Study: # 7812 entitled Lofexidine for management of opioid withdrawal with XR-NTX treatment

PI: Frances R. Levin, MD
NCT# NCT04056182

Protocol created/approved 8-12-2019
Data Analysis Plan created 8-15-2019

New York State Psychiatric Institute

Institutional Review Board

August 12, 2019

To: Dr. Frances Levin

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

Subject: Approval Notice

Your protocol # **7812** entitled: **LOFEXIDINE FOR MANAGEMENT OF OPIOID WITHDRAWAL WITH XR-NTX TREATMENT** Protocol version date 08/12/2019 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **August 12, 2019 to June 2, 2020.** (Reviewed at the Full Board meeting on June 3, 2019.)

Consent requirements:
☐ Not applicable:
☐ 45CFR46.116 (f) waiver of consent
√ 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 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 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 or events 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 (US WORLDMEDS)

Encl: CF (version date 8/1/19 in compliance with revised Common Rule), HIPAA

EN/AW/kpz

Signed copy on file at IRB

Protocol Title:
Lofexidine for Management of Opioid Withdrawal with XR-NTX Treatment

Version Date:
08/12/2019

Protocol Number:
7812

First Approval:
08/12/2019

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
06/02/2020

Contact Principal Investigator:
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Co-Investigator(s):
John Mariani, MD

Research Chief:
Frances Levin, MD

Cover Sheet

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

Division & Personnel

Division

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

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
✓ Medication-Free Period or Treatment Washout
✓ Internet-based Data Collection or Transmission

Population

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

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

Research Support/Funding

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

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is in preparation
Source of Funding
Industry
Sponsor
US WORLDMEDS
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
✓ NYSPI
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
Yes
✓ Hospital, clinics and other healthcare facilities

Hospitals,clinics and other healthcare facilities

Select from the list
or type in location(s)..
STARS-3 Columbus Circle, Suite 1408, New York, NY 10019

Lay Summary of Proposed Research

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This is an open-label pilot trial to evaluate the safety and tolerability of lofexidine in the management of opioid withdrawal symptoms while initiating outpatient treatment with naltrexone. Lofexidine is a non-opioid prescription medicine used in adults to help with the symptoms of opioid withdrawal that may happen when a person stops taking an opioid suddenly. The initiation procedure will be a flexible detoxification lasting 2 to 10 days concluding with the injection of XR-Naltrexone (Vivitrol). Vivitrol is a long-acting injection that contains enough medicine to last for one month blocking the effects of opioids. Lofexidine will be fixed-flexible dosing started on day 1 with maximum dose being three 0.18mg tablets taken orally 4 times daily at 4-to 6-hour intervals. Lofexidine treatment will continue throughout the detoxification, up to 10 days, and will be discontinued with a gradual dose reduction over 2 to 4 days. Precipitated withdrawal symptoms are treated with lofexidine, clonazepam, and other comfort medications.

Background, Significance and Rationale

Background, Significance and Rationale

Opioid use disorder (OUD) continues to be the driving force behind rising rates of drug overdoses in the United States (SAMHSA; 2017), and even though efforts to provide evidence-based OUD treatment with

medications have increased over the past decade rates of OUD still increased and a significant treatment gap remains (Jones et.al ; 2015). The most recent addition to treatment options for OUD is an extended-release preparation of naltrexone (XR-naltrexone), an opioid antagonist approved by the FDA in 2010 as Vivitrol for the prevention of relapse following opioid detoxification. The main advantage of XR-naltrexone is that it is long acting, protecting individuals from relapse for approximately a month, and circumventing the need for daily medication taking that would often lead to non-compliance with oral naltrexone. Treatment with XR-naltrexone has been associated with improved treatment retention, abstinence from opioids and reduced craving compared with placebo (Kruptisky et al.; 2011), and once initiated, its effectiveness appears to be comparable to buprenorphine a partial agonist, another FDA-approved treatment that can be used outside of the specialty treatment setting (Tanum et al; 2017; Lee et.al 2017).

However, one of the main barriers to initiating XR-naltrexone in active opioid users is the need for a 7 to 10-day abstinence from opioids prior to the first dose (Vivitrol, Package Insert). This means that individuals wishing to start XR-naltrexone first need to undergo detoxification, usually including 4-7 days of a buprenorphine or methadone taper, followed by 7-10 days of an opioid "washout." Unfortunately, many find this extended wait period difficult, due to persisting withdrawal symptoms and cravings, and are unable to complete it.

