by making finger presses on a computer mouse.

- Each laboratory session is about 4 hours long.

- Like all research, your decision to participate is up to you; taking part is voluntary.

Risks of Study Participation:

- If you decide to participate in this study, there are possible side effects and potential risks you should know about, and these are detailed in the consent form.

- The major risk of study participation is related to amphetamine administration. There have been reports of death and potentially a heart attack associated with amphetamine use. On rare occasions amphetamine use has been associated with chest pain, temporary hallucinations (seeing and hearing things that were not present), disorientation, seizures and muscle stiffness. You may also experience: excitation, restlessness, anxiety, headache, dry mouth, diarrhea, constipation, rapid pulse, loss of appetite, fluttering of the heart, irregular heart beats, and occasionally nausea, dizziness, sedation, or tremors.

Benefits

This study is not designed to benefit you directly. The genetic results will not be available to you or your doctors. However, research studies such as this one may help scientists investigating risk factors for drug abuse, and in the development of treatment medications.

Compensation

You will be compensated for your time and effort. As in all research, it is your choice to participate in this study and you do not have to participate if you do not want to. Also, you may stop participating at any time. Please read the Consent Form carefully and ask the study physician any questions or concerns you might have.

You can contact Dr. Jermaine Jones at (646) 774-6113 with any questions.

Consent Form

Study Purpose: The goal of this research study is to collect information on the effects of amphetamine type drugs and how they interact with the medication naltrexone. As a part of this study we will look at differences in people's DNA in an attempt to try to understand differences in how people respond to drugs. The cells of your body contain a molecule called deoxyribonucleic acid, or DNA for short. DNA is passed down from your parents and carries a code, in the form of genes, which determines your physical characteristics, such as the color of your hair and eyes; and risk for some diseases. Just as differences in our genetic code help explain why we all look different, these differences can also help to explain why some medications are effective for some people but not for others.

You are being asked to participate because you have some history of use of amphetamine drugs or other stimulants. By participating, you will help researchers meet the goals of the study. This study is being funded by the National Institute on Drug Abuse. Dr. Jermaine Jones is the principal investigator and the person in charge of the study. Study procedures will be conducted at the New York State Psychiatric Institute (NYSPI).

Details about this study are discussed below. It is important that you understand this information so that you can decide if you want to be in this research study. You will be given a copy of this consent form. You should ask the researchers, or staff members who may assist them, any questions you have about this study at any time. This consent form may contain words that you do not understand. Please ask the study doctor or the staff to explain any words or information that you do not understand. You may take home an unsigned copy of this consent form to think about or discuss with your family or friends before making your decision to participate in the study.

The study will enroll up to 70 people at NYSPI.

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 to withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute.

Alternative Treatments/Alternatives to Participation: This is not a treatment study. Information **is** being collected for research purposes only. The alternative to participating would be not to participate. Referrals will be given to you at the end of the study if you are interested in treatment for your drug use. This genetic study is intended to learn about treating drug abuse and not about you. We will not be providing you with any information about your DNA or your risk for developing inherited illnesses.

Study Procedures: If you decide to participate you will undergo the following procedures:

You will participate in a total 4 laboratory sessions. On the morning of each laboratory session a urine sample will be collected to test for recent drug use, and for pregnancy (in women). If either test is positive you will not be eligible to participate. Each laboratory session will take approximately 4 hours to complete. On Day 1 you will receive an intranasal amphetamine drug and an oral drug prior to it. The oral drug will be an FDA-approved opioid receptor blocker (naltrexone) or placebo (sham medication without any effects). Whether you get naltrexone or placebo will be randomly determined (like flipping a coin), and you will not be told which one you get that day. For the next 3 hours after these drugs are given, you will be asked to answer questions on the computer about how the drug makes you feel (such as "I feel high" or "I feel a good drug effect") and the way you might behave in pretend situations involving sex. At the end of the session, you will complete a field sobriety test. If you are not too high or intoxicated, we

will call a car service or taxi to take you to your home address. If medical staff feels you are overly intoxicated, you will be asked to wait with us until we feel it's safe for you to leave.

On the following day (Day 2) you will return to NYSPI and have the opportunity to work for the intranasal drug by making finger presses on a computer mouse. Like at the end of Day 1, you will be asked to complete a field sobriety test before leaving NYSPI. You will repeat these two sessions (Day 1 & 2) again at least 3 days apart. For safety, we will monitor your heart rate, blood pressure and electrical activity of the heart throughout both sessions.

We will ask for you to return about thirty days after your last session to complete a brief follow-up visit.

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. Whole blood samples can be used to make a cell line (cells from participants' blood will be cultured and kept alive forever to further study their DNA). The purpose of establishing a cell line is to create a source of DNA for storage in a repository for future research. The research on DNA and drug abuse will continue for a long time, and so your DNA may be available to researchers indefinitely. However, you may indicate at the end of this form how your genetic sample is used (check one). For the current study, samples will only be kept for a maximum of 5 years. If you change your mind about having your DNA used in future related research, you can tell us to remove and destroy the samples any time during or after the study. However, if you consent to having your sample used to create cell lines, you will not be able to withdraw consent to its use, since identifying information will be removed**.**

Study Risks

Amphetamine Administration: Amphetamine drugs are considered to have a high potential for abuse and there have been reports of death and potentially a heart attack associated with their use. In addition, on rare occasions amphetamine use has been associated with chest pain, temporary hallucinations (seeing and hearing things that were not present), disorientation, seizures and muscle stiffness. You may also experience: excitation, restlessness, anxiety, headache, dry mouth, diarrhea, constipation, rapid pulse, loss of appetite, fluttering of the heart, irregular heart beats, and occasionally nausea, dizziness, sedation, or tremors.

The risks of snorting methamphetamine have not been well characterized. In addition to likely nasal tissue irritation and bleeding, we cannot rule out the possibility of more significant adverse effects including loss of smell, lung damage, inflammation and infection.

Naltrexone Administration: Naltrexone may mildly impair the functioning of the liver. This effect on the liver will improve after naltrexone is discontinued. Naltrexone may also cause stomach upset, nausea, and vomiting. In addition, administration of naltrexone may increase blood sugar levels, which may produce symptoms such as dizziness, increased breathing, dehydration, sedation, and seizures. If you regularly use opioid medications like oxycodone or heroin, naltrexone may cause you to experience withdrawal symptoms.

Behavioral Tasks Risks: You may feel uncomfortable discussing sexual behaviors.

Pregnancy Risks: If you are female in your childbearing years, you will be asked to take a pregnancy test to ensure that you are not pregnant. If you are pregnant or trying to become pregnant, there may be risks to you or your unborn child. If you are nursing an infant, there may be risks to the infant. Females must be either post-menopausal, surgically sterilized, or use an acceptable method of contraception (double barrier method like a condom with a spermicidal lubricant) to participate in this study.

Risks to Privacy: As in any research study, it is possible that personal information about you could become known to other people. The investigators will take precautions to prevent this from happening. Your name will not appear on any questionnaires or test that you complete during the study. Instead, all questionnaires and tests you complete will be coded with a study code number.

Unknown/Unforeseeable Risks: In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this study drug. If you experience any symptoms you believe to be related to the study drug you should call the study staff at 646-774-6243**.**

Study Benefits: You are not expected to benefit directly from participation in this study.

New Information: You will be informed verbally and in writing of any new information, findings or changes to the way the research will be performed that might change your willingness to continue your participation in this study.

Compensation: You will receive $125 for each of the four completed laboratory sessions and $50 for the follow-up visit. With the additional money you could earn during the laboratory sessions, you could make up to $610. Failure to comply with the study could result in dismissal from the study. If you are dismissed from the study or decide to withdraw from the study, you will still receive the payment for the parts 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 were paid. Please note that payment for this study may affect your eligibility for Medicaid and other city and state support services. No information about which study you participated in will be provided to the IRS**.**

Confidentiality: All written information acquired in this study will be stored in locked files and will be kept confidential to the extent permitted by law. All computer-stored information will be "coded"—labeled only with a code and on password-protected computers. These code numbers will not use a name or any other identifying features. Your name and other personal identifying information will be stored in an electronically secure database at New York Psychiatric Institute that is accessible only to the members of the research team.

We have applied for a Certificate of Confidentiality issued by the National Institute on Drug Abuse. With this certificate, the researchers cannot be forced to release any research information in which you are identified, even under a court order or subpoena, without your written consent. The Certificate does not prevent the researchers from reporting suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others. Such information will be reported to the appropriate authorities. You should understand that 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. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. Records will be available to research staff, and Federal, State, and Institutional regulatory personnel (who may review records as part of the routine audits).

Your genetic information will be kept confidential and de-identified. All records containing links and identifying 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. Jones, 646 774-6113) or you can go to the following website http://www.genome.gov/10002328.

In Case of Injury

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.

Questions

The investigators will answer to the best of his/her ability any questions that the participant may have now or in the future about the research procedures, or about the subject's response to the procedures. You may contact the Principal Investigator, Dr. Jermaine Jones who can be reached at (646) 774-6113, if you have any questions. You will be given a copy of this consent form to take home with you. You will be notified of any significant new findings that may relate to your willingness to continue to participate in this study.

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 human subjects in research studies. You may call the IRB Main Office at (646) 774-7155 during regular office hours.

Documentation of Consent

Dr. Jones **may** ☐**, may not** ☐ use my genetic sample can be used for the current study.

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

Dr. Jones **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 and understand the preceding information describing this medical research study. The study doctor or the study staff has explained it to me in detail and all of my questions have been answered to my satisfaction.

I understand that I will receive a signed copy of this consent form for my records. I voluntarily agree to participate in the research study described above.

Name of Participant_____

Signature of Participant_____ Date_____

Statement of the Investigator (M.D.)

I have examined the participant named above for the purpose of determining whether he/she is capable of understanding the purpose, nature, risks, benefits and alternatives (including non-participation) of the research, making decisions about participation, and understanding that the decision about participation in the research will involve no penalty or loss of benefits to which the patient is otherwise entitled, for Dr. Jermaine Jones' research project "Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse." On the basis of this examination I have arrived at the conclusion that this participant has this capacity at this time.

Printed Name_____

Signature_____Date_____

PI: **JONES, JERMAINE D**	Title: Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse	
Received: 07/15/2015	FOA: PA14-013	Council: 01/2016
Competition ID: FORMS-C	FOA Title: Functional Genetics, Epigenetics, and Non-coding RNAs in Substance Abuse (R21)	
1 R21 DA040225-01A1	Dual:	Accession Number: 3845406
IPF: 1590919	Organization: NEW YORK STATE PSYCHIATRIC INSTITUTE	
Former Number:	Department: 110 NYPI Substance Abuse	
IRG/SRG: GHD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 150,000 Year 2: 125,000	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Jermaine Jones	Research Foundation for Mental Hygiene, Inc.	PD/PI
Sandra Comer PhD	Research Foundation for Mental Hygiene, Inc.	Co-Investigator
Shanthi Mogali	Research Foundation for Mental Hygiene, Inc.	Co-Investigator
Henry Kranzler MD	University of Pennsylvania	Consultant

Appendices

BDI,CGI,DAST,TSR,MEDICAL HISTORY QUESTIONNAIRE,Intake Questionnaire,Substance Use Inventory,RAB,Self-Report ASI_1,SCI

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
DA040225

b. Agency Routing Number

2. DATE SUBMITTED
2015-07-15

Application Identifier
PD/2015/01123

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: 1672049940000

Legal Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Substance Abuse
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007

Person to be contacted on matters involving this application
Prefix: Ms. First Name*: Janelle Middle Name: Rene Last Name*: Greenhill Suffix: MPH
Position/Title: Director of Administration
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007
Phone Number*: 646-774-6500 Fax Number: 646-774-6540 Email: nga@rf.cpmc.columbia.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1141410842A2

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
93.279
TITLE: Drug Abuse and Addiction Research Programs

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

12. PROPOSED PROJECT
Start Date* Ending Date*
04/01/2016 03/31/2018

13. CONGRESSIONAL DISTRICTS OF APPLICANT
NY-013

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Jermaine Middle Name: D Last Name*: Jones Suffix:
Position/Title: Research Scientist IV
Organization Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Substance Abuse
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007
Phone Number*: 646-774-6113 Fax Number: 646-774-6111 Email*: jonesje@nyspi.columbia.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$445,500.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$445,500.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: Ms. First Name*: Janelle Middle Name: Rene Last Name*: Greenhill Suffix: MPH
Position/Title*: Director of Administration
Organization Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Facilities and Admini
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007
Phone Number*: 646-774-6500 Fax Number: 646-774-6540 Email*: nga@rf.cpmc.columbia.edu

Signature of Authorized Representative*
Ms. Janelle Rene Greenhill MPH

Date Signed*
07/15/2015

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

424 R&R and PHS-398 Specific Table Of Contents

Number of Attachments in Appendix: 10

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Research Foundation for Mental Hygiene, Inc.
Duns Number:	1672049940000
Street1*:	Research Foundation for Mental Hygiene, Inc
Street2:	1051 Riverside Drive
City*:	New York
County:	NY
State*:	NY: New York
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	10032-1007
Project/Performance Site Congressional District*:	NY-013

File Name

Additional Location(s)

Funding Opportunity Number: PA-14-013. Received Date: 2015-07-15T14:35:23.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 00006105

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project Summary 7-15-15_1.pdf
8. Project Narrative*	Project Narrative 7-15-15_1.pdf
9. Bibliography & References Cited	References 7-13-15.pdf
10.Facilities & Other Resources	Facilities_Resources_Jones.pdf
11.Equipment	

Funding Opportunity Number: PA-14-013. Received Date: 2015-07-15T14:35:23.000-04:00

PROJECT SUMMARY

There is thought to be over 75 milliion abusers of amphetamines (AMPHs) and cocaine worldwide. Unlike drugs such as heroin, alcohol or nicotine, there is no FDA-approved medication to facilitate the treatment of psychostimulant abuse. Several preclinical and clinical studies have provided data suggesting that naltrexone (NTX) may have potential for this indication. However, a review of the literature reveals conflicting findings that require resolution. Several clinical studies have shown that genetic variation moderates the effects of a number of medications used to treat substance use disorders. A recent meta-analysis concluded that the *OPRM1* A118G SNP (rs1799971) significantly moderates the treatment efficacy of NTX in treating alcohol abuse, increasing the treatment efficacy by over 2 fold among G-allele carriers (AG/GG). The proposed application would be the first to investigate the moderating effect of this genotype in the efficacy of NTX to treat stimulant abuse. More specifically, we propose investigating the interaction between NTX and intranasal (IN) methamphetamine (50mg/70kg). Participants who meet DSM-V criteria for moderate-to-severe stimulant use disorder will complete testing sessions where the abuse liability of IN methamphetamine (M-AMPH) is assessed following pretreatment with NTX (0, 25, 50 mg). Naltrexone's effects upon the abuse potential of IN M-AMPH will be assessed using self-report measurements of positive subjective effects and drug self-administration. Medication effects on these validated predictors of abuse will be compared between A118G A allele homozygotes (AA) and G-allele carriers (AG/GG; an anticipated 25% of the total sample), in order to assess genetic moderation of treatment outcome. The advantage of this approach is that it may help to define individuals in which the treatment exerts its greatest effects. As a secondary aim of the study we will simultaneously assess for possible moderating effects of several functionally relevant genetic variants to predict the how NTX alters the subjective and reinforcing effects of IN M-AMPH [*ANKK1* (rs1800497); *DβH* (rs1611115); *DRD2* (rs2283265); *OPRM1* (rs6912029); *SLC6A3* (rs28363170)]. This study therefore utilizes a focused approach to assess the influence of a genetic polymorphism whose influence has been substantiated by other investigations, and an exploratory approach to assess the individual and combined influence of several likely genetic moderators. Combined, the two studies in this proposal will contribute to the assessment of the clinical utility of NTX for treating psychostimulant abuse, and may help identify gene x pharmacological interactions contributing to the personalization of treatment.

Project Narrative

The proposed investigation will be the first study assessing genetic modulation of naltrexone's effects upon the abuse liability of a stimulant drug (methamphetamine). An exploratory study will concurrently assess the ability of several functionally relevant gene variants to predict pharmacological treatment efficacy. In addition to its contribution to the further development of the first pharmacotherapy for stimulant abuse, this study may identify gene x pharmacological interactions contributing to the personalization of stimulant abuse pharmacotherapy.

Clinical Resources

New York State Psychiatric Institute (NYSPI) and the Columbia University Medical Center (CUMC) Department of Psychiatry together form an active academic medical center and leading teaching hospital that have attracted a distinguished group of research scientists who provide leadership across the breadth of modern psychiatry. The Department of Psychiatry is one of the largest in the country in terms of faculty size as well as state, federal, and foundation research support, and includes over 400 clinical and basic science faculty. The New York State Psychiatric Institute is located in New York City, where it is easily accessible by public transportation and fully equipped to conduct clinical research. The facilities at the NYSPI include 36 clinical research beds, 4 residential research beds, 22 clinical beds, 5 research clinics, animal quarters, a computer center, a research library, and over 100,000 square feet of laboratory space. The clinic space is configured with individual psychotherapy offices, classrooms, subject testing rooms, and medical examination facilities. The NYSPI Pharmacy has a Class IV Institutional License that allows for the distribution of controlled substances for research conducted within the Division. The NYSPI is the primary site for the Division on Substance Abuse and the proposed application, as well as numerous R01's to various Division faculty. The Division on Substance Abuse consists of over thirty individuals who are involved in the Division's numerous research protocols and clinical services. The clinical staff is comprised of psychiatrists, consulting internists and cardiologists, doctoral-level psychologists, master-level therapists, and nurses. Research in the Division focuses on antecedents and consequences of substance use and abuse, with particular emphasis on the development and testing of novel approaches to the treatment of substance abuse.

Laboratory Resources

The Central Reference Laboratory of the Nathan Kline Institute (NKI) for Psychiatric Research will perform blood and urine testing for the proposed project. The Central Reference Laboratory serves as the primary clinical laboratory for all clinical facilities of the New York State Office of Mental Health. Specimens are sent by express mail or private courier. The laboratory is equipped with standard instruments: centrifuges, spectrophotometer, shaker, high-pressure liquid chromatograph, scintillation spectrometer, as well as other specialized equipment.

The Human Genetics Resources Core of Columbia University will provide *DNA isolation and storage services* for the current proposal. Under the direction of Dr. Richard Mayeux the HGRC is designed to facilitate genetic research in human populations campus-wide. It has three components: 1) Cell and DNA Repository for tissue culture, cell banking and DNA isolation and storage); 2) Database Management Systems for tracking of laboratory and clinical research information. This Core is a resource for all departments, centers and institutes that wish to perform genetic research in human populations. As such, it represents a key component of human genetics research at Columbia University Medical Center.

The Taub Institute Genomics Core of Columbia University will act as our SNP genotyping service laboratory. Directed by Dr. Lorraine Clark, Taub provides all investigators at CUMC and NYSPI with PCR-based Genotyping, CNV Analysis, Gene Expression Analysis and Methylation Analysis; along with data analysis support for the coordination of statistical analysis of genetic data from human studies. The DNA facility has the latest sequencing technology including: Affymetrix GeneChip System, Illumina Iscan, Sequenom Mass Array Compact System, and NanoDrop-1000 Spectrophotometer. The facility can process Affymetrix Gene Chips using both expression and DNA genotyping products. Further expression data can also be obtained using the facility's real-time PCR instrument. Investigators are also able to consult with the facility director to determine the best method for their study, based on project goals, sample number and SNP density.

Computer

Computer users at NYSPI are provided with network maintenance consultation and connection to the internet and email. This includes access to PubMed, Medline, and the wide array of medical psychiatric, and substance abuse journals available in electronic form. Access also will be available to NYSPI computer facilities, which contain a variety of statistical and graphics (illustration, statistics-related) software.

Office

Office space is provided through Columbia University and NYSPI.

Major Equipment

No other major equipment will be needed.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Jermaine Middle Name D Last Name*: Jones Suffix:

Position/Title*: Research Scientist IV
Organization Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Substance Abuse
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10032-1007

Phone Number*: 646-774-6113 Fax Number: 646-774-6111 E-Mail*: jonesje@nyspi.columbia.edu

Credential, e.g., agency login: JONESJER

Project Role*: PD/PI Other Project Role Category:

Degree Type: PHD Degree Year: 2004

	File Name
Attach Biographical Sketch*:	Jones Biosketch 7-15-15.pdf
Attach Current & Pending Support:	

Tracking Number: GRANT11962274 Funding Opportunity Number: PA-14-013 . Received Date: 2015-07-15T14:35:23.000-04:00

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Sandra Middle Name D Last Name*: Comer Suffix: PhD

Position/Title*: Research Scientist Level V-NL
Organization Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Substance Abuse
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10032-1007

Phone Number*: (646) 774-6146 Fax Number: 212-543-5991 E-Mail*: comersa@nyspi.columbia.edu

Credential, e.g., agency login: scomer

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year: 1992

File Name
Attach Biographical Sketch*: Comer_Bio_7-13-15.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Shanthi Middle Name Last Name*: Mogali Suffix:

Position/Title*: Technical Specialist Level III
Organization Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Substance Abuse
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10032-1007

Phone Number*: 646-774-6147 Fax Number: E-Mail*: mogalis@nyspi.columbia.edu

Credential, e.g., agency login: SMogali

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: Degree Year:

File Name
Attach Biographical Sketch*: Mogali_Bio_Jones_R01_7_6_15.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Henry Middle Name R Last Name*: Kranzler Suffix: MD

Position/Title*: Professor of Psychiatry
Organization Name*: University of Pennsylvania
Department: Psychiatry
Division:
Street1*: Treatment Research Center
Street2: Perelman School of Medicine
City*: Philadelphia
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 19104-6178

Phone Number*: 215-222-3200 Fax Number: 215-386-6770 E-Mail*: kranzler@mail.med.upenn.edu

Credential, e.g., agency login: henrykranzler

Project Role*: Consultant Other Project Role Category:

Degree Type: MD Degree Year: 1982

	File Name
Attach Biographical Sketch*:	Kranzler Jermaine Jones R21 7-10-15.pdf
Attach Current & Pending Support:	

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME	POSITION TITLE
Jones, Jermaine Dionte	Research Scientist IV & Assistant Professor of Clinical Neurobiology
eRA COMMONS USER NAME (credential, e.g., agency login) **Jonesjer**	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Virginia: Charlottesville, VA	B.A.	98'-02'	Biology/Psychology
Old Dominion University: Norfolk, VA	M.S.	02'-04'	Psychology
American University: Washington, D.C	Ph.D.	04'-08'	Behavioral Neurobiology
Columbia University/NYSPI: New York, NY	Fellowship	08'-11'	Drug Abuse

A. Personal Statement.

The goal of the proposed study is to examine the influence of *OPRM1* gene variant (A118G, rs1799971) on the ability of naltrexone to alter the abuse liability of methamphetamine. An exploratory aim of the project will also assess the association between various relevant function gene variants on treatment response. I joined the Substance Abuse Division in 2008 as a post-doctoral fellow working in the Opioid Research Laboratory under Dr. Sandra Comer (Director). In 2011 I became a junior faculty member working on my K01 study investigating genetic contribution to the abuse potential of opioids. As a part of my K01 career development plan, I have attempted to develop a research niche within our Division investigating the pharmacogenetics of drugs abuse as it relates to changes in subjective effects (e.g. stronger positive subjective effects, weakened aversive effects) and treatment outcome. Since beginning my foray into this area of research 4 years ago, I have also completed coursework at Columbia's Mailman School of Public Health (P6385: Molecular Genetics and the Environment), The Jackson Laboratory (Genetics of Addiction) and the National Institute of General Medical Science (NIGMS) (Statistical Genetics). Since joining Columbia's Substance Abuse Division, I have gained significant expertise executing clinical investigations and combined with my recent endeavors in genetic research, I believe these experiences qualify me to oversee the completion of this project.

Most relevant to the current application

- **Jones J.D.,** & Comer S.D. (2015) A Review of Pharmacogenetic Studies of Drug Use Disorders. *Drug and Alcohol Dependence,* 152:1-14. PMCID: PMC4458176.
- **Jones J.D.,** Comer S.D., & Kranzler H.R. (2015) The Pharmacogenetics of Alcohol: A Critical Review. *Alcoholism: Clinical and Experimental and Research*, 39: 391-402. PMCID: PMC4348335
- **Jones J.D**., Luba R.L., Vogelman J., & Comer S.D. Evidence of Genetic Modulation of Opioid Withdrawal Severity. *Pharmacology, Biochemistry and Behavior* (Submitted).

