Study: # 7501 entitled LORCASERIN IN COMBINATION WITH XR-NALTREXONE FOR RELAPSE PREVENTION OPIOID USE DISORDER

PI: Frances R. Levin

NCT# NCT03169816

Study Protocol Date: May 25, 2017

NEW YORK STATE PSYCHIATRIC INSTITUTE

INSTITUTIONAL REVIEW BOARD

MEMORANDUM

May 25, 2017

TO: Dr. Adam M. Bisaga

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

SUBJECT: APPROVAL NOTICE

Your protocol # 7501 entitled **LORCASERIN IN COMBINATION WITH XR-NALTREXONE FOR RELAPSE PREVENTION OPIOID USE DISORDER** (version date 05-25-17) and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **May 25, 2017 to April 30, 2018.** (Reviewed by the Full Board on 05-01-17.)

Consent requirements:

☐ Not applicable:

☐ 45CFR46.116(d) waiver or alteration of consent (for the phone screen)

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

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

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

Field Monitoring Requirements: √ Routine ☐ Special:

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

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

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

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

CC: RFMH Business Office (U54DA037842-01; PI: Levin)
CU Grants & Contracts (subcontract)

ENC: CF, CF Cover Sheet, HIPAA form

EN/LG/Scr

Protocol Title:
Lorcaserin in Combination with XR-Naltrexone for Relapse Prevention Opioid Use Disorder

Version Date:
05/25/2017

Protocol Number:
7501

Clinic:
Substance Treatment And Research Services (STARS)

First Approval:
05/25/2017

Expiration Date:
04/30/2018

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
Within the division/department, what Center or group are you affiliated with, if any?
SUBSTANCE TREATMENT AND RESEARCH SERVICES

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
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ Off-label Use of Drug or Device

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?
Yes
Describe internal account
U54DA037842-01 Shared Pharmacotherapeutic Strategies for Cannabinoid & Opioid Use Disorders
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
No
Who is the PI of the grant/contract?
Levin, Frances, MD
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
Shared Pharmacotherapeutic Strategies for Cannabinoid & Opioid Use Disorders
Grant Number

U54DA037842-01
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)
Columbia University

Study Location

Indicate if the research is/will be conducted at any of the following
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

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We propose to recruit patients with **Opioid Use Disorder (OUD)** seeking treatment into our program of outpatient detoxification and naltrexone induction followed by a relapse-prevention treatment with **Extended release-naltrexone (XR-NTX)** . Eligible participants will be randomly assigned to adjunctive treatment with lorcaserin (N = 40), or placebo (N = 20) with weekly therapy. Lorcaserin **or placebo** 10 mg bid will be started on Day 1 of the study to address acute withdrawal, then maintained over the next 5 weeks, and stopped after the second XR-naltrexone is administered. Patients will be seen twice weekly for monitoring and offered two injections of naltrexone; at the end of oral naltrexone induction (end of week 1) and four weeks later (week 5). The primary outcome measure will be the proportion of patients successfully retained to receive the second naltrexone injection. Patients retained to this point tend to stay on treatment and do well long term, hence this is the most clinically relevant outcome to evaluate treatment initiation.

Background, Significance and Rationale

Background, Significance and Rationale

Opioid Use Disorder (OUD) has reached epidemic proportions in the US with more than 2.5 million individuals affected, and substantial morbidity, including fatal overdose, now a leading cause of accidental death. Ironically, while opioid dependence is among the most severe addictions, it also has the most effective medication treatments. Yet, most patients with OUD are not engaged in any form of treatment and those in treatment do not continue with the medication for a sufficient period of time to assure sustained abstinence. The immediate goal of this proposal is to help improve the acceptability and effectiveness of the new treatment strategy, opioid withdrawal followed by a relapse prevention using extended-release injectable formulation of naltrexone (XR-naltrexone), in order to ultimately expand the availability of effective treatment options for opioid dependence.

