Protocol Title:
Buprenorphine Stabilization and Induction onto Vivitrol for Heroin-dependent Individuals

Version Date:
10/10/2018

Protocol Number:
7699

Clinic:
BSU Clinical Service

First Approval:
10/10/2018

Expiration Date:
09/16/2019

Contact Principal Investigator:
Adam Bisaga, MD
Email: amb107@columbia.edu
Telephone: 646-774-6155

Research Chief:
Frances Levin, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting a new protocol

Division & Personnel

Division

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

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
None

Procedures

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

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Psychotherapy Trial

Population

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

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Adults over 50

Research Support/Funding

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

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Industry
Sponsor
Alkermes
Is the study investigator initiated?
Yes
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
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Vivitrol is an important option for those desiring detoxification and abstinence from opioids. Initiation of Vivitrol in individuals dependent on opioids is challenging, as they must undergo detoxification followed by several days of washout before Vivitrol can be administered. Moreover, most patients do not have access to an inpatient treatment facility to accomplish this process therefore feasible and effective outpatient procedures are necessary to accomplish this transition in many patients.

We have developed an outpatient procedure to accomplish Vivitrol induction on outpatient basis over 5-7 days but we observed that regular users of heroin have low rates of successful induction. Therefore, new strategies are needed for this difficult-to-treat population. We propose to evaluate a new longer approach that involves a three-week period of stabilization on buprenorphine and a slow dose reduction followed by a week-long period of opioid withdrawal concurrent with rapid escalation of oral naltrexone doses.

Background, Significance and Rationale

Background, Significance and Rationale

Vivitrol is an important option for those desiring detoxification and abstinence from opioids. Initiation of Vivitrol in individuals dependent on opioids is challenging, as they must undergo detoxification first followed by several days of washout before Vivitrol can be administered. Moreover, most patients do not have access to an inpatient treatment facility to accomplish this process therefore feasible and effective outpatient procedures are necessary to accomplish this transition. We have developed an outpatient procedure to accomplish this transition in 5 to 7 days which has a success rate of 56%. However regular users of heroin have 2.3 lower odds ratio of successful transition than users of prescription opioids. Heroin users are now becoming a growing population of individuals seeking treatment and some of them are interested in treatment with Vivitrol. Therefore, new strategies are needed for this difficult-to-treat population.

We have been piloting an alternative method of Vivitrol induction for participants who were not successful with a 5 to 7 days method. Many of those individuals are regular users of heroin and we have observed that the main reason for treatment failure in this population was the ongoing use of heroin during the week of oral naltrexone induction. Based on our observation of more than 200 individuals that we treated on outpatient basis over the past several years we believe that there are two distinct phenomena that contribute to the maintenance of heroin use in these individuals: 1) use of heroin for its euphoric effects (positive reinforcement) and 2) use of heroin to avoid withdrawal (negative reinforcement). We hypothesize that many heroin users are unable to cope with removal of both sources of reinforcement during an abrupt stopping of heroin. Therefore, we propose a treatment approach that would separate those two sources of reinforcement, in the first stage treatment will target positive reinforcing effects of heroin and in the second stage it will target adverse effects of opioid withdrawal (negative reinforcing effects). The proposed approach involves a three-week period of stabilization on buprenorphine followed by a week-long period of opioid withdrawal concurrent with rapid escalation of oral naltrexone doses.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
We hypothesize that a short-term treatment with buprenorphine prior to initiating treatment with naltrexone will increase the proportion of heroin-dependent patients successfully inducted onto Vivitrol.

Description of Subject Population

Sample #1

Specify subject population
Adults using heroin who meet criteria for opioid use disorder
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
45
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown
Both males and females will be recruited. All eligible subjects are accepted; however, past experience with recruitment for other studies in this population suggests that the sample will be 75% male, 60% Caucasian, 30% Hispanic or Latino, and 10% Black or African-American.
Description of subject population
Adult heroin users who currently meet DSM-5 criteria for opioid use disorder.

Recruitment Procedures

Describe settings where recruitment will occur
All potential participants will be evaluated at the Substance Use and Research Center (SURC) at the New York Psychiatric Institute.
How and by whom will subjects be approached and/or recruited?
All patients will be seen by one of our psychiatrists or psychologists for a screening evaluation and mental status examination as part of routine admission procedures, Patients who are opioid dependent and appear to meet criteria are told about the study and offered further evaluation. Final informed consent for the study will be obtained after full psychiatric and medical workup is complete. Procedures for training staff physicians in each protocol and consent form include initial presentations by the Principal Investigator at weekly staff meetings, and weekly discussion of inclusion/exclusion criteria and study eligibility for each screening participant.
How will the study be advertised/publicized?
Once approved by the IRB, advertisements for the study will be placed in local newspapers and radio stations. Additionally, prospective participants are recruited by word of mouth through liaison to other local clinical services.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

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

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Adult heroin users who meet criteria for current opioid use disorder
Create or insert table to describe the inclusion criteria and methods to ascertain them

1. Individuals between the ages of 18-60 (clinical interview)

2. Meets DSM-5 criteria of current opioid use disorder with six consecutive months of reported heroin use, supported by a positive urine for opiates indicating regular use of heroin

3. Seeking treatment for opioid use disorder with Vivitrol (Clinical interview)

4. Capable of giving informed consent and complying with study procedures (clinical interview)

5. In otherwise good health based on complete medical history and physical examination, laboratory tests, and EKG (Medical history and physical examination by psychiatrist, laboratory tests (serum Chem-20 and CBC, urinalysis) ECG)

6. BMI between 18-40 (clinical interview, vitals)

Create or insert table to describe the exclusion criteria and methods to ascertain them
1) Reported treatment with methadone in the last 3 months or positive urine toxicology for methadone on the day of consent (clinical interview)

2) Maintenance on, or regular use of buprenorphine or other prescription opioids (clinical interview)

3) Pregnancy, lactation, or failure in a sexually active woman to use adequate contraceptive methods. (Clinical interview by psychiatrist and medical history by psychiatrist, urine pregnancy test, serum HCG)

4) Active medical illness which might make participation hazardous, such as untreated hypertension, acute hepatitis with AST or ALT > 3 times normal, AIDS (CD4 count under 200 currently or medically ill with an opportunistic infection), unstable diabetes, cardiovascular disease. (medical history and physical examination by psychiatris, laboratory tests: serum Chem-20 and CBC, urinalysis, ECG)

5) Active psychiatric disorder which might interfere with participation or make participation hazardous,including DSM-5 Schizophrenia or any psychotic disorder, severe Major Depressive Disorder, or suicide risk or 1 or more suicide attempts within the past year. (MINI interview by therapist, clinical interview and mental status exam by psychiatrist, contact with collateral information as needed and available).

