Study: # 7764 entitled An Open-Label Pilot Study of Sublocade as Treatment for Opiate Use Disorder

PI: John Mariani, MD
NCT# NCT03861338
Protocol approved: 2-27-2019

New York State Psychiatric Institute

Institutional Review Board

February 27, 2019

To: Dr. John Mariani

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

Subject: Approval Notice

Your protocol # **7764** entitled: **AN OPEN-LABEL PILOT STUDY OF SUBLOCADE AS TREATMENT FOR OPIATE USE DISORDER** Protocol version date 02/27/2019 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **February 27, 2019 to January 27, 2020.** (Reviewed at the Full Board meeting on January 28, 2019.)

Consent requirements:
☐ Not applicable:
√ 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 (internal U54DA03784201; NIDA U54DA037842-01 subcontract to CU)

Encl: CF (version date 2/11/2019 in compliance with revised Common Rule), HIPAA

EN/AHW/alw

Signed copy on file at IRB

Protocol Title:
An Open-Label Pilot Study of Sublocade as Treatment for Opiate Use Disorder

Version Date:
02/27/2019

Protocol Number:
7764

First Approval:
02/27/2019

Clinic:
Substance Treatment And Research Services (STARS)

Expiration Date:
01/27/2020

Contact Principal Investigator:
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Co-Investigator(s):
Frances Levin, 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.
This project is a single-site trial.

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
✓ Use of Investigational Drug or Device
✓ 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?
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?
Yes
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
✓ 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

Lay Summary of Proposed Research

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The proposed study is a 12-week, open-label pilot study of sublocade (extended-release burprenorphine, BXR) as treatment for opiate use disorder (OUD) testing positive for Highly Potent Synthetic Opioids (HPSO). We plan to enroll 10 participants into the study. Outpatients seeking treatment for OUD will be screened, and those eligible and consenting will be inducted onto sublingual buprenorphine (target dose 16mg to 24mg). On the fourth day after starting the buprenorphine induction, participants will receive BXR 300mg by subcutaneious injection. Participants will be seen twice per week for urine collection for toxicology and research assessments and will have Medication Management counseling weekly during one of these visits. BXR will be administered monthly and dosing will be according to the FDA prescribing instructions of 300mg for the second dose and 100mg for the third. The aim of this study is to determine if BXR injection using standard dosing is a feasible treatment for patients with OUD who are positive for HPSO.

Background, Significance and Rationale

Background, Significance and Rationale

The US opioid epidemic continues to evolve with high-potency synthetic opioids (HPSO) now driving higher overdose fatality rates. There has been a five-fold increase in the US HPSO fatal overdose rate from 2013 (3,105) to 2016 (approximately 20,000) out of the approximately 42,000 overdose deaths due to opioids. Fentanyl analogs and other high-potency synthetic opioids (e.g., U-47700) are now commonly found in heroin and counterfeit prescription painkiller pills. In New York City, approximately one-half of all overdose deaths in 2017 involved fentanyl analogues. The high potency (e.g., carfentanyl is 10,000 times more potent than morphine) of these agents presents a new challenge for clinical treatment. Due to the rapidly changing nature of the illicit drug supply, the effectiveness of commonly used pharmacotherapies for opioid use disorder (OUD) (e.g., buprenorphine, methadone, naltrexone) in treating users of high-potency synthetic opioids is unknown. Experience at our research clinic in New York City is that nearly 80% of patients self-reporting heroin use are positive for fentanyl analogs, typically without their knowledge. Our experience with an ongoing clinical trial utilizing buprenorphine and extended-release injectable naltrexone is that the use of these treatments is more problematic in patients with OUD who test positive for fentanyl analogues, and our success rates are lower than compared to our own historical clinical trial controls. The increasing number of overdose deaths combined with lower efficacy of standard therapies creates an urgent need to develop new strategies for the HPSO using patient.