B. Positions and Honors.

Positions and Employment

2003-2004 Health Education Coordinator, Old Dominion University
2007-2008 Adjunct Lecturer, University of the District of Columbia
2008-2011 Post-Doctoral Fellow, Columbia University/NYSPI
2011-Present Adjunct Lecturer, City College of New York

2011-Present Adjunct Lecturer, St. John's University
2011-Present Assistant Professor of Clinical Neurobiology, Columbia University/NYSPI

Professional Memberships

2002-2004 Virginia Academy of Science
2004-2007 Society for Neurosciences (SfN)
2006-2008 International Behavioral Neuroscience Society (IBNS)
2007-Present American Psychological Association
2009-Present College on Problems of Drug Dependence (CPDD): Associate Member
2012-Present International Study Group Investigating Drugs as Reinforcers

Honors

2004 Johns Hopkins University: Ivor and Colette Royston Research Program Award
2005 American Psychological Association: Diversity in Neuroscience Pre-doctoral Fellowship
2005 Marine Biological Laboratory: Summer Program in Neuroscience Fellowship
2006 The College of Problems on Drug Dependence: Primm-Singleton Travel Fellowship
2007 International Behavioral Neuroscience Society: Travel Award Recipient
2009 Jackson Laboratory Short Course on Mammalian Genetics: Scholarship Recipient
2010 NIDA Genetic Approaches to Understand Drug Abuse and Addiction Meeting: Travel Award
2010 International Narcotics Research Conference: Young Investigator Travel Award
2012 CPDD Minority Early Stage Investigator Conference Stipend: Award Recipient
2012 American College of Neuropsychopharmacology: Travel Award
2013 College on Problems of Drug Dependence: Early Career Investigator Award
2014 Association for Medical Education and Research in Substance Abuse: Travel Award
2014 Society for Neuroscience, Frontiers in Addiction Research: Travel Award
2015 American Psychological Association (APA): International Conference Travel Grant
2015 Society of Addiction Psychology/NIDA: Early-Career Investigator Award

C. Contribution to Science

1. Critical, constructive analyses of the drug abuse literature through summary, classification, analysis and comparison.

As a young investigator, I feel my greatest contributions to the field has come from my efforts to gather, summarize and critique relevant studies in order to discuss the state of a significant research question. As with any area of research, rarely does a single study answer a research question sufficiently to lead to scientific consensus. All study methodologies (e.g., preclinical, clinical, laboratory, outpatient) have inherent limitations, along with the unique limitations of each individual investigation (e.g., sample size, generalizability, treatment duration etc., etc.). Therefore, reviews combining data across multiple studies provide a better framework for answering a research question, and are more likely to inform clinical care. To this affect, I have written a number of reviews in order to provide myself and other substance abuse researchers with a better understanding of several important topics.

- **Jones J.D.,** & Comer S.D. (2015) The Epidemiology of Pain and Opioid Abuse. In Matthews, A.M., and Fellers, J. *Treating Comorbid Opioid Use Disorder in Chronic Pain*. New York, NY: Springer.

- **Jones J.D**., & Comer S.D. (2013) A review of human drug self-administration procedures. *Behavioural Pharmacology* 24(5-6): 384-395. PMCID: PMC4080726

- **Jones J.D**., Mogali S. & Comer S.D. (2012) Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug and Alcohol Dependence* 125(1-2):8-18. PMCID: PMC3454351

- Cooper Z.D., **Jones J.D**. & Comer S.D. (2012) Glial Inhibitors: A novel pharmacological approach to modulating the behavioral effects of abused substances. *Expert Opin Investig Drugs* 21(2); 169-178. PMCID: PMC3314383

2. Mediators and moderators of the abuse liability of opioids.

Since completing my graduate training, most of my research has involved assessing the factors that mediate and moderate the reinforcing and subjective effects of opioids. In our controlled, clinical laboratory setting, my research has sought to better understand how factors such as: sex, genetic variation, route of administration, and state of dependence may lead to and/or maintain opioid abuse. Genetic moderation of the abuse liability of oxycodone is the focus of my K01 research study (DA030446). Additionally, my work has evaluated the ability of novel medications to alter laboratory measures of the reinforcing and positive subjective effects, as an indicator of their treatment potential. Overall, these studies have shown that the factors contributing to the abuse liability of opioids are multifaceted and nuanced, and it is difficult to produce attenuations in these effects that are clinically meaningful.

- **Jones J.D**., & Comer S.D. Novel Strategies for Reducing Opioid Abuse. Oral presentation at the International Narcotics Research Conference. Phoenix, AZ, June 2015.

- **Jones, J.D**., Sullivan, M.A., Manubay, J., Metz V., Mogali S., & Comer, S.D. (2015) The Effects of Pioglitazone, a PPARγ Receptor Agonist, on the Abuse Liability of Oxycodone. Addiction (Submitted).

- **Jones J.D**., Speer T., Nunes E., Comer S.D., Ross S., Rotrosen J. & Reid M.S. (2013) Opioid-like effects of the Neurokinin 1 antagonist aprepitant in patients maintained on and briefly withdrawn from methadone. American Journal of Drug and Alcohol Abuse 39(2): 86-91. PMCID: PMC3608205

- **Jones J.D**., Sullivan, M.A., Manubay, J.M., Vosburg, S.K., & Comer S.D. (2011) The subjective, reinforcing, and analgesic effects of oxycodone in patients with chronic, non-malignant pain who are maintained on sublingual buprenorphine/naloxone. Neuropsychopharmacology 36: 411–422. PMCID: PMC3055661

3. Ways to reduce the harms of opioid abuse.

As outlined in the proposal, opioid abuse is a significant cause of mortality and morbidity. My time as a fellow with the Division on Substance Abuse exposed me to the clinical aspects of drug use disorders. I feel my preclinical, genetic, and clinical background has given me a comprehensive view of the issues involved in drug abuse from susceptibility to treatment. As such, one of my areas of contribution has been to research ways to improve the lives of those suffering from opioid abuse. This area of study targets opioid abuse at its two most distal points, initiation and mortality. Among the relevant publications below is a study that provided the preliminary data for Dr. Comer's R01 grant "Risk and Benefits of Overdose Education and Naloxone Prescribing to Heroin Users (DA035207)." With this project (on which I am a co-investigator) we will attempt to study ways to improve overdose education and the availably of naloxone, in order to reduce opioid overdose fatality. The other work listed below suggests that we may circumvent the development of iatrogenic opioid abuse by preventing misuse of opioid analgesics, and highlights the unaddressed medical needs of those with active opioid use disorders.

- **Jones J.D**., Atchison J., Madera G., & Comer S.D. (2015) Need and utility of a polyethylene glycol marker to ensure against urine falsification among heroin users. *Drug and Alcohol Dependence*. doi: 10.1016/j.drugalcdep.2015.05.021. PMCID: NIHMSID694927

- **Jones J.D**., Roux P., Stancliff S., Matthews W., & Comer S.D. (2014) Brief overdose education can significantly increase accurate recognition of opioid overdose among heroin users. *International Journal of Drug Policy* 25:166-170. PMCID: PMC3864124

- Gudin J.A., Mogali S., **Jones J.D**., Comer S.D. (2013) Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgraduate Medicine* 125(4): 115-130. PMCID: PMC4057040

- Roux R., **Jones J.D**., & Comer S.D. (2013) Hepatitis C infection in non-treatment seeking heroin users: The burden of cocaine injection. *American Journal on Addictions* 22(6): 613-618. PMCID: PMC4059002

For my complete bibliography see:
http://www.ncbi.nlm.nih.gov/sites/myncbi/jermaine.jones.1/bibliography/41161959/public/?sort=date&direction=descending.

D. Research Support.

Active

K01 DA030446-04 (Jones) NIDA: 2011
Mentored Research Scientist Development Award
The research component of this grant investigates the contribution of genetic factors to the abuse potential of opioids. This grant also provides academic mentorship and support to help junior scientists become independent researchers.
Role: Principal Investigator

R01 DA035207-01 (Comer) NIDA: 2014
This study examines the risk and benefits of current NYSDOH overdose education and naloxone prescribing to heroin users.
Role: Co-investigator

U54 DA037842-01 (Evans, Levin) NIDA: 2014
Cooperative Agreement Specialized Center Grant
Project 3 (PI: Comer) of the Division of Substance Abuse center grant involves testing of various novel compounds as possible therapeutics to treat opioid use disorders.
Role: Junior Investigator

Completed

Reckitt-Benckiser (S.D. Comer): 2009 thru 2011
Reinforcing Effects of Intranasal Buprenorphine versus Buprenorphine/Naloxone in Buprenorphine-Maintained Intranasal Drug Users. The purpose of this study in to compare the reinforcing effects of intranasally administered buprenorphine alone, and buprenorphine in combination with naloxone, in order to determine the abuse liability of Suboxone (buprenorphine/naloxone combination) through this route of administration.
Role: Investigator

T32 DA007294 (F.R. Levin) NIDA: 2008 thru 2011
Research Fellowship in Substance Abuse Disorders

This grant provides research and academic psychiatrists/psychologists with the skills and clinical experience necessary to advance our knowledge about the etiology and treatment of substance abuse disorders.
Role: Fellow

R01 DA022222 (S.D. Comer) NIDA: 2008 thru 2011
Sustained-Release Naltrexone for Opioid Dependence: Longitudinal Study In Humans
The purpose of this study is to examine the safety, effectiveness, and time course of a sustained-release implantable formulation of naltrexone for the treatment of heroin dependence.
Role: Investigator

R01 DA016759 (S.D. Comer) NIDA: 2008 thru 2011
Prescription Opioid Effects in Drug and Non-drug Abusers
This grant examines the reinforcing, subjective, performance, and physiological effects of prescription opioid medications (oxycodone, codeine) in drug and non-drug abusers under conditions of pain and no pain.
Role: Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME	POSITION TITLE
Comer, Sandra D.	Professor of Clinical Neurobiology Research Scientist VI
eRA COMMONS USER NAME scomer	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Vanderbilt University, Nashville, TN	B. S.	1987	Psychology
University of Michigan, Ann Arbor, MI	M.S.	1988	Biopsychology
University of Michigan, Ann Arbor, MI	Ph.D.	1992	Biopsychology
Univ. of Minnesota, Minneapolis, MN		1993	Substance Abuse

A. Personal Statement

Stimulant abuse is a serious public health concern that is associated with increased morbidity and mortality. Although naltrexone has shown some promise for treating stimulant use disorder, clinical trials have yielded contrasting results. The studies proposed in the current application may address this problem by identifying populations of individuals who may who respond better or worse to naltrexone pharmacotherapy. For 20 years, my laboratory has investigated the pharmacological and behavioral factors affecting drug abuse in humans. My research has focus primarily on populations of opioid users (recreational prescription opioid users, chronic pain patients, and heroin users), but has also included populations of stimulant users. Many of my studies have examined the ability of medications (including naltrexone) to alter the abuse liability of addictive drugs. Thus, I can attest to my ability to provide oversight for the proposed application. Dr. Jones, who has been a member of my laboratory for the last 7 years, has expertise in clinical laboratory studies of abuse liability, and is the burgeoning investigator in our division on addiction genetics (the focus of his K01 grant). I believe that the proposed studies are particularly exciting because they may reveal new information regarding how we test new medications for stimulant abuse.

Publications most relevant to the current application:

- Askalsky P, Kalapatapu RK, Foltin RW, **Comer SD**. (2015) Butyrylcholinesterase levels and subjective effects of smoked cocaine in healthy cocaine users. Am J Drug Alcohol Abuse. 41(2):161-165.
- **Comer SD**, Mogali S, Saccone PA, Askalsky P, Martinez D, Walker EA, Jones JD, Vosburg SK, Cooper ZD, Roux P, Sullivan MA, Manubay JM, Rubin E, Pines A, Berkower EL, Haney M, Foltin RW. (2013) Effects of acute oral naltrexone on the subjective and physiological effects of oral D-amphetamine and smoked cocaine in cocaine abusers. Neuropsychopharmacology. 38(12): 2427-2438.
- **Comer SD**, Haney M, Foltin RW, Fischman MW. (1996) Amphetamine self-administration by humans: modulation by contingencies associated with task performance. Psychopharmacology (Berl). 127: 39-46.Jones JD,
- **Comer SD**. (2015) A Review of Pharmacogenetic Studies of Drug Use Disorders. Drug and Alcohol Dependence, 152:1-14.

B. Positions and Honors

Positions and Employment

1993-present	Research Scientist III-VI, Division on Substance Abuse, New York State Psychiatric Institute
1993-2001	Assistant Professor of Behavioral Biology, Dept. of Psychiatry, College of Physicians & Surgeons of Columbia University, New York, NY
2001-2009	Associate Professor of Clinical Neurobiology, Dept. of Psychiatry, College of Physicians & Surgeons of Columbia University, New York, NY

2009-present	Professor of Clinical Neurobiology, Dept. of Psychiatry, College of Physicians & Surgeons of Columbia University, New York, NY

Honors and Awards

1987-1991	University of Michigan Minority Merit Fellowship
1990	University of Michigan, Society for the Stimulus Properties of Drugs Young Investigator Travel Award
1991-1992	University of Michigan, Psychology Departmental Associate
1991	University of Michigan Doctoral Dissertation Fellowship
1992	University of Michigan, International Narcotics Research Conference Travel Award
1993	University of Minnesota, International Study Group Investigating Drugs as Reinforcers Student Paper Competition Award
2004	Joseph Cochin Young Investigator Award, College on Problems of Drug Dependence
2015-2016	President, College on Problems of Drug Dependence

C. Contribution to Science

1. Assessing Medications to Treat Heroin and Prescription Opioid Abuse

A primary focus of my laboratory has been to investigate potential treatment medications for opioid abuse and dependence using human laboratory models. The basic tenet of our Division's model is that in order to determine the potential utility of a medication, its effects on drug-taking behavior must be studied directly. My research has investigated the effects of selective opioid receptor antagonists (naltrexone) and partial agonists (buprenorphine) on a range of opioid effects (self-administration, subjective ratings, and physiological measures). This research successfully demonstrated the clinical utility of these medications to antagonize the effects of heroin.

- Sullivan MA, Vosburg SK, **Comer SD.** (2006) Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. Psychopharmacology (Berl). 189(1): 37-46.
- **Comer SD**, Walker EA, Collins ED. (2005) Buprenorphine/naloxone reduces the reinforcing and subjective effects of heroin in heroin-dependent volunteers. Psychopharmacology (Berl). 181(4): 664-675.

Opioids present risks from both physiological (e.g., respiratory depression, physical dependence) and public health (e.g., individuals in pain) perspectives. Accordingly, my research has also focused on ways to decrease the abuse/misuse of opioid analgesics among patients under long-term opioid therapy to treat chronic pain. This research has identified factors and treatment strategies that may help prevent the development of abusive patterns of opioid use during pain treatment.

- Roux P, Sullivan MA, Cohen J, Fugon L, Jones JD, Vosburg SK, Cooper ZD, Manubay JM, Mogali S, **Comer SD.** (2013) Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. Pain. 154(8): 1442-1448.
- **Comer SD**, Sullivan MA, Vosburg SK, Kowalczyk WJ, Houser J. (2010) Abuse liability of oxycodone as a function of pain and drug use history. Drug Alcohol Depend 109(1-3): 130-138.

2. Investigating Novel Pharmacological Approaches to Altering the Abuse Liability of Drugs

More recently, my search for new pharmacotherapies has moved beyond opioid replacement and antagonism. As the clinical utility of opioids is attributed to the same physiological effects responsible for their abuse potential, I have attempted to investigate novel targets to tease the two apart. This work has tested compounds targeting the NMDA receptors, along with various glial cell modulators. Though many compounds have shown modulatory effects, none have sufficiently attenuated the reinforcing or euphorigenic effects of opioids to show immediate clinical promise.

- Cooper ZD, Johnson KW, Pavlicova M, Glass A, Vosburg SK, Sullivan MA, Manubay JM, Martinez DM, Jones J.D., Saccone PA, **Comer SD.** (2015) The effects of ibudilast, a glial activation inhibitor, on opioid withdrawal symptoms in opioid-dependent volunteers. Addict Biol. doi: 10.1111/adb.12261.

- Cooper ZD, Jones JD, **Comer SD**. (2012) Glial modulators: a novel pharmacological approach to altering the behavioral effects of abused substances. Expert Opin Investig Drugs. 21(2): 169-178.
- Vosburg SK, Sullivan MA, **Comer SD**. (2011) Evaluation of the reinforcing and subjective effects of heroin in combination with dextromethorphan and quinidine. J Opioid Manag. 7(6): 451-461.
- **Comer SD**, Sullivan MA. (2007) Memantine produces modest reductions in heroin-induced subjective responses in human research volunteers. Psychopharmacology (Berl). 193(2): 235-245.

3. Moving Towards a Better Understanding of Substance Abuse

Another line of my research has examined the varying conditions that affect the abuse liability of opioids. These studies have systematically examined the relative abuse potential of several natural opiates (e.g., morphine) and synthetic opioids (e.g., heroin, oxycodone, and buprenorphine), via different routes of administration, among varying conditions (e.g., morphine-maintained, buprenorphine-maintained) and populations (e.g., Rx opioid users, normal healthy volunteers, chronic pain patients). This work has shown the nuanced nature of the abuse liability of opioids and provided clinicians with recommendations to mitigate risk, and investigators with recommendations to improve assessment.

- **Comer SD**, Metz VE, Cooper ZD, Kowalczyk WJ, Jones JD, Sullivan MA, Manubay JM, Vosburg SK, Smith ME, Peyser D, Saccone PA. (2013) Comparison of a drug versus money and drug versus drug self-administration choice procedure with oxycodone and morphine in opioid addicts. Behav Pharmacol. 24(5-6): 504-516.
- **Comer SD**, Sullivan MA, Vosburg SK, Manubay J, Amass L, Cooper ZD, Saccone P, Kleber HD. (2010) Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers. Addiction. 105(4): 709-718.
- **Comer SD**, Ashworth JB, Sullivan MA, Vosburg SK, Saccone PA, Foltin RW. (2009) Relationship between rate of infusion and reinforcing strength of oxycodone in humans. J Opioid Manag. 5(4): 203-212.
- **Comer SD**, Sullivan MA, Whittington RA, Vosburg SK, Kowalczyk WJ. (2008) Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. Neuropsychopharmacology. 33(5): 1179-1191.

4. Understanding How Sex Impacts the Utility and Abuse Potential of Opioids.

My colleagues and I have developed a laboratory model to investigate the responses to experimentally induced painful stimuli in men, normally-menstruating women, and women maintained on monophasic oral contraceptives. These studies have shown sex differences in sensitivity to pain, and demonstrated that some opioid medications are more effective and longer lasting in females.

- Manubay JM, Davidson J, Vosburg SK, Jones JD, **Comer SD**, Sullivan MS. (2015) Sex differences among opioid-abusing patients with chronic pain in a clinical trial. J Addiction Medicine. 9(1): 46-52.
- **Comer SD**, Cooper ZD, Kowalczyk WJ, Sullivan MA, Evans SM, Bisaga AM, Vosburg SK. (2010) Evaluation of potential sex differences in the subjective and analgesic effects of morphine in normal, healthy volunteers. Psychopharmacology (Berl). 208(1): 45-55.
- Kowalczyk WJ, Sullivan MA, Evans SM, Bisaga AM, Vosburg SK, **Comer SD**. (2010) Sex differences and hormonal influences on response to mechanical pressure pain in humans. J Pain. 11(4): 330-342.
- Kowalczyk WJ, Evans SM, Bisaga AM, Sullivan MA, **Comer SD**. (2006) Sex differences and hormonal influences on response to cold pressor pain in humans. J Pain. 7(3): 151-160.

5. Contributing to the Development of Scientific Consensus on Important Drug Abuse Topics.

It has been a long-held belief of mine that good science is a community effort. It begins with peer-review during the publication processes to ensure quality, followed by independent replication to ensure consistency,

and ends with a pool of credible data addressing a research question. From this existing body of scientific knowledge, consensus may begin to emerge. As an established investigator on drug abuse, I consider it my duty to contribute my knowledge and experience to panels attempting to best provide consensus recommendations concerning appropriate research methods and clinical management.

- Smith SM1, Dart RC, Katz NP, Paillard F, Adams EH, **Comer SD**, Degroot A, Edwards RR, Haddox JD, Jaffe JH, Jones CM, Kleber HD, Kopecky EA, Markman JD, Montoya ID, O'Brien C, Roland CL, Stanton M, Strain EC, Vorsanger G, Wasan AD, Weiss RD, Turk DC, Dworkin RH (2013) Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain. 154(11): 2287-2296.
- O'Connor AB, Turk DC, Dworkin RH, Katz NP, Colucci R, Haythornthwaite JA, Klein M, O'Brien C, Posner K, Rappaport BA, Reisfield G, Adams EH, Balster RL, Bigelow GE, Burke LB, **Comer SD**, Cone E, Cowan P, Denisco RA, Farrar JT, Foltin RW, Haddox JD, Hertz S, Jay GW, Junor R, Kopecky EA, Leiderman DB, McDermott MP, Palmer PP, Raja SN, Rauschkolb C, Rowbotham MC, Sampaio C, Setnik B, Smith SM, Sokolowska M, Stauffer JW, Walsh SL, Zacny JP. (2013) Abuse liability measures for use in analgesic clinical trials in patients with pain: IMMPACT recommendations. Pain 154(11): 2324-2234.
- **Comer SD**, Zacny JP, Dworkin RH, Turk DC, Bigelow GE, Foltin RW, Jasinski DR, Sellers EM, Adams EH, Balster R, Burke LB, Cerny I, Colucci RD, Cone E, Cowan P, Farrar JT, Haddox JD, Haythornthwaite JA, Hertz S, Jay GW, Johanson CE, Junor R, Katz NP, Klein M, Kopecky EA, Leiderman DB, McDermott MP, O'Brien C, O'Connor AB, Palmer PP, Raja SN, Rappaport BA, Rauschkolb C, Rowbotham MC, Sampaio C, Setnik B, Sokolowska M, Stauffer JW, Walsh SL (2012) Core outcome measures for opioid abuse liability laboratory assessment studies in humans: IMMPACT recommendations. Pain. 153(12): 2315-2324.
- Turk DC, O'Connor AB, Dworkin RH, Chaudhry A, Katz NP, Adams EH, Brownstein JS, **Comer SD**, Dart R, Dasgupta N, Denisco RA, Klein M, Leiderman DB, Lubran R, Rappaport BA, Zacny JP, Ahdieh H, Burke LB, Cowan P, Jacobs P, Malamut R, Markman J, Michna E, Palmer P, Peirce-Sandner S, Potter JS, Raja SN, Rauschkolb C, Roland CL, Webster LR, Weiss RD, Wolf K. (2012) Research design considerations for clinical studies of abuse-deterrent opioid analgesics: IMMPACT recommendations. Pain 153(10): 1997-2008.