The recent advent of XR-naltrexone has improved adherence to naltrexone and approximately 50% of patients started on injectable naltrexone are successful in treatment at 6 months, comparable with outcome of buprenorphine-assisted treatment but with lower rates of continuing opioid use. However, in order to safely initiate treatment with XR-naltrexone, an opioid dependent patient needs to undergo opioid withdrawal (detoxification) and be rapidly inducted onto the medication, which involves additional withdrawal discomfort. We developed an outpatient detoxification and naltrexone induction procedure, which has high patient acceptability and success rates, but the problems of withdrawal discomfort, persistent craving, and resulting dropout before the first XR-naltrexone dose persist. We have also shown that in addition to acute opioid withdrawal during the induction, subacute withdrawal symptoms, craving, and insomnia persist during the first several weeks after the first XR-naltrexone dose and may contribute to early dropout (after 1-2 injections). Thus, withdrawal discomfort and persistent craving is a likely common element underlying both failure of induction and early attrition from naltrexone treatment.

We are pursuing a program of research to develop pharmacological strategies that will increase success of induction and increase retention on XR-naltrexone. Here, we propose to conduct a pilot trial to test lorcaserin, a 5HT2c receptor (5HT2cR) agonists which recently become available for clinical use. Variety of 5HT2cR agonists, including lorcaserin, were found to be effective in preclinical models predictive of their efficacy in treatment of neuropsychiatric disorders including effects on mood, anxiety, impulsivity, learning and memory, psychosis, and food intake. Recently emerging area of research include studies indicating that 5HT2cR agonists may be effective in treatment of substance use disorders as these agents were found to: decrease self-administration of drugs of abuse, reduce reinstatement of drug-seeking behavior induced by stress as well as pharmacological and environmental cues, reduce motivational aspects of drug withdrawal, and reduce impulsive responding. Recent data suggest effectiveness of lorcaserin in alleviating opioid withdrawal **(Gobert et al., 2000; Wu et al., 2015; Zang et al., 2016).** Encouraging findings from preclinical models was confirmed by the recent positive results of the smoking cessation clinical trial **(Shanahan et al., 2016).** Consequently, there is strong support to suggest a first, proof-of-concept clinical trial of lorcaserin as a treatment of OUD and studying its potential to improve relapse-prevention effects of XR-naltrexone seems to be most fitting with the available evidence.

Specific Aims and Hypotheses

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Specific Aim #1: To determine whether lorcaserin, compared to placebo, increases the proportion of patients successfully inducted onto injectable naltrexone and retained to receive the second monthly injection.

Specific Aim #2: To determine whether lorcaserin, compared to placebo, reduces severity of acute withdrawal and craving during detoxification and induction prior to the first injection and protracted withdrawal after the first injection.

This will be the first clinical trial of lorcaserin for treatment of opioid withdrawal and the facilitation of naltrexone induction. If found effective, adjunctive lorcaserin would be a significant advance in the initiation of treatment with XR-naltrexone. As such, this method would have the potential to expand the population of individuals with OUD for whom naltrexone is a viable treatment option.

Description of Subject Population

Sample #1

Specify subject population
Adults ages 18-60 with current Opioid Use Disorder
Number of completers required to accomplish study aims
40
Projected number of subjects who will be enrolled to obtain required number of completers
60
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 that the sample will be 75% male, 60% Caucasian, 30% Hispanic or Latino, and 10% Black or African-American.
Description of subject population
Adults ages 18-60 with current Opioid Use Disorder.