Despite the known effectiveness of buprenorphine sublingual (BSL) maintenance treatment, retention and continued non-prescribed opioid use remain significant limitations. Two recent large trials comparing BSL to other OUD pharmacotherapies found that around 50% or more of patients treated with BSL dropped out of treatment by 3 to 6 months. The first long-acting injectable buprenorphine (Sublocade™) became commercially available in 2018 after receiving an FDA Fast Track and Priority Review designation. This monthly buprenorphine formulation, which is available in two doses (100 mg and 300 mg), can achieve serum buprenorphine concentrations in excess of that achieved by BSL 24 mg per day. Moreover, if an unexpected drug holiday is experienced, at two weeks past the injection due date, μ-opioid receptor remains above 70%, providing some measure of protection against relapse to opioid use. While the Sublocade™ buprenorphine extended-release (BXR) injection product has not yet been compared to BSL treatment for the treatment of OUD, the pharmacologic advantages of BXR can be expected to improve treatment retention and outcome. The extended-release injection aspect should improve compliance and reduce relapse by providing more continuous buprenorphine serum levels as compared to the sublingual formulation. We hypothesize that the BXR injection will have particular benefit for individuals using fentanyl analogues and other HPSO because by providing continuous therapeutic serum buprenorphine levels there will be substantially less opportunity for non-compliance and relapse. Even in the case of a delayed injection, therapeutic levels of buprenorphine will be present for up to two weeks.

We propose an open-label, uncontrolled pilot study, in which patients seeking treatment for OUD who are positive for fentanyl analogues at screening (N = 10) will be inducted onto BSL and then receive BXR injection, with a primary outcome comparison of end of study opioid use compared to baseline. To our knowledge, this would be the first trial to examine the use of this BXR injection formulation for the treatment of OUD patients positive for fentanyl analogues, and the first pharmacotherapy trial of any agent for the treatment of patients with OUD testing positive for HPSO.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Aim 1: To determine if BXR injection using standard dosing is a feasible treatment for patients with OUD who are positive for HPSO.

Primary Hypothesis: BXR treatment will be associated with decreased opioid use for OUD patients positive for HPSO. The primary outcome measure will be opioid use during the last two weeks of the study compared to baseline as measured by a combination of urine toxicology and self-report.
Secondary Hypotheses: BXR injection will be associated with reduce symptoms of craving and symptoms of withdrawal as compared to baseline.

If found promising, the results of this pilot trial would support advancement of conducting a controlled trial, with the potential to improve the effectiveness of OUD pharmacotherapy for this subgroup more vulnerable to fatal overdose.

Description of Subject Population

Sample #1

Specify subject population
Adults with OUD testing positive for HPSO
Number of completers required to accomplish study aims
5
Projected number of subjects who will be enrolled to obtain required number of completers
10
Age range of subject population
18-65

Gender, Racial and Ethnic Breakdown
We plan to enroll 10 participants into the study. Both males and females will be recruited. All eligible participants are accepted; however, past experience with recruitment for opioid use disorders suggests that the approximate gender distribution for this study will likely be 20% female and 80% male. Previous and ongoing opiate studies at STARS have had samples comprised of approximately 50% Caucasians, and 50% ethnic minorities distributed as 24% African-American and 22% Hispanic-American, and 4% other. We anticipate a similar representation in this project. We will make every effort to recruit minority patients in order to ensure the generalizability of our findings to the overall treatment population.
Description of subject population
Prospective subjects will be 10 men or non-pregnant women of any ethnicity or race, aged 18-65. Enrolled

subjects will be individuals with OUD who test positive for HPSO.

Recruitment Procedures

Describe settings where recruitment will occur
The project will be completed at the Substance Treatment and Research Services (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 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 OUD
Create or insert table to describe the inclusion criteria and methods to ascertain them

1. Individuals between the ages of 18-65	1. legal identification
2. Voluntarily seeking treatment for opioid use	2. self-report
3. Meets current DSM-5 criteria for OUD as a primary diagnosis, with at least moderate severity	3. clinical interviews; MINI assessment
4. Test positive for HPSO use	4. urine toxicology
5. Able to provide informed consent and comply with study procedures	5. clinical assessment, MMSE (individuals over 60 years old)