For my complete bibliography of 106 total career publications see:

http://www.ncbi.nlm.nih.gov/pubmed/?term=comer+SD

D. Research Support

Ongoing Research Support:

R21 DA040436- 01 (Comer) **07/15/2015 thru 07/30/2017**
NIDA
Dynamic Contrast-enhanced MRI to Measure Blood-Brain Permeability in Substance Abusers
This study will test if BBB permeability is directly correlated with increased magnitude of positive subjective responses, as well as methamphetamine self- administration.
Role: Principal Investigator

R01 DA035207-01A1 (Comer) **09/15/2014 thru 05/30/2019**
NIDA
Risks and Benefits of Overdose Education and Naloxone Prescribing to Heroin Users
This study assessed the impact of NYSDOH overdose education programs on opioid overdose in New York City along with way to improve the medical intervention among heroin users who witness an overdose event.
Role: Principal Investigator

U54 DA037842-01 (Levin) **09/01/2014 thru 05/30/2019**
NIDA

Shared Pharmacotherapeutic Strategies for Cannabinoid and Opioid Use Disorders
The goal of Project 3 is to examine a series of medications that may have utility in treating opioid use disorder, using our laboratory model and our decision algorithm to logically evaluate candidate medications to be tested in clinical settings.
Role: PI of Project #3

Protocol #6883R (Comer) **01/01/2014 thru 09/30/2015**
Reckitt-Benckiser
Reinforcing Effects of Intravenous Bup versus Bup/Nal in Hydromorphone-Maintained Heroin Users
The purpose of the study is to evaluate the reinforcing effects of various intravenous doses of buprenorphine compared to buprenorphine/naloxone in heroin-dependent individuals Intravenous heroin, naloxone, and placebo will be used as positive, negative, and neutral control conditions, respectively.
Role: Principal Investigator

Protocol #6817 (Comer) **10/15/2013 thru 09/30/2015**
Marker-Test Diagnostics, Inc.
The Utility of a Polyethylene Glycol Labeling Procedure for Identifying Fraudulent Urine Samples
Role: Principal Investigator

Protocol #6021(Comer) **04/28/2007 thru 06/30/2015**
Avigen/MediciNova, Inc.
The Safety, Tolerability and Preliminary Efficacy of AV411, a Glial Inhibitor, in Heroin Abusers
AV411 was hypothesized to decrease withdrawal symptoms during the detoxification phase and is expected to increase the duration and magnitude of oxycodone-induced analgesia during laboratory sessions.
Role: Principal Investigator

Recently Concluded Support:

R01 DA016759-10 (Comer) **09/20/2003 thru 04/30/2015**
NIDA
Prescription Opioid Effects in Drug and Non-drug Abusers
This study examined the reinforcing, subjective, performance, and physiological effects of two commonly prescribed opioid medications (oxycodone, codeine) in two studies.
Role: Principal Investigator

R01 DA031022-03 (Comer & Bisaga) **09/30/2010 thru 06/30/2014**
NIDA
Pioglitazone for the Treatment of Opioid and of Nicotine Dependence
The objective was to test the ability of pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist to reduce abuse of heroin (Study 1), and cigarette smoking (Study 2).
Role: Multi Principal Investigator

P50 DA009236-20 (Kleber) **09/30/1994 thru 05/31/2014**
NIDA
Novel Medications Approaches for Substance Abuse
Project 1: Laboratory Models: Pharmacotherapies for Opioid Dependence (PI: Comer)
This aim of this project was to examine the ability of glial activation inhibitors (ibudilast and minocycline) and a peroxisome proliferator-activated gamma receptor (PPAR-gamma) agonist (pioglitazone) to alter the abuse liability of opioids.
Role: PI of Project #1

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Mogali, Shanthi

eRA COMMONS USER NAME (credential, e.g., agency login): SMogali

POSITION TITLE: Instructor of Clinical Psychiatry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Fisk University: Nashville, TN	B.A.	1998-2001	Biology
Meharry Medical College: Nashville, TN	M.D.	2001-2005	Medicine
Emory University School of Medicine: Atlanta, GA	Residency	2005-2009	Psychiatry
Columbia University/ NYSPI: New York, NY	Fellowship	2009-2011	Addiction Psychiatry

A. Personal Statement

I am a board certified addiction psychiatry physician and currently serve as an Instructor of Clinical Psychiatry at Columbia University that entails research, clinical and teaching roles. In 2009 I came to Columbia Medical Center as a research fellow in Dr. Levin's T32 substance abuse fellowship and graduated in 2011. As a fellow, I expressed an interest in medication development for opioid dependence and began working closely with Dr. Sandra Comer in the Opioid Research Laboratory. Under Dr. Comer's mentorship, I was awarded pilot funding through Dr. Kleber's P50 Center grant to examine the physiological, subjective and analgesic effects of oxycodone-induced responses when combined with minocycline, a microglial inhibitor. These data have been analyzed and the manuscript is in progress. Currently, I am working with Dr. Comer and Dr. Jermaine Jones as the research psychiatrist for their ongoing opioid studies in the Opioid Research Laboratory. I also have a role in educating medical students, residents, and fellows in the diagnosis and treatment of substance abuse disorders. Overall, my goal is to actively contribute to the field of substance abuse research by examining novel medications that may deter drug abuse. This grant, if funded, will allow us to evaluate for possible genetic modulation of the efficacy of naltrexone to attenuate the subjective and reinforcing effects of stimulant drugs. I will be responsible for the medical and psychiatric oversight, and ensuring the safety of our participants throughout screening and testing. Given my academic training, research among drug-abusing populations and history of productive collaborations with Drs. Jones, and Comer, I am in a strong position to help assure the successful completion of this project.

Publications most relevant to the current application

1. Comer, SD., **Mogali, S.**, Saccone, PA., Askalsky, P., Martinez, D., Walker, E., Jones, JD., Vosburg, SK., Cooper, ZD., Roux, P., Sullivan, MA., Manubay, JM., Rubin, E., Pines, A., Berkower, EL., Haney, M., and Foltin, RW. (2013) Effects of acute oral naltrexone on the subjective and physiological effects of oral d-amphetamine and smoked cocaine in cocaine abusers. Neuropsychopharmacology. Jun 5: 1-12. PMCID: PMC3799062

2. **Mogali, S.,** Jones, J.D., Manubay, J.M., Sullivan, M.A., & Comer S.D (2014) Effects of minocycline on oxycodone-induced responses in humans. Drug and Alcohol Dependence. July 1: e153.

3. Jones, JD., Sullivan, MA., Vosburg, SK., Manubay, JM., **Mogali, S.,** Metz, V., Comer, SD. (2014) Abuse potential of intranasal buprenorphine versus buprenorphine/naloxone in buprenorphine-maintained heroin users. Addict Biol. Jul 25. PMCID: PMC4305506

B. Positions and Honors

Board Qualifications

2011- Present	General Psychiatry, American Board of Psychiatry and Neurology, Certificate No. 62563
2012- Present	Addiction Psychiatry, American Board of Psychiatry and Neurology, Certificate No. 2168

Positions and Employment

2009	On call physician, Psychiatry Admissions, Georgia Regional Hospital, Georgia
2009	On call physician, Child and Adolescent Psychiatry, Gwinnett/Rockdale/Newton Crisis Stabilization Program, Georgia
2009	On call physician, Psychiatry Emergency Department Annex, Atlanta VA Hospital, Georgia
2011- Present	Instructor of Clinical Psychiatry, New York State Psychiatric Hospital, New York
2011- Present	Instructor of Clinical Psychiatry, Columbia University, New York
2014- Present	Medical Director, Center for Motivation and Change: Berkshires, Massachusetts

Professional Memberships

2007-2009	Indo- American Psychiatric Association
2007-2011	American Psychiatric Association (APA)
2009-2012	College on Problems of Drug Dependence (CPDD): Associate Member

Honors

1998-2001	Howard Hughes Research Scholar for Undergraduate Microbiology, Fisk University
2002-2005	Merit Based General Endowed Scholarship providing full tuition for Medical College Education
2008	Indo-American Psychiatric Association Outstanding Resident Award Nominee
2011	Columbia University, Substance Abuse Division Pilot Study Grant: Funding Recipient
2011	NIDA Director's Travel Award, College on Problems of Drug Dependence

C. Contribution to Science

1. Extended-release injection naltrexone has proved promising in the treatment of opioid dependence. Treatment is often difficult as patients are not able to complete successful detoxification for induction onto agonist treatment. My most recent publication further investigated this problem by evaluating pre-treatment patient characteristics as predictors of successful completion of a rapid naltrexone induction procedure prior to XR naltrexone treatment. These findings may be used to guide primary care providers to recognize appropriate patients for rapid naltrexone induction. I served as the primary author and conducted literature searches, designed the investigation, and gathered data for analysis.

   Mogali, S., Khan, NA., Drill ES., Pavlicova M., Sullivan, MA., Nunes ES., Bisaga, A. (2015) Baseline Characteristics of patients predicting suitability for rapid naltrexone induction. Am J Addict. April; 24: 258-64. PMID: 25907815

2. As a fellow, I expressed an interest in medication development for opioid dependence and began working closely with Dr. Sandra Comer in the Opioid Research Laboratory. Under Dr. Comer's mentorship, I was

awarded pilot funding through Dr. Kleber's P50 Center grant to examine the physiological, subjective and analgesic effects of oxycodone-induced responses when combined with minocycline, a microglial inhibitor. In brief, these data suggest that microglial inhibitors may play a role in deterring substance abuse by attenuating the subjective responses that may influence the abuse liability of oxycodone.

Mogali, S. Jones, J.D., Manubay, J.M., Sullivan, M.A., & Comer S.D (2014) Effects of minocycline on oxycodone-induced responses in humans. Drug and Alcohol Dependence. July 1: e153.

A complete list of my published work can be found at:
http://www.ncbi.nlm.nih.gov/pubmed/?term=mogali+s

D. Research Support

Active

U54 DA037842-01 (Levin) NIDA: 09/01/14 thru 06/30/19
Shared Pharmacotherapeutic Strategies for Cannabinoid & Opioid Use Disorders
Project 3: Laboratory: Pharmacotherapies for Opioid Use Disorder (PI: Comer)
The goal of Project 3 is to examine a series of medications that may have utility in treating opioid use disorder, using our laboratory model and our decision algorithm to logically evaluate candidate medications to be tested in clinical settings.
Role: Research Psychiatrist

R01 DA035207-01A1 (Comer) NIDA: 09/15/14 thru 08/31/19
Risks and Benefits of Overdose Education and Naloxone Prescribing to Opioid Abusers
Fatal and nonfatal opioid overdoses have increased substantially in recent years. The current proposal seeks to evaluate a potential solution to this serious public health problem: namely, opioid overdose education and naloxone prescribing to substance abusers. Both a retrospective and a prospective study will be conducted to examine the risks and benefits of this novel approach.
Role: Research Psychiatrist

Completed

R01 DA016759-09 (Comer) NIDA: 09/20/03 thru 04/30/15
Prescription Opioid Effects in Drug and Non-drug Abusers
This study will examine the reinforcing, subjective, performance, and physiological effects of two commonly prescribed opioid medications (oxycodone, codeine) in two studies.
Role: Research Psychiatrist

R01 DA031022-04 (Comer) NIDA: 09/30/10 thru 06/30/14
Pioglitazone for Treatment of Opioid and Nicotine Dependence
The objective is to test the ability of pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist that is FDA-approved for use in the management of type 2 diabetes mellitus, to reduce abuse of heroin (Study 1), and cigarette smoking (Study 2). Pioglitazone will be tested in combination with buprenorphine/naloxone (Study 1) and with the nicotine patch (Study 2).
Role: Research Psychiatrist

P50 DA009236-20 (Kleber) NIDA: 09/30/94 thru 05/31/14
Project 1: Laboratory Models: Pharmacotherapies for Opioid Dependence (PI: Comer)
This aim of this project is to examine the ability of glial activation inhibitors (ibudilast and minocycline) and a peroxisome proliferator-activated gamma receptor (PPAR-gamma) agonist (pioglitazone) to alter the abuse liability of opioid medications.
Role: Research Psychiatrist

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME	POSITION TITLE
Henry R. Kranzler, M.D	Professor of Psychiatry
eRA COMMONS USER NAME henrykranzler	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Monmouth University, West Long Branch, NJ	B.A.	1976	Anthropology
Rutgers University, New Brunswick, NJ	M.A.	1980	Anthropology
UMDNJ, Robt. Wood Johnson Medical School,	M.D.	1982	Medicine
Univ of CT School of Medicine, Farmington, CT	Residency	1986	Psychiatry
Univ of CT Alcohol Res Ctr, Farmington, CT	Post Doc.	1987	Alcohol Research

A. Dr. Kranzler is an addiction psychiatrist whose research focuses on the genetics and pharmacological treatment of alcohol and drug dependence. The proposed project is a logical extension of work that he has done on the phararmacogenetics of substance dependence. For the past 4 years, he has served as a co-mentor on Dr. Jones' K01 pharmacogenetics grant and will serve as a consultant on the proposed project, meeting with Dr. Jones in person annually and through telephone meetings and email throughout the grant period. Dr. Kranzler will provide input on the implementation of the study, assisting in dealing difficulties that may arise, and in the analyses and report writing based on the research findings. He will also be involved in planning and implementing any changes in design or procedures.

Publications most relevant to the current proposal:

1. O'Malley, S.S., Corbin, W.R., Leeman, R.F., DeMartini, K.S., Fucito, L.M., Ikomi, J., Romano, D.M., Wu, R., Toll, B.A., Sher, K.J., Gueorguieva, R., **Kranzler, H.R**. Reduction of alcohol drinking in young adults by naltrexone: a double-blind, placebo-controlled, randomized clinical trial of efficacy and safety. *J Clin Psychiatry*. e207-13. doi: 10.4088/JCP.13m08934. 2015.

2. Jones, J.D., Comer, S.D., & **Kranzler, H.R.** The Pharmacogenetics of Alcohol: A Critical Review. *Alcoholism: Clinical and Experimental and Research*, 39: 391-402, 2015.

3. Bi, J., Gelernter, J., Sun, J., **Kranzler, H.R.** Comparing the utility of homogeneous subtypes of cocaine use and related behaviors with DSM-IV cocaine dependence as traits for genetic association analysis. *Am J Med Genet B Neuropsychiatr Genet.*165B(2):148-56. 2015.

4. Chen, A.C., Morgenstern, J., Davis, .CM., Kuerbis, A.N., Covault, J., **Kranzler, H.R,.** Variation in Mu-Opioid Receptor Gene (OPRM1) as a Moderator of Naltrexone Treatment toReduce Heavy Drinking in a High Functioning Cohort. *J Alcohol Drug Depend*.1(1):101. 2013.

B. Positions and Honors.

1998–2010 Professor (with Tenure), Department of Psychiatry, Univ. of CT School of Medicine (UCSOM)
2010 Professor, Department of Genetics and Developmental Biology, UCSOM
2010–present Emeritus Professor of Psychiatry and Genetics and Developmental Biology, UCSOM
2010–present Professor (with Tenure), Dept. of Psychiatry, University of Pennsylvania Perelman School of Medicine (PSOM)
2013–present Director, Center for Studies of Addiction, PSOM

Recent Honors: 2006 Frontiers of Science Lectureship, American Psychiatric Association

2007 Frank J. MacDonell Lectureship, Department of Psychiatry, University of Michigan School of Medicine
2008 Medical Sciences Graduate Students' Association Lectureship, University of Calgary
2009 Distinguished Fellow, American Academy of Addiction Psychiatry
2009 Fellow, American College of Neuropsychopharmacology
2010 Alumnus of the Year, Monmouth University, West Long Branch, NJ
2013 Keynote Speaker, Visions in Pharmacology, University of Toronto
2014 Editor-in-Chief, *Alcoholism: Clinical and Experimental Research*
2014 James H. Tharp Award for Alcoholism Research (selected by the American Society of Addiction Medicine)
2014 Dan Anderson Award (selected by the Hazelden/Betty Ford Foundation)
2015 Scott Mackler Award for Excellence in Substance Abuse Teaching, PSOM

Editorial Boards: *Addiction Biology*
Addictive Disorders and Their Treatment
Drug and Alcohol Dependence
Experimental and Clinical Psychopharmacology
International Journal of Neuropsychopharmacology

C. Contributions to Science

1. Dr. Kranzler's contributions to science have been in three major areas: alcohol pharmacotherapy research; the identification or characterization of specific genes influencing the risk for dependence on alcohol and drugs; and genetic moderators of the response to the pharmacological treatment of alcohol use disorders. His contributions to alcohol pharmacotherapy include the use of a targeted approach to opioid antagonist treatment and the development of long-acting naltrexone as a treatment option for alcohol dependence. In 1994, naltrexone was approved by the U.S. Food and Drug Administration (FDA) to treat alcohol dependence. Dr. Kranzler subsequently showed that the medication could be used on an "as needed" basis (Kranzler et al. 1997) and completed two placebo-controlled trials comparing targeted with daily drug administration (Kranzler et al. 2003), the study design for which he shared with investigators at Biotie Therapies, a pharmaceutical company in Turku, Finland. Their initial study of nalmefene using this approach led to the multi-center studies in the European Union that were the basis for the approval in 2012 of nalmefene by the European Medicines Agency. Dr. Kranzler also pioneered the use of long-acting naltrexone to treat alcohol dependence (Kranzler et al. 1998; Kranzler et al. 2004) and was a major contributor to the multi-center trial of a long-acting formulation of the medication (Garbutt et al. 2005) that led to its approval in 2006 by the FDA to treat alcohol dependence.

1. **Kranzler, H.R**., Tennen, H., Penta, C., Bohn, M. Targeted naltrexone treatment in early problem drinkers. *Addictive Behaviors*, 22:431-436, 1997.

2. **Kranzler, H.R.**, Modesto-Lowe, V., Nuwayser, E.S. Sustained-release naltrexone for alcoholism treatment: A preliminary study. *Alcoholism: Clinical and Experimental Research*, 22:1074-1079, 1998.

3. **Kranzler, H.R**., Armeli, S., Tennen, H., Blomqvist, O., Oncken, C., Petry, N., Feinn, R. Targeted naltrexone for early problem drinkers. *Journal of Clinical Psychopharmacology*, 23:294-304, 2003.

4. Garbutt JC, **Kranzler HR**, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW for the Vivitrex® Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence. *JAMA*, 293:1617-1625, 2005.

2. Dr. Kranzler's contributions to understanding the genetic basis of alcohol and drug dependence have included a series of candidate gene studies (e.g., Covault et al. 2004, 2008), linkage analyses (e.g., Gelernter et al. 2006), and genomewide association studies (e.g., Gelernter et al. 2014). Current activity in this area includes a whole genome sequencing study focusing on cocaine dependence.

1. Covault, C., Gelernter, J., Hesselbrock, V., Nellissery, M., **Kranzler, H.R.**: Allelic and haplotypic association of *GABRA2* with alcohol dependence, *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, 129B:104-109, 2004.

2. Covault J, Gelernter J, Jensen K, Anton R, **Kranzler HR**. Markers in the 5′ region of *GABRG1* associate to alcohol dependence and are in linkage disequilibrium with markers in the adjacent *GABRA2* gene, *Neuropsychopharmacology*, 33:837-848, 2008. (PMCID: PMC2743531)

3. Gelernter J, Panhuysen C, Wilcox M, Hesselbrock V, Rounsaville B, Poling J, Weiss R, Sonne S, Farrer L, **Kranzler HR**: Genomewide linkage scan for opioid dependence and related traits. *American Journal of Human Genetics*, 78:759-769, 2006. (PMCID: PMC1474044)

4. Gelernter J, **Kranzler HR**, Sherva R, Almasy L, Koesterer R, Anton R, Preuss UW, Ridinger M, Rujescu D, Wodarz N Zill P, Han S, Zhao H, Farrer LA. Genome-wide association study of alcohol dependence: significant findings in African- and European-Americans including novel risk loci, *Molecular Psychiatry*, 19:41-49, 2014. (PMCID: PMC24166409)

3. Dr. Kranzler's most recent work has focused on topiramate, a glutamate antagonist with demonstrated efficacy in the treatment of alcohol dependence. He and colleagues found that the medication is efficacious only in a subgroup of individuals who are homozygous for an allele of rs2832407 in the *GRIK1* gene, which encodes a kainate receptor subunit. The specific single nucleotide polymorphism that moderates the response to topiramate treatment was identified through association to alcohol dependence (Kranzler et al. 2009) and shown to be a significant pharmacogenetic predictor of reductions in heavy drinking (Kranzler et al. 2014a). Most recently, we found persistent effects of topiramate in rs2832407*C-allele homozygotes during a six-month post-treatment follow-up period (Kranzler et al. 2014b) and evidence that the effects of topiramate on heavy drinking in the genotype-responsive group are mediated by self-efficacy to resist heavy drinking (Kranzler et al. 2014c).

1. **Kranzler HR**, Gelernter J, Anton RF, Arias AJ, Herman A, Zhao H, Burian L, Covault J: Association of markers in the 3' region of the GluR5 kainate receptor subunit gene (*GRIK1*) to alcohol dependence. *Alcoholism: Clinical and Experimental Research*, 33:1–6, 2009. (PMID: 19320626; PMCID: PMC2772659)

2. **Kranzler HR**, Covault J, Feinn R, Armeli S, Tennen T, Arias AJ, Gelernter J, Oncken C, Pond T, Kampman KM. Topiramate treatment for heavy drinkers: Moderation by a *GRIK1* polymorphism, *American Journal of Psychiatry*, 171: 445-452, 2014a. (PMCID: PMC3997125)

3. **Kranzler HR**, Wetherill R, Feinn R, Pond T, Gelernter J, Covault J. Posttreatment effects of topiramate treatment for heavy drinking, *Alcoholism: Clinical and Experimental Research* 38:3017-23, 2014b. (PMCID: PMC4293099)

4. **Kranzler HR**, Armeli, Wetherill R, Feinn R, Tennen H, Gelernter J, Covault J, Pond T. Self-efficacy mediates topiramate-induced reduction of drinking, which is moderated by *GRIK1* genotype. *Addiction Biology*, 2014c Dec 15 [Epub ahead of print].

For a full list of Dr. Kranzler's publications, which include 362 articles (published or in press), a full listing of which is at http://www.ncbi.nlm.nih.gov/pubmed/?term=kranzler+hr

D. Research Projects Ongoing:

R01 AA017535 (Gelernter/Kranzler) **9/15/09 - 8/31/15**
NIH/NIAAA (**NCE)**
Genetics of Alcohol Dependence in African-Americans

The purpose of this proposal is to identify specific risk genes in African-Americans that contribute to the development of alcohol dependence. Dr. Kranzler directs the UPenn site and oversees phenotypic assessment across both the Yale and UPenn sites.

R01 DA030976 (Wilhelmsen/Kranzler) **9/30/10 – 5/31/16**
NIH/NIDA **(NCE)**
Deep sequencing studies for cannabis and stimulant dependence

The purpose of this study is to conduct deep sequencing of existing DNA and refinement of phenotypic information to enhance gene finding efforts for cannabis, methamphetamine, and cocaine dependence. Dr.

Kranzler oversees analyses related to subtypes of cocaine dependence as phenotypes and will participate in the analysis of the sequence data.

R01 AA021164 (Kranzler)
NIH/NIAAA **4/1/12 – 3/31/17**
2/2 Pharmacogenetic Treatment for Alcoholism

This study examines genetic variants as moderators of the response to ondansetron treatment of alcohol dependence. It is a collaborative R01 being conducted at two sites: the University of Pennsylvania and the University of Maryland.

R01 DA012690 (Gelernter) **8/5/00 – 8/31/18**
NIH/NIDA
Genetics of Opioid Dependence
Risk for opioid dependence is influenced by genes. The main object of this study is to find genes that influence risk for opioid dependence by sequencing the entire exome (the part of the genome that is known to serve a coding function), in groups of people who are of European or African ancestry, with and without opioid dependence.

Research Grant (McKay) **4/1/14 – 3/31/19**
Department of Defense
Preventing risky drinking in veterans treated with prescription opioids

The major goals of this project are: 1) To compare the effectiveness of a 12-month integrated prevention intervention with standard care over an 18-month follow-up period, for veterans treated with prescription opioids and who are engaging in risky/hazardous drinking, as defined by NIAAA guidelines; and 2) To examine secondary outcome measures, moderator effects, and mediation effects.

R01 CA184315 (Kranzler) **8/15/14 – 7/31/19**
NIH/NCI
Placebo-controlled trial of bupropion for smoking cessation in pregnant women

The major goals of this project are: 1) conduct a 10-week placebo-controlled trial of bupropion 300 mg/day in 360 pregnant smokers who are at 13–24 weeks gestation and generally from low-income, under-served communities; 2) assess changes in depression symptoms and craving as mediators of bupropion's effect on quit rates; and 3) explore genetic, metabolic, and social/behavioral moderators of the efficacy of bupropion on cigarette abstinence and safety.

R01 AA023192 (Kranzler) **8/15/14 – 7/31/19**
NIH/NIAAA
Pharmacogenetic Analysis of Topiramate Treatment of AUD

The major goals of this project are: 1) To examine the moderating effect of rs2832407 in *GRIK1* on the efficacy of topiramate 200 mg/day in reducing the frequency of heavy drinking; and 2) To examine daily processes, including expectancies regarding the positive effects of drinking and their interaction with genotype and medication group, to predict the intensity of nighttime drinking.

COMPLETED (PAST 3 YEARS)

R01 AA011330 (Gelernter/Kranzler)
NIH/NIAAA **3/1/09 – 2/28/15**
Genetics of Alcohol Dependence in American Populations

The purpose of this proposal is to identify genes predisposing to alcohol dependence. It involves recruitment of a sample of alcohol-dependent cases and screened controls. Dr. Kranzler directs the UPenn site and oversees phenotypic assessment across both the Yale and UPenn sites.

K24 AA13736 (Kranzler) **4/01/08 – 9/30/14**
NIH/NIAAA
Novel Approaches to Alcoholism Pharmacotherapy and Risk
Midcareer Investigator Award in Patient-Oriented Research

This Mid-Career Investigator Award (K24) enabled Dr. Kranzler to mentor beginning clinical investigators, continue his career development, and conduct research on the pharmacotherapy of alcoholism and the genetics of alcohol and drug dependence.

P60 AA03510 (Hesselbrock) **12/1/07 - 11/30/12**
NIH/NIAAA
Center for Research on the Etiology and Treatment of Alcohol Dependence

The focus of this center is on the systematic exploration of the alcohol dependence syndrome, including its etiology, patterning and treatment. Dr. Kranzler serves as Principal Investigator of a component of the center, entitled “Topiramate Treatment of Heavy Drinkers.”