6) Physiologically dependent on alcohol or sedative- hypnotics with impending withdrawal. Other substance use diagnoses are not exclusionary. (MINI interview by therapist, Clinical interview by psychiatrist)

7) History of allergic or adverse reaction to buprenorphine, naltrexone, naloxone, clonidine, or clonazepam. (Clinical interview by psychiatrist)

8) Chronic **neurocognitive disorder** (Clinical interview by psychiatrist)

9) History of accidental drug overdose in the last 3 years as defined as an episode of opioid-induced unconsciousness or incapacitation, whether or not medical treatment was sought or received.
(MINI interview by therapist, clinical interview by psychiatrist)

10) Painful medical condition that requires ongoing opioid analgesia or anticipated surgery necessitating opioid medications (Clinical interviewpsychiatrist)

11) Fentanyl only use, supported by a urine toxicology that is positive for fentanyl only and negative for all other opioids. (Clinical interview, urine toxicology)

12) Court mandated to treatment (clinical interview)

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
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
Potential participants will sign the **screening consent page of the study consent** form prior to initiating the screening process. Following review of screening informed consent, an evaluation team consisting of a Masters level research psychologist and psychiatrist meets with potential participants. The baseline evaluation includes a full battery of self-report measures, a structured psychiatric evaluation (MINI interview), Hamilton depression scale, a physical examination, and laboratory assessments. Medical screening and laboratory work, include vital signs, a physical examination, ECG, serum chemistry, liver function tests, complete blood count, and urinalysis obtained by study personnel. Pregnancy tests will be conducted for women.
Describe Study Consent Procedures
After the screening evaluation, the study physician will review the study inclusion/exclusion criteria to determine if the participant is eligible for the study based on the screening materials. If the participant is eligible for the study, they will be given the consent form to read, and review with the consenting physician. The study consent will only be signed after all of the participant's questions are asked, and after all the risks and benefits are explained to and understood by the participant. Study related procedures will only be initiated after the consent form is signed by both the participant and consenting physician.
Indicate which of the following are employed as a part of screening or main study consent procedures

✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Bisaga, Adam, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Buprenorphine induction/stabilization/taper: Buprenorphine induction will be conducted at the SURC center. After consenting to the study, participants will receive buprenorphine, dispensed weekly, that they will take daily. Participants will be stabilized on, and tapered off, buprenorphine over a 3-week period. Reductions will occur in a graded fashion, with the stabilization dose reduced to 4mg, according to the following schedule:

- **Day 0 (Study Consent + ancillary medications).** Participants will be advised to abstain from opioids for at least 12-16 hours prior to taking their first dose of buprenorphine/naloxone in the clinic the next day.
- **Day 1:** After a COWS of 6-10, participants will receive buprenorphine/naloxone 2/0.5mg. If tolerated, the patient will receive an additional 4mg onsite, with 2mg to take home that evening. Patients will receive a total of 8/2mg on Day 1.
- **Days 2-7**: 8/2 mg buprenorphine/naloxone
- **Days 8-14**: 6/1.5 mg buprenorphine/naloxone
- **Days 15-21**: 4/1 mg buprenorphine/naloxone

Participants will attend the center twice weekly and will be assessed for opioid and other substance use (urine toxicology and self-report), vital signs, opioid withdrawal symptoms, opioid cravings, and dose adjustments of buprenorphine will be made as needed by study physicians. This approach to buprenorphine taper is intended to resemble standard clinical practice, in which patients seeking transition off buprenorphine undergo a slow taper. The purpose is in part to provide a slow transition with minimal withdrawal symptoms. Participants will have at least two study visits a week during the buprenorphine taper, but may be seen more regularly at the center if deemed clinically necessary. Participants will be required to submit at least one opioid negative urine (except for buprenorphine) during the last two weeks of the buprenorphine taper. **Participants who are not able to submit at least one opioid negative urine**

during the last two weeks of the buprenorphine taper will be offered buprenorphine to resume in the clinic and will be provided with referrals.

Naltrexone induction procedure: Participants who successfully complete the taper must then complete a two-day washout (abstinence from opioids, buprenorphine). During this 48-hour period, participants will report to the center daily for vital sign monitoring and to receive standing doses of ancillary medications (clonidine, clonazepam, zolpidem, prochlorperazine) to alleviate withdrawal and discomfort with additional doses as needed. After abstinence of >/= 48 hours from the last buprenorphine dose, to allow for mu receptor availability, participants will begin the naltrexone induction, using a 3 day ascending taper of oral naltrexone and once the final oral dose of naltrexone 15 mg is tolerated, participants will receive Vivitrol injection.

The administration of naltrexone will occur within a detoxification suite, consisting of a private room outfitted with two comfortable reclining lounge chairs, adjustable lighting, and an entertainment system. Participants will be monitored by clinical staff frequently, with vital signs checks and withdrawal assessments. Transportation home by car service will be provided at the end of the day for any patient deemed to have this clinical need.

On Day 1 of the naltrexone induction, participants a pre-treated with prochlorperazine, clonidine, and clonazepam, followed by the first dose of naltrexone 1.5mg. If the first dose of naltrexone is tolerated, a second dose of 1.5mg will be administered. Ascending split doses of naltrexone will be titrated up slowly, until the final total dose of 15mg has been given on Day 3 (Day 1: 1.5-3mg, Day 2 : 3-6mg, Day 3: 15mg). Ancillary medications will be offered daily during the induction week and will include clonidine for myalgias, prochlorperazine for nausea, clonazepam to reduce anxiety and dysphoria, and trazodone or zolpidem for insomnia. Participants will be provided take-home doses of ancillary medications in small doses for one week post-administration of Vivitrol. Once a total of 15mg of naltrexone has been tolerated (at least 1.5 hr. observation), the participant may receive 380mg IM Vivitrol. As noted in the section for Procedures for Missed Doses of Vivitrol, if relapse is suspected (the participant reports opioid use, and/or has a positive UDS for opioids) and there is a risk that the participant has developed physical dependence (e.g., delay in receiving scheduled injection or subjective effects suggesting that the block is incomplete) a naloxone challenge will be administered before the participant receives their next injection.

For female participants, a urine pregnancy test will be obtained on the day of Vivitrol administration. If at any time during the study a female participant has a positive urine pregnancy test, this will be reported to the FDA and IRB, the participant will be discontinued from the study, and transitioned to a treatment program in the community.

If a participant is unable to receive Vivitrol on induction Day 3, because they were unable to receive naltrexone due to opioid intoxication or severe withdrawal, the participant will be given up two additional days to attempt the oral naltrexone titration and Vivitrol induction. **If a patient fails to succeed with the naltrexone initiation procedure, the study team will provide the patient with a weekly supply of buprenorphine, and will be provided with a referral.**

Vivitrol Injections: Vivitrol will be administered as an intramuscular injection (380mg) in one buttock by one of the research psychiatrists or research nurse, who are currently trained and administer Vivitrol in other

protocols. Participants will be offered a second injection 4 weeks post administration of the first injection, and a 3rd injection 4 weeks later.

Procedures for Missed Doses of Vivitrol: If a patient misses a scheduled second or third injection and takes an opioid during at least two of the seven days following the date of the scheduled injection, relapse will be suspected(the participant reports recent opioid use, and/or has a positive UDS for opioids) , a naloxone challenge may be preformed, if appropriate, using 0.8mg naloxone IM. The patient is followed clinically and withdrawal symptoms are assessed over the next hour. If the challenge is negative, the administration of Vivitrol will be resumed. However, because there are blood levels and partial blockade beyond four weeks after the initial administration of Vivitrol, vulnerability to relapse may be more gradual, and the instance of mild or equivocal reactions to the naloxone challenge more common. In this instance, a second challenge within 72 hours, will be attempted, and if tolerated, the next injection of Vivitrol can be given. Patients who fail two consecutive naloxone challenges are considered to have relapsed and are referred for inpatient detoxification or agonist maintenance, as deemed clinically appropriate and in accordance with the patient's wishes. **Patients who fail two negative naloxone challenges will be given a week supply of buprenorphine and will be provided with referrals.**

Missing a scheduled Vivitrol injection is the most important threat to the success of Vivitrol maintenance. In the event of a patient missing a scheduled injection, staff will immediately attempt to contact the patient to re-establish commitment to the naltrexone treatment and reschedule the injection within a 24-48 hour period. If the patient cannot attend the treatment center within a two-day time-frame, or cannot be located, the treatment team will use previously obtained locator information in an effort to locate the patient through emergency contacts and try to get them in for a visit.

Study Visits
Participants will be seen in the center twice weekly during the buprenorphine stabilization phase and daily on weekdays during the induction phase (Days 1-5) . Once XR-NTX has been administered, participants will continue to be seen at the center twice weekly for **12** weeks. At each visit the patient will meet with the research assistant to complete research ratings. Research nurse collects safety measures and inquires about side effects. Side effects of study medications are reviewed weekly during the visit with a research psychiatrist, or more frequently if clinically indicated, and study psychiatrist will adjust medication dose if necessary.