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	1. clinical interviews
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	2. clinical interviews
3. Methadone maintenance treatment	3. self-report; urine toxicology
4. Buprenorphine maintenance treatment	4. self-report; urine toxicology
5. Known history of allergy, intolerance, or hypersensitivity to candidate medication (buprenorphine)	5. clinical assessment,

	self-report
6. Pregnancy, lactation, or failure to use adequate contraceptive methods in female patients; male participants are required to use adequate forms of birth control as the exposure to Sublocade on sperm and subsequent fetal development are not known.	6. serum pregnancy test, self-report
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	7. clinical assessment, vital signs, laboratory tests
8. Legally mandated to substance use disorder treatment	8. self-report
9. Current physiological dependence on alcohol or sedative-hypnotics that would require a medically supervised detoxification-other substance use diagnoses are not exclusionary	9. clinical assessment
10. Individuals, who in the clinicians judgment, have a history of failed trial of buprenorphine or sublocade (e.g. history of severe opioid intoxication or overdoses despite adequate adherence to buprenorphine or sublocade), or other features of the history that strongly suggest the patient is not a good candidate for outpatient treatment with buprenorphine.	10. clinical assessment

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.
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
Dakwar, Elias, 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
Williams, Arthur
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Screening and Diagnosis: Uniform screening procedures will be used. A standardized telephone screen is followed by an appointment for those who meet general study criteria. No identifying information is recorded until the subject completes the study explanation and consent process; evaluation follows consent using standardized measures. Common, standardized intake and evaluation training will be conducted for all procedures and instruments. Points at which assessments will be made are listed in Table 1. Data collected will be entered or uploaded and maintained in the clinical trials secure electronic database and coded with a unique identifier assigned to each participant. Hospital charts, and Departmental, HIPPA-compliant Research Subject Registration System (KISMER) will, however, contain participants’ names.

Eligibility Determination via Physical Examination and Psychiatric Evaluation: Review of history, physical, and laboratory evaluations and the medical-psychiatric evaluation note lead to final determination

of eligibility will be done by the study psychiatrist trained on the protocol.

The MINI International Neuropsychiatric Interview (MINI): will be performed during screening as part of a complete psychiatric diagnostic assessment.

Medical Screening and Evaluation: Medical examination and laboratory work will follow consent. ECGs, blood draws, and urinalyses will be obtained by a lab technician. All tests are conducted using accepted clinical techniques and samples (e.g. bloods) are collected using universal precautions. Pregnancy tests will be conducted for women. A Health Survey will be conducted with special attention devoted to cardiovascular function. A cardiologist is available for STARS participants and will review any abnormal ECGs, and determine whether or not a patient can be safely enrolled in the trial.

Physiological Measures:

- *Medical History and Physical Exam:* A comprehensive medical history and physical examination will be performed during the screening process.
- *Pregnancy Testing*: Serum pregnancy testing will be performed on all females during screening and urine pregnancy tests will be performed at baseline and weeks 4, 8, and 12
- *Serum laboratory examination*: Complete blood count, electrolyte, and liver function tests will be performed during the screening process and follow up at weeks 4, 8, and 12
- *Urinalysis*: Laboratory urinalysis (glucose, protein, ketones, pH, specific gravity, and microscopic analysis) will be performed during the screening process and follow up at weeks 4, 8, and 12
- *Urine Toxicology*: Urine samples will be collected during screening and a full urine toxicology will be tested and at each study visit during the trial. Participants will provide urine twice weekly
- *Electrocardiogram (ECG)*: will be completed at baseline
- *Vital Signs and weight/BMI*: Temperature, pulse, blood pressure, and weight with calculated BMI will be measured at each visit for data collection and safety monitoring purposes.