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:	Dr.
First Name*:	Jermaine
Middle Name:	D
Last Name*:	Jones
Suffix:	

2. Human Subjects

Clinical Trial?	● No	○ Yes
Agency-Defined Phase III Clinical Trial?*	● No	○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

○ Yes ● No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

Funding Opportunity Number: PA-14-013. Received Date: 2015-07-15T14:35:23.000-04:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ❍ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ❍ Yes ❍ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Modular Budget

OMB Number: 0925-0001

Budget Period: 1

Start Date: 04/01/2016 End Date: 03/31/2017

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium F&A*	150,000.00
Consortium F&A	0.00
Total Direct Costs*	150,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)
1.	Modified TDC	62.00	150,000.00	93,000.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, Ryan McCarthy, (212) 264-2069

Indirect Cost Rate Agreement Date: 01/15/2015

Total Indirect Costs: 93,000.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 243,000.00

Funding Opportunity Number: PA-14-013. Received Date: 2015-07-15T14:35:23.000-04:00

PHS 398 Modular Budget

Budget Period: 2

Start Date: 04/01/2017 End Date: 03/31/2018

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium F&A*	125,000.00
Consortium F&A	0.00
Total Direct Costs*	125,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)
1.	Modified TDC	62.00	125,000.00	77,500.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, Ryan McCarthy, (212) 264-2069

Indirect Cost Rate Agreement Date: 01/15/2015

Total Indirect Costs: 77,500.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 202,500.00

Funding Opportunity Number: PA-14-013. Received Date: 2015-07-15T14:35:23.000-04:00

PHS 398 Modular Budget

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium F&A for Entire Project Period ($)	275,000.00
Section A, Total Consortium F&A for Entire Project Period ($)	
Section A, Total Direct Costs for Entire Project Period ($)	275,000.00
Section B, Total Indirect Costs for Entire Project Period ($)	170,500.00
Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period ($)	445,500.00

2. Budget Justifications

Personnel Justification	Jones_R21_Just_7_15_15.pdf
Consortium Justification	
Additional Narrative Justification	Jones_Additional Narrative Justification.pdf

Funding Opportunity Number: PA-14-013. Received Date: 2015-07-15T14:35:23.000-04:00

Budget Justification

The Research Foundation for Mental Hygiene/New York State Psychiatric Institute (RFMH/NYSPI) implemented a new policy governing the proposing of effort for those investigators who possess an appointment at RFMH/NYSPI and an academic appointment at the University and an academic appointment at Columbia University ("Joint Appointees"). Joint Appointees previously proposed their effort on RFMH/NYSPI projects based on a percentage of their total professional effort across Columbia University and RFMH/NYSPI, on an integrated basis. As of Spring 2014, RFMH/NYSPI has transitioned to a new model based upon the method utilized by those with joint Veterans Affairs/academic appointments*. Under the new model, Joint Appointees propose their effort on RFMH/NYSPI projects based on a percentage of their RFMH/NYSPI effort only. However, for informational purposes, the budget justification also will indicate what the effort would be if it were calculated based on total professional effort (TPE) across both institutions.

* As described in the NIH Guide for Grants and Contracts, vol. 18, no. 27, August 11, 1989.

PERSONNEL

Jermaine D. Jones, Ph.D., Principal Investigator: (1.20 cal months, Yrs 1-2, no salary requested until 6/1/2016). Dr. Jones is a Research Scientist IV at the Research Foundation for Mental Hygiene, Inc. (RFMH) as well as an Assistant Professor of Clinical Neuroscience in the Department of Psychiatry's Division on Substance Abuse at Columbia University's College of Physicians and Surgeons. Dr. Jones is currently the recipient of a K01 award from NIDA entitled: "Contribution of Various Genetic Polymorphisms to Oxycodone's Abuse Liability". He received his Ph.D. in the summer of 2008 and began his 3-year fellowship in the Division on Substance Abuse in the fall of 2008. He has been working with Dr. Comer since he began his fellowship and has become proficient at conducting abuse liability assessments in clinical populations, and is a developing researcher on the genetics of addiction. Dr. Jones will assume all scientific responsibility for the study. Currently, Dr. Jones has a K01 award (K01 DA030446) that ends on 5/31/2016; he will be paid salary beginning 6/1/2016. From 4/1/2016 thru 5/31/2016, Dr. Jones' effort on this grant will be subsumed by his K award. The effort listed by Dr. Jones in this submission is based solely upon his effort at RFMH.

Sandra D. Comer, Ph.D., Co-Investigator: (TPE: 0.22 cal months, Yrs 1-2; RFMH/NYSPI Effort: 0.36 cal months,). Dr. Comer is a Research Scientist VI at the Research Foundation for Mental Hygiene, Inc. (RFMH), a Research Scientist 5 at the New York State Psychiatric Institute (NYSPI), as well as a Professor of Clinical Neurobiology at Columbia University's College of Physicians and Surgeons. She has been performing substance abuse research with humans for over 20 years and has over 25 years research experience working with opioids. Dr. Comer will supervise Dr. Jones concerning the scientific aspects of the study, data analysis and manuscript writing. The effort listed by Dr. Comer in this submission is based upon her effort at RFMH/NYSPI. If the effort were figured based on Dr. Comer's total professional effort at RFMH/NYSPI and Columbia University it would be 0.22 cal months effort.

Shanthi Mogali, M.D., Co-Investigator: (0.60 cal months, Yrs 1-2). Dr. Mogali is a board certified Addiction Psychiatry physician and Technical Specialist III at the Research Foundation for Mental Hygiene, Inc. She is also an Instructor in Clinical Psychiatry in the Division on Substance Abuse at Columbia University's College of Physicians and Surgeons. She has over 10 years of psychiatric clinical experience and has worked with Drs. Jones and Comer since joining the Division on Substance Abuse in 2009. Dr. Mogali will oversee clinical assessment during screening, medical supervision of the laboratory sessions and assessment/reporting of adverse events. The effort listed by Dr. Mogali in this submission is based solely upon her effort at RFMH.

Janet Murray, N.P., Research Nurse (1.20 calendar months, Yrs 1-2): Janet Murray has been with the Division of Substance abuse for 10 years and has worked with both the Cocaine and Opioid research units. Having worked with Drs. Jones and Comer for over 8 years, Ms. Murray is very familiar with the behavioral observation techniques and laboratory procedures involved in clinical laboratory studies. She will be responsible for various aspects of medical screening of potential participants, along with administering study drug, and safety monitoring during laboratory session. The effort listed for Ms. Murray in this submission is based solely upon her effort at RFMH.

Rachel Luba, B.A., Research Assistant: (11.00 cal months, Yrs 1-2). Ms. Luba is a Research Support Assistant II at the Research Foundation for Mental Hygiene (RFMH) and has been with the Division on Substance Abuse for 2 years and has been trained in: participant recruitment, data management and behavioral observation techniques by Drs. Jones and Comer. On the upcoming project, she will be responsible for scheduling participant visits, performing assessments, and managing data collection from the laboratory sessions. The effort listed by Ms. Luba in this submission is based solely upon her effort at RFMH.

The fringe rate at the Research Foundation for Mental Hygiene, Inc. (RFMH) is 35%. The IDC rate at RFMH is calculated at 62% of modified total direct costs (MTDC). Except where specifically noted, a 3% cost of living increase is assumed for all salary expenses except where individuals have reached the NIH salary cap. The Research Foundation for Mental Hygiene operates on an April 1st thru March 31st fiscal year and has institutionally mandated cost of living salary increases on April 1st of each year. All salary figures presented in the budget reflect these cost of living adjustments

CONSULTANT

Henry Kranzler, M.D.: Dr. Kranzler is currently a Professor of Psychiatry and Director of the Center for Studies of Addiction at the Univ. of Pennsylvania, Perelman School of Medicine. He has served as principle investigator or co-investigator on over 12 NIDA- or NIAAA-funded studies investigating genetic contribution to drug use disorders. He has also co-authored over 110 publications related to the study of addiction genetics. In addition to frequent electronic communications, in person meetings between Dr. Jones and Dr. Henry Kranzler are anticipated to occur once every three months. We have budgeted $500 per visit for Dr. Kranzler's honoraria and are requesting **$2,000** per year for Yrs 1-2 (4 visits per year @ $500/visit (5 hours @ $100/hr = $500)) = $2,000 per year). Dr. Kranzler currently serves as the Co-mentor on Dr. Jones' K01 grant, and formerly functioned as an advisor on the NYSPI Division on Substance Abuse recently completed Center Grant (P50 DA009236-20).

PARTICIPANT FLOW

Over the proposed 2-year funding period, approximately 70 participants will be enrolled (based on previous inpatient studies of this duration we anticipate a negligible dropout rate). Approximately 10 participants will be enrolled during each 3-month period (average 35 participants per year).The final 3 months of the funding period will be devoted to data analysis and publication.

SUPPLIES

Study Supplies**:** Based upon our previous investigations we anticipate needing $10 for each participant to purchase supplies such as: paper, case books, syringes, Band-Aids, alcohol wipes, gloves, etc. Therefore we have requested **$350** per year for study supplies (35 participants per year x $10/participant).

Urine Toxicology Tests**:** Urine testing will be performed at each screening visit for all potential study participants to assess for recent drug use. We are requesting **$420** each year for urine toxicology tests. The breakdown for each year is as follows: $4 per test, 3 tests per participant x 35 screened participants/yr).

Pharmacy Medication Expense**:** Medications will be prepared and stored in the Research Pharmacy at NYSPI. Over the life of the study, we will need to purchase: Naltrexone 50mg – 5 bottles @ $19.52/bottle = $97.60; and Methamphetamine – 21 bottles @ $304.77/bottle = $6,400.17, for a total of $6,497.77. Therefore, we are requesting **$3,248.89** per year to cover the cost of medication. Per the NYSPI pharmacy directive, the costs for Administrative Expenses will increase at 4% per year in Year 2.

TRAVEL

PI Travel Expenses**:** The results of this study will be of interest to many in the field of substance abuse research and treatment. Therefore we are requesting **$2,500** to cover the cost of travel, food and lodging for the primary investigator to attend the annual meeting of the College of Problems on Drug Dependence or the International Behavior and Neural Genetics Society.

OTHER EXPENSES

Pharmacy Administrative Fees**:** In addition to the cost of medications (see **SUPPLIES** above), the NYSPI pharmacy charges us for: a yearly administrative fee ($600/yr), the manufacturing of capsules ($52.50/yr) and for prescription dispensing ($15.63/Rx, 10 Rx's per participant, 35 participants/yr = $5,470.50). Therefore, we are requesting **$6,123** per year for pharmacy administrative expenses. Per the NYSPI pharmacy directive, the costs for Administrative Expenses will increase at 4% per year in Year 2.

Volunteer Compensation: requesting $2,625 + $19,250 = **$21,875** per year (see below)

- Screenings: Participants will receive $25 for each of the three screening assessments. Based upon previous efforts to recruit this participant population, we anticipate needing to screen approximately 80 potential study candidates over 2 years to obtain our target N. So for each year we are requesting $2,625 for screenings: ($25 x 3 screening visits x 35 participants per year = $2,625).
- Laboratory sessions: Those volunteers who are enrolled in the laboratory testing will earn between $25-$50 per day [$50 per day if they complete all 5 session ($25/day completion incentive)]. Participants also have the option of earning up to $18 during each self-administration session (i.e., via drug vs money procedure). There are a number of factors involved in estimating the cost associated with this portion of the study (e.g., # enrolled vs completers, drug vs. money preference etc. etc.,) however, we estimate the total payment to be ≈$550 per participant x 35 enrolled participants/yr= $19,250.

DNA Isolation**:** In order to conduct analyses on the genetic polymorphisms of interest, we will extract DNA from blood samples collected from all study participants. The Columbia University Medical Center has a Human Genetics Resources Core that will isolate the DNA at a cost of $45 per sample. We will store these samples in our -20°C freezer. Thus, we are requesting **$1,575** per year to extract DNA from our blood samples (35 participants per year x $45).

DNA Analysis**:** Blood samples collected from all study participants will be assessed for the alleles of interest at a cost of approximately $10 per sample. Therefore, we are requesting **$350** per year to fund genotyping expenses (35 participants per year x $10 per sample).

Advertising/Recruitment**:** In order to obtain participants we plan to advertise this study in three journals that have proven to be the most effective in our previous recruitment efforts (AM New York, The Village Voice and the New Jersey Journal). We plan to post an ad in one of the 3 journals every other week through the funding period weeks on and off throughout the duration of the study. We will also utilize free recruitment sources such as craigslist.org and researchmatch.org. We are requesting **$11,105** for both years for advertising expense.

Additional Narrative Justification

Though our anticipated Direct Cost expenses for Y1 ($133,575.78) and Y2 ($141,423.69) are very similar, we will be requesting (6) six modules of $25,000 each in Y1 ($150,000) and (5) five modules of $25,000 each in Y2 ($125,000) in order to be in compliance with the funding limits of the R21 award.

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	Introduction to revised application 7-15-15.pdf
2. Specific Aims	SpecificAims 7-15-15.pdf
3. Research Strategy*	Research Strategy 7-15-15.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	Protection of Human Subjects 7-15-15.pdf
6. Inclusion of Women and Minorities	Inclusion of Women and Minorities 7-15-15.pdf
7. Inclusion of Children	Inclusion of Children 7-15-15.pdf
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	Letter of Support_Kranzler_1.pdf
13. Resource Sharing Plan(s)	Data Sharing Plan 7-14-15.pdf
Appendix (if applicable)	
14. Appendix	SCID.pdf BDI.pdf CGI.pdf DAST.pdf TSR.pdf MEDICAL HISTORY QUESTIONNAIRE.pdf Intake Questionnaire.pdf Substance Use Inventory.pdf RAB.pdf Self-Report ASI_1.pdf

INTRODUCTION TO THE REVISED APPLICATION

This is a resubmission of the R21 application entitled *Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stumulant Abuse*. Overall, the committee was very positive and noted several strengths of each component of the grant including: "outstanding environment," "clinically significant" area of study and "innovative" research plan. The committee also noted several areas needing improvement and clarification. This letter only addresses the major points of criticism; however, each individual critique has been addressed.

Critiques of the Investigators: Reviewers raised concern that **none of the research team has significant human genetics research experience/publication history** and that data from my currently funded pharmacogenetics grant would make the reviewers "more confident". Response: To address this concern, I have added Dr. Hank Kranzler as a paid consultant on the grant. Dr. Kranzler has served as the principle investigator or co-investigator on over 12 NIDA/NIAAA- funded studies investigating genetic contribution to the abuse and treatment of substance use disorders and has authored over 110 publications related to the study of addiction genetics. Dr. Kranzler currently serves as the co-mentor or my K01 grant (DA030446) *Contribution of Various Genetic Polymorphisms to the Abuse Liability of Oxycodone.* In addition to agreeing to assist in the successful completion of the proposed study, Dr. Kranzler has lent his expertise to revising the research plan based on the initial grant review. Since the original submission, I have also significantly improved my pharmacogenetics authorship with publications in *Drug and Alcohol Dependence*, and *Alcoholism: Clinical and Experimental Research*. I have also submitted data from my K01 study for publication, this data also served as preliminary data for a pharmacogenetics R01 grant submission (DA040906) on which I was principal investigator.

Critique of the Research Plan: Concerning the research plan, the reviewers were concerned that the **inclusion criteria related to (ab)use of psychostimulants was too broad,** and would lead to significant variability in subjective response to the study's challenge drug and the relative value of the drug to the alternative monetary reinforcer, confounding both assessments of abuse liability. Response: To address this concern, the investigators decided to modify the target study sample to individuals with more severe and current abuse of psychostimulant drugs (i.e., meet current DSM-V criteria for moderate-to-severe stimulant use disorder, specifically cocaine or amphetamines, yet are NOT seeking treatment for their drug use). Accordingly, to match these participants with more stimulant abuse experience, we have changed the test drug and route of administration. We will now test naltrexone's (NTX) ability to attenuate the self-administration and positive subjective experience of intranasally administered methamphetamine (M-AMPH, 50mg/70kg). We have significant experience testing this population and this drug/route in our clinical laboratory procedures, and are confident that among this new population there will be significantly less variability in the effects of the IN test drug. Additionally, the current route of administration better models how amphetamines and other stimulants are abused in the real world (vs. the oral administration that all previous NTX+AMPH lab studies have used).

Our experience in testing potential medication effects under these specific subject and dosing parameters has also allowed us to carefully select an appropriate monetary alternative reinforcer to test the drug against. Therefore, we are confident that data we obtain on the ability of NTX to shift participants' responding from drug reinforcer to the monetary reinforcer will have predictive validity of its treatment potential. This addresses another of the reviewers' concerns that **findings in these clinical laboratory setting may not translate to treatment potential in the real world.** Laboratory models of self-administration synthesize the physiological, behavioral, and cognitive aspects of a drug's effects, and translate them into a quantifiable indicator of abuse liability, drug-taking behavior itself. In general, drugs of abuse are thought of as reinforcers, because they produce rewarding subjective feelings thereby increasing the likelihood/occurrence of the behavior(s) that lead to their delivery (Catania, 1971; Brady and Lucas, 1984). Within the context of self-administration clinical studies, the abuse potential of a drug have typically been quantified in terms of: ratings of "liking" and/or "good drug effect," the amount of effort they are willing to devote to receive the drug, and/or the choice of drug vs. a nondrug alternative reinforcer. Data from our lab and many others has shown the value of human self-administration procedures in the development of treatment medications for substance abuse, and demonstrated their predictive validity (Carpenter et al., 2009; Comer et al., 2008; Jones et al., 2013).

Finally, the reviewers were conflicted as to whether a design approach that studies **a single possible genetic moderator, or one that investigates several, would be the most clinically meaningful**. As such, the new study design is capable of doing both. Response: While the moderating effect of the *OPRM1* A118G SNP (rs1799971) remains the primary target (because interaction with NTX has been the substantiated by other studies), in order to recruit sufficient numbers for a between subjects genetic analysis for this SNP (major allele vs minor allele-carriers) we will obtain a sufficient sample size for an exploratory polygenetic assessment of several possible genetic variants selected for functional relevance and minor allele frequency. Although the results of the polygenetic analysis will not provide the same specificity in determining the moderating contribution (effect size of each variant), it may provide an indication as to which genes/variants deserve more targeted investigation.

SPECIFIC AIMS

Overview: It is estimated that worldwide there are over 75 milliion abusers of amphetamines and cocaine. Despite the public health significance of psychostimulant abuse, there remains no FDA-approved medication to facilitate treatment. In addition to treating alcohol abuse, naltrexone (NTX) has shown some promise in treating stimulant abuse (for which there are no pharmacotherapies). The abuse liability of amphetamines (AMPH) and other psychostimulants is most commonly attributed to their enhancement of mesolimbic dopaminergic transmission (Di Chiara & Imperato 1988). Additionally however, there is evidence that stimulant drugs modulate the endogenous opioid system (Wang and McGinty, 1995; Fagergren et al, 2003). In addition to being a non-specific opioid antagonist, NTX inhibits dopamine (DA) neurons within the ventral tegmental area and diminishes dopamine function within the nucleus accumbens and nearby basal brain regions (Brahen et al 1977; Herridge et al 1988; Martin et al 1973).

Preclinical and clinical studies have provided data suggesting that NTX may be effective at reducing the (ab)use of AMPHs, however, a review of the literature reveals conflicting findings that require resolution. The introduction to genetic techniques to the study of drug abuse has helped to identify a number of genomic loci and variants that may moderate variability in treatment response. A recent meta-analysis concluded that the *OPRM1* A118G SNP (rs1799971) significantly moderates the treatment efficacy of NTX for alcohol abuse, increasing effectiveness by over 2 fold among G-allele carriers (AG/GG). The proposed application would be the first to investigate the utility of NTX for treating stimulant abuse, while taking into account the possible moderating effect of rs1799971 variation. More specifically, we propose investigating the interaction between oral NTX and intranasal (IN) methamphetamine (M-AMPH; 50mg/70kg), a commonly prescribed (Desoxyn) and abused amphetamine-type stimulant (Brant et al., 2014). By administering this dose of M-AMPH via a route with faster pharmacokinetics (intranasal), the proposed investigation will better model how amphetamine drugs are abused in the real world (Bolin et al., 2013; Choi et al., 2001; Karila et al., 2010; Hart et al., 2008). Therefore, this investigation will provide a more externally valid assessment of NTX's treatment potential in comparison to previous studies.

Potential participants who meet DSM-V criteria for stimulant use disorder will complete testing sessions where IN M-AMPH effects are assessed following pretreatment with NTX (0, 25, 50 mg). Naltrexone pretreatment effects upon the abuse liability of M-AMPH will be assessed using self-report measurements of positive subjective effects and drug self-administration. Medication effects on these validated predictors of abuse potential will be compared between A118G A allele homozygotes (AA) and G-allele carriers (AG/GG) in order to evaluate genetic moderation of treatment outcome. In an exploratory endeavor, data from all participants (N =72) will be used to concurrently assess the ability of 5 functionally relevant genetic variants to predict NTX's treatment efficacy [*ANKK1* (rs1800497); *DβH* (rs1611115); *DRD2* (rs2283265); *OPRM1* (rs6912029), *SLC6A3* (rs28363170)].

This investigation will seek to address the following specific aims:

- Primary Aim: Compare the ability of NTX to alter the subjective and reinforcing effects of IN M-AMPH between groups of *OPRM1* A118G SNP carriers (AA vs AG/GG).

  We hypothesize that G-allele carriers will report dose-dependent reductions in positive subjective and reinforcing effects following NTX pretreatment. In comparison, AA homozygous participants will report significantly less NTX effects on these measures.

- Exploratory Aim: Assess the association between various functionally relevant candidate genes and NTX treatment response.

  We predict that the presence or absence of one or more of the target genetic variants will be significantly associated with (and predict) change in the positive subjective and reinforcing effects of M-AMPH following 0 mg NTX and 50 mg NTX pretreatment.

Impact: The proposed investigation will be the first study assessing genetic modulation of naltrexone's effects upon the abuse liability of a stimulant drug (methamphetamine). The exploratory study will concurrently assess the ability of several functionally relevant gene variants to predict pharmacological treatment efficacy. In addition to its contribution to the further development of the first pharmacotherapy for stimulant abuse, this study may identify gene x pharmacological interactions contributing to the personalization of stimulant abuse pharmacotherapy.

SIGNIFICANCE

The Challenge of Stimulant Abuse: Abuse of stimulants is a serious public health problem. Of the approximately 210 million illicit drug users worldwide, approximately 54.8 million abuse amphetamines (AMPH) and approximately 21 million abuse cocaine (COC; United Nations Office on Drugs and Crime, World Drug Report, 2014). In the United States, cocaine use has declined but the use of amphetamine-type drugs is on the rise. The rate of AMPH use in the United States now exceeds the historic level reached by cocaine in the period 2000-2006.

A Potential Solution: The abuse liability of AMPH and other psychostiumlants is most commonly attributed to its enhancement of mesolimbic dopaminergic transmission (Di Chiara & Imperato 1988). Additionally however, there is evidence that stimulant drugs modulate the endogenous opioid system (Wang and McGinty, 1995; Fagergren et al, 2003). One medication that has shown promise as a pharmacotherapy for stiumlant abuse is naltrexone (NTX). In addition to being a non-specific opioid antagonist, NTX inhibits dopamine (DA) neurons within the ventral tegmental area and diminishes dopamine function within the nucleus accumbens and nearby basal brain regions (Brahen et al 1977; Herridge et al 1988; Martin et al 1973).

Consistent with these data, opioid receptor antagonism by NTX has been shown to attentuate the behavioral and neurochemical effects of AMPH. In rodent models, NTX significantly attenuated AMPH-induced: dopamine release (at a dosage of 5.0 mg/kg) and locomotor behavior (at 3 mg/kg), AMPH-potentiated brain stimulation reward (at 0.5 mg/kg) and amphetamine-induced reinstatement of drug seeking (at 0.1 and 0.3 mg/kg) (Schad et al.,1995, Häggkvist et al., 2010; Häggkvist et al., 2009; Todtenkopf et al., 2009). The modulatory effect of NTX on amphetamine-induced behaviors has also been observed in rhesus monkeys, where 0.01–1 mg/kg of the drug dose-dependently decreased amphetamine self-administration (Jimenez-Gomez et al., 2011).

The data from preclinical models have been corroborated using various human laboratory studies. Three clinical amphetamine challenge studies have shown reductions in the subjective effects of d-amphetamine (D-APMH) following acute pretreatment with NTX (50 mg, orally) (Jayaram-Lindstrom et al., 2004; 2008a; Marks et al., 2014). Combined, these findings strongly suggest that NTX may be useful in treating amphetamine abuse, and has led to its being tested in clinical trials. Jayaram-Lindstrom and colleagues (2005) found encouraging results in an open-label trial of NTX (50 mg), reporting significantly lower amphetamine use during treatment compared to pre-treatment. In a later randomized, placebo-controlled trial, these investigators found that NTX (50 mg) significantly increased mean numbers of negative urine samples and continuous abstinence more than placebo (Jayaram-Lindstrom et al., 2008b). However, Grant et al. (2010) failed to find a robust treatment response in NTX-treated participants (at dosages of 50-150 mg/day).

The data have also been inconsistent in trials of sustained-release NTX formulations. Tiihonen et al. (2012) assessed the efficacy of a NTX implant in individuals with comorbid opioid and amphetamine dependence. Naltrexone outperformed the placebo implant on retention and the proportion of drug-free urine samples. In another trial among patients with problematic amphetamine use, abstinence rates were 2.27 times greater among patients with NTX plasma levels >2 ng/ml. In contrast to these findings, one of the largest clinical trials of extended-release NTX for amphetamine abuse showed a lack of a treatment effect of the active formulation vs. placebo (Rúnarsdóttir and Hansdóttir, Annual Meeting of the College on Problems of Drug Dependence, June, 2013).