At each visit the patient meets with the research assistant to complete research ratings, including self-report of withdrawal, mood, and drug use. The patient provides a urine sample under observation by a staff member at each visit. The sample is tested immediately for opiates with the iScreen system (Instant Technologies, Inc.). Vital signs are also taken. All data are then brought to the therapist and therapy session is held.

Participants may come to the center to be seen as frequently as needed. In particular, any participant who is experiencing protracted opioid withdrawal will be offered clinical contact on a frequent, even daily, basis. For clinical matters arising in the evenings or on weekends, participants will have access to the 24-hour emergency telephone service, staffed by physicians familiar with this protocol who can address patients' concerns.

Behavioral Therapy
Participants will receive counseling focused on medication adherence, education about management of withdrawal symptoms, on correct medication usage and the importance of adherence to study procedures and abstinence from any substance use outside of the protocol. All participants will receive behavioral therapy once weekly during the stabilization and post-induction phase, and daily (Mon-Fri) during the naltexone induction phase. Physician will meet with participants during each visit during the induction process and weekly during the buprenorphine stabilization, and post-induction phases. The goals of these counseling sessions are to: educate and support the patient as he or she stabilizes on XR-NTX, provide a motivational platform to discuss pharmacological and nonpharmacological strategies for the management of opioid withdrawal symptoms, provide education regarding any medication side effects, and increase patient's motivation to adhere to the XR-naltrexone and to remain on it with the provider in the community after the completion of the study.

Buprenorphine/naloxone will be offered to participants if they relapse to opioids or if they are unable to tolerate study procedures at any point in the study, as well as at the end of study if they no longer wish to continue treatment with Vivitrol.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

1) Development of serious psychiatric symptoms as indicated by the Clinical Global Impression (CGI) improvement score of 6 (much worse than baseline) or greater for 2 consecutive weeks.

2) If the participant's continued opioid use places him/her at risk for self-destructive behavior or other harm as indicated by a CGI improvement score of 6 or more (much worse than baseline) for 2 consecutive weeks, or as determined by clinical judgement .

3) Development of serious medical condition(s) that may or may not be related to study participation as assessed by weekly visits with the psychiatrist, vital sign measurements, and weekly urine toxicology.

4) If the participant becomes pregnant as assessed by monthly urine pregnancy testing.

Participants may be also removed from the trial if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment (drop out criteria are defined above). Subjects who develop serious psychiatric symptomatology (e.g. psychosis, suicidal ideation, severe depressive symptoms) during the study period will be dropped from the study and appropriate clinical referrals will be made. This would include, but not be limited to, patients who become unconscious after using, engage in destructive or violent behavior while intoxicated, report driving while intoxicated, or develop medical complications from their opioid use. In all cases where subjects are discontinued from the study, the clinical research staff will assume clinical responsibility for the subjects until clinical referrals are operational.

In the case that the patient is removed from the research trial for medical reasons, or is requesting withdrawal from the study, he/she will be retained in open treatment for the remaining study period. Upon removal of a patient from the trial due to clinical deterioration, the patient will be referred for appropriate follow-up treatment, in the most instances either intensive outpatient or residential treatment. The PI or a study psychiatrist is available 24 hours/day by phone and/or beeper in case of emergency.

If a patient is discontinued from the study, or decides to withdraw, or relapses during study participation, the patient will get treated with buprenorphine until they are linked with a referral for continuing buprenorphine treatment. Participants will receive a one-week supply of buprenorphine at a time during the transition process.

Buprenorphine will be also offered to participants if they are unable to continue with Vivitrol treatment at the end of the study. If additional injections of Vivitrol are available, they will also be offered to patients at the end of the treatment study.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Urine samples will be collected at every visit, and we will use onsite testing to provide immediate feedback on opiate use to the participant and the treatment team. Blood chemistry will be obtained at baseline and end of study. Urine pregnancy tests will be obtained at baseline and prior to each administration of XR-NTX.

Assessment Instruments

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

MINI- International Neuropsychiatric Interview (MINI) (30 minutes) (Screening Visit)
Psychiatric Interview (30 minutes) (Screening visit)
Medical History (Screening visit)
Physical Exam (Screening and End of Study Visits)
Urine sample for toxicology (5 min) (Daily during induction phase; bi-weekly during stabilization and post induction)
Clinical Global Impression Scale- Observer (CGI-O) (5 min) (Weekly)
Hamilton Depression Scale (HAM-D) (5 min) (Weekly)
Clinical Opiate Withdrawal Scale (COWS) (2 minutes) (Daily during induction phase; bi-weekly during stabilization and post induction)
Subjective Opioid Withdrawal Scale (SOWS)(2 minutes)(Daily during induction phase; bi-weekly during stabilization and post induction)
Systematic Assessment for Treatment Emergent Effects (SAFTEE) (3 min) (Weekly)
Concomitant Medications Form (3 min) (Weekly)
Locator Form (5 minutes) (Baseline)
Craving Scale (2 min) (Daily during induction phase; bi-weekly stabilization and post induction)

Vital Signs Nursing Form (3 min) (Daily during induction phase; bi-weekly during stabilization and post induction)
End Study Form (5 min)(End of Study)

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
A delay of up to 2 weeks is possible prior to enrollment.
Maximum duration of delay to standard care or treatment of known efficacy
Up to two weeks.
Treatment to be provided at the end of the study
All participants who remain active in treatment will have an End-of-Study visit, within a week of the final study day (28 days after second XR-NTX injection), during which final ratings measures, and toxicology will be obtained. Participants will receive a third injection of XR-NTX at the end of study. At the conclusion of the protocol, the participants will be offered supportive therapy for at least one additional month or until an appropriate referral for on-going treatment is made. If the patient is interested to continue on XR-NTX, we will try to work with the patient's insurance to provide coverage to continue XR-NTX. Most insurance plans cover Vivitrol, and we have devloped a network of providers who we have referred patients to. If the patient is unable to find a provider to administer injection but we were able to secure the medication through patient's insurance and the patient is at risk to become unblocked we will administer the injection.

Participants who had no response to naltrexone treatment, such as those who continued using opioids while on naltrexone as well as those who stopped taking naltrexone (missed scheduled injections) and/or resumed opioids after missing naltrexone, are considered to be at very high risk of a full relapse and overdose. These individuals will be immediately directed toward either inpatient detoxification followed by a residential treatment, or toward agonist maintenance with either buprenorphine/naloxone or methadone. Methadone maintenance treatment is widely available in the community; however, access to buprenorphine treatment is more restricted.

In order to minimize the risk of relapse due to the lack of access to the medication and the gap between treatment providers we would like to offer 2-week supply buprenorphine/naloxone 8mg to participants who are in the process of being referred out to either inpatient treatment or an agonist maintenance program. We will continue to provide additional support including frequent, daily if needed visits at our center for a maximum of 2 weeks.