We previously demonstrated that transition from active opioid use (heroin or prescription opioid) to XR-naltrexone could be achieved in 7 days on an outpatient basis, using a regimen of buprenorphine, clonidine and other ancillary medications, and gradual up-titration of oral naltrexone beginning with very low doses (Sullivan et.al; 2016). Further shortening the delay to first XR-naltrexone administration, may enable more patients to successfully initiate treatment. However, a shorter procedure may produce more severe withdrawal symptoms. The use of clonidine in the management of opioid withdrawal in previous trials was found to be effective in relieving symptoms, but dosing was limited due to side effects such as hypotension and bradycardia.

Lofexidine is an alpha-2-adrenergic receptor agonist that was recently approved in the United States for the treatment of opioid withdrawal symptoms. The use of lofexidine as treatment to relieve opioid withdrawal syndrome (OWS) followed the observed benefits of its analog, clonidine, to relieve OWS. There is very limited evidence comparing directly lofexidine to clonidine. Four small controlled studies showed that at the doses that are comparable in relieving acute OWS severity (lofexidine 1.2-1.6 mg/d and clonidine 0.9-1.2 mg/d) patients treated with lofexidine had less hypotensive adverse effects. One study showed that lofexidine was more effective than clonidine in treating or preventing more severe withdrawal during transition onto naltrexone.

Therefore we aim to evaluate the safety and tolerability of lofexidine in the management of opioid withdrawal symptoms while initiating treatment with naltrexone during an outpatient detoxification.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Aim 1: To evaluate the safety and tolerability of lofexidine using standard dosing in the management of opioid withdrawal symptoms while initiating outpatient treatment with naltrexone.

Description of Subject Population

Sample #1

Specify subject population
Adults with current Opioid Use Disorder
Number of completers required to accomplish study aims
10
Projected number of subjects who will be enrolled to obtain required number of completers
20
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 suggest that the sample will be 75% male, 55% Caucasian, 30% Hispanic-American, 10% African-American, and 5% other minorities based on data from previous trials.
Description of subject population
Prospective participants must be adult (18 to 60 years of age) and meet criteria for current opioid use disorder by history and urine toxicology. Other substance use diagnoses are not exclusionary since multiple substance abuse is common in this population, and such an exclusion would rule out a large proportion of the population and limit the generalizability of the study. However, physiological dependence on alcohol or sedative-hypnotics with impending withdrawal is exclusionary. Maintenance on methadone or other long-acting agonist (e.g. buprenorphine) is exclusionary. Prospective participants cannot have concurrent psychiatric or medical conditions that would interfere with participation (e.g. mania, psychosis, pregnancy or failure to use adequate contraception).

Recruitment Procedures

Describe settings where recruitment will occur
All screening and study procedures will occur at the Substance Treatment and Research Services (STARS) of the Division on Substance Abuse (STARS Downtown) situated on 3 Columbus Circle, 14th Floor, Suite 1408, NY, NY 10019.
How and by whom will subjects be approached and/or recruited?
Screening for this study will be covered by the Substance Treatment and Research Service (STARS) umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that

they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this "phone screen" information will be forwarded to the clinician to facilitate the first meeting.

All patients will receive an explanation of the study risks, benefits, treatments, procedures, and option for alternative treatments. Patients who wish to participate will be asked to sign the treatment consent form following resolution of any questions and clear indication that they understand the nature of the study and consent form.

How will the study be advertised/publicized?

We will recruit individuals with OUD through newspapers, radio, subway ads and public service announcements coordinated by the NYSPI Public Relations Office. This method has proven successful in several clinical trials at STARS. All advertisements will be sent to the Institutional Review Board for approval. The first phase of recruitment is a structured telephone interview when the initial contact is made. Individuals interested in receiving treatment for OUD will be asked to come to STARS for additional screening as per protocol #6582R. Those patients who meet criteria for OUD and all other inclusion/exclusion criteria will be asked if they are interested in participating in the study.

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?

Yes

Describe concurrent research involvement

Screening for this study will be covered by the Substance Treatment and Research Service (STARS) umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this "phone screen" information will be forwarded to the clinician to facilitate the first meeting.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Adults with 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 present for at least six months, supported by a positive urine for opioids on day of consent (MINI interview, Clinical interview, and urine toxicology)
3. Seeking treatment for opioid use disorder (Participant self-report, MINI interview, Clinical interview)
4. Capable of giving informed consent and complying with study procedures (clinical interview)
5. History of opioid withdrawal (MINI interview, Clinical interview)