Recruitment Procedures

Describe settings where recruitment will occur
All potential participants will be evaluated at the Substance Treatment and Research Service (STARS) clinic at the New York State 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 at STARS (Evaluation of Potential Substance Abuse Participants, IRB # 6582R, PI: Mariani). Patients who are opiate 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. The physicians listed above work regular weekly shifts at STARS, know the protocol well, and are able to explain study consent to the participant. 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 study will be placed in local newspapers and radio stations. Additionally, prospective participants are recruited by word of mouth and 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?
Yes
Describe concurrent research involvement
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 at STARS as part of proocol #6582R, PI: Mariani; Evaluation of Potential Substance Abuse Participants.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
All participants
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**

(MINI interview by therapist, Clinical interview with psychiatrist, DSM-5 criteria review, and urine toxicology)

3. Seeking treatment for opioid use disorder
(Participant self-report, MINI interview by therapist, Clinical interview by psychiatrist)

4. Capable of giving informed consent and complying with study procedures
(Clinical interview by psychiatrist)

5. Not underweight; defined as BMI≥18.5
(Calculation of BMI using weight and height of participant)

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

1. Lifetime history of DSM-5 diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder
(MINI interview by therapist, Clinical interview by psychiatrist)

2. Current DSM-5 criteria for any other psychiatric disorder that in the investigator's judgment is unstable, would be disrupted by the study medication, or is likely to require pharmacotherapy or psychotherapy during the study period. Concurrent treatment with other psychotropic medication is exclusionary.
(MINI interview by therapist, Clinical interview and mental status exam by psychiatrist, contact with collateral information as needed and available)

3. Individuals who meet DSM-5 criteria for any substance use disorders - severe, other than opioid and nicotine use disorder. Physiological dependence on alcohol or sedative-hypnotics is exclusionary.
(MINI interview by therapist, Clinical interview by psychiatrist)

4. A recent history of binge-use of alcohol or sedative-hypnotics (using large amounts in a short time to severe intoxication or blackouts).
(Clinical interview by psychiatrist)

5. Pregnancy, lactation, or failure to use adequate contraceptive method in female patients who are currently engaging in sexual activity with men.
(Clinical interview by psychiatrist, physical examination and medical history by psychiatrist or NP, urine pregnancy test, serum HCG)

6. Unstable medical conditions, such as AIDS, cancer, uncontrolled hypertension (blood pressure > 140/90), uncontrolled diabetes, pulmonary hypertension or heart disease.
(Medical history and physical examination by psychiatrist or NP, laboratory tests (serum Chem-20 and CBC, urinalysis), ECG)

7. Legally mandated to participate in a substance use disorder treatment program.
(Participant self-report, Clinical interview by psychiatrist)

8. Current or recent history of significant violent or suicidal behavior, risk for suicide or homicide **(MINI interview by therapist, Clinical interview by psychiatrist)**

9. Currently meets DSM-5 diagnosis for an eating disorder with low body weight (BMI <20)
(MINI interview by therapist, Clinical interview by psychiatrist)

10. History of accidental opioid overdose in the last three years or any other significant history of overdose following detoxification within past 10 years defined as an episode of opioid-induced unconsciousness, whether or not medical treatment was sought or received.
(MINI interview by therapist, Clinical interview by psychiatrist)

11. Elevated liver function tests (AST and ALT > 3 times the upper limit of normal) or impaired renal function (GFR<60 ml/min)
(Laboratory tests -serum Chem-20)

12. Known history of allergy, intolerance, or hypersensitivity to lorcaserin, naltrexone or any other study medications
(Participant self-report, Clinical interview by psychiatrist)

13. . Concurrent use of migraine medications containing ergotamine (Cafergot, Ergomar) or dihydroergotamine (Migranal), 5HT2B receptor agonists like cabergoline, or medications metabolized by CYP2D6 (thioridazine, tamoxifen, metoprolol, aripiprazole, codeine)
(Clinical interview by 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
Potential participants will sign the general screening (#6582R) consent form prior to initiating the screening

process. Following review of screening informed consent, an evaluation team consisting of a Masters- or Doctoral-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 at STARS. Pregnancy tests will be conducted for women.
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
Brezing, Christina, MD
Evans, Elizabeth, MD
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Shulman, Matisyahu
Vaezazizi, Leila
Williams, Arthur
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 and informed consent using the IRB-approved consent form will be obtained by the research psychiatrist.