Clinical Treatment Alternatives

Clinical treatment alternatives
The major alternatives to long-term treatment of opiate dependence is a "drug-free" treatment on either an outpatient or residential basis, or agonist maintenance with methadone or buprenorphine, all available by referral. Other options available in the community include either hospital-based detoxification (often agonist-assisted) to a "drug-free" state, which is available to the patients by referral, or outpatient methadone detoxification, which is available at some methadone clinics. Regardless of treatment, the risk of relapse to illicit opioid use is very high once the detoxification is completed without medication-based relapse prevention treatment. XR-naltrexone is FDA-approved for relapse prevention treatment of opioid use disorder. During the initial informed consent process, patients will be informed about alternative treatments and their availability, and that they are free to choose among the options, at baseline or at any time during the study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Side Effects, Risks, and Interactions of Buprenorphine
Buprenorphine has been associated with adverse effects typical of opioid agonist drugs (e.g. sedation, constipation, insomnia, headache, nausea), although as a partial agonist such effects are typically less pronounced than they would be with a full agonist. The most common adverse event associated with the sublingual administration is oral hypoesthesia. Other adverse events were constipation, headache, intoxication, disturbance in attention, palpitations, insomnia, sweating, and blurred vision. Buprenorphine by itself has little tendency to suppress respiration and is associated with a low risk of overdose, a safety advantage. However, there is a risk of overdose if buprenorphine is combined with sedative drugs such as benzodiazepines or alcohol, analogous to the risk of combining such sedating medications with a full agonist like methadone. As a partial agonist, buprenorphine can precipitate an acute opioid withdrawal reaction if taken within 12--18 hours of another short--acting full opioid agonist, or within 48--72 hours of a longer--acting full opioid such as methadone.

Discontinuation of buprenorphine is associated with opioid withdrawal symptoms ranging from mild-moderate to more severe reactions. Study physicians have extensive experience, in both research and clinical settings, in administering buprenorphine and in the management of opioid withdrawal symptoms. The use of buprenorphine is also associated with the risk of using the medication for the purposes of intoxication. In the present study we will use buprenorphine/naloxone combination product, which has lower abuse liability. If sublingual buprenorphine is used parenterally, there is a risk of precipitated opioid withdrawal. Such an event, if it were to occur, would be short-lived and not life threatening. Participants will be warned of this risk and advised not to use the medication in this manner. If it is determined that patients have been abusing their buprenorphine in such a manner, they will be declared to have failed BUP discontinuation, and a new treatment plan will be developed by the patient’s clinical team, with possibilities including transfer to buprenorphine or methadone maintenance. To minimize the risk of diversion,

medication will be dispensed for short time intervals (1-2 weeks of medication at a time).
Buprenorphine is metabolized principally by CYP3A4. Co-administration of other CYP3A4 inhibitors (e.g. anti-- retrovirals efavirenz, delavirdine, atazanavir or atazanavir/ritonavir; the anti-fungal agent ketoconazole;; antibiotics erythromycin or clarithromycin) may cause an increase in systemic levels of buprenorphine, although this does not usually have clinically significant effects. When a patient being prescribed buprenorphine is also receiving other medications, the prescribing physician will check for potential interactions ahead of time and monitor during treatment.

Side Effects of Extended--Release (XR), Injectable Naltrexone
The most common side effect associated with injectable naltrexone is injection site reaction. XR-naltrexone is administered as a gluteal intramuscular injection and injection site reactions, mostly pain, and occur in approximately 5% of patients in opioid treatment studies. These reactions are generally mild and include pain, tenderness, indurations, bruising, pruritus and swelling. Generally these reactions last 1-3 days. Rare skin reactions at the site of the injection have been reported, including sterile abscesses, which may relate to inadvertent injection into fatty tissue, rather than muscle. Patients will be informed of this risk, and baseline physical evaluation will include examination of the buttock for excessive adiposity. If a patient is examined by a physician and found to have an abscess, necrosis, cellulitis or extensive swelling, an appropriate surgical referral will be made.
Naltrexone has been associated with reversible hepatocellular injury indicated by elevated liver enzymes when administered at doses substantially greater than the 380 mg im per month, dose recommended for relapse prevention treatment of opiate dependence and proposed for the present study. When used in the recommended dose range in opiate--dependent patients, this risk is remote (Brahen et al., 1988; Brewer and Wong, 2004). Naltrexone is therefore contraindicated in patients with acute hepatitis or liver failure, and such patients are excluded from the study. Patients with hepatic enzyme levels greater than three times the upper limit of normal are excluded. Injectable naltrexone achieves higher blood levels than oral naltrexone initially, but these should remain lower than levels associated with hepatitis. If naltrexone--induced hepatitis were to occur in the setting of long--acting preparation, where the naltrexone would be only very slowly eliminated, this would prolong exposure to the offending agent. However, the experience with injectable naltrexone also suggests it is safe. In our studies with extended-release naltrexone several patients experienced elevation in liver enzymes, which were determined to be related to hepatitis C. In the proposed study we will use a long--acting, injectable preparation of naltrexone (Vivitrol 380 mg). Several recent reports have documented that naltrexone pose significantly lower risk of hepatotoxicity than previously suspected, even among alcohol-- and opioid--dependent persons including those with HCV and/or HIV infection (Lucey et al., 2008; Mitchell et al., 2012; Tetrault et al., 2012; Vagenas et al., 2014). These reports were used to support decision taken by FDA in July of 2013 to remove the Boxed Warning on the hepatotoxicity. Other adverse events seen most frequently in association with XR-naltrexone treatment for opioid dependence include nasopharingitis, insomnia and toothache (Vivitrol; Package Insert).

If a patient misses scheduled injection of Vivitrol and resumes regular opiate use, then receiving injectable naltrexone will precipitate opiate withdrawal, which may be quite severe in proportion to the time since the last injection and the level of opiate dependence. The physician will evaluate the patient and perform a naloxone challenge test to determine whether or not naltrexone can be safely resumed. If the naloxone challenge is positive (withdrawal is precipitated), then the patient will be removed from the study and offered another treatment option such as agonist maintenance (buprenorphine or methadone) according to clinical judgment and the patient’s preferences.

Self-administration of large doses of opiates may over-ride the blockade produced by naltrexone resulting in opiate overdosage with its attendant risks including respiratory depression and death. Patients will be warned of the severe danger of using opiates, including trying to over-ride the blockade. Also patients who have topped naltrexone and resume opiates will not be tolerant initially, so that the quantities of opiates self-administered prior to treatment, when they were tolerant, may be quite dangerous in the non-tolerant state. Patients will be warned of this. Patients who self-administer opiates to the point of somnolence or stupor will be removed from the trial and referred to inpatient detoxification. In the event of a medical emergency requiring opiate analgesia, a patient on naltrexone will require higher doses of opiates than normally administered. Patients will be informed of this and will be given a naltrexone medication card to carry in their wallet.

Risks of the Rapid Naltrexone Induction Procedure:
In this procedure withdrawal is then precipitated through administration of oral naltrexone and treated with clonidine (an alpha-2 adrenergic receptor agonist which reduces sympathetic nervous system output produced by opiate withdrawal), clonazepam (a benzodiazepine which reduces the anxiety and dysphoria and permits sleep) and other adjunctive medications. In the proposed protocol the risk of severe withdrawal has been minimized by starting naltrexone at the very low dose. Opiate withdrawal causes agitation, elevated pulse and blood pressure and other signs of sympathetic arousal, and sometimes confusion. Clonidine may produce somnolence or hypotension. Clonazepam commonly may produce somnolence. The procedure is contraindicated in patients with unstable medical problems or histories of hypersensitivity to any of the medications used, and these are exclusions in the proposed study. The procedure is conducted in the outpatient setting that permits monitoring of patients for up to 8 hours daily to permit close monitoring of vital signs and mental status.

Pregnancy
Buprenorphine and naltrexone are Pregnancy category C agents, although the safety of buprenorphine in pregnancy has been supported in clinical trials (Jones et al., 2010). Female participants will be required to use adequate methods of birth control (condom with spermicide, diaphragm with spermicide, birth control pills) to be included in the study and will be strongly encouraged to use more effective methods like a subdermal implant, IUD, or a depot contraceptive injection. Serum pregnancy tests will be evaluated at baseline and urine for pregnancy will be tested as clinically indicated during treatment according to standard clinical procedures. If a female patient does become pregnant she will be withdrawn from study medication and offered continuing treatment with methadone or buprenorphine, which remains the current treatment of choice for pregnant opioid dependent patients.