Medication and rationale:
Study Days 1-3: Buprenorphine induction: Study procedures will begin with all participants being inducted onto BSL. For buprenorphine to be safely administered, participants must be in withdrawal from opioids. Individuals will be instructed to abstain from opioids starting at consent and begin buprenorphine medication the day after consent. The day after consent, patients will return to the STARS clinic and be administered a Clinical Opiate Withdrawal Scale (COWS). If found to be in mild withdrawal (COWS score > 6), participants will be started on buprenorphine 2 mg followed by further doses of buprenorphine up to 8 mg on day 1. Because HPSO use may lead to a delayed onset of opioid withdrawal syndrome, the first day that buprenorphine is administered may not be up to three days after a participants last opioid use. Whichever day the first dose of BSL is administered will be considered the first day of the induction. The buprenorphine dose will be advanced to a target dose of 24 mg per day on a fixed-flexible schedule, with stabilization at a lower dose if the patient does not tolerate side effects at higher doses. Adequate dosing of buprenorphine is important to its effectiveness, and 16 mg to 24 mg per day is considered the target according to most guidelines.

COMFORT MEDICATIONS: Participants will be given comfort medications to help manage their withdrawal for the first two weeks of the treatment study as needed. Comfort medications prescribed will be

clonidine, clonazepam, prochlorperazine, and zolpidem. Participants will be told that medications may cause some side effects such as sleepiness, lowered blood pressure (which may produce dizziness or a tendency to feel faint), or upset stomach. Participants will be instructed that they should use caution when driving a vehicle or operating appliances or machinery during this time.

Study Day 4: Participants will receive BXR under open-label conditions.
Maintenance Buprenorphine Dosing with BXR treatment: After successful induction onto sublingual buprenorphine, participants will receive BXR (Sublocade) 300 mg subcutaneous injection as per FDA—approved prescribing instructions. The second injection of Sublocade 300 mg will be administered 28 days later. The third injection will occur 28 days subsequent to the second injection at a dose of 100 mg.

Assessment of Side Effects and Medication Compliance: The research nurse and psychiatrist will query about side effects related to the study medication. Reported side effects and other treatment emergent events since the past visit will be recorded; additionally, the severity of the side effect/treatment emergent event, the action taken, and the continuation or resolution of the side effect/treatment emergent event will be documented.

Ongoing assessments: Participants will be asked to provide urine at each visit. They will be asked to complete self-report forms weekly throughout the treatment trial. At each visit, the research staff will monitor vital signs (heart rate and blood pressure) and inquire about medication-related side effects. The Side Effect Questionnaire consists of 2 parts: 1) self-reported side effects obtained by the nurse using an open format and 2) a checklist of symptoms rated from absent to severe, incorporating the major organ systems (e.g., gastrointestinal, neurological, cardiovascular). Serum laboratory and urinalysis will be repeated at weeks 4 and 8 of the trial. Patients may be removed from the study if they repeatedly miss study visits.

Medication Preparation and Dispensing: The New York State Psychiatric Institute Pharmacy is a dedicated, specialized facility that prepares medication for clinical trials including our ongoing STARS trials. STARS has worked exclusively with NYSPI pharmacy on ordering, preparing and dispensing medications to participants. There are a standard set of procedures with regards to this process. First medications are ordered from the pharmacy for each individual participant the week they will be dispensed. The medications provided from the NYSPI pharmacy are only from current, non-expired medication sources. The NYSPI pharmacy provides labeling on all medication bottles or kits that includes the relevant medication, study, participant, and expiration information. Before medication is dispensed to any participant, there is a standard medication dispensation checklist for quality assurance, which requires the study physician and one other staff member to confirm medication name, dosage, quantity, directions/frequency of administration, participant ID, study week, and expiration date. This is reviewed with the participant.

The co-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 co-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 co-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.

At week 12 or at the conclusion of a participants involvement in the study (if they do not stay in the study for the entire 12 weeks) they will be offered supportive therapy for one additional month or until an appropriate referral for on-going treatment is made. If they do not stay in the study for the entire 12 weeks, we will ask them to show up for the final appointment to make sure they are healthy, to complete interviews, and paperwork that were begun while they were in the study.