This is a 2-arm, randomized, placebo-controlled trial to obtain initial data regarding **feasibility and tolerability** of lorcaserin for increasing successful initiation onto XR-naltrexone. Sixty volunteers will be offered outpatient detoxification followed by a treatment with XR-naltrexone. Participants will be offered two injections of XR-naltrexone and weekly therapy. We selected adherence with naltrexone injections as the primary outcome because it is the most clinically meaningful outcome of this treatment.

The study will be entirely outpatient. Upon study entry, participants will begin clinic visits at the Substance Treatment and Research Service (STARS) clinic. All participants will visit the clinic twice weekly to

provide urine toxicology, report on adverse events, and complete additional assessments (Table 1), 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. Participants come to the clinic daily visits to the clinic for safety, clinical monitoring and management of withdrawal. On Study Day -1, following the consent procedure, participants will be sent home with ancillary medications (clonidine, clonazepam, zolpidem) and will be instructed to abstain from opioids for 12-24 hours prior to Study Day 1and they may use ancillary medication if needed. Buprenorphine is initiated usually on Day 1 after an overnight abstinence, given first as a test 2 mg dose followed by additional 4 mg dose in the clinic and 2 mg dose to take at night if discernible withdrawal symptoms are present. Before the buprenorphine dose, participants will be assessed for the severity of withdrawal using COWS, and will require a COWS score of 6 or greater, prior to administration of buprenorphine. On Day 2 patients are started on clonidine, clonazepam and if needed prochloperazine for nausea. At the end of each clinic visit patients are sent home with additional ancillary medications to manage residual symptoms (clonidine, clonazepam and zolpidem). On Day 3 oral naltrexone is started at very low 1 mg dose, with and additional 3 mg dose administered 3 hours later. On Day 4 12.5 mg is administered and the patient's response is monitored. On Day 5 the target 25 mg of oral naltrexone is given at which point it is safe to administer the injection of naltrexone. On Days 1-5 COWS/SOWS assessments will be completed prior to administration of daily medications, 60 minutes after administration of oral naltrexone, and at the end of the study visit. All participants will receive naltrexone injections (Vivitrol 380 mg i.m.) under open label condition.

Compliance will be supported by observed ingestion of powdered doses of naltrexone as suspension in water. If opioid use occurs in combination with missed doses, a naloxone challenge will be administered to confirm that oral naltrexone will be tolerated; if necessary, an additional day of adjuvant medication only will be given. In patients at risk for greater withdrawal symptoms (e.g. history of severe withdrawal, substantial methadone use or more severe dependence (> 6 bags per day), or a strong reaction to the first daily dose of naltrexone), the procedure may be slowed down by 1 or 2 days.

Ancillary medications: A standing order of these medications will be available to patients and will include clonidine for myalgias (MDD= 0.3mg), prochlorperazine for nausea (MDD= 30mg), clonazepam to reduce anxiety and dysphoria (MDD= 1.5mg), zolpidem for insomnia (MDD=10mg).
Participants will be provided take-home doses of ancillary medications in small doses and on a tapering schedule for two weeks (including the detoxification week) to alleviate any protracted opiate withdrawal. Additional doses will be offered as clinically determined for participants experiencing continued withdrawal symptoms.

Study Medications Dosing: Study medications (lorcaserin or placebo) will be administered under double-blind conditions. Starting with day 1 of the induction period and during the subsequent six weeks of outpatient treatment all participants will receive two oral capsules (lorcaserin or matched placebo) twice daily. During the induction the first daily dose of lorcaserin **or placebo** 10mg will be given on Day 1 in the clinic 1 hour after the first dose of 2mg buprenorphine has been administered and the evening dose will be

taken at home at night. On Days 2-5, locaserin **or placebo** 10mg will be administered approximately 30 minutes prior to oral naltrexone.