Risks of Relapse
Treatment with buprenorphine is also associated with a high risk of relapse (Raistrick et al. 2005), and a remote risk of opioid overdose if the patient uses a significant amount of opioids after losing tolerance. Risk minimization procedures include exclusion of patients with a history of overdose in the past 3 years , regular monitoring of urine toxicology and opioid use, and referral for agonist treatment or inpatient detoxification if relapse occurs.

Blood Tests
Blood drawing may cause slight discomfort at site of needle entry, resulting in a small bruise.

Naloxone Challenge Test
This test will be performed under the supervision of a study physician and will take approximately 45 min to complete. The risks of a dose of 0.2-0.8 mg naloxone administered IM are the signs and symptoms associated with opioid withdrawal ("gooseflesh," "vomiting," "tremor," "uncontrollable yawning," etc.). These will be assessed every 10 min. for up to 45 min. During the procedure, we will measure blood pressure and heart rate before and up to 30 min. after the naloxone dose.

Describe procedures for minimizing risks
Exclusion Criteria: The exclusion criteria of this study are designed to minimize the risks to participants. Patients are excluded if they have severe psychiatric illness (mood disorder with functional impairment or suicide risk, schizophrenia) which might interfere with their ability to participate in the outpatient therapy. A history of recent drug overdoses will be exclusionary. Pregnancy, lactation, or failure to practice a reliable birth control method is exclusionary, and patients are instructed to inform their psychiatrist immediately if they suspect they may be pregnant. Urine HCG is tested during screening and monthly throughout the trial. Serum (quantitative) pregnancy test will be obtained during screening. The baseline medical evaluation includes physical examination, blood chemistry profile (including liver function tests), complete blood count, urinalysis (including HCG), and electrocardiogram, urine toxicology, and naloxone challenge if opiate dependence diagnosis is unclear. The evaluating psychiatrist reviews all these and takes a medical history.

Any disorders which might make buprenorphine-clonidine-naltrexone or naltrexone maintenance hazardous, such as uncontrolled hypertension, diabetes, heart disease, hepatitis with transaminase levels greater than three times the upper limit of normal, renal disease, or advanced AIDS are exclusionary. Participants with uncertain hepatitis status and unexplained liver enzyme elevation > 3 times the upper limit of normal will be offered hepatitis panel testing to determine study eligibility. Patients with acute hepatitis infection and increasing liver function tests during screening will be excluded from study participation. The patient will be assisted in obtaining appropriate medical evaluation and treatment, and may be eligible for the research study once the problem is controlled. History of an allergic reaction to any of the medications used is an exclusion criterion.

Patient Education: All patients will be informed through the informed consent form and discussions with the research psychiatrist and therapist of the possible side effects and risks enumerated above. In addition, at weekly visits the psychiatrist will query side effects in general, and events of specific concern including missing naltrexone doses in conjunction with resumed opiate use or heavy opiate use in an effort to override the blockade, and the risk of overdose and death in these situations. Therapists will also be trained to query for such events and bring them to the attention of the psychiatrist who will follow up. Patients will give informed consent before entering the study. Patients are instructed to call us if any untoward effects occur and are given the phone number of our 24-hour answering service.

Patient Monitoring and Removal from Study: The psychiatrist and/or therapist will assess appropriateness for continuation in the research study on a continuous basis, and will remove from the trial patients with significant clinical deterioration or noncompliance of a type which could be dangerous. If a patient is removed from the research trial for medical reasons, he/she will be retained in open treatment for the remaining of the study period and will be offered a supply of buprenorphine while transitioning to other

treatment. Upon removal of a patient from the trial due to clinical deterioration, the patient will be referred for appropriate follow-up treatment, in most instances either inpatient detoxification or residential treatment, or methadone maintenance. The PI, Co-PI, or a study psychiatrist is available 24 hours/day by phone and/or beeper in case of emergency.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Patients will be asked to divulge information, such as their drug use or legal, psychiatric or medical problems, which are sensitive and could have adverse social consequences if released. This would include information released to insurance companies, family members, or made public in any way. Patient records are kept in locked files and released only with the patient's signed consent. We will obtain a Federal Certificate of Confidentiality to further safeguard the confidentiality of the participants enrolled in the trial. The Certificate of Confidentiality will allow investigators and others with access to research records to refuse to disclose information that could identify subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. Contact with family members or significant others will only be with the patient's express written consent. All computer data are stored without names or other uncoded identification.
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
Participants may benefit from many of the components of the treatment that they receive, induction onto injection naltrexone, naltrexone maintenance, and components of behavioral therapy.

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 $40 at each study visit to cover the cost of transportation and time spent completing study related forms. Therefore if a patient attends every study visit, they can earn up to $1,720.

References

References

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM,Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the combine study: a randomized controlled trial. JAMA 295(17): 2003-17.

Brahen, L. S., Capone, T. J., & Capone, D. M. (1988). Naltrexone: lack of effect on hepatic enzymes. The Journal of Clinical Pharmacology, 28(1), 64-70.

Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA 293(12): 1617-25.

Gerra, G., Fantoma, A., & Zaimovic, A. (2006). Naltrexone and buprenorphine combination in the treatment of opioid dependence. Journal of psychopharmacology, 20(6), 806-814.

Gowing, L., Ali, R., & White, J. M. (2009). Buprenorphine for the management of opioid withdrawal. The Cochrane Library.

Hammig, R., Kremter, A., Strasser, J., von Bardeleben, U., Gugger, B., Walter, M., Duresteler, K.M., Vogel, M. (2016). Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Subst Abuse Rehabil 20:7:99-105.

Hser, Y. I., Evans, E., Grella, C., Ling, W., & Anglin, D. (2015). Long-term course of opioid addiction. Harvard review of psychiatry, 23(2), 76-89.

Hulse GK, O'Neil G, Arnold-Reed DE (2004). Methadone maintenance vs. implantable naltrexone treatment in the pregnant heroin user. Int J Gynaecol Obstet. 85(2): 170-1.

Hulse, G. K., & O'Neill, G. (2001). Methadone and the pregnant user: a matter for careful clinical consideration. Australian and New Zealand Journal of Obstetrics and Gynaecology, 41(3), 329-332.

Raistrick, D., West, D., Finnegan, O., Thistlethwaite, G., Brearley, R., & Banbery, J. (2005). A comparison of buprenorphine and lofexidine for community opiate detoxification: results from a randomized controlled trial. Addiction, 100(12), 1860-1867.

Reece, A. S. (2009). Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine. Journal of substance abuse treatment, 37(3), 256-265.

Resnick, R.B., Kestenbaum, R.S., Washton, A., Poole, D. (1977). Naloxone-precipitated withdrawal: a method for rapid induction onto naltrexone. Clin Pharmacol Ther, 21(4):409-13.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
7699_10.1.18_UNBOLDED.pdf
Upload copy(ies) of bolded Consent Form(s)
7699_10.1.18_BOLDED.pdf
Upload copy(ies) of the HIPAA form
kait2.0_hipaa_8.16.18.pdf
Upload any additional documents that may be related to this study
7699 COVERSHEET_10.1.18 BOLDED.pdf

Buprenorphine Stabilization and Induction onto Vivitrol for Heroin-dependent Individuals
Principal Investigator: Dr. Adam Bisaga, MD (646)774-6155

Overview: Below is a summary of the study that you are being asked to participate in. 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, which you will have to sign if you decide to participate in the study. The consent form contains detailed information about the study and about the risks which you will discuss it with others before deciding to take part. And remember that, even if you agree to participate, you can change your mind at anytime.

Voluntary Participation: This is a voluntary study, and you do not have to participate if you do not want to. You may stop participating at any time. You can choose to stop participating at any time.