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

1) Meets DSM-5 criteria for substance use disorder other than opioid as the primary diagnosis (clinical interview)
2) Having a comorbid psychiatric diagnosis that might interfere with participation or make participation hazardous, such as an active psychotic disorder or current suicide risk (clinical interview)
3) Methadone maintenance or long-acting agonist (buprenorphine) treatment (self-report; urine toxicology)
4) Buprenorphine maintenance treatment (self-report; urine toxicology)
5) Known history of allergy, intolerance, or hypersensitivity to candidate medication (lofexidine, naltrexone, naloxone) (clinical assessment)
6) Pregnancy, lactation, or failure to use adequate contraceptive methods in female patients (Clinical interview, medical history, urine pregnancy test, serum HCG)
7) Unstable medical conditions, which might make participation hazardous such as uncontrolled hypertension (blood pressure >150/100), acute hepatitis, uncontrolled diabetes, or elevated liver function tests (AST and ALT >3 times the upper limit of normal)
8) Legally mandated to substance use disorder treatment
9) Currently physiological dependence on alcohol or sedative-hypnotics that would require a medically supervised detoxification-other substance use diagnoses are not exclusionary (clinical assessment)
10) Painful medical condition that requires ongoing opioid analgesia or anticipated surgery necessitating opioid medications (Clinical interview; psychiatrist)

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?
Yes
Indicate NYSPI IRB #
6582R
Describe Study Consent Procedures

Screening for this study will be covered by the Substance Treatment and Research Service (STARS)umbrella screening protocol #6582R (PI: John Mariani, MD). Trained research assistants and administrative assistants under the supervision of the principal investigator conduct the initial phone screening. Under protocol #6582R, patients who contact STARS interested in research trial participation are informed that they will be asked questions of a personal nature and asked to provide verbal consent for such questions. A "phone screen" form is completed by the phone screener, which asks basic demographic information, contact information (for scheduling purposes) and description of substance use to determine whether an in-person evaluation appointment is appropriate. Individuals are also informed that if they make an initial screening appointment this “phone screen” information will be forwarded to the clinician to facilitate the first meeting.

Once screening has been completed, eligible participants will meet with the research psychiatrist for consent to protocol #7812. Only research psychiatrist's will obtain consent.

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
Blevins, Derek
Brezing, Christina, MD
Iqbal, Muhammad
Kidd, Jeremy
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Shulman, Matisyahu, MD
Srivastava, A Benjamin
Wai, Jonathan, MD

Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Potential subjects will undergo a screening visit which will include a demographics questionnaire, medical history, physical examination, psychiatric evaluation, laboratory testing, and electrocardiogram. The MINI International Neuropsychiatric Interview (MINI) will be conducted to determine current DSM-5 diagnoses. Eligible participants will be offered the opportunity to participate in the research treatment study, using the IRB-approved consent form obtained by the research psychiatrist.

This is an open-label pilot trial to evaluate the safety and tolerability of lofexidine in the management of opioid withdrawal symptoms while initiating outpatient treatment with naltrexone. The initiation procedure will be a flexible detoxification lasting 2 to 10 days concluding with the injection of XR-Naltrexone (Vivitrol). Lofexidine will be fixed-flexible dosing started on day 1 with maximum dose being three 0.18mg tablets taken orally 4 times daily at approximately 4-to 6-hour intervals. Lofexidine treatment will continue throughout the detoxification, up to 10 days, and will be discontinued with a gradual dose reduction over 2 to 4 days (Table 2). Precipitated withdrawal symptoms are treated with lofexidine, clonazepam, and other adjuvant medications as detailed below.

The study will be entirely outpatient. Upon study entry, participants will begin clinic visits at the Substance Treatment and Research Service (STARS) clinic. After the detoxification period (2-10 days) where participants will attend the clinic daily, participants will then attend the clinic twice per week for the next 4 weeks and then once per week for the last 4 weeks. All participants will visit the clinic weekly to provide urine toxicology, report on adverse events, and complete additional assessments. All participants will also receive medical management, a medication adherence focused psychosocial intervention that facilitates compliance with study medication and other study procedures, and promotes abstinence from opioids and other substances.

Detoxification and Induction onto Injectable Naltrexone: The detoxification-naltrexone induction will be performed at the STARS outpatient research clinic, which is outfitted with a detoxification suite. After study consent and prior to initiating any study procedures, a urine will be collected and tested for pregnancy. A negative urine pregnancy is required at admission as detoxification and naltrexone treatment would not be recommended during pregnancy.

Participants come to the clinic daily for safety assessments, clinical monitoring, and management of withdrawal. Patients will be seen at the clinic preferably in the morning on Day 1 to initiate the lofexidine-naltrexone procedure. On Study Day 1, following the consent procedure, participants will start lofexidine and will be instructed to begin to abstain from opioids. Vital signs will be checked post 1 hour of initial lofexidine dose to see if there is an effect on blood pressure. Participants will continue to receive lofexidine 0.18mg #3 QID (approximately 9am, 1pm, 5pm, 10pm). Administration of lofexidine is withheld in case of dizziness or lightheadedness complaints, low blood pressure (SBP < 90 or DBP < 60), or orthostatic blood pressure changes (from lying down to standing up drop of SBP ≥ 20 mmHg, DBP ≥ 10 mmHg). If there are

changes in blood pressure or reported dizziness/lightheadedness we will hold off on lofexidine dosing, hydrate the participant and repeat blood pressure after 30 to 60 minutes to determine how long the lofexidine dose will be held. If vital signs and reported side effects return to normal ranges lofexidine dose will be continued as per protocol. If vital signs and reported side effects remain lofexidine medication will be held until the next study visit. We will counsel all participants in the importance for adequate oral hydration during the consent process and throughout the study.