Medical Management Psychosocial Intervention: Phase II pharmacotherapy clinical trials should employ a psychosocial intervention to promote adherence to the study medication regimen and study visit schedule, without inflating the placebo response rate. The psychosocial intervention for this study will be Medical Management used for Project COMBINE (Anton et al., 2006), modified for opiate use disorder. All participants will have a manual-guided (Pettinati et al., 2005) supportive behavioral treatment session with the research psychiatrist each week. This psychosocial intervention facilitates compliance with study medication and other study procedures, promotes abstinence from marijuana and other substances, and encourages mutual-support group attendance. Dr. Mariani will provide ongoing supervision to other study physicians to prevent therapeutic drift. All study psychiatrists will be trained in providing Medical Management and refresher training sessions will be provided every 6 months. As director of Columbia's Substance Treatment and Research Service, Dr. Mariani has extensive experience conducting and supervising Medical Management and other similar medication adherence focused psychosocial intervention models.

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 (AEF). The signs and symptoms, time of onset, duration, severity, medical intervention, follow-up procedures, and suspected relationship to study drug will be reported. Any AE (clinical signs and symptoms or laboratory test) associated with 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, NIDA, and the Food and Drug Administration.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early 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 (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 as assessed by weekly visits with the psychiatrist, vital sign measurements, and lab testing

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

5) Substantial worsening depression or development of any active suicidality as measured with the HAM-D.

*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 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 available.

Blood and other Biological Samples

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

Laboratory evaluation: Complete blood count, electrolytes, blood chemistries, including liver function tests and routine urinalysis will be performed during the screening process, weeks 4, 8, and 12. Approximately 16 teaspoons of blood (approximately 80 ml) will be taken during the entire study. This is less than the amount given for a blood donation.

Urine Drug Testing: A urine sample will be collected at each visit (daily during the first week and twice-weekly during weeks 2-12). Each sample will be tested for naturally occurring (e.g., morphine, heroin), semi-synthetic opioids, and buprenorphine. HPSO will be tested for once weekly due to expense.

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 (twice-weekly). Each sample will be tested for naturally occurring (e.g., morphine, heroin), semi-synthetic opioids, and buprenorphine. HPSO will be tested for once weekly due to expense.

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 (Bisaga et al., 2011).

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).

Quality of Life: The Quality of Life Enjoyment and Satisfaction Questionnaire- Short From (QLES-Q-SF) is a 16-item self-report questionnaire, assessing the degree of enjoyment and satisfaction experienced by subjects in different areas of daily functioning based on a 5-point scale. It will be collected at baseline and weekly thereafter (Endicott et al. 1993).

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.

NIDA/VA Serious Adverse Event Form and NIDA Serious Adverse Event Tracking and Reporting System (SAETRS, on line): Whenever a serious adverse event occurs the event is described and reported IRB and to the NIDA project officer. SAETRS is a web-based application that helps collect, track, store, analyze and report serious adverse events (SAETRS).

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

Please attach copies, unless standard instruments are used
study assessments 1.24.19.pdf

Off label and investigational use of drugs/devices

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

Drug #1

Name of the drug
sublocade
Manufacturer and other information

Other name: Buprenophine extended-release
Manufacturer: Indivior

Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

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 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

Discharge and aftercare planning and implementation will be incorporated into the study. Participants will be given appropriate referrals when the study is completed and will be offered 4 weeks of continued meetings with the physician 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.

Participants will be offered to be transferred back to sublingual burprenorphine with clinical dosing during the 4 weeks of continued aftercare with the research physician. This discussion and decision, along with ongoing meetings with the physician will be documented in the clinical chart.

Clinical Treatment Alternatives

Clinical treatment alternatives
Participants will be informed of alternatives to participation in the proposed trial, including referrals in the community, residential or inpatient, or medical treatment.