Alternatives: Other treatments are available, including methadone maintenance, buprenorphine maintenance, inpatient or other outpatient detoxification programs. **Maintenance with either buprenorphine or methadone is the recommended treatment.** Methadone or buprenorphine maintenance are thought to be more effective treatments for heroin or other opioid dependence than behavioral therapy and/or outpatient naltrexone treatment.

Procedures: If you decide to participate in this study, you will initially be assessed for your suitability to participate. You will be asked to attend the research center for an initial screening visit, where you will be seen by the trial doctor who will check that you are suitable for the study, ask some questions about your medical and psychiatric history, general health, treatment history, blood draws, and undergo a physical exam. Once you have given your consent to participate in this trial, you will begin your 3-week stabilization on buprenorphine/naloxone after abstaining from opioids for 12-16 hours. You will come to the clinic twice-weekly complete study assessments, and to meet with your therapist. If you are able to abstain from heroin with the help of buprenorphine/naloxone you will be detoxified off it over 5-day period when you will receive increasing doses of oral naltrexone and additional medications to help with withdrawal symptoms. On Day 5 of the detox week, you will receive an injection of naltrexone (Vivitrol). After the detox is completed, you will receive an intramuscular injection naltrexone, a long-acting form of naltrexone that lasts in your system for approximately 4 weeks. You will be asked to stay at the clinic for at least one hour after receiving this injection, for clinical observation. After receiving the intramuscular injection naltrexone, you will continue to receive counseling in the clinic for 12 additional weeks. During each visit, you will fill out several questionnaires and answer questions about your alcohol use and other drug use. Once each week, you will have a 30-minute session with a therapist and a psychiatrist.

Risks: There are expected, and potential risks and discomforts associated with participating in this study, including: Withdrawal symptoms (nausea, vomiting, diarrhea, muscle and abdominal cramping, irritability, anxiety, insomnia) during the first week. If you have stopped taking opioids, or just completed detoxification, or you stop taking naltrexone, you may be more sensitive to heroin and other drugs. Therefore, amounts of heroin and other drugs that you took routinely in the past may be very dangerous, causing overdose; you could die from this. Naltrexone does not block the effects of other drugs (e.g. cocaine, tranquilizers, alcohol) and does not reduce the risks in using these substances. Naltrexone can cause irritation to the liver, difficulty sleeping, depression, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, headaches, rise in blood sugar levels, dizziness, increased breathing, dehydration, sedation, and epileptic seizures.

Compensation: During the study, you will receive $40 in cash **per visit** to help pay for your transportation costs and for completing study related assessments. You can earn up to $1720 if you attend every study visit.

Benefits: You may benefit directly from the treatment you receive with reduction in your drug use and improvement in problems related to your drug use.

Questions: If you have any questions, contact the research psychiatrist (Dr. Adam Bisaga (646-774-6155).

NEW YORK STATE PSYCHIATRIC INSTITUTE
COLUMBIA UNIVERSITY DEPARTMENT OF PSYCHIATRY
Informed Consent for Participation in Research

Buprenorphine Stabilization and Induction onto Vivitrol for Heroin-dependent Individuals

I. Purpose and Overview

You are being asked to take part in a research study evaluating a new approach to treating opioid use disorder. As part of this outpatient treatment you will first be treated with buprenorphine/naloxone (Suboxone), a medication for opioid use disorder, for 3-weeks. If you are able to remain abstinent form heroin during that period, you will be detoxified off opioids over the 5-day period using increasing doses of oral naltrexone and additional medications to help with withdrawal symptoms. At the conclusion of this procedure you will receive an injection of naltrexone (Vivitrol) to prevent relapse. You will receive two additional injections of naltrexone every four weeks for the total of three injections and you will also be receiving individual therapy during the 12-weeks of the study.

Vivitrol is a long-acting injection that contains enough medicine to last for one month blocking the effects of opiates and craving. It has no opiate-like effects and is not a controlled substance. Vivitrol has been approved by the Food and Drug Administration (FDA) for the relapse prevention to opioid dependence following detoxification. You are being asked to participate in this study because you are currently dependent upon opiates and meet other study entry criteria. The purpose of this research is to develop new procedure for initiating treatment with naltrexone. This study is funded by Alkermes, a company that manufactures Vivitrol.

II. Voluntary

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

III. Alternative Treatments/Alternatives to Participation

You do not need to participate in this research study to receive treatment for your opioid use disorder or to receive treatment with Vivitrol or buprenorphine. Other treatments are available, including methadone maintenance, buprenorphine maintenance, inpatient or other outpatient detoxification programs. Maintenance with either buprenorphine or methadone is the recommended treatment.

IV. Procedures

Screening

The study begins with a screening visit. The medical examinations and laboratory tests for screening may be done on one day or over multiple days. You and the study doctor will arrange

those times. If you agree to be in this study, you will sign this form before any study procedures are done.

In order to participate in the study, you must first have a psychiatric and medical screening, which will include questions about your drug use, health, and other problems you may be having. Depending on the results of that, you may also have a cardiogram (a test to measure the electrical activity of your heart), blood tests, a physical exam, and a urine toxicology screen. After the initial screening visit(s), you will be told whether you may be eligible for this research treatment study. The screening process may take between a few days to a few weeks depending on the frequency of your visits. If you are not eligible, or if you are not interested in taking part in the research treatment, then the clinician will assist you in finding treatment for your problems elsewhere.

Buprenorphine/naloxone Stabilization and Taper

You will receive a weekly supply of buprenorphine/naloxone that you will take daily according to the following schedule: a stable dose of 8/2 mg (Days 1-7), 6/1.5mg (Days 8-14), and 4/1 mg (Days 15-21). During this time, we ask that you come to the clinic twice per week so that the staff can assess for withdrawal symptoms and make dose adjustments of the buprenorphine /naloxone if needed. The purpose of the stabilization and taper is in part to provide a slow transition with minimal withdrawal symptoms.

Detox

You will have a 2-day washout period following your last dose of buprenorphine/naloxone. We will ask you to come to the clinic for both days during this period, so that staff can check you for withdrawal symptoms, administer medications to minimize withdrawal, and evaluate readiness for oral naltrexone. You will be asked to abstain from opioid use for two days between your last dose of buprenorphine/naloxone and your first day of oral naltrexone-assisted detox, and to continue to do so for the rest of this week. If you do use heroin or other opiate drugs during this period, you may receive a naloxone challenge to determine whether it is safe to continue with the rest of the detox schedule. After the 2-day washout period, you will receive the first dose of oral naltrexone, and will receive increasing doses up to 15 mg over three days, followed by an intramuscular injection naltrexone. At each outpatient visit during the detox, you will need to provide an observed urine sample, which will be tested for opiates as well as other drugs. You will have your vital signs checked by the staff. In addition, you will receive medications to reduce the discomfort of withdrawal from opioids. These include: clonidine (a medicine used to treat high blood pressure), clonazepam (for anxiety), prochlorperazine (anti-nausea drug), and zolpidem or trazodone (for insomnia). If you experience significant withdrawal while at the clinic, you will be strongly encouraged to remain at the clinic for observation, and your medication dosage and the length of the detox may be modified. If your withdrawal symptoms are more severe, your detox can be extended for 1-2 day, to allow for more time to tolerate oral naltrexone.

You will be free to leave the clinic each day once you have received all necessary medication doses and have been evaluated for medical stability by the psychiatrist. If you experience fatigue or medication side effects, car transportation home will be provided to you.