Participants will be monitored by clinical staff frequently, with vital signs checks and withdrawal assessments. Starting day 1 participants will be sent home with ancillary medications (clonazepam, zolpidem) and will be instructed that they may use ancillary medication if needed.

Ancillary medications: A standing order of additional medication targeting withdrawal symptoms will be available to patients and will include clonazepam 1 mg tid and zolpidem 10 mg QHS. Ancillary medications will be offered daily during the induction week and will include clonazepam to reduce anxiety and dysphoria, and zolpidem for insomnia. Participants will be provided take-home doses of ancillary medications in small doses and on a tapering schedule for two weeks (after the detoxification week) to alleviate any protracted opioid withdrawal. Additional doses will be offered as clinically determined for participants experiencing continued withdrawal symptoms.

Naloxone challenge and Vivitrol injection: The purpose of the naloxone challenge is to determine if the participant is likely to tolerate a Vivitrol injection. The timing of naloxone challenge is based on a number of clinical factors including time since the last opioid use, pattern of recent opioid use, severity of tolerance and withdrawal symptoms, and response to ancillary medications used for the treatment of withdrawal. We will make the decision to administer naloxone on the COWS score, as well as the other factors noted above. The COWS score may be suppressed by other medications, and could also be suppressed by use of opioids. Therefore a global assessment of the participant's progress through the induction period will be taken into account when deciding to administer naloxone, using the COWS as the final indicator of readiness. **If a participant reports continued use of opioids, then naloxone challenge will not be administered because it would be very likely to precipitate withdrawal. However, if the urine test for opioids is positive, but the patient reports not having used any opioids in the recent days, then clinical judgment will be exercised as to whether to administer the naloxone challenge. This judgment would balance the risk of a brief episode of withdrawal precipitated by naloxone, against the potential benefit that the patient passes the naloxone challenge (no exacerbation of withdrawal symptoms) can receive injection naltrexone.**

Once a participant has a COWS < 6, they qualify for a naloxone challenge. Discussion of the naloxone challenge risks/benefits will be discussed with study staff and the naloxone consent form will be signed prior to the challenge. The challenge will be conducted over a 60 minute time frame. Individuals will be asked the last opioid use, route, and amount. A naloxone dose of 0.8mg will be given as an injection in the participants upper arm muscle. Participants will then be monitored for withdrawal and changes in vital signs for the next 60 minutes using the standard COWS (5 minutes, 20 minutes, and 60 minutes after naloxone dose). Once the participant completes the naloxone challenge and has no increase in COWS withdrawal score $\geq$ 10 they may receive XR-naltrexone injection (Vivitrol 380mg) on Day 2-10. Following the naltrexone injection, the patient will be required to remain at the clinic for at least 1 hour prior to discharge, to monitor for any increased withdrawal symptoms or side effects.

This outpatient detoxification/naltrexone induction medication protocol is outlined in Table 2, below. Evaluation of withdrawal severity (COWS) and vital signs, will be obtained at least twice per day (at the beginning and end of their study visit). Additional COWS can be administered as per clinical judgment of the study physician and nurse practitioner.

For female participants, a urine pregnancy test will be obtained on the day of each vivitrol administration. If at any time during the study a female participant has a positive urine pregnancy test, this will be reported to the IRB and the study sponsor, US WorldMeds and the participant will be discontinued from the study. We will follow our study discontinuation procedure as outlined below to transition these individuals to a treatment program in the community.

Outpatient Treatment Post-Detoxification

Study Visits

Participants will have two weekly clinic visits during the first month of treatment and one weekly visit during the second month. 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 opioids. Vital signs are also taken. Once a week participant will meet with a study psychiatrist for safety and tolerability evaluation, along with medical management therapy.

Participants may come to the clinic 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.

Outpatient medications

On the day after the XR-naltrexone injection participants will receive tapering doses of lofexidine for 2-4 days. During the subsequent 8-week course of outpatient treatment, patients receive additional injection of Vivitrol 380 mg, at week 4.

Medication Management

All participants will receive medical management once weekly during the post-induction phase, a medication adherence focused psychosocial intervention that facilitates compliance with study medication and other study procedures, and promotes abstinence from opioids and other substances. Overdose prevention education including a naloxone kit will be given to each patient.