Genetic Variation as a Moderator of Treatment Response: In addition to the role that methodological differences among studies (e.g., in medication dosage, subject population, treatment duration, sample size) may have played in these findings, genetic variation may also have contributed to the inconsistency in treatment response. In support of this possibility is the fact that the heritability (proportion of observable differences in a trait between individuals that is due to additive genetic effects) of substance abuse is among the highest of any psychiatric disorder 40–80% (Agrawal et al., 2012; Kendler et al., 2000; Tsuang et al., 1996; Tsuang et al., 2001; Uhl et al., 1999). The burgeoning area known as pharmacogenetics examines the moderating effects of genes on drug response, most commonly in laboratory studies or clinical trials.

One relevant finding from pharmacogenetic research involves a single nucleotide polymorphism (SNP) in exon 1 of the mu opioid receptor gene (*OPRM1*). An A to G substitution (A118G, rs1799971) alters the receptor's amino acid sequence by substituting aspartic acid for asparagine (Asn40Asp40). A recent meta-analysis of one of the most commonly studied medication (NTX) x genotype (A118G) interactions in the treatment of alcohol dependence revealed a robust modulatory effect of this genotype on treatment outcome. In their meta-analysis of NTX pharmacogenetic clinical trials, Chamorro et al. (2012) concluded that G-allele carriers (AG or GG) were ~2 times less likely to relapse than A-allele homozygotes when treated with NTX. Human laboratory studies have generally been consistent with the findings from clinical trials. Alcohol challenge studies have shown G-allele carriers to be more sensitive to the stimulant and hedonic effects of alcohol (Ray et al., 2010; Ray and Hutchison, 2004), and to show a greater blocking effect on these responses when treated with NTX (Bujarski et al., 2012;

Ray et al., 2012; Setiawan et al., 2011). In light of the data showing a significant modulatory role of the A118G SNP (rs1799971) on NTX's effects on alcohol, the current application is to examine whether the SNP moderates NTX's effects on amphetamines.

INNOVATION

The proposed study will be the first investigation of NTX as a treatment for stimulant abuse to incorporate genetic variability as factor in treatment response. The primary design feature will be a prospective evaluation of NTX's ability to attenuate the reinforcing and positive subjective effects of intranasal (IN) methamphetamine (M-AMPH) in rs1799971 A-allele homozygotes (AA) and G-allele carriers (AG or GG). In an exploratory regression analysis we will concurrently assess the simultaneous impact of several genetic variants with relevant functional significance, whose moderating effects on NTX have yet to be extensively investigated. The relative moderating effects of these genetic variants may be small individually, and therefore not detectable when they are assessed alone. We will use a novel, polygenic approach to identify their combined contribution, which may serve as the basis for more targeted genetic analysis. Additionally, using intranasal amphetamine dosing will allow us to assess NTX's effects on a more clinically relevant route of administration, which has previously not been tested in the clinical laboratory. Finally, by using common, validated methods to assess, diagnose, and test study participants, this study will contribute resources for use by all investigators studying addiction genetics. This type of candidate-gene pharmacogenetic study has the potential to enhance clinical care of substance use disorders (SUDs) by identifying risk factors and providing clinically useful predictors of pharmacotherapeutic outcome.

APPROACH

Design Overview

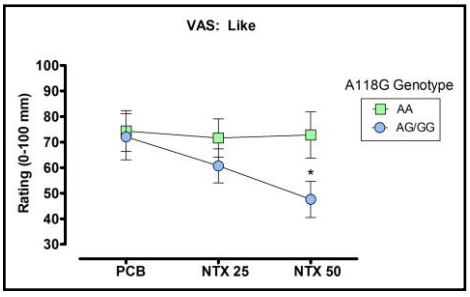
Primary Study: The proposed study will compare the ability of NTX to alter the abuse potential of IN M-AMPH in individuals differentiated on the basis of the *OPRM1* A118G SNP. Participants will be stimulant abusers of (Caucasian or of European decent, not seeking treatment) and consistent with most research on this genetic variant (Arias et al. 2014; Hendershot et al., 2014; Kim et al., 2009; Schacht et al., 2013) comparison genotypes will be grouped into A homozygotes (AA) vs. variant G-allele carriers (combined AG and GG). We plan to enroll 72 participants in the proposed study. Based on previous research we anticipate that 25% of the total sample will be G-allele carriers (Chamorro et al., 2012; Chen et al., 2013; Orsziet al., 2009; Ray et al., 2009). A random subset of major allele carriers, equal in number to the final count of G-allele carriers (anticipated ~17) who complete the study, will be utilized as their comparator group. This will ensure equal N's for the between-genotypes comparisons.

Participants who pass the extensive medical and psychological screening will be admitted to the inpatient unit of Columbia University Medical Center/ New York State Psychiatric Institute (NYSPI) for testing (see *Recruitment*). Following a 1-2 day washout, participants complete three lab sessions assessing the effects of pretreatment with 3 doses of NTX (0, 25 and 50 mg) in combination with IN M-AMPH (50mg/70 kg) in random order. The drug route/dose was chosen because our Division's previous work has shown that it elicits robust self-administration and positive subjective among stimulant-dependent populations (Comer et al., 1996; Hart et al., 2001; 2002; 2008; Kirkpatrick et al., 2012) (further justification is provided in the *Design Considerations* section). Our extensive experience testing this drug/dose in our clinical drug self-administration procedures also provides us with a validated, comparable alternative monetary reinforcer to test it against (U.S. $18). See Jones et al., 2013 for a review of the relevance and utility of laboratory models of drug administration. Naltrexone pretreatment is administered at 900hrs, followed by the IN administration of the sample M-AMPH dose (50mg/70kg) and $18 (1000hrs, "Sample" session). The Sample session is followed by comprehensive quantification of the subjective, cognitive and physiological M-AMPH effects (see *Assessments*). On the following day, participants return to the lab to complete a self-administration or "Choice" session where they are asked to choose between 1/6th of the drug dose or dollar amount they sampled the day before (i.e., ~8 mg or $3). Sample and Choice sessions are

Table 1: Sample Study Design

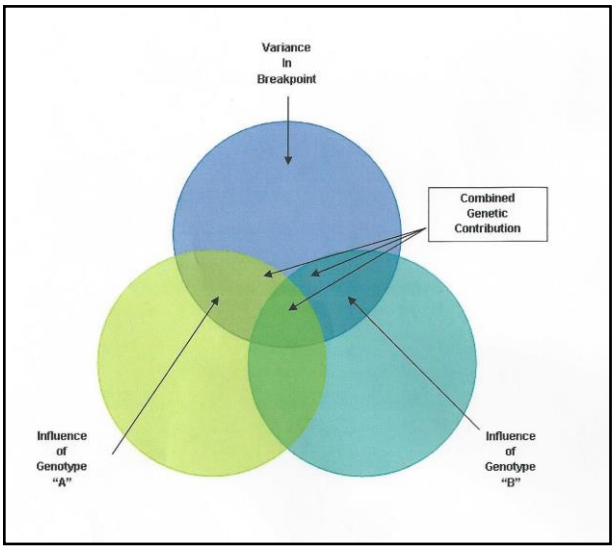
Week 1						Week 2					
Dose Time	**Mon**	**Tue**	**Wed**	**Thu**	**Fri**	**Dose Time**	**Mon**	**Tue**	**Wed**	**Thu**	**Fri**
	Admission	Washout	Testing	Testing			Testing	Testing		Testing	Testing
9:00 AM			**NTX 0mg**	**NTX 0mg**		9:00 AM	**NTX 50mg**	**NTX 50mg**		**NTX 25mg**	**NTX 25mg**
10:00 AM			Sample: 50mg vs $18	Choice: 50mg vs $18		10:00 AM	Sample: 50mg vs $18	Choice: 50mg vs $18		Sample: 50mg vs $18	Choice: 50mg vs $18
11:00 AM						11:00 AM					
12:00 PM						12:00 PM					
1:00 PM						1:00 PM					
2:00 PM						2:00 PM					
3:00 PM						3:00 PM					
4:00 PM						4:00 PM					
5:00 PM						5:00 PM					

completed on successive days (vs. the same day) in order to prevent carry over effects that we have previously observed with amphetamine self-administration (Comer et al., 1996; 2001). In the 6-trial, progressive ratio, choice procedure, after a choice is made between two options by clicking on its visual representation on the computer screen, the participant must complete the operant task requirement (finger presses on a computer mouse). The operant response requirement for each of the two options increases independently. The initial ratio requirement for each option will be 100 responses, which then increases progressively each time the option is selected (100, 200, 400, 800, 1200, 1600). At the end of the self-administration task (approximately 4 PM), the participant will receive whatever (s)he had chosen. Money is added to the study payment, and the IN M-AMPH is given to the participant by a physician. Within this context the abuse potential of the drug is quantified in terms of the amount of effort participants are willing to devote to receive the drug, and/or the choice of drug vs. the monetary alternative reinforcer (Catania, 1971; Brady and Lucas, 1984). The effects of NTX pretreatment on the positive subjective and reinforcing effects of D-AMPH will be compared between the two A118G genotypes (AA vs AG/GG). These data are expected to reveal a genotype by drug interaction, fictionalized in Figure 1 to the right.



Exploratory Study: An exploratory analysis will utilize combined data from all participants. A multiple regression will be employed to identify the possible combined moderation influence of a number of genetic variants on measures of methamphetamine's abuse potential (drug self-administration) and NTX's treatment efficacy (reduction in drug self-administration). Accordingly, a number of pharmacogenetic studies have found only combined effects of two or more variants (Chen et al., 2014; Dahl et al., 2006; David et al., 2007; Johnson et al., 2013; Johnstone et al., 2004; Quaak et al., 2012; Ray et al., 2014; Swan et al., 2007; Uhart et al., 2013). In this analysis, we have selected 5 target gene variants to use as predictor variables in a multivariate model to predict NTX's effects on the changes in the M-AMPH abuse liability measures discussed above (i.e., the change in score between 0mg and 50mg NTX testing sessions). This analysis will explore the relative contribution of each of the individual genetic variants along with their combined effect (see Figure 2 below). The candidate genotypes were chosen based upon prior evidence of an association with amphetamine abuse, demonstrated functional relevance to the effects of psychostimulants and a minor allele frequency of greater than 15%:

- Ankyrin repeat and kinase domain containing 1 gene, *ANKK1* (rs1800497): Adjacent to *DRD2*, associated with dependence on amphetamines and cocaine (Noble et al., 1993; Persico et al., 1996) and pharmacotherapy treatment outcome (Spellicy et al. (2013),
- Dopamine Beta Hydroxylase gene, *DβH* (rs1611115): Accounts for up to 52% of the variation in DβH enzyme levels, shown to moderate cocaine pharmacotherapy treatment outcome (Deinum et al., 2004; Khonke et al., 2002; Kosten et al., 2013),
- D2 DA Receptor gene, *DRD2* (rs2283265): Shown to interact with psychostimulant pharmacological treatment response (Spellicy et al, 2013),
- Dopamine transporter (DAT) gene, *SLC6A3* (rs28363170): Associated with altered DAT expression and DA clearance (Fuke et al., 2001),
- Mu opioid receptor gene, OPRM1 (rs6912029): Shown to moderate NTX treatment response (Al-Eitan et al., 2012).



Recruitment and Screening: Recruitment for this study will occur primarily through advertisements in local newspapers. Potential applicants will first complete a telephone interview via which we will obtain information on demographics (name, telephone number, race, age, sex), medical, psychological, personal history, and details on their use of various prescription and illicit drugs. Participants who meet study criteria based on the telephone interview will be scheduled to come to NYSPI for additional screening procedures. After signing the screening consent form, participants will be evaluated by a team of research psychologists, nurses, and physicians. Screening procedures will include self-report and clinically-administered inventories. In total, screening procedures typically require 3-4 visits to complete.

Screening assessments include:

- *Beck Depression Inventory (BDI-II; Beck et al., 1972).* The BDI-II is a 21-item self-report instrument that measures the severity of depression. Each item is rated on a 4-point scale ranging from 0 to 3.
- *State-Trait Anxiety Inventory (STAI; Spielberger, 1983).* The STAI is a self-report questionnaire consisting of two self-rated subscales, 20 items each, that rate trait anxiety and state anxiety. Both the Trait and State subscales will be completed at screening.
- *Structured Clinical Interview for DSM-IV or DSM-V expected to be available in 2015 (SCID; First et al., 1995*). A semi-structured clinician administered interview used to derive major DSM-IV Axis I psychiatric diagnoses.
- *Substance Use Inventory (Comer et al., 2008)*. This locally-developed self-report questionnaire will be used to determine quantity (i.e., dollars spent per day) and frequency (i.e., days) of substance use including: opioids, cocaine, alcohol, marijuana, amphetamines, sedatives, and phencyclidine.

Other screening assessments include: medical history evaluation, physical examination, ECG, laboratory testing (including hematology, clinical chemistry, and thyroid panel), breathalyzer, urinalysis, urine pregnancy testing and 11-panel urine drug toxicology. After reviewing screening results, a research psychiatrist will make the final decision as to whether the participant is eligible for the study. For those who agree to participate, informed consent for the study will be obtained and a training session, which is designed to familiarize participants with the study procedures, will be scheduled.

All participants must meet all of the following inclusion criteria to be enrolled into the study:

- Male or female age 21 to 50 years.
- Meet DSM-5 criteria for moderate-severe stimulant use disorder (endorse 4 or more of the criteria listed in the DSM-5). In the past 12 months, used any of the commonly abused stimulants recreationally including methamphetamine, cocaine, or Ecstasy at least twice in one week; participants will be exposed to the same or less stimulant administration than they normally would outside of the laboratory.
- In otherwise good health based on complete medical history, physical examination, vital signs measurement, ECG, and laboratory tests (hematology, blood chemistry, and urinalysis) within normal ranges.
- Able to give written informed consent to participate.

Participants will not be enrolled in the study if they meet any of the following exclusion criteria:

- Currently seeking treatment for a substance use disorder.
- DSM-V criteria for moderate-to-severe substance use disorders (except those involving cocaine, amphetamines and nicotine).
- Active psychiatric disorder that might interfere with participation or make participation hazardous.
- Lack of effective birth control; currently pregnant or breastfeeding.
- Uncontrolled neurological, cardiovascular, renal, and hepatic diseases, active tuberculosis, or any other disorder that might make administration of study medications hazardous.
- Gastrointestinal or renal disease that would significantly impair absorption, metabolism or excretion of study drug, or require medication or medical treatment.
- Current treatment with a psychotropic medication.
- History of allergy, adverse reaction, or sensitivity to amphetamine.
- Pseudocholinesterase deficiency.

Genotyping: After being consented at their initial visit to NYSPI, ~30 cc of venous blood will be collected in 8.5 ml ACD vacutainer tubes. Within 24 hr of their collection, blood samples will be transferred to Columbia's Human Genetics Research Core where DNA will be isolated and stored at -20° C. Extracted DNA will be batched and sequenced by Columbia's Taub Institute using PCR-based methods. Whole blood samples from each participant will also be sent to the NIDA Center for Genetic Study (NCGS) repository for the creation of cell lines, DNA, plasma or RNA for use among the broader scientific community. In addition to blood samples, we will also provide the NCGS with de-identified clinical data collected as a part of this investigation including: sex, race/ethnicity, age, SCID or psychiatric evaluation results.

Laboratory Session Tasks and Measures:

- *Reinforcing effects:* M-AMPH breakpoint (the point at which operant responding ceases) and % of drug vs. money choices.
- *Subjective Effects*: Two questionnaires will be used to assess subjective drug effects. A 26-item visual analog scale (VAS) will be used to assess subjective and physiological drug effects such as "I feel a good effect" and "I feel high". Participants rate each item on the scale from 'Not at all' (0 mm) to 'Extremely' (100 mm). In addition, a 6-item drug effects questionnaire (DEQ) will be used to measure drug effects (strength of drug effects, good effects, bad effects, willingness to take the drug again, drug liking, and similarity to other drugs). Participants select among a series of possible answers ranging from 0 ('No Effect') to 4 ('Very Strong Effect').

- *Cognitive effects*: The cognitive battery consists of two performance tasks: a 10-min divided attention task (DAT) and a 3-min digit-symbol substitution task (DSST, McLeod et al. 1982). The divided attention task consists of concurrent pursuit-tracking and vigilance components. Participants track a moving stimulus on the video screen using the mouse and signal when a small black square appears at any of the four corners of the video screen. The DSST consists of nine 3-row by 3-column squares (with one black square per row) displayed across the top of the computer screen. For each trial, a randomly generated number indicates which of the nine patterns should be emulated on a keypad by the participant. Participants will be required to emulate as many patterns as possible by entering the pattern associated with randomly generated numbers appearing on the bottom of the screen.
- *Physiological Measures:* For safety, oxygen saturation (%SpO_2), respiration (breaths per minute), heart rate, and blood pressure (systolic and diastolic) will be measured every 5 minutes.
- *Criteria for Terminating a Session & Criteria for Discontinuation/Dropout:* See the *Protection of Human Subjects* section for medical criteria our Division has used extensively in order to ensure the safety of participants receiving intranasal psychostimulants.

Discharge and Follow-up: Participants will be paid $25/inpatient day, with a $25/day bonus for completing the study. At the conclusion of the study, participants will be given an exit interview during which the study will be described. Those who are interested in treatment for their drug use at the end of the study will be offered referrals to studies at our Substance Treatment and Research Service or other treatment providers. All participants will return to NYSPI weekly for payments, and at 1 and 3 months for follow-up visits.

Design Considerations

Drugs and Dosing: Methamphetamine was selected for the proposed study because it a commonly abused and prescribed (Desoxyn) amphetamine-type stimulant (Brant et al., 2014). There are also data to suggest that globally, ampetamines are being used as a substitute for cocaine, therefore data obtained here with M-AMPH may also be applicable to cocaine-abusing populations (United Nations Office on Drugs and Crime, 2014).The dose of M-AMPH (50mg/70kg) selected for this study has also been shown to be highly rewarding in stimulant-abusing participants (Kirkpatrick et al., 2012). By administering this dose of M-AMPH via a route with faster pharmacokinetics (intranasal), the proposed investigation will better model how amphetamine drugs are abused in the real world (Bolin et al., 2013; Choi et al., 2001; Karila et al., 2010; Hart et al., 2008). Therefore, this investigation will provide a more externally valid assessment of NTX's treatment potential in comparison to previous studies that have used an oral route of AMPH administration. Oral doses of 25 mg and 50 mg of NTX were chosen based on the existing literature. Oral doses of 50 mg of NTX produce plasma levels sufficient to saturate mu opioid receptors for over 72 hr (Lee et al. 1988). This finding, given the possibility of side effects, precludes the need to test higher doses (Anton et al. 2006; Garbutt 2010; Pfohl et al. 1986). The acute dosing of NTX replicates the dosing procedure of many of the NTX+AMPH challenge studies cited in the *Significance* section. Additionally, observations of robust reductions in amphetamine's reinforcing and positive subjective effects by NTX, obtained in the laboratory setting are predictive of treatment response in clinical treatment settings (Haney et al., 2008; Jayaram-Lindstrom et al., 2004; 2008 a;b).

Focus on A118G: In the current proposal, only one genetic variant was chosen for *a priori*, quasi-experimental, between-groups testing, due to its substantiated moderating effect on the efficacy of the test drug (NTX). An alternative approach would be to test the effects of NTX on M-AMPH among a participant sample, then perform *a posteriori* comparisons of outcome between genotypes for many possible moderating variants. However, this approach would necessitate hundreds of participants to control for multiple testing well beyond the financial feasibility of any single clinical laboratory study. This statistical control is often ignored and is thought to lead to false positives and the failure to replicate among pharmacogenetic studies (Hart et al., 2013; Jones et al., 2015 A, B; Munafo et al., 2007). The exploratory aim of the proposed study attempts to simultaneously assess several possible genetic moderators (but whose influence is not as substantiated as the primary genetic target) using the combined study sample. Although this approach will not allow for specific determination of the effect size of each individual variant, positive results may serve as the basis for a more direct genotype comparison.

Aims:

- Primary Aim: Compare the ability of NTX to alter the subjective and reinforcing effects of intranasal M-AMPH between groups of *OPRM1* A118G SNP carriers (AA vs AG/GG).
- Exploratory aim: Assess the moderation of the subjective effects of M-AMPH by various functionally relevant candidate genes.

Statistical Analyses

Outcome Measures

Abuse Liability: The primary outcome measure of the reinforcing effects of the test drug (IN OXY) will be the drug **break point** assessed during the "choice" self-administration session (the point at which responding for the drug ceases). In addition to this measure we will utilize peak (maximal drug effect throughout the session) observation of positive subjective drug effects (e.g., VAS assessed drug **"Liking")** measured during the "sample" session (continuous variables). The distributions of all continuous variables will be checked for normality, and transformations will be employed, if necessary, before applying specific parametric techniques. Before performing specific analyses (described below), we will examine all outcomes for outliers. The distribution of demographic variables (e.g., gender, age) and measures of drug use will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals.

Data Analysis Plan

Primary Hypothesis and Testing: SNP rs1799971 G-allele carriers will report dose-dependent reductions in positive subjective (i.e., "Liking" and reinforcing (i.e., lower breakpoint) following NTX pretreatment. In comparison, AA homozygous participants will report significantly less NTX effects on these measures. These data will be analyzed with a mixed-model analysis of variance (ANOVA) test comparing medication effects (PCB, NTX 25, NTX 50) between the two genotype groups (AA vs AG/GG). If a significant interaction is found with this omnibus ANOVA, planned comparisons (t-tests) will be used to specify where significant differences exist. All tests for main effects (Genotype, NTX Dose) will be performed at two-tailed significance α=5%; all tests for interaction effects will be performed at significance level α=15%. Any comparison where homogeneity is violated will not be considered significant. Because we expect that the minor allele carriers will make up only 25% of the total sample (N=72), a random subset of the major allele carriers, equal in number to the final count of G-allele carriers (anticipated ~17) will be utilized as their comparator group. Although some between-groups statistical tests are robust against unequal sample sizes, differential sample size combined with the likely possibility of differential group variance, could easily double or triple the alpha error rate (Lipsey, 1990). Because sex has been shown to moderate the efficacy of NTX (Setiawan et al., 2011) participants will be stratified according sex to ensure comparable numbers of males and females in the AA and AG/GG groups.

Exploratory Hypothesis and Testing: The presence or absence of one or more of the target genetic variants will be significantly associated with (and predict) change in the positive subjective and reinforcing effects of M-AMPH following 0 mg NTX and 50 mg NTX pretreatment. Multiple regression analysis will be used to identify which individual or combination of the 5 genetic variants best predicts those who respond to NTX (i.e., is there a genetic profile that may moderate the effect size of NTX's treatment efficacy). A bivariate analysis will first be used to select eligible factors for the multivariate model (demographic variables will also be assessed in this model). To avoid situations where strong confounds could hide important predictors, a liberal *p*-value of <0.20 will used as a selection criterion for inclusion in the multivariate model. A stepwise backward selection procedure will then be used, based on a p <0.05 to identify the best multivariate model. Area under the curve (AUC) will be calculated to determine the robustness of the model. This statistical approach has provided significant data in other behavioral pharmacogenetic studies (Jones et al., Submitted).

Genetic Analyses: For each polymorphism, a test for Hardy–Weinberg equilibrium will be performed to test for deviation from Hardy–Weinberg equilibrium by using the SNPstat software (Solé et al., 2006). For all the selected polymorphisms, we will consider both a log-additive, a dominant, or a recessive mode of inheritance. The Akaike information criterion (AIC) will be used to select the genetic model that best fits the data (i.e., the model with the lowest AIC score).

Power Analysis: Power for the current study is based on previous investigations demonstrating a moderating effect of A118G on the effects of NTX. Effect size estimates concerning the impact of this SNP are derived from two alcohol pharmacogenetic challenge studies finding greater NTX attenuation of subjective ratings of "High," and "Euphoria" among G-allele carriers (Ray et al., 2012; Setiawan et al., 2011). Based on mean differences observed for NTX's effects between AA and AG/GG groups in these two studies, a Cohen's *d* effect size of 1.0 was estimated (assuming that each group varies 1.1 standard deviations from its mean). Given this effect size, a sample size of 17 per genotype would allow us ~90% power to detect a 20 mm difference in NTX's effects on ratings of M-AMPH "Liking" between the AA and AG/GG groups. This power analysis is also applicable to the exploratory study. To achieve an N of 17 minor-allele carriers, we plan to test 72 participants in total. This sample size would allow us to asses an effect size contribution from genetics variables as small as 0.12 (f^2) in a regression model (R^2). When this effect size was imputed into G* Power 3.1.7 with the number of genetic variables under investigation in the exploratory analysis (5), a sample size of 72 participants should allow ~85% power to detect a significant model. Because of the exploratory nature of this study, an α of 5% was used. Adjusting the alpha for all predictor variables to account for multiple testing would assume that the predictor variables are independent, which is not likely. However, once the data are collected, the investigators will be able to determine the relatedness of the predictor variables and adjust the alpha accordingly (i.e., Bonferroni adjusted α). Thus, with regard to both study aims, these calculations suggest that this study is suitably powered.