Outpatient Treatment

After the detox is completed, you will receive an intramuscular injection naltrexone, a long-acting form of naltrexone that lasts in your system for approximately 4 weeks. You will be asked to stay at the clinic for at least one hour after receiving this injection, for clinical observation. After receiving the intramuscular injection naltrexone, you will continue to receive counseling in the clinic for 12 additional weeks. During each visit, you will fill out several questionnaires and answer questions about your alcohol other drug use. Once each week, you will have a 30-minute session with a therapist and a psychiatrist. These sessions will help you work on your treatment goals. You will also have your vital signs monitored at every visit. You will be offered two additional injections at Weeks 4 and 8 after the first injection.

You may be given a naloxone challenge test if we have concerns that you are still dependent on opioids or if you have relapsed, prior to administering Vivitrol. In order to determine whether or not you are dependent on opioids, we may administer up to 0.8 mg naloxone intramuscularly (injection in your upper arm muscle), which – if you have recently used opiates - may produce a number of withdrawal symptoms, such as nausea, sweating, diarrhea, and anxiety. These symptoms will usually wear off between 20-30 minutes. If the symptoms persist, we will offer you medications such as clonidine and clonazepam, to help alleviate the symptoms.

If, during the course of treatment, you relapse to heroin or other opioid dependence and are unable to give an opioid-free urine and/or restart naltrexone, you will be provided with referrals to alternative treatment programs. We will offer you buprenorphine/naloxone if you relapse to opioids or if you are unable to tolerate study procedures at any point in the study. If you use heroin during the study but are able to receive your next injection as determined by the naloxone challenge, you will continue in the program.

The most serious risk of study participation is that you will lose tolerance to opiates (the effect of heroin, fentanyl, or another opiate on the body is much stronger), and this means that resuming use of opiates after detoxifying could cause you to stop breathing and die. If you complete the detox and receive intramuscular injection naltrexone monthly, it will help to protect you against death due to opioid overdose, because it blocks the effects of opioid drugs. But if you stop taking naltrexone injections, restarting opiates could result in accidental overdose or death.

End of Study

At 12 weeks after your first intramuscular injection naltrexone, you will be asked to meet for an hour with the psychologist to answer questions about how you have been doing, have another physical examination and blood tests, complete some questionnaires, and you will be referred for further treatment as part of an after-care plan outside the clinic. You will work with your therapist after you receive your last injection of Vivitrol in study week 8 to develop a follow-up care plan to continue your treatment**.** After the study is completed, if you have trouble transitioning to your follow-up care provider, you can meet with your therapist weekly for up to a month until you have transitioned into the follow-up treatment.

If you remain abstinent throughout the study, we strongly encourage you to continue treatment after study completion and will work with you to help find another treatment provider. If you find difficult to remain abstinent (e.g., have strong cravings or use opioids) we will offer you a

two-week supply of buprenorphine/naloxone. We will also provide you with referrals for Vivitrol, buprenorphine, methadone, and behavioral treatment options. In the event that you decide to discontinue from the study, or are withdrawn from the study, you will be treated with buprenorphine/naloxone until you have been transitioned to another buprenorphine treatment program or provider.

The doctors conducting this research study are also responsible for your clinical care. If during the course of the study, you have a medical emergency or require urgent medical care, the research medical staff will consult with your treating physician(s) regarding any information relevant to your medical care. In the event of an emergency or if you have questions while in the study, you can reach the clinic at (646) 774-6174 during regular business hours or (914) 419-8921 in the evenings or on weekends.

V. Risks and Inconveniences

The most serious risk of study participation is that you will lose tolerance to opiates (the effect of heroin or another opiate on the body is much stronger), and this means that resuming use of opiates after detoxifying could cause you to stop breathing and die. If you complete the detox and receive intramuscular injection naltrexone monthly, it will help to protect you against death due to opioid overdose, because it blocks the effects of opioid drugs. But if you stop taking naltrexone injections, restarting opiates could result in accidental overdose or death.

Opioid detox carries a moderately high risk of relapse and a risk of opioid overdose if you use a large amount of opioids or if you use opioids that contain fentanyl after losing tolerance**.** We will seek to minimize these risks by monitoring you closely with urine drug tests and asking about any opioid use. If you do relapse, you will be given referrals for methadone or buprenorphine maintenance or inpatient detox and follow-up treatment.

<u>Buprenorphine/naloxone</u>

During the buprenorphine/naloxone induction and taper you may experience withdrawal symptoms such as difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint muscle pain, headaches, or runny nose. We do not expect that your will require additional medications, as withdrawal symptoms are usually mild during a buprenorphine/naloxone taper. However, you will be evaluated by medical staff during each daily detox visit, and if you develop significant withdrawal symptoms, these will be addressed. Possible medications that may be given include clonidine, clonazepam, trazodone, and zolpidem. You may experience discomfort despite their use.

You may also experience a rapid and sudden onset of withdrawal symptoms if you crush your take-home buprenorphine/naloxone pills and either inject or snort them. These symptoms would be very uncomfortable but short-lived and not life-threatening, and your psychiatrist would evaluate you for them, as well as provide you with referrals to alternative treatment.

Clinic staff will be monitoring you carefully to make sure you are receiving the optimal dose of buprenorphine/naloxone during each day of the induction, stabilization and taper. If you decide to take more buprenorphine/naloxone than prescribed during the first week of the study, or decide to inject buprenorphine/naloxone, the combination with the additional medications we

may be giving you to help with withdrawal symptoms, such as clonazepam, could put you at risk of death.

Opioid medications, like buprenorphine/naloxone, can interact with medicines, such as antidepressants and migraine medicines, meant to increase the effects of serotonin, a chemical in the brain. This interaction causes a serious response in the brain called serotonin syndrome. If you are taking an opioid along with a medicine that increases serotonin and develop symptoms such as agitation, hallucinations, rapid heart rate, fever, excessive sweating, shivering or shaking, muscle twitching or stiffness, trouble with coordination, and/or nausea, vomiting, or diarrhea, you should seek medical attention immediately. These symptoms generally start within several hours to a few days of taking an opioid with a medicine that increases the effects of serotonin in the brain, but symptoms may occur later, especially after either medication is increased in dose.

Taking opioids may lead to a rare, but serious condition where not enough of the hormone called cortisol is produced, particularly during stressful conditions when cortisol is usually produced. Consult your study doctor or seek medical attention (ensure that you communicate that you are participating in a clinical trial) if you experience symptoms such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. Long-term use of opioid pain medications may lead to decreased sex hormones. Inform your study doctor if you experience signs or symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.

Naloxone Challenge Test

Prior to receiving the intramuscular injection naltrexone, you may be given a naloxone challenge test if we have concerns that you are still dependent on opioids. In order to determine whether or not you are dependent on opioids, we may administer up to 0.8 mg naloxone intramuscularly (by injection), which – if you have recently used opiates - may produce a number of withdrawal symptoms. You may experience certain effects such as: sweating, restlessness, stomach pain, diarrhea, headache, anxiety, nausea, vomiting dizziness, runny nose, yawning, muscle aches, or tremors. We will monitor your reactions to naloxone for up to 45 minutes.

Naltrexone

Naltrexone will be administered two days after your last dose of buprenorphine/naloxone which may precipitates withdrawal. The withdrawal symptoms are then treated with clonidine, clonazepam, trazodone, prochlorperazine and zolpidem, but despite their use, you may experience significant discomfort. The side effects of these medications may include insomnia or possible sleepiness, lowered blood pressure which may produce dizziness or a tendency to feel faint, nausea, vomiting, diarrhea, muscle and abdominal cramping, irritability, anxiety, and an allergic reaction involving a narrowing of the airways in the lungs, similar to what people with asthma sometimes develop.

Once you are stabilized on naltrexone, this medicine generally has few side effects. It can cause irritation to the liver or may occasionally cause or contribute to depressive symptoms. Additional side effects may include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint muscle pain, or headaches. It is important to note that these symptoms may represent persisting withdrawal symptoms, and the psychiatrist who is monitoring you can prescribe medications to reduce the discomfort.