Procedures for missed doses of XR-naltrexone

If a patient misses a scheduled second 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 performed, if appropriate, using 0.8 mg 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 treatment combined with medication 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. Buprenorphine is not included in the standard detoxification procedure for this study, but introduced as bridge medication. We will work with patients and make every effort to stabilize patients on buprenorphine at the clinic until a referral is secure. Patients will be at risk of overdose if they are not stabilized on one of the effective medications. Thus we will work hard with them to secure placement. Please see our study discontinuation procedure below.

Missing a scheduled XR-naltrexone 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 Discontinuation Procedure:

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. We will work with patients and make every effort to stabilize patients on buprenorphine at the clinic until a referral is secure. These individuals will be immediately directed toward either inpatient treatment such as residential treatment in combination with medication (methadone, buprenorphine, and/or Vivitrol), 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 clinic for a maximum of 2 weeks.

Discussion of treatment recommendations as well as risks and benefits of accepting and refusing referrals will take place and will be documented. Such a plan will be formalized and approved by a study physician no later than 4 weeks prior to planned treatment termination (by study week 4). If a patient misses discharge-planning visits, the discharge plan will be sent to the patient in the mail. If a patient has not made a successful transfer of care by the end of follow-up period, despite full compliance with recommendations, additional visits may be offered to enable appropriate placement.

Managing controlled substances: The PI, Dr. Frances R. Levin, obtained her own NYS Controlled Substance license and DEA Researcher Registration number. This project will be run under both the PI, Dr. Frances R. Levin's NYS Controlled Substance license (0401417) and her DEA Researcher Registration # RL0507941 and the NYS/OMH license (0400081) and NYSPI DEA Researcher Registration (PN0093461) held by the NYSPI Pharmacy Department. The drug stock of controlled substances for each project will be ordered, maintained and prepared under the Institutional registration at the NYSPI Pharmacy (OMH/NYS

Controlled Substance license # 0400081).

Packaged drugs (kits) will be transferred to the Principal Investigator (Dr. Frances R. Levin) using a DEA 222 form with the address where the study will take place (e.g. 3 Columbus Circle, Suite 1408, NY, NY 10019). Drugs or kits for individual patients will be transferred from the Institutional registration (#0400081) to the investigator registration using DEA 222 forms and transported by Marcia Loughran, FNP (supervisor of controlled substance activity) to the 3 Columbus Circle Suite 1408, NY, NY 10019 research site. Drug will then be kept in the wall mounted, double-door, double-locked storage cabinets at 3 Columbus Circle until it is given to the participant.

You can upload charts or diagrams if any
7812 detox medication flow chart-table 2.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation

We have operationalized the criteria for study dropout during the study as follows:
1. Participant is unable to pass a naloxone challenge during the 10 day induction period.
2. 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 or psychiatric or medical deterioration that cannot be managed safely in the context outpatient treatment offered at the study (in cases where the investigator determines that the participant needs immediate study discontinuation).*
3. If the participant's continued opioid or other drug 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. In cases where the investigator determines that the participant needs immediate study discontinuation for continued opioid or other drug use, participants will be provided with referrals.*
4. 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.
5. If the participant becomes pregnant as assessed by monthly urine pregnancy testing

*Any occurrence of CGI score of 6 or 7 at any time will trigger a clinical evaluation and then clinical judgment as to whether the patient should be discontinued, rather than a definitive discontinuation criterion. Such evaluations will be documented in the clinical chart.

Referrals for treatment in the community will be provided for the appropriate level of care.

Participants may be 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. A patient who's continued opioid use places them at risk for self-destructive behavior or otherwise places them at significant risk will be discontinued from the study. 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.

Please see Study Discontinuation Procedure in Study Procedures section for full details.

Blood and other Biological Samples

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

Approximately 10 cc of blood is drawn at baseline for blood chemistries, CBC, and pregnancy (females).

Urine will be collected at each study visit.

Assessment Instruments

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

Assessment of Drug Abuse Severity

Clinical Global Impression Scales for Substance Abuse: This is a clinician-rated and self-rated instrument that rates global severity and improvement on 7-point scales for opioid use. On the improvement scale a rating of 1 = "very much improved" requires abstinence, and a rating of 2 = "much improved" requires at least a 75% reduction in substance use since beginning study medication. The opioid change score is dichotomized such that patients scoring 1 or 2 are rated "responders" and all others "non-responders." A similar approach will be used to assess severity and improvement for global symptoms weekly by the study physician.

Timeline Follow-back (TLFB) Assessment: The Timeline Follow-Back method will gather self-reported opioid use data for each day during the 28 days prior to study enrollment and each day during the study period. Other substance (including nicotine and alcohol) use self-report data will also be gathered during the TLFB interview.

Urine Drug Testing: A urine sample will be collected under direct observation at each visit.