Double Blind Treatment Period: Participants will be seen in the clinic at twice per week during weeks 2-7. At each visit the patient completes research ratings and the nurse collects vital signs and BMI, inquires about side effects, and obtains a urine sample under observation (Table 1). At each visit to STARS the patient meets with the research assistant to complete research ratings, including self-report of withdrawal, mood, and drug use. Side effects are reviewed at least weekly during the visit with a psychiatrist who will adjust medication dose if necessary. All participants will receive manualized, weekly therapy that it is derived from counseling aspects of BNT, emphasizing relapse prevention and adherence to medication. (Rothenberg et al., 2002). Participants will receive a 1-week supply of **lorcaserin or placebo** at a time.

Compliance with Lorcaserin/**placebo**: Timeline Followback (TLFB) pill count interview and weekly incentive for medication bottle return will be used to both enhance and measure medication compliance. To emphasize adherence to study medication and enhance reliability of the TLFB pill count, a $10 cash card incentive is provided for return of both medication bottles and unused medications (if not taken). Whether or not the patient ingested medication is not tied to compensation for bottle and pill return. The results of the TLFB pill count and medication bottle return are discussed with participants by the research psychiatrist to enhance adherence.

Extended Release (XR) Injectable Naltrexone: Use of opiates presents different concerns in the management of patients receiving XR-naltrexone maintenance. Failure mode with XR-naltrexone is similar that a patient misses a scheduled injection, resumes heroin, and becomes re-addicted. However, because of the long duration of action of XR-naltrexone (full blockade lasts up to **one month** after the last injection with a partial blockade for another week) a grace period of at least 7 days can be expected during which the injection can be rescheduled without risk of relapse. 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 the psychiatrist 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 half-hour. If the challenge is negative, the administration of XR-naltrexone will be resumed. If positive, then XR-naltrexone risks of precipitating withdrawal, and the injection will be postponed. However, because there are blood levels and partial blockade beyond Week 5, 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 24-48 hours will be attempted, and if tolerated, the next injections can be given. **A urine pregnancy test will be obtained for female participants prior to administration of XR-Naltrexone.**

Procedures for Missed Doses of Long-acting Naltrexone: Missing a scheduled Vivitrol 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 48-hour period. If the patient cannot attend the treatment clinic within that 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 get him/her in for a clinic visit. If opioid use occurs in

combination with a missed Vivitrol injection, a naloxone challenge will be administered to confirm that the next long-acting naltrexone injection will be safely tolerated.

Evaluation of Depression :Participants who meet criteria for a mood disorder (MDD) of mild to moderate severity will be followed closely during detoxification and subsequently. Mood will be assessed both in therapy sessions and in weekly MD visits, with repeated Ham-D scales. If a patient demonstrates significant depressive symptoms which persist following detoxification, we will offer the participant the option of beginning an antidepressant If deemed clinically warranted.

Managing controlled substances: Currently the study is run under the NYS Controlled Substance license # 0400081 held by the NYS OMH and the DEA Researcher Registration # PN0093461 held by the NYSPI Pharmacy Department. Dr. Bisaga has obtained his own NYS Controlled Substance license and applied for a federal DEA research license. When he will obtain DEA Researcher Registration # the projects will be run under both his research specific NYS license, his DEA Researcher Registration and the NYS/OMH license and NYSPI DEA Researcher Registration. 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. Adam Bisaga) 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
Naltrexone Lorca Study Process Image-4.24.17.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Study Discontinuation

Drop out criteria during the screening and study period include:

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.
3) Development of serious medical condition(s) that may or may not be related to study participation (e.g., significant weight loss, serotonin syndrome) as assessed by weekly visits with the psychiatrist, vital sign measurements, weekly weight-ins, and monthly serum and urine laboratory studies
4) If the participant becomes pregnant as assessed by monthly urine pregnancy testing

5) Weight loss resulting in the participant becoming underweight (BMI<18.5). BMI will be calculated weekly.

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. 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 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 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.