PROTECTION OF HUMAN SUBJECTS

1. Risks to the Subjects

Human Subjects Involvement and Characteristics

Prospective research participants will be normal healthy men and non-pregnant women who will be evaluated according to the following inclusion/exclusion criteria:

All participants must meet all of the following inclusion criteria to be enrolled into the study:

- Male or female age 21 to 50 years
- DSM-V criteria for moderate-to-severe stimulant use disorder
- In otherwise good health based on complete medical history, physical examination, vital signs measurement, ECG, and laboratory tests (hematology, blood chemistry, urinalysis) within normal ranges
- Able to give written informed consent to participate

Participants will not be enrolled in the study if they meet any of the following exclusion criteria:

- Currently seeking treatment for a substance use disorder
- DSM-V criteria for moderate-to-severe substance use disorders (except those involving cocaine, amphetamines and nicotine)
- Active psychiatric disorder that might interfere with participation or make participation hazardous
- Lack of effective birth control; currently pregnant or breastfeeding.
- Uncontrolled neurological, cardiovascular, renal, and hepatic diseases, active tuberculosis, or any other disorder that might make administration of study medications hazardous
- Gastrointestinal or renal disease that would significantly impair absorption, metabolism or excretion of study drug, or require medication or medical treatment
- Current treatment with a psychotropic medication
- History of allergy, adverse reaction, or sensitivity to amphetamines
- Pseudocholinesterase deficiency

Sources of Research Material

Screening evaluation and research forms completed by research staff and participants include:

- Blood sampling: (1) comprehensive metabolic panel collected during screening (2) identification of target genetic variants.
- Urine samples: to document drug and/or alcohol use, pregnancy testing, and urinalysis for general health.

All data will be obtained specifically for research purposes and coded with a unique identifier assigned to each participant. Consent forms will contain participants' names.

Potential Risks

Blood Drawing: During the screening assessments, two 30 cc venous blood samples will be collected, one for medical evaluation and another for genetic testing. Blood drawing may cause mild discomfort at the site where the needle is inserted, and it poses a small risk of bruising at the site as well as an extremely low risk of infection.

Psychological Distress: The structured interviews, rating scales, and questionnaires should add no physical risk. However, because many of the interviews and assessments are time consuming to complete and involve topics of a sensitive nature, some people have found them to be physically or emotionally tiring. Patients are informed prior to study entry that they can refuse to answer any questions and that they

can request to stop at any time. If a participant becomes agitated during any of the interviews or assessments, he or she will be provided with therapeutic assistance.

Amphetamine administration: Amphetamine-type stimulants (including methamphetamine) are used clinically for the treatment of ADHD and narcolepsy. Doses between 5 and 60 mg per day in divided doses are typically used for the treatment of narcolepsy. The major risks of intranasal M-AMPH administration are increased blood pressure and heart rate. Other side effects include excitation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, dry mouth, diarrhea, constipation, and weight loss. Less common side effects include seizures, blurred vision, increased thought disorders, psychosis, and hallucinations. Our Division has safely administered psychoactive stimulants including cocaine, amphetamine and methamphetamine via oral, smoked, intravenous and intranasal routes in numerous studies without significant medical complications (Comer et al., 1996, 2001, 2013; Collins et al., 2007; Hart et al., 2001, 2008; Foltin et al., 2004). Only prospective participants who use stimulants in a quantity greater than that we plan to administer in the proposed study will qualify for inclusion.

Naltrexone Administration: Naltrexone may mildly impair the functioning of the liver. This effect on the liver will resolve after naltrexone is discontinued. Naltrexone may also cause stomach upset, nausea, and vomiting. In addition, administration of naltrexone may increase blood sugar levels, which may produce symptoms such as dizziness, increased breathing, dehydration, sedation, and localized seizures. Only two active NTX doses are administered as a part of the proposed investigation, therefore we anticipate a very small likelihood of these adverse effects.

Subsequent Drug Use: The possibility of study participants increasing their drug use as a result of their participation in the proposed study is small. Previous studies have shown that administration of drugs of abuse to drug-abusing volunteers does **not** lead to increased drug use after study participation:

- Bigelow GE, Brooner RK, Walsh SL, Preston KL, Liebson IA. (1995) Community outcomes following research exposure to cocaine or opioids. In: IHL, editor. Problems of Drug Dependence 1994: Proceedings of the 56th Annual Scientific Meeting. Washington DC: NIH; p. 354.
- Elman I, Krause S, Karlsgodt K, Schoenfeld DA, Gollub RL, Breiter HC, et al. (2001) Clinical outcomes following cocaine infusion in nontreatment-seeking individuals with cocaine dependence. Biol Psychiatry 49: 553–555.
- Fischman MW, Schuster CR, Resnekov L, Shick JF, Krasnegor NA, Fennell W (1976) Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 33: 983–989.
- Pratt WM, Davidson D. (2005) Does participation in an alcohol administration study increase risk for excessive drinking? Alcohol 37: 135–141.

Analysis of our own 1 month follow-up data across 5 recently completed inpatient studies where drugs were administered found that participation decreases drug use and facilitates entry into treatment. More specifically, 42% of our study completers were not using heroin 1 month after study completion and 55% decreased their heroin use from 5.9 bags per day at baseline to 2.9 bags per day at the 1-month follow up visit. In addition, 21% initiated buprenorphine or methadone treatment, 6% enrolled in a detox program, and 25% were referred to treatment [Roux et al., (2012) Impact of inpatient research participation on subsequent drug use patterns: implications for ethics and public health. Addiction 107: 642-649]. A similar follow-up analysis of studies where cocaine was administered yielded similar results. Cocaine use significantly decreased at 1 month (-$165.13/week) and 3 months (-$118.59/week) after study participation ($p<0.001$). This decrease was not accompanied by a change in other drug use, e.g., a compensatory increase in alcohol, marijuana or nicotine use [Kalapatapu RK et al., (2012) Substance use after participation in laboratory studies involving smoked cocaine self-administration. Drug Alcohol Depend 120(1-3): 162-167]. These results are not surprising because those who volunteer for our studies generally have relatively long histories of drug use and are, by inclusion criteria, regular users who have no desire to cut down or stop their use. The amount of drug they receive is also less than what they would be administering outside of the laboratory.

Inpatient Housing: The problems associated with living in the hospital have been minimal in the participants we have tested in other research studies. We describe the isolation, boredom and inactivity at length prior to signing the consent form. The risks involved in exposure to the laboratory are believed to be negligible. In numerous previous studies, participants have not found the experimental procedures or laboratory per se to be stressful or difficult. Of course, participants are free to leave the study at any time and care is taken to be sure that this is understood. During the last few days 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 at STARS or Narcotics Anonymous.

Pregnancy: Female participants must not be pregnant to be included in the study. Urine pregnancy tests are performed at each screening visit and immediately prior to admission.

Confidentiality: Potential participants divulge information that is sensitive and may have adverse social consequences if released. This would include information released to insurance companies, health care agencies, or family members, or information made public in any way. A Certificate of Confidentiality will be obtained for the current study and procedures for protecting confidentiality of records will be followed. Specifically, all data records containing identifying information will be kept in locked files and on password-protected computers. 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 their identifying information. The contract 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 uncoded identification. Patients will be identified only through a numerical code in all electronic databases.

Genomic Information: Participants will be notified that these samples will be used for an investigation into the association between drug abuse and genotype, and that these samples will be archived for up to 15 years for future investigations. Participants will also be informed of the Genetic Information Nondiscrimination Act (GINA) that generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate based upon genetic information.

2. Adequacy of Protection Against Risks

Screening: 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.

The following procedures and exclusionary criteria are designed to minimize the risks to participants:

- Participants are excluded if they have severe psychiatric illness(es) (e.g. mood disorder with functional impairment or suicide risk, schizophrenia) that might interfere with their ability to participate in the study or their capacity to provide informed consent
- Current treatment with psychotropic medications is exclusionary due to possible adverse interactions with study medications
- Pregnancy is exclusionary due to the possible effects of the study medication on fetal development
- History of an allergic reaction to any medication administered as a part of this study
- The evaluating study psychiatrist physician reviews all medical assessments along with medical history to determine if any would make study procedures hazardous

Participant Education

All participants will be informed of the possible side effects and risks mentioned above, which will also be included in an informed consent document. For eligible participants, the study PI and research psychiatrist will describe the study in detail including study procedures, and possible risks and benefits of participation. Participants may sign the consent form only after reading it, having any questions answered, and being given a copy to keep.

Consent Procedures

Participants will provide informed consent to screening and all study procedures prior to testing. Participants are instructed to call us if any untoward effects occur after the laboratory session and are given an emergency contact number.

Participant Monitoring and Removal from the Study

The research team will continually assess the participant's health throughout the inpatient period and will remove participants from the study if physical or mental deterioration is observed. The medical criteria below have previously been approved by NIDA to be used to terminate a laboratory session during which amphetamines were administered, and an individual's participation in the entire trial.

- **Criteria for Terminating a Session:** The occurrence of any of the following abnormalities in a participant's vital signs will result in the immediate ending of a laboratory session: (a) Systolic blood pressure > 180 mm Hg, sustained for longer than 6 minutes (> 3 consecutive readings), (b) diastolic blood pressure > 120 mm Hg, sustained for longer than 6 minutes (> 3 consecutive readings), and (c) heart rate > (220 – subject age x 0.85) bpm, sustained for longer than 6 minutes (> 3 consecutive readings).
- **Criteria for Discontinuation/Dropout:** If two sessions are terminated due to abnormal vital signs, the participant will be discontinued from the research study and informed as to the reason that their participation is being ended and they will be counseled as described below for completers Upon removal of a participant from the study, he or she will be provided with the appropriate follow-up treatment by the study physician and research nurse.

Confidentiality

Information about participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Records are kept in locked files and released only with the participant's consent. All data are stored without names or other coded identification. Participants will be identified only through a numerical code in databases, while a paper code list will be kept under lock and key by the principal investigator. Before any screening procedures are initiated, participants sign an IRB-approved HIPAA acknowledgement form. A Certificate of Confidentiality will also be obtained for this study.

3. Potential Benefits of the Proposed Research to the Subjects and Others

Although there are minimal direct benefits to the participants, we conclude that the scientific benefits of the proposed research outweigh the potential risks.

4. Importance of the Knowledge to be Gained

Currently little is known about how genetic factors modulate naltrexone's effects on stimulant drugs. The proposed clinical investigation will be the first study assessing genetic modulation of naltrexone's ability to alter the abuse liability of a commonly abused stimulant (M-AMPH). The study could identify an important Gene x Pharmacological interaction, contributing to the personalization of stimulant abuse pharmacotherapy. In addition we may also learn more concerning genetic risk factors for stimulant abuse.

5. Data and Safety Monitoring Plan

Adverse Event (AE)

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries are also regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the study physician to be of clinical significance

Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs inpatient stay
- Results in persistent or significant disability or incapacity
- An important medical event

All adverse events reported by the participant or observed by the research staff will be individually listed on our Adverse Event Form (AEF). The signs and symptoms, time of onset, duration, severity, medical intervention, follow-up procedures, and suspected relationship to study drug will be reported. Any AE (clinical signs and symptoms or laboratory test) associated with M-AMPH or naltrexone administration whether or not considered drug related, will be documented by the study physician or nurse. Both the principal investigator and study physician provide ongoing review of the data and safety of the study participants during daily communication with the research staff, as well as at weekly lab meetings. In addition, ongoing and annual review of any serious adverse event is monitored by the IRB of the New York State Psychiatric Institute, NIDA, and the FDA. The co-investigator, Dr. Comer, has served as a regular member of the IRB at the NYSPI since 2001, so she is intimately familiar with adverse and serious adverse events reporting requirements.

INCLUSION OF WOMEN AND MINORITIES

Because the minor allele of the study's primary target variant (A118G) is significantly less common among African-Americans (7%) than non-Hispanic Caucasians (28.7%) or Hispanics (27.8%)(Hastie et al., 2012), it will not be feasible to recruit an adequate number of participants of African ancestry to test the study's primary hypothesis. Further, it is not feasible to combine African-ancestry and European-ancestry participants in the same analysis because to do so would result in confounding due to population genetic differences. Thus, we will enroll only participants who self-identify as White/Caucasian or as being of European ancestry. Of this sample, we anticipate that approximately 30% will self-identify as Hispanic/Latino. Based on previous experiences with recruiting stimulant abusers in the NYC area, we anticipate that 15% of our sample will be female (see Targeted/Planned Enrollment Table).

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	0	0	**0**
White	14	30	7	19	**70**
More than One Race	0	0	0	0	**0**
Total	**14**	**30**	**7**	**19**	**70**

Study 1 of 1

Funding Opportunity Number: PA-14-013. Received Date: 2015-07-15T14:35:23.000-04:00

INCLUSION OF CHILDREN

Adolescents less than 21 years of age will be ineligible for participation in this study. More data on naltrexone's safety and methamphetamine's abuse potential in adolescents should be garnered before this procedure is attempted with younger participants. Additionally, adolescents < 21 who suffer from stimulant use disorder may require significantly different pharmacotherapeutic strategies than adults.

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Perelman School of Medicine
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June 27th, 2015

Jermaine Jones, Ph.D.
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Division of Substance Abuse
1051 Riverside Drive
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Dr. Jones,

I am glad to provide this letter to support the R21 application "Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse." I believe Dr. Jones has developed a very innovative way of evaluating the contribution of genetic involvement in efficacy of naltrexone to treat stimulant abuse. Over the past 25 years, I have been an active investigator in the genetics of substance abuse and have conduced: linkage, association, GWAS and candidate-gene studies.

I have worked with Dr. Jones over the past 4 years a co-mention on his K01 grant "Genetic Contribution to the Abuse Liability of Oxycodone." I have also previously worked with Columbia's Division of Substance Abuse as an advisor on their P50 Center Grant (PI Herbert Kleber, MD). I have worked with Dr. Jones to refine the research plan of this proposal and believe the proposed study could have a significant impact on our understanding of genetic contribution to opioid use disorder. Dr. Jones is a very promising young investigator whose progression towards developing a pharmacogenetic research niche within his division I have helped foster over the past few years. I look forward to working with him on this exciting project. As I have discussed with Dr. Jones, I will be available to discuss and troubleshoot any issues that may arise during data collection, and assist with analysis for any interim analyses and the final study report. I am excited to continue our cooperative research endeavors, and hope that this application is funded.

Sincerely,

Henry R. Kranzler, MD
Professor of Psychiatry /Director
Center for Studies of Addiction
University of Pennsylvania
Perelman School of Medicine
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Data and Resource Sharing

NIH requires data sharing for all investigator-initiated grants with direct costs exceeding $500,000 in any single year. This grant does not meet these criteria. However data from the studies in this R21 application will be shared in a number of ways. First, this protocol will be registered through the Protocol Registration System operated by the National Library of Medicine (NLM). The Protocol Registration System maintained by NLM will allow us to update information about the ongoing trial. The NLM publishes this information on their ClinicalTrials.Gov website. By providing details about this study, we also satisfy clinical trial registration requirements of the International Committee of Medical Journal Editors (ICMJE).

Secondly, as a NIDA-funded human genetics study, this investigation will also be included among those participating in the NIDA Center for Genetic Studies (NCGS). Accordingly, the principal investigator (Dr. Jermaine Jones) will send the NCGS repository whole blood samples from each participant to possibly create cell lines, DNA, plasma or RNA. In addition to blood samples, the NCGS will also receive de-identified clinical and phenotypic data that will be collected as a part of this investigation including: subject ID, sex, ethnicity, age, DSM-V diagnosis, SCID or psychiatric evaluation results, along with Addiction Severity Index (ASI), Drug Abuse Screening Test (DAST-10) and Clinical Global Impression (CGI) scores. This data will be verified as needed, and regular updates will be provided throughout the grant award period. Blood samples, along with clinical and phenotypic data will be sent to the repository every 6 months and available for distribution 12 months after the termination of the grant period (including extensions). The PI will also apply for membership to the NIDA Genetics Consortium (NGC) and attend NGC meetings. A copy of the Informed Consent documents will also be provided to the NCGS/NGC to be searched or distributed to qualified investigators. Annual updates of all IRB-approved modifications to these documents will be sent to the NCGS.

Lastly, data will also be shared via posters and talks at national and international conferences, such as the College on Problems of Drug Dependence (CPDD), Behavioral Pharmacology Society (BPS), the American College of Neuropsychopharmacology (ACNP), and International Behavioral Neuroscience Society (IBNS). Research manuscripts reporting the findings from the specific aims outlined in this study will be submitted for publication in peer-reviewed journals. Taken together, we feel this constitutes an acceptable mechanism for sharing data.

Name: _____ Date:_____

Interviewer:_____

How did you find out about our research? _____

How old are you? _____

Prescription Stimulant Use Information

Have you ever used prescription stimulants like (Adderral or Ritalin)? Y N

For medical purposes? Recreational purposes? Both? (Circle one)

Why did you 1st start using them? _____ How long have you used RxOs _____

What types have you tried before (name and dose of pills)? _____

How are/did you use them (route of admin table):

		Current						
	Life-time	Always	Very Often	Often	Some-times	Never	Don't know	Refuse to answer
oral								
chew								
IN								
IV								
smoke								

How many days per week do you use ? _____

How many pills do you use each day? _____

How many pills are prescribed each day? _____

How many pills do you use at a time? _____

Prescription Opioid Use Information

Have you ever used prescription opioids? Y N

For medical purposes? Recreational purposes? Both? (Circle one)

Why did you 1st start using them? _____ How long have you used RxOs _____

What prescription opioids are you using currently (name and dose of pills)? _____

How are you using them (route of admin table):

		Current						
	Life-time	Always	Very Often	Often	Some-times	Never	Don't know	Refuse to answer
oral								
chew								
IN								
IV								
smoke								

How many days per week do you use ? _____

How many pills do you use each day? _____

How many pills are prescribed each day? _____

How many pills do you use at a time? _____

How long do you go between doses? _____

How long can you go without? _____

What happens (withdrawal symptoms)? _____

Have you ever used **Methadone?** Y N RX? Frm Street? Both?

Do you currently use Methadone? Y N RX? Frm Street? Both?

Have you ever used **Suboxone?** Y N RX? Frm Street? Both?

Do you currently use Suboxone? Y N RX? Frm Street? Both?

Do you have Medicaid? Y N

What other medications are you currently taking? _____

Obtaining RxOs

Do you buy prescription drugs on the street? _____

How much do you pay per pill (drug and dose?) _____

Do you sell your pills? _____

Do you go to more than one doctor to get RxOs? _____

How many docs and what specialty? _____

Do you get them from friends or family? _____

Please specify: _____

Do you get them in any other ways? _____

Which other ways? _____

What side effects? _____

What do you like about RxOs? _____

Heroin Use Information

Have you ever used heroin? Y N

Have you ever used heroin for pain control? Y N

If yes, could you provide some details? What kind of pain? For how long? Was it effective?

Do you still use it for pain? Y N notes: _____

During the last 30 days

How may days per week do you use heroin? _____

How many bags a day do you use? _____

How much do you spend each day on H (avg & range)? _____

How many bags at a time do you use? _____

How long do you usually go between hits? _____

How long can you go without? _____

What happens (withdrawal symptoms)? _____

How long have you used H? _____

What do you like about H? _____

Do you usually do it alone? _____ with others? _____

Where do you usually buy it? _____

Routes of H administration

	LIFETIME	CURRENT USE						
		Always	Very Often	Often	Some-times	Never	Don't know	Refuse to answer
IV								
IM								
smoke								

Other Drug Use Information

Do you currently drink alcohol? Y N

	LIFETIME	CURRENT USE						
		Always	Very Often	Often	Some-times	Never	Don't know	Refuse to answer
Beer:								
Wine:								
Hard liquor:								

	Never	Monthly or less	2-4 x/mo	2-3 x/wk	> 4 x/wk
How often do you have a drink containing alcohol? If > 4, how many days/wk exactly?_____					
How many units of alcohol do you drink on a typical day when you are drinking?	1 to 2	3 to 4	5 to 6	7 to 8	10+
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	LT Mnthly	Mnthly	Wkly	Daily or almost daily

During the last 30 days, did you use some following drugs ?

	Marijuana	Cocaine/ crack	Benzos	Ecstasy
Route of administration (IN, SM, IV, PO, …)				
How often do you use? (days/wk? days/mo?)				
How much do you use per episode of use?				

	Other Club Drugs	MethAMPH	Hallucinogens	Barbiturates
Route of administration (IN, SM, IV, PO, …)				
How often do you use? (days/wk? days/mo?)				
How much do you use per episode of use?				

Do you smoke cigarettes? Number/day? Brand? _____

How do you feel about your drug use?

Always chasing it _____ Distressed _____

Have to avoid withdrawals _____ Seeking treatment _____

OK with it _____

If I gave you $100 dollars today to spend only on drugs, what would you buy?

Smile _____ Easy _____

Pause _____ Hard _____

Cocaine _____ MJ _____

Heroin _____ EtOH _____
Rx Opioids _____ RxAMPH _____

Do you combine any drugs?

Cocaine + MJ _____ Why?_____ RxO + Benzos _____ Why?_____
EtOH + Cocaine _____ Why?_____ RxO + Alcohol _____ Why?_____
H + Cocaine _____ Why?_____ RxO + Cocaine _____ Why?_____
H + Benzos _____ Why?_____ RxO + Other _____ Which other?_____

Why do you combine drugs? _____

What's the longest you've gone without X in the past month?

Cocaine _____ MJ _____
Heroin _____ Etoh _____
Rx Opioids _____ RxAMPH _____

Education:

GED _____ HS _____
Grade school _____ College _____

Job: _____
Flexible: _____

Jail (# days or years):

Misdemeanor _____ Drug Possession _____
Juvenile Delinquent _____ Weapon _____
Skill in avoiding _____ Probation _____
Lucky never got caught _____ Parole _____

Do you have any kids? _____
Who will take care of them during the study? _____

Have you ever been tested for HCV infection? Yes No Was the last test.... + -
Have you ever been tested for HIV infection? Yes No Was the last test... + -

Mood:

Depressed _____ Romantic problems _____
Anxious _____ OK _____

Appearance:

Neat _____ Sloppy _____
Clear _____ Dreamy _____

Arms:

OK _____ Too many track marks _____

Other comments/concerns: _____

Clinical Summary: _____

MEDICAL HISTORY QUESTIONNAIRE

DO YOU:

CURRENT	PAST	NONE		COMMENTS
			wear glasses or contact lenses	
			wear a hearing aid	
			have trouble sleeping	
			have trouble eating	
			cough up blood	
			walk in your sleep	
			have an history of tuberculosis	
			have any history of asthma	
			have any history of heart trouble	

IS THER ANY HISTORY IN YOUR FAMILY INVOLVING:

CURRENT	PAST	NONE		COMMENTS
			high blood pressure	
			heart problems	
			diabetes	
			tuberculosis	
			sickle cell anemia	
			cancer	

			emotional problems	

HAVE YOU EVER HAD, OR DO YOU CURRENTLY HAVE:

CURRENT	PAST	NONE		COMMENTS
			scarlet or rheumatic fever	
			swollen or painful joints	
			frequent or severe headaches	
			dizziness or fainting spells	
			eye trouble	
			ear, nose or throat trouble	
			hearing loss	
			severe tooth or gum trouble	
			lung disease	
			an allergic reaction to medication or drugs	
			sinus problems	
			hay fever	
			diabetes	
			head injury	
			skin disease	
			thyroid trouble	
			shortness of breath	
			pain or pressure in the chest	
			chronic cough	
			palpitation or pounding heart	
			high blood pressure	

			cramps in your legs	
			frequent indigestion	
			stomach, liver or intestinal trouble	
			gall bladder trouble or gallstones	
CURRENT	PAST	NONE		COMMENTS
			jaundice or hepatitis	
			adverse reaction to drug or medicine	
			broken bones	
			tumor, growth, cyst, cancer	
			rupture, hernia	
			hemorrhoids	
			frequent or painful urination	
			bedwetting since age 12	
			kidney stone or blood in urine	
			sugar in urine	
			changes in urination pattern	
			V.D.- syphilis, gonorrhea	
			recent weight gain or weight loss	
			arthritis, rheumatism, or bursitis	
			bone, joint or other deformity	
			lameness	
			loss of finger or toe	
			painful shoulder or elbow	
			recurrent back pain	
			"trick" or locked knee	
			foot trouble	

			paralysis	
			blood disease	
			epilepsy, fits, convulsions	
			motion sickness	
			depression or excessive worry	
			nervous trouble of any sort	
			loss of memory, amnesia	
			periods of unconsciousness	
			seeing or hearing things that aren't there	
			suspicious or paranoid thoughts	

Have you had any diseases or medical conditions that you feel are related to your use of drugs? If so, when/ what

Have you had an X-ray within the last 3 months? Yes_____ No _____ Date & Place _____

_____

Do you currently use prescribed medications? Yes _____ No _____Type & Reason _____

_____

Do you have any allergies to medications? Yes _____ No _____ Specify _____

_____

Do you have any allergies to foods? Yes _____ No _____ Specify _____

_____

Have you ever been treated for mental illness? Yes _____ No _____ Specify _____

_____

Are you pregnant or possibly pregnant? Yes _____ No _____

Are you using birth control? Yes _____ No _____ Type _____

HOSPITALIZATIONS DURING THE PAST 3 YEARS: (most recent first)