Craving Visual Analog Scale: A visual analog scale is used for patients to rate the intensity of craving for opioids experienced since the previous visit.

Clinical Opiate Withdrawal Scale (COWS): The COWS is a 11-item scale reliably eliciting severity of common physical and psychological symptoms of opiate withdrawal (Wesson, 2003). It will be used to examine occurrence of symptoms of opioid withdrawal and will be collected at each visit.

Miscellaneous Measures

Hamilton Depression Scale (HAM-D): In addition to mood symptoms, the HAM-D has items that measure anxiety, low appetite, irritability, and insomnia, which are symptoms of subacute opioid withdrawal of particular interest for this study (Hamilton 1960).

Assessment of Side Effects and Medication Compliance

Systemic Assessment for Treatment Emergent Events (SAFTEE): The psychiatrist or research nurse queries the patient and logs side effects and other treatment emergent events since the past visit, recording severity, action taken, and whether the side effect(s) is continuing or resolved.

Assessing Medication Compliance: (1) The study psychiatrist during each weekly evaluation queries and records patients' self-reported compliance and missed doses. (2) Compliance is also monitored with pill counts conducted by the research nurse.

Reporting of Adverse Events

All adverse events (AE) reported by the participant or observed by the investigator will be individually listed on the Adverse Event Form (SAFTEE). 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 the use of study drug, whether or not considered drug related, will be documented by the study psychiatrist.

All AEs reports will be reviewed by the study physicians and PI. In the event of any "serious" and/or "unexpected" adverse drug experiences, the PI will notify the Psychiatric Institute IRB and the study sponsor, US WorldMeds.

Please see table of study assessments for complete detail of assessments.

Please attach copies, unless standard instruments are used
study assessments.pdf

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
Active treatment of known efficacy (induction onto Vivitrol) begins when patients have signed study consent and begin outpatient treatment at STARS. A delay of up to 2 weeks is possible prior to enrollment.
Maximum duration of delay to standard care or treatment of known efficacy
The maximum delay is up to two weeks. Screening, diagnostic and medical evaluation to determine eligibility are generally completed within 3 to 5 days. It may take another week to complete a longer evaluation (for example if input is needed from another treating physician), or for patients to arrange to be

absent from work or family responsibilities. Clinical staff are in regular contact with patients during this time, and patients are informed of other treatment options available in the community.
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 (approximately 28 days after second XR-NTX injection), during which final ratings measures, and toxicology will be obtained. 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 developed 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 treatment such as residential treatment in combination with medication (methadone, buprenorphine, Vivitrol), 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.

We will use buprenorphine as a bridge if a participant cannot or does not want to take vivitrol. 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 will offer a 2-week supply of buprenorphine/naloxone, up to 24mg per day (as per clinical judgment) to participants who are in the process of being referred out to either inpatient treatment or an agonist maintenance program.

Discussion of treatment recommendations as well as risks and benefits of accepting and refusing referrals will take place and will be documented. Such a plan will be formalized and approved by a study physician no later than 4 weeks prior to planned treatment termination (by study week 4). If a patient misses discharge-planning visits, the discharge plan will be sent to the patient in the mail .
If a patient has not made a successful transfer of care by the end of follow-up period, despite full compliance with recommendations, additional visits may be offered to enable appropriate placement.

Clinical Treatment Alternatives

Clinical treatment alternatives

The major alternatives for long-term treatment of opioid use disorder are treatment on either an outpatient or residential basis, agonist maintenance with methadone or buprenorphine, or Vivitrol which are all available by referral. Stabilization on one of the effective medications (methadone, buprenorphine, Vivitrol) is recommended. Other options available in the community include either hospital-based treatment (often agonist-assisted), which is available to the patients by referral, or outpatient methadone treatment.

Regardless of treatment, the risk of relapse to illicit opiate 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 opiate dependence.

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 and Risks of buprenorphine: *We will use buprenorphine as a bridge if a participant cannot or does not want to take Vivitrol. 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 will offer a 2-week supply of buprenorphine/naloxone, up to 24mg per day (as per clinical judgment) to participants who are in the process of being referred out to either inpatient treatment or an agonist maintenance program.*
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. Study physicians have extensive experience, in both research and clinical settings, in administering buprenorphine and in the management of opioid withdrawal symptoms.

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. In addition, Vivitrol could result in withdrawal symptoms at the first dose. Study physicians will inform participants of this risk prior to receiving the injection.

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 (see Preliminary Studies) 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 options such as agonist maintenance (buprenorphine or methadone) according to clinical judgment and the patient's preferences (please see Study Discontinuation Procedure in Study Procedures section for full details).

Self-administration of large doses of opiates may over-ride the blockade produced by naltrexone resulting in opiate over dosage 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 stopped 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 treatment in combination with medication (methadone, buprenorphine, Vivitrol).