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 screening and at Week 7 (End of Study) for blood chemistries and CBC. A blood serum pregnancy test will be obtained for all female participants during screening. **A urine sample will be collected for a urinalysis at screening. At each study visit a urine sample will be collected for urine toxicology.**

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)
Risk Assessment Battery (5 min; screening)
Clinical Global Impression Scale- Observer (CGI-O modified from Guy 1976) (5 min; 1x week)
Urine sample for toxicology (5 min; daily)
Hamilton Depression Scale (HAM-D) (5 min; 1x week)
Clinical Opiate Withdrawal Scale (COWS) (2 minutes; 3x/daily during detox, 1x week)
Systematic Assessment for Treatment Emergent Effects (SAFTEE) (3 min; 1x week)
Concomitant Medications Form (3 min; 1x week)
Locator Form (5 minutes; baseline)
The Subjective Opiate Withdrawal Scale (SOWS) (5 min; 1x week)

The State-Trait Anxiety Inventory (STAI) (5 min; 1x week)
Craving Scale (3 min; daily)
Vital Signs Nursing Form (3 min;daily)
Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Lorcaserin (Belviq)
Manufacturer and other information
Lorcaserin (Belviq) is a weight-loss drug developed by Arena Pharmaceuticals. It has serotonergic properties and acts as an anorexiant.
Approval Status
IND is approved
IND#
134870
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Bisaga, Adam, MD

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 (detoxification) begins when patients have signed study consent and are randomized to begin outpatient detoxification 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
Up to two weeks.
Treatment to be provided at the end of the study
Study Discharge/Aftercare Plan:
Discharge and aftercare planning and implementation will be incorporated into the study. A Discharge Plan will be completed by a clinician and approved by a study physician prior to the End of Study visit. After the End of Study, participants will continue in a follow-up phase with once weekly clinic visits with their therapist for up to one month in order to facilitate transition and permit overlap with another treatment

program for aftercare. Discussion of treatment recommendations as well as risks and benefits of accepting and refusing referrals will take place and will be documented.

Clinical Treatment Alternatives

Clinical treatment alternatives

The major alternatives for long-term treatment of opiate dependence are "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 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

Potential Risks

Study Medication Risks: One of the main risks associated with participation is drug administration. Lorcaserin (or Belviq©) was approved by the FDA for treating obesity, is generally well tolerated, and has low abuse potential, though it is a schedule IV substance. The target daily dose of lorcaserin in the proposed study (20 mg) is the current FDA approved dose for the treatment of weight management. In clinical trials, headache was the only reported side effect to occur at a frequency much greater than placebo. Other possible side effects of lorcaserin include: constipation, dry mouth, headache, nausea, and dizziness. Some rare but serious side effects include hypoglycemia in patients with Type 2 diabetes, serotonin syndrome, agitation, confusion, hallucinations, arrhythmias, cardiac valve disease, depression, thoughts of suicide, and an erection lasting longer than 4 hours.

The combination of lorcaserin with other serotonergic medications (e.g., 5HT3 antagonist antiemetics, bupropion, triptans, SSRIs, SNRIs, TCAs, St. John's Wart, tryptophan), medications that impair the metabolism of serotonin (e.g., MAO inhibitors, dextromethorphan, tramadol, lithium), or antidopaminergic medications (e.g., antipsychotics) may enhance serotonergic effects, and this could result in rare but serious serotonin syndrome reaction. Signs of serotonin syndrome include: mental

status changes (e.g., anxiety, agitated delirium, restlessness, and disorientation); easy startle, autonomic manifestations (e.g., diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhea); and neuromuscular hyperactivity (e.g., tremor, muscle rigidity, myoclonus, hyperreflexia, and bilateral Babinski sign).

The combination of lorcaserin with ergot derivatives is contraindicated. The use of these drugs together may increase the risk of developing valvular heart disease in addition to enhancing serotonergic effects that may result in serotonin syndrome. The combination of lorcaserin with 5HT2B-R agonists (e.g., cabergoline) is contraindicated due to the increased risk of cardiac valvulopathy. Lorcaserin is a moderate CYP2D6 inhibitor and may decrease the clearance of drugs metabolized by CYP2D6, and thus raise these other drug levels increasing the risk of toxicity.Lorcaserin is contraindicated in pregnancy due to the fact that weight loss offers no clinical benefit in pregnancy and is advised against.