NAME OF FACILITY	DATES INVOLVED	REASON

Initials:_____ Date _____

Initials:_____ Marital Status:_____ Age:_____Sex:_____ Date: _____
Occupation:_____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for the group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad
1 I feel sad much of the time
2 I am sad all the time
3 I am so sad or unhappy that I can't stand it

2. Pessimism

0 I am no discouraged about my future
1 I feel more discouraged about my future than I used to be
2 I do not expect things to work our for me
3 I feel my future is hopeless and will only get worse

3. Past Failure

0 I do not feel like a failure
1 I have failed more than I should have
2 As I look back, I see a lot of failures
3 I feel I am a total failure as a person

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to
2 I get very little pleasure from the things I used to enjoy
3 I can't get any pleasure from the things I used to enjoy

5. Guilty Feelings

0 I don't feel particularly guilty
1 I feel guilty over many things I have done or should have done
2 I feel quite guilty most of the time
3 I feel guilty all of the time

6. Punishment Feelings

0 I don't feel I am being punished
1 I feel I may be punished
2 I expect to be punished
3 I feel I am being punished

7. Self-Dislike

0 I feel the same about myself as ever
1 I have lost confidence in myself
2 I am disappointed in myself
3 I dislike myself

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be
2 I criticize myself for all of my faults
3 I blame myself for everything bad that happens

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself
1 I have thought of killing myself but I would not carry them out
2 I would like to kill myself
3 I would kill myself if I had the chance

10. Crying

0 I don't cry anymore than I used to
1 I cry more than I used to
2 I cry over every little thing
3 I feel like crying, but I can't

11. Agitation

0 I am no more restless or wound up than usual
1 I feel more restless or wound up than usual
2 I am so restless or agitated that it's hard to stay still
3 I am so restless or agitated that I have to keep moving or doing something

12. Loss of Interest

0 I have not lost interest in other people or activities
1 I am less interested in other people or things than before
2 I have lost most of my interest in other people or things
3 It's hard to get interested in anything

13. Indecisiveness

0 I make decisions about as well as ever
1 I find it more difficult to make decisions than usual
2 I have much greater difficulty in making decisions than I used to
3 I have trouble making any decisions

14. Worthlessness

0 I do not feel I am worthless
1 I don't consider myself as worthwhile and useful as I used to
2 I feel more worthless as compared to other people
3 I feel utterly worthless

15. Loss of Energy

0 I have as much energy as ever
1 I have less energy than I used to have
2 I don't have enough energy to do very much
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern

1a I sleep somewhat more than usual
1b I sleep somewhat less than usual

2a I sleep a lot more than usual
2b I sleep a lot less than usual

3a I sleep mores of the day
3b I wake up 1-2 hours early and can't get back to sleep

17. Irritability

0 I am no more irritable than usual
1 I am more irritable than usual
2 I am much more irritable than usual
3 I am irritable all he time

18. Changes in Appetite

0 I have not experienced any change in my appetite

1a My appetite is somewhat less than usual
1b My appetite is somewhat greater than usual

2a My appetite is much less than before
2b My appetite is much greater than usual

3a I have no appetite at all
3b I crave food all the time

19. Concentration Difficulty

0 I can concentrate as well as ever
1 I can't concentrate as well as usual
2 It's hard to keep my mind on anything for very long
3 I find I can't concentrate on anything

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual
1 I get more tired or fatigued more easily than usual
2 I am too tired or fatigued to do a lot of the things I used to do
3 I am too tired or fatigued to do most of the things I used to do

21. Loss of interest in Sex

0 I have not noticed any recent change in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

_____ Subtotal Page1
_____ Subtotal Page 2

Table 1:Testing Schedule	
Sample Session Events (Day 1)	
-60 (1000 hrs)	Physiological monitoring [(Blood Pressure, HR: every 5 minutes; ECG: continuous)], Urine Drug/Pregnancy Test **Oral Naltrexone Administration (0 mg or 50 mg)**
-30	**Baseline:** Physiological, Subjective, and Performance Effects
0	**Sample: Intranasal M-AMPH, 30 mg + $15**
15	Subjective Effects
30	Subjective, and Performance Effects
45	Subjective Effects
60	Subjective and Performance Effects
75	Subjective Effects
90	Subjective and Performance Effects
105	Subjective Effects
120	Subjective and Performance Effects
135	Subjective Effects
150	Subjective and Performance Effects
165	Subjective Effects
180 (1400 hrs)	Subjective and Performance Effects
Sobriety Check and Discharge	

24-Hour Interval

Choice Session Events (Day 2)	
-60 (1000 hrs)	Self-Administration Task begin
0	**M-AMPH and/or Money Administration** Physiological monitoring [(Blood Pressure, HR: every 5 minutes; ECG: continuous)]
180 (1400 hrs)	**Sobriety Check and Discharge**

Table 2: Overall Study Design

Week 1						Week 2					
M	T	W	Th **Sample (0 mg NTX)**	F **Choice**	Sa-Su	M	T **Sample (50 mg NTX)**	W **Choice**	Th	F	Sa-Su

New York State Psychiatric Institute Institutional Review Board
Request for HIPAA Waiver of Authorization and/or Waiver of Consent

Use this form if you are requesting to waive or alter some or all of the elements of consent and/or of HIPAA authorization requirements.

IRB Protocol Number: 7347 Name of Principal Investigator: Jermaine Jones, PhD

Title of Study: Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

Please indicate and explain nature of request below:

☒ Partial Waiver for telephone screens. **Waiver to obtain verbal consent**
☐ Partial Waiver for internet survey research.

☐ Full Waiver for the purpose of accessing an existing database or records (paper or electronic) to identify potential subject or to conduct above research.

Describe the identifiable information that you will be collecting or accessing under this waiver (Be specific to allow the IRB to determine whether the information includes any of the 18 HIPAA identifiers or any other method of identifying the individuals):

- Age
- Sex
- Current and previous drug use behavior.
- Previous medical and psychiatric diagnoses.

The study, or phase of the study for which the waiver is being sought, should present no more than minimal risk to the subject, including risk to their confidentiality. Please explain how your study, or the phase of the study for which the waiver is being sought, meets the following criteria:

1. Explain why the waiver or alteration will not adversely affect the rights and welfare of the subjects. Verbal Consent will be obtained and the procedures detailed for maintaining confidentiality still apply.

2. Explain why is it not practical to obtain consent and/or authorization from subjects? Participants first respond to study advertisements via telephone.

3. Can the research practicably be conducted without access to, and use of, the individually identifiable information? If not, why? No, a number of inclusion and exclusion criteria require data that need to be verified such as age.

4. Indicate how you plan to protect the identifiers from improper use and disclosure. Check all that apply:

☒Electronic safeguards where only study staff has access and the database meets all security requirements as outlined in the NYSPI Security Plan (e.g. password protection, data encryption, firewall, no outside transmission of data, restricted access etc).
☒Physical safeguards where only study staff has access to areas with study information and NYSPI recommendations for physical security are in place (locked cabinets, locked filing room, restricted access etc).
☐No identifiers, links or codes will be retained that permit data to be identified.
☐Other:

5. Describe your plan to destroy the identifiers at the earliest opportunity:
   ☒Identifiers will be destroyed if the patient does not meet criteria for admission to the study
   ☐Identifiers will be retained until potential subjects sign consent and authorization and complete the study. Destruction of all identifiers will be consistent with federal, state and Institute policies, and or other contractual agreements.
   ☐ N/A as I will not record identifiers or create links or codes to connect the data

6. Where applicable: Describe how subjects will be provided with additional pertinent information after participation. Upon their first in-person visit to PI, the study procedures are described in detail.

By submitting this application you are certifying that the protected health information or other identifiable information will not be reused or disclosed except as required by law, for authorized oversight of the research, or for other research that has been reviewed and approved by the IRB with specific approval regarding access to this protected health information.

☒Agree ☐Do not agree

FOR THOSE REQUESTING ACCESS TO MEDICAL RECORDS MAINTAINED AT NYSPI

Please also complete the following to describe selection criteria for your request:

Selection Criteria for records required (e.g. diagnosis, age, date of admission)

Dates of required records: from / / through / /

Anticipated sources of information (check all that apply)
☐ Paper medical records, Owner

☐ OMH EMR and/or DUKE EMR

☐ Other (describe)

Number of records needed: Number ____ ☐ ≥ 50 ☐ < 50

Jermaine Jones

From: Pollock, Jonathan (NIH/NIDA) [E] <jpollock@nida.nih.gov>
Sent: Tuesday, September 06, 2016 4:51 PM
To: Jermaine Jones
Subject: RE: R21DA040225-01A1

Jermaine,

You may change the protocol as described below.

Jonathan

Jonathan D. Pollock, Ph.D.
Chief
Genetics, Epigenetics, and Developmental Neuroscience Branch
Division of Neuroscience and Behavior
National Institute on Drug Abuse, NIH
6001 Executive Blvd, Rm. 4267
Bethesda, MD 20892
Tel. 301-435-1309
Email. jpollock@mail.nih.gov
Skype: Dogmacentral1

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Tuesday, September 06, 2016 4:49 PM
To: Pollock, Jonathan (NIH/NIDA) [E] <jpollock@nida.nih.gov>
Subject: FW: R21DA040225-01A1

Hello Dr. Pollock,

Just checking to see if you had a chance to review these proposed edits to this study?

Jermaine

From: Jermaine Jones
Sent: Wednesday, August 31, 2016 11:54 AM
To: Pollock, Jonathan (NIH/NIDA) [E]
Subject: RE: R21DA040225-01A1

Hello Dr. Pollock

I'm finalizing the IRB submission for this award and there are a few methodological changes from the original proposal that I would like to implement. Some changes are intended to make the study more feasible, and others to improve safety. I've outlined them below. Also, in one of our phone conversations you mentioned that you had a number of idea of ways that may help address this research question,?

1. I'd like to decreased the intranasal (IN) methamphetamine (M-APMH) dose from 50mg/70kg to 30mg. We currently have another study where an IN 50mg dose led to prolonged tachycardia in a participant just a few months ago. Though our division has given the 50 mg dose in previous studies without this issue, I believe that the 30mg dose will still illicit the robust positive subjective/reinforcing effects that we need while significantly decreasing the likelihood of a repeat of this adverse event.

2. Similarly, in order to minimize the number of methamphetamine exposures, I would like to drop the 25 mg naltrexone (NLTX) condition and complete sample and choice self-administration sessions on the same day. This will allow us to test the effects of naltrexone on M-AMPH in two sessions (0mg NLTX + M-AMPH)(50 mg NLXT + M-AMPH) as opposed to the 6 exposures proposed in the original application. I originally included the 25 mg NLTX dose because we always like to observe a dose-response medication effect, if possible. However, this isn't essential to the aims of the project. I also believe this design will also simplify the comparisons across genotypes. We've safely performed IN M-AMPH sessions (up to 50mg/70kg) on an outpatient basis so this should not put the participants at any increased risk (Kirkpatrick et al., 2012).

Please let me know how you fell about these edits and any more you feel should be included in the IRB submission.

I'm working from home today but I'm available by phone the rest of the week, if you would like to discuss this.

Thanks,
Jermaine
646 774-6113

From: Jermaine Jones
Sent: Wednesday, March 02, 2016 9:56 AM
To: Pollock, Jonathan (NIH/NIDA) [E]
Subject: RE: R21DA040225-01A1

Hello Dr. Pollock,

I apologize for not being able to call you back on Monday. I had to rush out to catch a flight. I'm back in the office Thursday, would you have time to speak then?

Jermaine

From: Pollock, Jonathan (NIH/NIDA) [E] [jpollock@nida.nih.gov]
Sent: Thursday, February 25, 2016 4:16 PM
To: Jermaine Jones
Subject: RE: R21DA040225-01A1

Jermaine,

In the morning call me at 240-409-4873.

Jonathan

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Thursday, February 25, 2016 4:16 PM
To: Pollock, Jonathan (NIH/NIDA) [E] <jpollock@nida.nih.gov>
Subject: RE: R21DA040225-01A1

Sure,

Thanks

From: Pollock, Jonathan (NIH/NIDA) [E] [mailto:jpollock@nida.nih.gov]
Sent: Thursday, February 25, 2016 4:14 PM
To: Jermaine Jones
Subject: RE: R21DA040225-01A1

Jermaine,

Please call me Monday.

Jonathan

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Thursday, February 25, 2016 4:13 PM
To: Pollock, Jonathan (NIH/NIDA) [E] <jpollock@nida.nih.gov>
Subject: R21DA040225-01A1

Hello Dr. Pollock,

I'm wondering if you have time tomorrow to discuss this grant and its likelihood of being funded?

Thanks,
Jermaine Jones, PhD
Assistant Professor of Clinical Neurobiology
Columbia University College of Physicians and Surgeons
1051 Riverside Dr
New York, NY 10032
(646) 774-6113

Form of Notice by CU Faculty IND/IDE Holder

Study Title: Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

IRB Protocol No: 7347

IND/IDE Number: 133276

CU Faculty IND/IDE Holder: Jermaine Jones, PhD

Principal Investigator (if different from IND/IDE Holder): Click here to enter text.

The undersigned IND/IDE holder will be acting as the Sponsor-Investigator, or the Sponsor with the undersigned Principal Investigator, of the above named study. The undersigned IND/IDE holder acknowledges that as a Sponsor-Investigator or Sponsor of such study, he/she has additional responsibilities under the FDA regulations and confirms that he/she has adequate resources to fulfill such responsibilities in full compliance with such regulations.

NOTE: This form should be submitted to the IRB of record and the Clinical Trials Office.

IND/IDE Holder:

Name: Jermaine Jones, PhD

Signature:

Date: **January 3, 2017**

Acknowledged (if applicable):

Principal Investigator

Name: Click here to enter text.

Signature:

Date: Click here to enter a date.

Approved:

Department Chair

Name: Frances Levin, MD

Signature:

Date: January 3, 2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 127115

IND ACKNOWLEDGEMENT

Sandra Comer, PhD
1051 Riverside Drive
Unit 120
New York, NY 10032

Dear Dr. Comer:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Please note the following identifying data:

IND NUMBER ASSIGNED: 127115

SPONSOR: Sandra Comer, PhD

PRODUCT NAME(S): methamphetamine

DATE OF SUBMISSION: June 24, 2015

DATE OF RECEIPT: July 1, 2015

You may not initiate studies in humans until 30 days after the date of receipt shown above unless we notify you sooner that you may proceed. If, on or before July 31, 2015, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will immediately notify you verbally or in writing that (1) clinical studies may not be initiated under this IND ("clinical hold") or (2) certain restrictions apply to clinical studies under this IND (“partial clinical hold”). If we place your human studies on clinical hold, you will be notified in writing of the reasons and the information necessary to correct the deficiencies. In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have subsequently notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **IND 127115** submitted on June 24, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

  If your IND is not in eCTD format:

  - you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

  - if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

  - if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format via the ESG. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

IND REPORTING AND SUBMISSION PROCEDURES

CDER has developed a web page that provides information regarding IND application reporting and submission procedures, which also includes information regarding product development for clinical investigations and expanded access for clinical treatment. The web page may be found at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm

CHARGING FOR AN INVESTIGATIONAL DRUG

We remind you that, under 21 CFR 312.8(a)(3), you may not charge for this investigational drug without prior written authorization from FDA.

GOOD LABORATORY PRACTICE

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR 58). If such studies have not been conducted in compliance with these regulations, provide a statement describing in detail all differences between the practices used and those required in the regulations.

ENVIRONMENTAL ASSESSMENT

Box 13, item 7 of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. Information on environmental assessments is available in the guidance "Environmental Assessment of Human Drugs and Biologics." This document is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development (i.e., phase 1 or 2), we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry "Guidance for

Industry Assessment of Abuse Potential of Drugs," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, call me, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Christopher Hilfiger
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER M HILFIGER
07/07/2015

Jermaine Jones

From: Darkwah, Mavis <Mavis.Darkwah@fda.hhs.gov>
Sent: Friday, December 23, 2016 3:01 PM
To: Jermaine Jones
Subject: RE: IND 133276 Documents Request

Importance: High

Dear Jermaine,

Based on the information provided via reference, we are able to allow you to provide a commitment to submit the updated COA when available. It should be submitted before initiating the study.

Regards,

Mavis

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Thursday, December 22, 2016 11:44 AM
To: Darkwah, Mavis
Subject: RE: IND 133276 Documents Request

Hello Mavis,

I've attached the following documents:

- Categorical Exclusion request
- Letter of Authorization from Dr. Comer
- Certificate of Analysis for the Lactose Powder/Placebo
- Certificate of Analysis (COA) for Naltrexone

I'm having a bit of trouble with the Methamphetamine COA. For the COA the manufacturer needs to know a specific Lot number to provide the corresponding COA. I can't get the Lot number until we actually purchase the product from them. Because this is a Schedule II drug, our Pharmacy does not want to purchase it without final IRB approval. My current IRB approval is pending authorization from the FDA. I've been making calls all week to see how I can get around this conundrum. Do you have any suggestions?

Jermaine
646 774-6113

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, December 19, 2016 11:56 AM
To: Jermaine Jones
Subject: RE: IND 133276 Request for teleconference

The telecon is scheduled for 9 am (eastern), tomorrow, December 20. Use the following call-in number, and let me know if Dr. Comer is able to join us.

toll free: 1-855-828-1770
Meeting ID: 744 292 298
Meeting Password: 123456

Regards,

Mavis

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Sunday, December 18, 2016 4:42 PM
To: Darkwah, Mavis
Subject: RE: IND 133276 Request for teleconference

I'm available on Tuesday at that time, but I'm still waiting to hear from Dr. Comer.

Jermaine

From: Darkwah, Mavis [Mavis.Darkwah@fda.hhs.gov]
Sent: Friday, December 16, 2016 3:52 PM
To: Jermaine Jones
Subject: RE: IND 133276 Request for teleconference

Thank you. We would like to speak with both you and Dr. Comer. Please let me know if December 20, 2016, 9 am (Eastern) or December 21, 2016, Wednesday 1 pm (Eastern) work for both of you, or please propose a date and time next week that will work for both of you.

Regards,

Mavis

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Friday, December 16, 2016 2:19 PM
To: Darkwah, Mavis
Subject: Re: IND 133276 Request for teleconference

I'm out on Monday for an eye procedure. Any time on Tuesday outside of 12-1:30 would work.

Jermaine

Sent from my iPhone

On Dec 16, 2016, at 2:13 PM, Darkwah, Mavis <Mavis.Darkwah@fda.hhs.gov> wrote:

> Dear Jermaine,
>
> We would like to have a brief teleconference with you to clarify few questions we have for your IND after our preliminary review. The proposed date and time is Monday, December 19, 3:15 pm (Eastern). Please let me know if this date and time will work for you as soon as possible.

Regards,

Mavis

Mavis Y. Darkwah, PharmD
LCDR, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

Jermaine Jones

Subject: FW: IND 133276 Information Request

Importance: High

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Friday, December 16, 2016 2:31 PM
To: Jermaine Jones
Subject: RE: IND 133276 Information Request
Importance: High

Dear Jermaine,

Please address the information request below:

There is a discrepancy between the 1571 form submitted with your IND, which identifies you as the Sponsor of this IND, and the "Form of Notice by CU Faculty IND/IDE Holder" which you submitted on 12/5, which indicates that Dr. Comer is taking responsibility for this protocol under her IND 127115.

Please clarify whether this protocol is to be conducted under IND 133276 with you as the Sponsor, or under 127115 with Dr. Comer as the Sponsor.

If the protocol is to be conducted under a separate IND with you as the Sponsor, all data supporting your protocol must reside in your IND, or a right of reference (also known as a letter of authorization) must have been provided by the Sponsor of another application allowing us to refer to their data to support the review of your application. At this point, we have no such authorization to refer to another application, so you must supply all data necessary for our review. The form you submitted is a not a letter of authorization.

Therefore,

Provide an updated COA for the methamphetamine product to be used in the study. The COA provided is from 2011.
Provide the composition of the Placebo and a certificate of analysis.
Provide a statement of categorical exclusion from an environmental analysis, with no known extraordinary circumstances, per 21 CFR 25.31(e).

Respond via email as soon as possible, preferably by COB, December 19, 2016, and follow up with an official submission to the IND.

Regards,

Mavis

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Wednesday, December 14, 2016 2:23 PM
To: Darkwah, Mavis
Subject: RE: IND 133276 Information Request

Hello Mavis

I would describe it as a randomized, double-blind, placebo-controlled, two-period, between-groups design. This design was chosen because the study's primary endpoint is a comparison of naltrexone's effects on methamphetamine, between two genotype groups. We need all participants to complete both sessions (naltrexone + METH) (placebo+METH) in order to determine how naltrexone interacts with methamphetamine (placebo-controlled). Based on the previous literature we are anticipating that naltrexone will somewhat attenuate methamphetamine's effects but the degree to which (calculated as a % change from placebo to active) will significantly vary between the two genotype groups (between-groups). Randomization of the order of the two sessions controls for the effects of repeated METH administration (randomized). Participants and research assistants working directly with the participants will both be blind with respect to receiving naltrexone or placebo, to control for expectancy (double-blind). However, for safety, participants and staff will always be aware that methamphetamine is being administered.

Jermaine

From: Darkwah, Mavis [Mavis.Darkwah@fda.hhs.gov]
Sent: Wednesday, December 14, 2016 10:04 AM
To: Jermaine Jones
Subject: RE: IND 133276 Information Request

Dear Jermaine,

Please confirm that the study design is a randomized, double-blind, placebo-controlled (for the naltrexone), two-period, crossover design. If our understanding of the study design is incorrect, please explain the rationale for the study design chosen.

Regards,

Mavis

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Wednesday, December 14, 2016 9:08 AM
To: Darkwah, Mavis
Subject: Re: IND 133276 Information Request

Thanks Mavis,

Should I move forward with seeking final IRB approval?

Jermaine

Sent from my iPhone

On Dec 14, 2016, at 7:34 AM, Darkwah, Mavis <Mavis.Darkwah@fda.hhs.gov> wrote:

> Dear Jermaine,
>
> Your responses/proposal is acceptable.
>
> Regards,

Mavis

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Tuesday, December 13, 2016 10:11 AM
To: Darkwah, Mavis
Subject: RE: IND 133276 Information Request

Hello Mavis,

My responses are below:

1. I have revised the discontinuation parameters accordingly in my IRB protocol and in the IND application attached.
2. A) The following verbiage has been added to the CF "The risks of snorting methamphetamine have not been well characterized. In addition to likely nasal tissue irritation and bleeding, we cannot rule out the possibility of more significant adverse effects including loss of smell, lung damage, inflammation and infection. " I removed the medical terms since our IRB requires the CF language to be at an 8th grade reading level. I also did not include the language of "Snorting crushed drugs," as the methamphetamine we will be using for this study comes in a powder form, so we will not need to crush it. Additionally, there will be no concerns with the participant snorting any excipients from a crushed tablet, which should minimize nasal irritation and complications. We use this powder in another study (PI: Dr. Comer) and have not had any of the aforementioned complications.

   Our IRB protocol is electronic, once the FDA is satisfied with the required edits to the protocol I will submit them to the IRB for approval. Does this sounds like an acceptable course of action?

   Jermaine

From: Darkwah, Mavis [mailto:Mavis.Darkwah@fda.hhs.gov]
Sent: Monday, December 12, 2016 3:35 PM
To: Jermaine Jones
Subject: IND 133276 Information Request
Importance: High

Dear Jermaine,

We have completed our initial review of your IND and have the following preliminary comments:

1. Add subject discontinuation parameters as follows:
   Subjects will be terminated for:
   a. Systolic blood pressure > 180 mm Hg, sustained for longer than 6 minutes (> 3 consecutive readings)
   b. Diastolic blood pressure > 100 mm Hg, sustained for longer than 6 minutes (> 3 consecutive readings)
   c. Heart rate > (220 - subject age x 0.85) bpm, sustained for longer than 6 minutes (> 3 consecutive readings)
   d. The session will be terminated if significant ECG abnormality (e.g., >10 PVC's/hr, or multifocal PVS's, or significant ST changes, chest pain), or seizure are observed.

2. Include information in your informed consent that snorting methamphetamine has not been adequately tested for safety and may result in adverse effects, such as local tissue irritation, nasal tissue damage, anosmia, and possible lung complications. An example of an informed consent statement is provided below:

   > The risks of snorting methamphetamine have not been characterized. Snorting crushed drugs may cause irritation inside your nose, including pain, burning, itching, runny nose, bleeding, stuffiness, and other side effects which have not been tested with the specific drug you will snort in this study. In addition to likely nasal irritation and bleeding, we cannot rule out the possibility of more significant adverse effects include a potentially permanent loss of your sense of smell or damage to your lungs, including granulomas.

Respond via email as soon as possible, latest by COB December 15, 2016, and follow up with an official submission to the IND.