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.

Side-Effects and Risks of Lofexidine

Treatment with lofexidine may cause hypotension, dizziness, dry mouth, and bradycardia. Participants will be encouraged to hydrate orally when taking lofexidine. Blood pressure will be checked at each clinic visit. Lofexidine will be held if the patient's blood pressure falls below 90/60. Additional risks include syncope.

rebound hypertension and QT prolongation. ECG will be obtained during the screening and patients at risk for QT prolongation (e.g., moderate to severe renal or hepatic insufficiency) will be excluded.

Pregnancy:
Lofexidine is of unknown risk to a fetus. 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. Serum pregnancy tests will be evaluated at baseline, day 1 of the detoxification, monthly during the treatment study (prior to each injection), 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.

Assessments: 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.

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

Risks of Relapse
Treatment with naltrexone is also associated with a high risk of relapse, and a remote risk of opioid overdose if the patient uses a significant amount of opioids after losing tolerance. Individuals who use opiates are at risk for overdose, however we are using a standard treatment (e.g., Vivitrol) for opioid use disorder and there is no limitation in the labeling to justify excluding patients with a history of overdose. To minimization risk, we will monitor urine toxicology and opioid use at each visit, along with discussion of substance use weekly during the clinical assessment with the research psychiatrist.

We will work with relapsed patients who cannot resume and make every effort to stabilize patients on buprenorphine at the clinic until a referral is secure. Relapsed patients will be referred for inpatient treatment in combination with medication or outpatient buprenorphine or methadone maintenance. Self-administration of large doses of opiates may override 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 trying to override the blockade. Also patients who have stopped naltrexone for several days 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 who self-administer opiates to the point of somnolence or stupor will be removed from the trial and referred to inpatient treatment in combination with medication or to methadone maintenance treatment. As stated earlier, we will work with patients and make every effort to stabilize patients on buprenorphine at the clinic until a referral is secure. It is notable that XR-naltrexone in theory might protect against this risk, since naltrexone blood levels decline gradually over a period of weeks rather than the abrupt decline which

occurs when oral naltrexone is discontinued. 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.

Naloxone Challenge Test
This test will be performed under the supervision of a study physician and will take approximately 60 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.

Confidentiality: Patients applying for treatment divulge information that is sensitive and may have adverse social consequences if released. This would include information released to insurance companies, health care agencies, family members, or made public in any way. Procedures for protecting confidentiality of records will be followed.

Describe procedures for minimizing risks

Weekly Monitoring: Any study of medication efficacy carries risk. However, the investigators have conducted a series of studies administering medications to patients with opioid use disorder. Further, Dr. Bisaga has specifically conducted a study in our division in which the outpatient method of rapid naltrexone induction was developed. Other clinic physicians have extensive experience in administering oral and injectable naltrexone to opioid-dependent patients as well as experience providing treatment with buprenorphine.

Patients are seen weekly by a physician for evaluation of medication and side effects, medication compliance therapy, or dose adjustments or adverse effects, and for evaluation of safety and emergence of any safety related issues (e.g. pregnancy, clinical worsening including serious medical or psychiatric conditions, or worsening of substance use). Adverse Events and Serious Adverse Events will be carefully monitored during the study.

Procedures for Missed Doses of XR-naltrexone: If the patient misses a scheduled injection and takes an opioid during at least two of the seven days following the date of the scheduled injection, relapse will be suspected, and we will perform a naloxone challenge, if appropriate, using 0.8 mg naloxone, administered intramuscularly. The patient is followed clinically and withdrawal symptoms are assessed over the next hour. If the challenge is negative, the administration of XR-naltrexone will be resumed. If positive, the patient will have relapsed as XR-naltrexone may precipitate significant withdrawal so it cannot be resumed. However, because there are blood levels and partial blockade beyond 4 weeks after the last injection, vulnerability to relapse may be more gradual, and the instance of mild or equivocal reactions to naloxone challenge more common. In this instance, a second challenge within 72 hours will be attempted, and if tolerated, the next injections can be given. Buprenorphine or placebo will be resumed after the next XR-naltrexone dose is given. Patients who fail two consecutive naloxone challenges are considered to have relapsed and are referred for inpatient treatment in combination with medication or agonist maintenance, as

deemed clinically appropriate and in accordance with the patient's wishes. We will work with patients and make every effort to stabilize patients on buprenorphine at the clinic until a referral is secure.