It is very important that you receive the intramuscular injection naltrexone. If you take small amounts of heroin or other opiates while on naltrexone, you should feel no opiate-like effects. However, it is possible to overpower naltrexone if you take large amounts of heroin or other

opiates such as fentanyl, and such an action can be fatal. Also, if you stop taking naltrexone, it is possible that you may be much more sensitive to opiates. This means that amounts of heroin or other opioids that you used to take routinely could cause you to overdose, stop breathing and die. Naltrexone does not block the effects of other drugs such as cocaine, tranquilizers, or alcohol, and it does not reduce the risks in using these substances, such as getting drunk, or getting high on cocaine or tranquilizer pills.

Vivitrol

Risks of Vivitrol are possible irritation (e.g., redness, swelling, possible scarring) or infection at the injection site. Injection site reactions have ranged from a small, painless area of hardness to pain, itching, redness, and swelling. These reactions have typically resolved spontaneously over a period of 1-3 weeks. Of the 1,000 naltrexone injections we have administered, three to date caused site swelling and an open sore to develop, which became infected and required a minor surgical procedure, antibiotic treatment and wound care. The wound healed completely over a period of approximately 3 months but resulted in a scar.

Another study risk is that naltrexone may impair the functioning of your liver. Short-term increase of liver enzymes can occur, but this is usually reversible. This effect on your liver will resolve after naltrexone leaves your body. In addition, administration of naltrexone may increase blood sugar levels, which may produce symptoms such as dizziness, increased breathing, dehydration, and seizures. If you experience any of these symptoms, it is important that you tell the investigator immediately.

In rare cases, patients who received injectable naltrexone reported developing a form of allergic pneumonia, experiencing shortness of breath. If you have trouble breathing, it is important that you let us know right away. In patients treated with the naltrexone injection, we have also observed hives, an allergic reaction of the skin with redness and itching. If you develop any of these symptoms it is important to let us know.

If you miss your visit to receive Vivitrol, and/or take opioids, you should come to the clinic immediately. There, you will be evaluated to determine if it is safe to restart the naltrexone. You may be asked to take an intramuscular injection of naloxone. If your body has become dependent on opioids, this dose will produce withdrawal symptoms lasting less than one hour. You may refuse the naloxone challenge but must be able to provide an opioid-negative urine or reconsider the challenge within 72 hours in order to determine whether you can safely restart naltrexone. If at this point, you are found to be dependent on opioids and unable to restart naltrexone, you will be provided with referrals to alternative treatment programs.

It is very important that you tell your study physician about any other medications you are taking (either prescription or non-prescription) before beginning naltrexone. It is also very important that, during the course of the study, you tell your research psychiatrist about any other medications you are prescribed or plan to take to avoid possible adverse reactions.

Comfort Medications

You will be given comfort medications to help manage your withdrawal during the detoxification. When you are taking the comfort medications (clonidine, clonazepam, prochlorperazine, and zolpidem), you should use caution when driving a vehicle or operating appliances or machinery. These medications may cause some side effects such as sleepiness, lowered blood pressure (which may produce dizziness or a tendency to feel faint), or upset stomach.

Other Risks

(For females) Both the detoxification procedure and outpatient naltrexone treatment may pose risk to a fetus. You will have a pregnancy test before beginning treatment and monthly thereafter to determine that you are not pregnant. You will be asked to use adequate birth control throughout your treatment such as: (a) hormonal contraception such as Depo-Provera, daily oral contraceptive, transdermal patch or Nuva ring, (b) intra-uterine devices, (c) sterilization, or (d) double barrier contraception, which is a combination of any two of the following methods: condoms, spermicide, diaphragm.

The only risk to the blood-drawing procedures used in this study is the possibility that slight discomfort and/or a small bruise or, rarely, a local infection may develop at the site of the needle puncture. This seldom occurs. If taking any medication orally, it is being dispensed to you in packages that are not childproof. Extra precautions need to be taken to keep the oral medication away from children.

You will be carefully monitored throughout your participation to minimize the chance of any serious adverse side effects. We will provide you with any significant new findings that may develop during the course of the study, which may relate to your willingness to continue study participation. If you suspect that you might be pregnant, you must inform the study team immediately.

VI. Benefits

You may benefit directly from the treatment you receive with reduction in drug use and improvement in problems related to your drug use. The findings of the study may help doctors know more about how to treat opioid dependence and help others with this problem.

VII. Confidentiality

We will do everything we can to keep others from learning about your participation in the research. To further help us protect your privacy, the investigators will obtain a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, the investigators cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for the purpose of audit or evaluation. A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note however, that if an insurer, employer or other outside party, learns of your participation, and obtains your consent to receive research information, then the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy. Finally, 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. Records will 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. 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. Electronic data are also coded and are stored on computers that are password protected. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

VIII. Study Compensation

During the study, you will receive $40 in cash per visit to help pay for your transportation costs and for completing study related assessments. Below is a breakdown of all the study visits:

- Screening: 1 visit = $40
- Consent: 1 visit= $40
- Buprenorphine Stabilization and Taper Phase General Visit: 6 visits (2 visits per week for 3 weeks)= $240
- Detox Week: 5 visits= $200
- Follow-up Visits: 16 visits= $640

Therefore, if you attend every study visit, you can earn up to approximately $1,720. 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.

IX. 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. Please be aware that:

1. The New York State Psychiatric Institute, Columbia University, Research Foundation for Mental Hygiene, and New York Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital.
2. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage.
3. No monetary compensation for wages lost as a result of injury will be paid to you by the New York State Psychiatric Institute, Columbia University, Research Foundation for Mental Hygiene, or by New York Presbyterian Hospital.
4. By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

X. Questions

The investigators will answer to the best of their abilities any questions you may have now or in the future about the study procedures or about your response to the procedures. You should contact the Principal Investigator, Dr. Adam Bisaga, at (646)744-6155 if you have any questions. If a medical emergency occurs at night or over the weekend, you should go to the nearest hospital emergency room and have them call (914) 419-8921 and ask for the doctor on call. If you have any questions about your rights as a research participant, want 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.

XI. Documentation of Consent for Screening

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

Print name : _____
(Participant)

Signed: _____Date: _____

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

Print name: _____
(Person Designated to Obtain Consent)

Signed: _____ Date: _____

Consent for Future Contact

You permit the Opioid Treatment Research Program staff to contact you in the future.

Print name : _____
(Participant)

Signed: _____Date: _____

XII. Documentation of Consent for Study Participation

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

Print name : _____
(Participant)

Signed: _____Date: _____

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

Print name: _____
(Person Designated to Obtain Consent)

Signed: _____ Date: _____

ADDENDUM 1
CONSENT FOR SIGNIFICANT OTHER CONTACT

It may be important for the staff at the clinic to discuss your problems with a close family member or friend to assess how you are doing, to help contact you if you miss a visit, or in case of an emergency. By signing this page, you consent to allow the staff to contact the following person(s) to discuss your case throughout the course of your treatment. You may refuse to grant this permission, and it will not affect your eligibility for treatment in this study.

Name:_____Relationship:_____

Address:_____

Phone Numbers:_____

Name:_____Relationship:_____

Address:_____

Phone Numbers:_____

Name:_____

Significant other contact information refused:____

Participant Signature:_____ Date_____

Investigator Signature:_____ Date_____

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

Protocol Number: 7699 **Principal Investigator:** Adam Bisaga, M.D.

Name of Study: Buprenorphine stabilization and induction onto Vivitrol for heroin-dependent individuals

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:

☑ The Sponsor of the Research,
Alkermes
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
Laboratory Corporation of America (Lab Corp.)

☐ 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):

  Adam Bisaga, M.D.
  1051 Riverside Drive, Unit 120
  New York, NY 10032
- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

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

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

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

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

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