Risks of the Buprenorphine-Clonidine-Naltrexone Procedure: In this procedure, opiate-dependent patients are stabilized briefly on the partial opiate agonist buprenorphine. During subsequent administration of naltrexone and throughout the detoxification, withdrawal symptoms are 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 prn medications such as zolpidem for insomnia. 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 conducted in a setting equivalent to a day hospital, with a STARS study physician present at all times, to permit close monitoring of vital signs and mental status. Naltrexone does not provide a blockade for other substances of abuse, such as cocaine, benzodiazepines, or
alcohol. Thus, patients remain at risk of experiencing intoxicating effects and/or overdose with these drugs. This risk is highlighted in the consent form. Rare cases of allergic pneumonia following depot administration have been reported. Patients are advised of this in the consent form and are urged to contact STARS staff immediately if they develop any trouble breathing. We have observed two cases of allergic hives in patients treated with naltrexone. This risk is highlighted in the study consent form.

Side Effects of Naltrexone: Naltrexone has been associated with reversible hepatocellular injury indicated by elevated liver enzymes when administered at doses substantially greater than the 50mg per day dose recommended for maintenance treatment of opiate dependence and proposed for the present studies. When used in the recommended dose range in opiate-dependent patients, this risk is remote (Brahen et al., 1988). 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 3 times the upper limit of normal are therefore excluded. XR-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 during treatment with naltrexone injections, where the naltrexone would be only very slowly eliminated, this would prolong exposure to the offending agent. However, the experience with long-acting injectable naltrexone also suggests it is safe. In our studies with long-acting naltrexone several patients experienced elevation in liver enzymes, which were determined to be related to hepatitis C. One patient in the XR-naltrexone trial developed diabetes mellitus, which was deemed unlikely to be study related.

During the outpatient detoxification phase of the study, patients will have daily doses of oral naltrexone supervised at STARS. If a patient misses one or more oral naltrexone doses and resumes regular opiate use, then taking a dose of naltrexone will precipitate opiate withdrawal, which may be quite severe. Patients will be warned not to take the naltrexone if they have missed their dose for more than three days in a row and resumed opiate use for more than one day. Patients will be advised to report to STARS for clinical assessment by a study physician. If history and urine toxicology findings suggest a lapse or possible relapse, a naloxone challenge may be necessary. If the naloxone challenge is positive (withdrawal is precipitated), then the patient will be managed according to guidelines described above (see section entitled Handling of Lapses and Relapses). Relapsed patients who cannot resume naltrexone are referred for inpatient detoxification 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 will be warned of this. Patients with a history of drug overdose in the past 3 years or an overdose after detoxification within 10 years will be excluded. Patients who self-administer opiates to the point of somnolence or stupor will be removed from the trial and referred to inpatient detoxification or to methadone maintenance treatment. 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 and will be given a naltrexone medication card to carry in their wallet.

Pregnancy: Both the buprenorphine-clonidine-naltrexone procedure and naltrexone maintenance are considered contraindicated in pregnancy. Several small case series (Hulse et al., 2001; 2004) are reassuring in suggesting favorable pregnancy outcomes in women detoxified and maintained on naltrexone while pregnant. However, standard practice suggests methadone or buprenorphine maintenance is the treatment of choice for opioid dependent pregnant women, and we do not consider the small size of these case series sufficient to amend that recommendation. Absence of pregnancy will be confirmed at baseline and monthly during the study with urinary HCG. For women, regular use of an adequate contraception method (diaphragm with spermicide, condom with spermicide, birth control pills) is required for inclusion in the study.

Other Risks: Blood draws may cause slight discomfort at the site of needle entry, can result in infection at the site if hygienic/sterile techniques aren't used, or can result in a small bruise.

Participants will receive cash compensation and incentives during the study that could pose a risk of providing more available funds to purchase illicit opioids.