Missing a scheduled XR-naltrexone injection is the most important threat to the success of XR-naltrexone maintenance. In the event of a patient missing a scheduled injection, the clinic 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 clinic within that two-day timeframe, or cannot be located, the treatment team will use previously obtained locator information in an effort to locate the patient through emergency contacts and get him/her in for a clinic visit.
Use of opiates presents concerns in the management of patients receiving XR-naltrexone. Failure mode with XR-naltrexone is that a patient misses a scheduled injection, resumes opioids, and becomes re-dependent. However, because of the long duration of action of XR-naltrexone (full blockade lasts up to 5 weeks after the last injection) a grace period of at least 7 days can be expected during which the injection can be rescheduled without risk of relapse.

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
We will apply for a Certificate of Confidentiality for this study from the National Institute of Health to offer protection for the privacy of participants by protecting identifiable research information from forced disclosure (e.g., through a subpoena or court order). The Certificate of Confidentiality will allow investigators and others with access to research records to refuse to disclose information that could identify participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the Federal, State, or local level. The Certificate of Confidentiality is granted for studies that collect information that, if disclosed, could damage participants' financial, employability, insurability, or reputation, or have other adverse consequences.

We use coded records (i.e. initials and numbers), store signed consent forms in a locked safe, and try, to the best of our ability to maintain confidentiality. Only coded records will be entered into the computer and the security of electronic data is ensured at the level of the server, the user, and the database. We do, however, point out to prospective patients, that we cannot assure that their drug histories and other personal records might not become known.
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. The participants may or may not benefit directly from the treatment they receive with reduction in drug use. There is the potential benefit of improvement of OUD with XR-NTX treatment. Often patients entering and remaining in treatment studies for opioid or other substance use disorders exhibit some improvement in personal, medical and psychiatric domains whether or not the specific medication is demonstrated effective.

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.
During the outpatient study, participants will earn $20 in cash per visit for transportation costs for attending study visits for the study period of approximately 10 weeks (2-10 detoxification and 9 weeks outpatient study visits). The maximum amount over the approximately 10 weeks an individual may potentially earn for attending all study visits is $460 (up to $200 during the detoxification and $260 for outpatient study visits). The $20 for transportation compensation will be given at each study visit.

References

References

Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and State Treatment Need and Capacity for Opioid Agonist Medication-Assisted Treatment. American journal of public health. 2015;105(8):e55-63.

Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377(9776):1506-13.

Lee JD, Nunes EV, Jr., Novo P, Bachrach K, Bailey GL, Bhatt S, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2017.
SAMHSA. National Survey of Substance Abuse Treatment Services (N-SSATS): 2016. Data on Substance Abuse Treatment Facilities. . Rockville, MD Substance Abuse and Mental Health Services Administration, 2017; 2017.
Sullivan M, Bisaga A, Pavlicova M, Choi CJ, Mishlen K, Carpenter KM, et al. Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine. Am J Psychiatry. 2017;174(5):459-67.

Tanum L, Solli KK, Latif ZE, Benth JS, Opheim A, Sharma-Haase K, et al. The Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. JAMA psychiatry. 2017.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
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IRB # 7812: "LOFEXIDINE FOR MANAGEMENT OF OPIOID WITHDRAWAL WITH XR-NTX TREATMENT"

Overview of Data Analytic Plan (created on 8/15/19)

Baseline demographics and non-efficacy outcomes, including retention, frequency of adverse events, and receipt of the first injection of naltrexone-xr will be tabulated and summarized for this open-label treatment group using means, standard deviations and percentages where appropriate. Opioid use (Timeline Follow-Back), craving for opioids (VAS scale), urine toxicology, and depression scores (HAMD) during detoxification and post detoxification will also be analyzed using similar models as in the primary hypothesis. PROC GLIMMIX in SAS® 9.4 will be used to conduct all analyses. All statistical tests will be two-sided with a level of significance of 5%.

Hypotheses testing:

Primary Hypothesis: Lofexidine will be associated with reduced symptoms of opioid withdrawal during the 2-10 days induction phase as compared to baseline (day 1).

To analyze the primary hypothesis, withdrawal severity (COWS) during the 2-10 days induction phase will be summarized using descriptive summaries and analyzed using longitudinal generalized linear mixed effects models with a main effect of time, adjusted by the baseline (day 1) withdrawal score. Based on the distribution of the outcome corresponding link function will be used (eg. log for skewed data etc). A random intercept will be used to account for the between subject variances and an autoregressive (AR1) covariance structure to account for the correlation of the repeated observations within subjects over time.

Secondary Hypotheses: Lofexidine used to manage opioid withdrawal symptoms will result in successful initiation of outpatient naltrexone-XR treatment by the completion of the induction phase and patients receiving first naltrexone-xr injection.

To analyze the secondary hypothesis, the proportion of subjects who complete the induction phase and receive the first naltrexone-xr injection will be calculated. A one-sample proportion test will be used to compare whether the sample proportion is significantly different from benchmark proportions of successful induction to naltrexone-xr. Additionally, 95% confidence interval will be computed to estimate the expected range of population proportion of successful induction.