Regards,

Mavis

Mavis Y. Darkwah, PharmD
LCDR, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158
Email: Mavis.Darkwah@fda.hhs.gov

Jermaine Jones

From: Sullivan, Matthew <Matthew.Sullivan@fda.hhs.gov>
Sent: Thursday, December 01, 2016 3:59 PM
To: Jermaine Jones
Cc: Darkwah, Mavis
Subject: RE: IND Submission 133276

Jermaine –

I'm assigning Mavis Darkwah as the Project Manager for this IND submission. She'll be your contact person here at FDA for this application going forward.

Thanks, and please let me know if you have any questions.

Matt

From: Sullivan, Matthew
Sent: Thursday, December 01, 2016 3:47 PM
To: 'Jermaine Jones'
Subject: RE: IND Submission 133276

In terms of the required forms, you have everything. You may not have enough of an argument to support the safety of IN methamphetamine, but if Dr Cormer can provide you with a Letter of Authorization to her IND, then any data contained therein will be available to support your application as well.

Matt

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Thursday, December 01, 2016 3:35 PM
To: Sullivan, Matthew
Subject: Re: IND Submission 133276

Thanks for the clarification. I'll proceed with sending you the CMC information for the methamphetamine and the naltrexone. With the exemption request I believe I included all of the required components for an IND, is there anything else you would need from me to proceed with the complete IND application for the study?

Jermaine

On Dec 1, 2016, at 2:54 PM, Sullivan, Matthew <Matthew.Sullivan@fda.hhs.gov> wrote:

> Hi Jermaine –
>
> Thanks. To clarify, each IND has a unique research focus that is established when an IND is initially opened. The research focus of IND 127115 is different than what you have proposed, so yours would need to be its own application. Further, we have no mechanism to exempt individual protocols under an IND. The whole IND is exempted (or not).

We understand that your research focus is on the naltrexone, but we evaluate all modalities proposed in a protocol. You propose two medications, so we have evaluate them both. As discussed, since you aren't using a methamphetamine approved via the IN route, we aren't able to exempt this IND.

Thanks, and let me know if you have further questions.

Matt

From: Jermaine Jones [mailto:jonesje@nyspi.columbia.edu]
Sent: Thursday, December 01, 2016 1:36 PM
To: Sullivan, Matthew
Subject: RE: IND Submission 133276

Hello Matthew,

Thanks for getting in touch with me so quickly. The IND exception request was only for the oral naltrexone. My co-investigator on this project (Dr. Sandra Comer) already has in IND for intranasal methaphetamine for another NIDA study (IND# 127115, using a methamphetamine powder we obtain from NIDA through RTI). I was planning to add this study to her IND. I've attached the form our IRB requires where she has agreed to this. I'll contact our pharmacy concerning the CMC information for the naltrexone and the placebo capsules they plan to use and will get this information to you soon.

Jermaine

From: Sullivan, Matthew [Matthew.Sullivan@fda.hhs.gov]
Sent: Thursday, December 01, 2016 12:36 PM
To: Jermaine Jones
Subject: IND Submission 133276

Dr Jones –

We have received your IND submission for Naltrexone. We note that you are also planning to administer intranasal methamphetamine. As there are no methamphetamine products approved for the IN route, we aren't likely able to exempt this submission. Can you please clarify for us why you feel that you would be eligible exemption in light of this?

Regardless, we will need CMC data on both the naltrexone product (and placebo) you intend to use, as well as the methamphetamine product. If you are converting an approved oral methamphetamine tablet, we will need an argument supporting the safety of the IN route as well as the pharmacy procedures you will be utilizing.

Thanks,
Matt

Matthew W. Sullivan, M.S.
Supervisory Regulatory Health Project Manager

Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

COLUMBIA UNIVERSITY
College of Physicians and Surgeons

Dec 22nd 2016

Mavis Y. Darkwah, PharmD
LCDR, USPHS Commissioned Corps
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
FDA/CDER/OND/ODE II
Ph: (240) 402-3158

Dear Dr. Darkwah

This letter serves as authorization for you to access any material submitted on behalf of IND# 127115 for Dr. Jermaine Jones' IND 133276. Please feel free to contact me with any questions at: sdc10@columbia.edu or (646) 774-6146.

Sincerely,

Sandra D. Comer, Ph.D.
Professor of Clinical Neurobiology
Division on Substance Use Disorders
Columbia University College of Physicians and Surgeons
1051 Riverside Drive, Unit 120
New York, NY 10032

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 133276

STUDY MAY PROCEED

Jermaine Jones, PhD
Columbia University College of Physicians and Surgeons
New York State Psychiatric Institute
l051 Riverside Drive, Unit 120
New York, NY 10032

Dear Dr. Jones:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Naltrexone Hydrochloride.

We have completed our safety review of your protocol, and have concluded that you may proceed with your proposed clinical investigation.

In addition, we have the following comment:

> Based on the information you have provided via reference, we are able to allow your study to proceed with the understanding that you have committed to provide an updated Certificate of Analysis for the methamphetamine drug substance when it becomes available to you. The Certificate should be submitted prior to starting the study.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

  If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development (i.e, phase 1 or 2), we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, contact Mavis Y. Darkwah, PharmD, Regulatory Project Manager, at (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON H HERTZ
12/29/2016

Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse
Screening Consent Summary Form

Purpose of Study

The goal of this research study is to collect information on the effects of amphetamine-type drugs, how they interact with the medication naltrexone, and how genetics may alter this interaction. Genetics is the study of how genes control characteristics like your hair and eye color. Just as differences in our genetic code help explain why we all look different, these differences can also help to explain why some medications are effective for some people but not for others.

You are being asked to screen for this study as a stimulant user. By participating, you will help researchers meet the goals of the study. This study is being funded by the National Institute on Drug Abuse. Dr. Jermaine Jones is the principal investigator and the person in charge of the study. All screening and study procedures will be conducted at the New York State Psychiatric Institute (NYSPI).

Participation in this screening 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. This is not a treatment study. Information is being collected for research purposes. Referrals for treatment are available at any time. 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 treatment referral will be arranged.

Study Procedures

You have been selected as a potential research volunteer. In order to participate in the study, you must first pass medical and psychiatric screening. This will include answering a general health questionnaire and other questionnaires relating to drug use; receiving an interview by a psychologist; and a physical examination. An electrocardiogram will be done to check the functioning of your heart. Blood samples are also collected to assess your general physical health, and urine samples are collected to test for drugs of abuse as well as pregnancy. If you are a woman, you will be given a pregnancy test. If you think you might be pregnant, please tell the investigator. You will be given another pregnancy test before each testing session, and if it is positive you will not be eligible to participate. Additionally, this study has a genetic component that requires the collection of a blood sample to extract DNA (described in detail in the Study Consent form). The cells of your body contain a molecule called deoxyribonucleic acid, or DNA for short. DNA is passed down from your parents and carries a code, in the form of genes, which determines your physical characteristics, such as the color of your hair and eyes.

If you are still eligible after the screening, the study will be described to you in detail and you will be given a detailed Study Consent form outlining all aspects of the study.

Risks

During blood drawing, there is a risk of slight discomfort and/or bruising at the site where the needle is inserted. Approximately 2 tablespoons will be taken for health testing. If you qualify for the study, another 2 tablespoons will be collected for genetic testing (4 total tablespoons). When someone donates blood, 32 tablespoons are taken on one occasion.

The structured interviews and questionnaires are time consuming to complete and involve topics of a sensitive nature.

As in any research study, it is possible that personal information about you could become known to other people. The investigators will take precautions to prevent this from happening. Your name will not appear on any questionnaires or tests that you complete during the study. Instead, all questionnaires and tests you complete will be coded with a study code number. The results from your individual genetic analyses will be kept confidential as described above.

Benefits
You are not expected to benefit directly from participation in this study. However, research studies such as this one may help scientists investigating risk factors for drug abuse, and **in** the development of treatment medications.

Confidentiality
We have applied for a Certificate of Confidentiality issued by the National Institutes on Drug Abuse (NIDA). With this Certificate, the researchers cannot be forced to release any research data in which you are identified, even under a court order or subpoena, without your written consent. The Certificate does not prevent the researchers from reporting suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others. Such information will be reported to the appropriate authorities.

You should understand that 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. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Records will only be available to research staff and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Your name and other personal identifying information will be stored in an electronically secure database at New York Psychiatric Institute. Electronic information is also coded and is stored on computers that are password protected. 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.

Compensation
As a result of participating in this screening you will receive $50 per screening visit, to a maximum of four visits. If you are enrolled in the study and complete all study procedures, you will earn between $650 and $800.

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. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator at (646) 774-6113 so that you can review the matter and identify the medical resources that may be available to you

Questions
The investigators will answer to the best of his ability any questions that you may have now or in the future about the research procedures. You may contact the Principal Investigator, Dr. Jermaine Jones, who can be reached at (646) 774-6113, if you have any questions. You will be given a copy of this consent form to take home with you. 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 human subjects in research studies. You may call the IRB Main Office at (646) 774-7155 during regular office hours.

Documentation of Consent

I voluntarily agree to participate in the research study described above.

Name of Participant_____

Signature of Participant_____ Date_____

Investigator, Physician, or Nurse

Printed Name_____

Signature_____Date_____

Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

Consent Summary Form

Below 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 need to sign if you decide to participate in the study. The consent form contains much more detailed information about the study and the risks you will need to consider in making your decision.

- You are being asked to participate in a research study that is attempting to collect information on the effects of an amphetamine drug, if they can be blocked by another medication, and how your genetics plays a role. Genetics is the study of how genes control characteristics like your hair and eye color. Just as differences in our genetic code help explain why we all look different, these differences can also help to explain why some medications are effective for some people but not for others.

- You will complete 4 laboratory sessions. During 2 of these sessions an amphetamine drug will be administered intranasally, along with an oral dose of the medication naltrexone. During the other 2 sessions you will have the opportunity to work for the drug or money by making finger presses on a computer mouse.

- Each laboratory session is about 4 hours long.

- Like all research, your decision to participate is up to you; taking part is voluntary.

Risks of Study Participation:

- If you decide to participate in this study, there are possible side effects and potential risks you should know about, and these are detailed in the consent form.

- The major risk of study participation is related to amphetamine administration. There have been reports of death and potentially a heart attack associated with amphetamine use. On rare occasions amphetamine use has been associated with chest pain, temporary hallucinations (seeing and hearing things that were not present), disorientation, seizures and muscle stiffness. You may also experience: excitation, restlessness, anxiety, headache, dry mouth, diarrhea, constipation, rapid pulse, loss of appetite, fluttering of the heart, irregular heart beats, and occasionally nausea, dizziness, sedation, or tremors.

Benefits

This study is not designed to benefit you directly. The genetic results will not be available to you or your doctors. However, research studies such as this one may help scientists investigating risk factors for drug abuse, and in the development of treatment medications.

Compensation

You will be compensated for your time and effort. As in all research, it is your choice to participate in this study and you do not have to participate if you do not want to. Also, you may stop participating at any time. Please read the Consent Form carefully and ask the study physician any questions or concerns you might have.

You can contact Dr. Jermaine Jones at (646) 774-6113 with any questions.

Consent Form

Study Purpose: The goal of this research study is to collect information on the effects of amphetamine type drugs and how they interact with the medication naltrexone. As a part of this study we will look at differences in people's DNA in an attempt to try to understand differences in how people respond to drugs. The cells of your body contain a molecule called deoxyribonucleic acid, or DNA for short. DNA is passed down from your parents and carries a code, in the form of genes, which determines your physical characteristics, such as the color of your hair and eyes; and risk for some diseases. Just as differences in our genetic code help explain why we all look different, these differences can also help to explain why some medications are effective for some people but not for others.

You are being asked to participate because you have some history of use of amphetamine drugs or other stimulants. By participating, you will help researchers meet the goals of the study. This study is being funded by the National Institute on Drug Abuse. Dr. Jermaine Jones is the principal investigator and the person in charge of the study. Study procedures will be conducted at the New York State Psychiatric Institute (NYSPI).

Details about this study are discussed below. It is important that you understand this information so that you can decide if you want to be in this research study. You will be given a copy of this consent form. You should ask the researchers, or staff members who may assist them, any questions you have about this study at any time. This consent form may contain words that you do not understand. Please ask the study doctor or the staff to explain any words or information that you do not understand. You may take home an unsigned copy of this consent form to think about or discuss with your family or friends before making your decision to participate in the study.

The study will enroll up to 70 people at NYSPI.

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 to withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute.

Alternative Treatments/Alternatives to Participation: This is not a treatment study. Information **is** being collected for research purposes only. The alternative to participating would be not to participate. Referrals will be given to you at the end of the study if you are interested in treatment for your drug use. This genetic study is intended to learn about treating drug abuse and not about you. We will not be providing you with any information about your DNA or your risk for developing inherited illnesses.

Study Procedures: If you decide to participate you will undergo the following procedures:

You will participate in a total 4 laboratory sessions. On the morning of each laboratory session a urine sample will be collected to test for recent drug use, and for pregnancy (in women). If either test is positive you will not be eligible to participate. Each laboratory session will take approximately 4 hours to complete. On Day 1 you will receive an intranasal amphetamine drug and an oral drug prior to it. The oral drug will be an FDA-approved opioid receptor blocker (naltrexone) or placebo (sham medication without any effects). Whether you get naltrexone or placebo will be randomly determined (like flipping a coin), and you will not be told which one you get that day. For the next 3 hours after these drugs are given, you will be asked to answer questions on the computer about how the drug makes you feel (such as "I feel high" or "I feel a good drug effect") and the way you might behave in pretend situations involving sex. At the end of the session, you will complete a field sobriety test. If you are not too high or intoxicated, we

will call a car service or taxi to take you to your home address. If medical staff feels you are overly intoxicated, you will be asked to wait with us until we feel it's safe for you to leave.

On the following day (Day 2) you will return to NYSPI and have the opportunity to work for the intranasal drug by making finger presses on a computer mouse. Like at the end of Day 1, you will be asked to complete a field sobriety test before leaving NYSPI. You will repeat these two sessions (Day 1 & 2) again at least 3 days apart. For safety, we will monitor your heart rate, blood pressure and electrical activity of the heart throughout both sessions.

We will ask for you to return about thirty days after your last session to complete a brief follow-up visit.

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. Whole blood samples can be used to make a cell line (cells from participants' blood will be cultured and kept alive forever to further study their DNA). The purpose of establishing a cell line is to create a source of DNA for storage in a repository for future research. The research on DNA and drug abuse will continue for a long time, and so your DNA may be available to researchers indefinitely. However, you may indicate at the end of this form how your genetic sample is used (check one). For the current study, samples will only be kept for a maximum of 5 years. If you change your mind about having your DNA used in future related research, you can tell us to remove and destroy the samples any time during or after the study. However, if you consent to having your sample used to create cell lines, you will not be able to withdraw consent to its use, since identifying information will be removed.

Study Risks

Amphetamine Administration: Amphetamine drugs are considered to have a high potential for abuse and there have been reports of death and potentially a heart attack associated with their use. In addition, on rare occasions amphetamine use has been associated with chest pain, temporary hallucinations (seeing and hearing things that were not present), disorientation, seizures and muscle stiffness. You may also experience: excitation, restlessness, anxiety, headache, dry mouth, diarrhea, constipation, rapid pulse, loss of appetite, fluttering of the heart, irregular heart beats, and occasionally nausea, dizziness, sedation, or tremors.

The risks of snorting methamphetamine have not been well characterized. In addition to likely nasal tissue irritation and bleeding, we cannot rule out the possibility of more significant adverse effects including loss of smell, lung damage, inflammation and infection.

Naltrexone Administration: Naltrexone may mildly impair the functioning of the liver. This effect on the liver will improve after naltrexone is discontinued. Naltrexone may also cause stomach upset, nausea, and vomiting. In addition, administration of naltrexone may increase blood sugar levels, which may produce symptoms such as dizziness, increased breathing, dehydration, sedation, and seizures. If you regularly use opioid medications like oxycodone or heroin, naltrexone may cause you to experience withdrawal symptoms.

Behavioral Tasks Risks: You may feel uncomfortable discussing sexual behaviors.

Pregnancy Risks: If you are female in your childbearing years, you will be asked to take a pregnancy test to ensure that you are not pregnant. If you are pregnant or trying to become pregnant, there may be risks to you or your unborn child. If you are nursing an infant, there may be risks to the infant. Females must be either post-menopausal, surgically sterilized, or use an acceptable method of contraception (double barrier method like a condom with a spermicidal lubricant) to participate in this study.

Risks to Privacy: As in any research study, it is possible that personal information about you could become known to other people. The investigators will take precautions to prevent this from happening. Your name will not appear on any questionnaires or test that you complete during the study. Instead, all questionnaires and tests you complete will be coded with a study code number.

Unknown/Unforeseeable Risks: In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this study drug. If you experience any symptoms you believe to be related to the study drug you should call the study staff at 646-774-6243**.**

Study Benefits: You are not expected to benefit directly from participation in this study.

New Information: You will be informed verbally and in writing of any new information, findings or changes to the way the research will be performed that might change your willingness to continue your participation in this study.

Compensation: You will receive $125 for each of the four completed laboratory sessions and $50 for the follow-up visit. With the additional money you could earn during the laboratory sessions, you could make up to $610. Failure to comply with the study could result in dismissal from the study. If you are dismissed from the study or decide to withdraw from the study, you will still receive the payment for the parts 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 were paid. Please note that payment for this study may affect your eligibility for Medicaid and other city and state support services. No information about which study you participated in will be provided to the IRS**.**

Confidentiality: All written information acquired in this study will be stored in locked files and will be kept confidential to the extent permitted by law. All computer-stored information will be "coded"—labeled only with a code and on password-protected computers. These code numbers will not use a name or any other identifying features. Your name and other personal identifying information will be stored in an electronically secure database at New York Psychiatric Institute that is accessible only to the members of the research team.

We have applied for a Certificate of Confidentiality issued by the National Institute on Drug Abuse. With this certificate, the researchers cannot be forced to release any research information in which you are identified, even under a court order or subpoena, without your written consent. The Certificate does not prevent the researchers from reporting suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others. Such information will be reported to the appropriate authorities. You should understand that 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. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. Records will be available to research staff, and Federal, State, and Institutional regulatory personnel (who may review records as part of the routine audits).

Your genetic information will be kept confidential and de-identified. All records containing links and identifying 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. Jones, 646 774-6113) or you can go to the following website http://www.genome.gov/10002328.

In Case of Injury

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.

Questions

The investigators will answer to the best of his/her ability any questions that the participant may have now or in the future about the research procedures, or about the subject's response to the procedures. You may contact the Principal Investigator, Dr. Jermaine Jones who can be reached at (646) 774-6113, if you have any questions. You will be given a copy of this consent form to take home with you. You will be notified of any significant new findings that may relate to your willingness to continue to participate in this study.

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 human subjects in research studies. You may call the IRB Main Office at (646) 774-7155 during regular office hours.

Documentation of Consent

Dr. Jones **may** ☐, **may not** ☐ use my genetic sample can be used for the current study.

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

Dr. Jones **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 and understand the preceding information describing this medical research study. The study doctor or the study staff has explained it to me in detail and all of my questions have been answered to my satisfaction.

I understand that I will receive a signed copy of this consent form for my records. I voluntarily agree to participate in the research study described above.

Name of Participant_____

Signature of Participant_____ Date_____

Statement of the Investigator (M.D.)

I have examined the participant named above for the purpose of determining whether he/she is capable of understanding the purpose, nature, risks, benefits and alternatives (including non-participation) of the research, making decisions about participation, and understanding that the decision about participation in the research will involve no penalty or loss of benefits to which the patient is otherwise entitled, for Dr. Jermaine Jones' research project "Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse." On the basis of this examination I have arrived at the conclusion that this participant has this capacity at this time.

Printed Name_____

Signature_____Date_____

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

Protocol Number: 7347 **Principal Investigator:** Jermaine Jones, Ph.D.

Name of Study: Using Pharmacogenetics to Better Evaluate Naltrexone for Treating Stimulant Abuse

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:
NYSPI/Columbia University College of Physicians and Surgeons

☑ The Sponsor of the Research,
National Institute 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):

     Dr. Jermaine Jones
     NY State Psychiatric Institute (Unit 120), New York, NY 10032
     646-774-6113
   - 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.**

I'm going to be asking you about problems or difficulties you may have had, and I'll be making some notes as we go along. Do you have any questions before we begin?

MDE	1	**In the last two months, has there been a period of time when you were feeling depressed or down most of the day nearly every day?** IF YES: **How long did it last? (As long as two weeks?**)	A two-week period in the past two months characterized by depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation (e.g. appears tearful).	NO	YES
MDE	2	**What about losing interest or pleasure in things you usually enjoyed?** IF YES: **Was it nearly every day? How long did it last? (As long as two weeks?)**	A two-week period in the past two months characterized by markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others)	NO	YES
MDE		Is the answer to either 1 or 2 YES?		NO ➔	YES – ***SCID***

ME	1	**Have you ever had a period of time when you were feeling so good, excited, or hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?** IF YES: (**Was that more than just feeling good? Did anyone say you were manic?)** **How long did that last (as long as one week)?**	A distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least one week (or any duration if hospitalization is necessary).	NO	YES
ME	2	If NO: **What about ever having a period of time when you were so irritable that you found yourself shouting at people or starting fights or arguments (Did you find yourself shouting at people you really didn't know)?** IF YES: **How long did that last (as long as one week)?**		NO	YES
ME		Is the answer to either 1 or 2 YES?		NO ➔	YES – ***SCID***

PD	**Have you ever had a panic attack, when you suddenly felt frightened or anxious or suddenly developed a lot of physical symptoms?**	NO ➔	YES – ***SCID***
OCD	**Have you ever been bothered by thoughts that didn't make any sense and kept coming back to you even when you tried not to have them?**	NO ➔	YES – ***SCID***
OCD	**Was there ever anything that you had to do over and over again and couldn't resist doing, like washing your hands again and again, counting up to a certain number, or checking something several times to make sure that you'd done it right?**	NO ➔	YES – ***SCID***
GAD	**In the last six months, have you been particularly nervous or anxious?**	NO ➔	YES – ***SCID***
ED	**Have you ever had a time when you weighed much less than other people thought you ought to weigh?**	NO ➔	YES – ***SCID***
VR	**Have you ever been arrested or convicted for assault or any violent offence? What about being involved in violence when you weren't arrested or charged with it?**	NO ➔	YES – ***Follow-up yourself***

PTSD	1	**Sometimes things happen to people that are extremely upsetting – things like being in a life threatening situation like a major disaster, very serious accident or fire, being physically assaulted or raped, seeing another person killed or dead or badly hurt, or hearing about something horrible that has happened to someone you are close to. At any time in your life, have any of these kinds of things happened to you?**	NO ➔	YES
PTSD	2A	If YES: **Sometimes these things keep coming back in nightmares, flashbacks, or thoughts that you can't get rid of. Has that ever happened to you?**	NO	YES
PTSD	2B	If NO: **What about being very upset when you were in a situation that reminded you of one of these terrible things?**	NO	YES
PTSD		Is the answer to 1 AND 2A and/or 2B YES?	NO ➔	YES – ***SCID***

Now I'd like to ask you about unusual experiences that people sometimes have.

SCHZ	1	**Has it ever seemed like people were talking about you or taking special notice of you?** If YES: **Where you convinced they were talking about you, or did you think it might have been your imagination?** If YES or NO: **What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?**	Delusions of reference – i.e. events, objects, or other people in the individual's immediate environment have a particular or unusual significant.	NO	YES
SCHZ	2	**What about someone going out of their way to give you a hard time, or trying to hurt you?**	Persecutory delusion, i.e. the individual (or his or her group) is being attacked, harassed, cheated, persecuted, or conspired against.	NO	YES
SCHZ	3	**Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?**	Grandiose delusion i.e., content involves exaggerated power, knowledge or importance, or a special relationship to a deity or famous person.	NO	YES

SCHZ	4	**Did you ever feel that something was very wrong with you physically even though your doctor said nothing was wrong…like you had cancer or some terrible disease?** **Have you ever been convinced that something was very wrong with the way that a part or parts of your body looked?**	Somatic delusion i.e. content involves change or disturbance in body appearance or functioning.	NO	YES
SCHZ	5	**Did you ever have any unusual religious experiences?**	Religious delusion	NO	YES
SCHZ	6	**Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (Were you awake at the time?** **If YES: What did you hear? How often did you hear it?**	Auditory hallucinations	NO	YES
SCHZ	7	**Did you ever have visions or see things that other people couldn't see? (Were you awake at the time?**	Visual hallucinations	NO	YES
SCHZ	8	**What about strange sensations in your body or on your skin?**	Tactile hallucinations	NO	YES
SCHZ		Is the answer to 1, 2, 3, 4, 5, 6, 7, or 8 YES?		NO ***END***	YES – ***SCID***

_____ was interviewed for participation in an opioid laboratory study. The candidate showed no indication of current depression or GAD, or lifetime panic disorder, OCD, PTSD, anorexia, mania or psychotic illness. The candidate denied a history of significant violence.

Signed: _____ Printed:_____

Date:_____