The structured interviews, rating scales, and questionnaires should add no physical risk. The major disadvantage is the time required to complete them and that some of the questions might be embarrassing to participants. Our past experience with these measures indicates that they are acceptable to participants.

However, some people have found them uncomfortable and/or tiring because the interviews/assessments are long and of a personal nature.
Describe procedures for minimizing risks

1) Screening Procedures

In order to minimize the risk associated with the study, subjects undergo a comprehensive medical and psychiatric evaluation during the screening procedure. The baseline medical evaluation consists of a physical examination, blood chemistry profile (including liver function tests), complete blood count, urinalysis, serum pregnancy test, urine toxicology and is designed, along with the clinical history, to detect chronic and/or unstable medical illnesses. A comprehensive psychiatric assessment is performed during the screening process, and is intended to detect and assess all past and current psychiatric disorders. The eligibility criteria (see above) are designed to minimize the medical and psychiatric risks to participants by excluding those for whom participation would place them at an increased risk. Special attention will be given to patient's concurrent use of medications. Participants on medications that meet exclusion criteria will not be included in the study. If participants have recently completed another study at STARS, we will ensure, as with other medications, that there are no drug-drug interactions with the possible recent exposure to other study medications or will ensure proper time for wash-out between studies.

2) Study Procedures

Participants will be informed about the possible side effects and risks (listed above) of taking lorcaserin both alone and in combination with other medications through extensive discussions with staff psychiatrist during the consent process. Participants will be told to contact the clinic if they experience any adverse effects and given the number for the 24-hr physician on-call. All participants, both those not taking and taking concurrent medications, will be monitored closely throughout the study for possible signs and symptoms of serotonin syndrome and weight loss. Participants' mental status and physical health are monitored weekly during the study period by a psychiatrist. Vital signs will be obtained at each study visit. Weight will be assessed weekly to monitor for possible excessive weight loss and used to calculate BMI. At clinic visits, a physician will assess participants for signs and symptoms of adverse effects of lorcaserin, noting which if any symptoms are present, the severity of the symptoms, make adjustments to study medication dose, discontinue study medication, or withdraw the participant from the study if needed.

Female participants who are engaging in sexual activity with men must use adequate methods of contraception which will be discussed repeatedly during the screening process. Serum pregnancy tests will be conducted during screening and urine pregnancy tests will be performed monthly during the study. If a female participant does become pregnant or wishes to become pregnant, study medication will be immediately discontinued, she will be withdrawn from the study, and offered continuing nonpharmacological treatment (psychotherapy).

3) Procedures to Minimize Other Risks:

With regards to the risks of blood draws, only staff trained in phlebotomy will draw blood from participants to minimize risks of infection. Participants will be warned of the possible associated discomfort and slight bruising following blood draws. They can decline blood draws at any time.

We aim to reduce the risk of using cash reimbursements and incentives to buy drugs by keeping reimbursements at a low monetary value. The monetary incentives for completion of study related activities are felt to be modest, appropriate, and limited. This payment schedule has been used successfully in treatment studies in our clinic and others with no observed effect of increased drug use.

With regards to risks associated with interviews, rating scales, and questionnaires, patients are informed that they may refuse to answer any questions and may ask to stop at anytime. If participants become upset during the interviews/assessments, assistance will be made available to them.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
In the course of treatment, patients may divulge information which is sensitive and may 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 consent. Contact with family members or significant others is made only with the patient's express consent. All mainframe computer and microcomputer data is stored without names or other uncoded identification. Patients will be identified only through a numerical code in both the mainframe and microcomputer databases, while a paper code list will be kept under lock and key by the PI and the Research Assistant. A Federal Certificate of Confidentiality will be obtained.
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 will receive up to 12 weeks of free treatment. A complete physical and psychiatric evaluation will be performed free of charge.

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 study, participants will be given **$20 for each study visit.** Additionally participants will receive $10 for returning study medication bottles (5 weeks of study medication) . Participants could earn as much as $410 total over the course of the study.

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