Alternative Treatments and Procedures: The primary effective treatments for OUD are buprenorphine, methadone and XR-NTX. The effectiveness of standard OUD pharmacotherapy for individuals with OUD positive for HPSO is unknown. Participants of the proposed study will receive an evidenced-based treatment for OUD, although clinical trial participation is a more restricted treatment environment than community-based clinical treatment. Several psychotherapy methods have been shown to be effective in augmenting OUD pharmacotherapy and include: Relapse Prevention Therapy, a form of CBT; Contingency Management, a prize- or voucher-based incentive treatment; Motivational Enhancement Therapy (MET), a form of Motivational Interviewing; the combination of CBT and MET together; and family therapy. During the study, participants are permitted to seek additional help from other providers (therapists and physicians outside of the study) which will be tracked using the modified treatment services review. Patients are informed that they may request referral for other treatment options and if a participant's condition worsen (see trial exit criteria), participants will be referred for clinical treatment.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Potential risks
High potency opioids like fentanyl carry an especially high risk of overdose and death even if the participant is on medication, or the medication may not fully protect against this risk. There are several sources and types of risk. Physical risks are those associated with obtaining blood samples (which may leave bruises) and medication administration. Psychological and social risks include revelation of sensitive material. Legal risks, not associated with the study per se, are inherent in the behavior of illicit drug use. The primary source

of study related risks in clinical trials of medications stem from the medication itself. The most serious risk of study participation is that participants will lose tolerance to opioids, and this means that resuming use of opioids after detoxifying could cause death. Buprenorphine will help protect against death due to opioid overdose, but ceasing buprenorphine and restarting opioids would result in accidental overdose and be fatal.

The following summarizes relevant information from the FDA approved prescribing information for buprenorphine sublingual tablets and the injectable formulation of buprenorphine (Sublocade®).

Risks associated with buprenorphine treatment
Risks of BXR (Sublocade™): There is a risk of serious harm or death with intravenous administration BXR, which is designed for subcutaneous injection. There is a risk of a localized skin reaction (pruritis) or pain at the injection site.

Risks of buprenorphine (BXR and BSL): Addiction, abuse, and misuse are important risks of buprenorphine: Buprenorphine can be abused in a manner similar to other opioids. Life-threatening respiratory depression and death have occurred in association with buprenorphine. There is a potential danger of self-administration of benzodiazepines of other CNS depressants while under treatment with buprenorphine. There is a risk of opioid withdrawal with abrupt discontinuation: Buprenorphine treatment is associated with a risk of hepatitis. Adverse reactions commonly associated with buprenorphine are constipation, headache, nausea, vomiting, increased hepatic enzymes, and fatigue. There is an increased risk of opioid withdrawal symptoms if the medication is initiated too soon after last opioid dose. Buprenorphine has a risk of opioid related side effects--e.g. nausea, constipation, sedation, respiratory depression (particularly when combined with alcohol or other sedating drugs); worsening of opioid use disorder if the medication does not prove effective or is discontinued by the patient, including functional impairment as well as risk of death from drug overdose.

Risk associated with the combination of buprenorphine and other opioids: There is also the possibility of unexpected reaction if patient's in the study use street opioids or other illicit drugs along with buprenorphine. This risk will be mitigated through weekly medical follow-up with patients throughout the study at medication management sessions which will include a formal assessment for adverse events at each medication management visit. Should unexpected adverse events occur, the study physician will use clinical judgement and shared decision making with the patient to determine the best course of action including lowering or discontinuing buprenorphine.

Pregnancy: Buprenorphine is a Pregnancy Category C agent, although the safety of buprenorphine in pregnancy has been supported in clinical trials (Zedler et al. 2016). Male and 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. There are risks of exposure to Sublocade on sperm and subsequent fetal development are not known. Serum pregnancy tests will be evaluated at baseline and urine for pregnancy will be tested as clinically indicated during treatment according to standard clinical procedures. If a female patient does become pregnant she will be exited the trial and offered continuing treatment with methadone or buprenorphine in a clinical setting, which are the current treatments of choice for pregnant opioid dependent patients.

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.

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

Procedures to Minimize Study Medication 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.

2) Study Procedures

Participants will be informed about the possible side effects and risks (listed above) of taking BXR or BSL both alone and in combination with other medications, alcohol, or illicit drugs through extensive discussions with staff psychiatrist(s) during the consent process. Participants will be monitored closely with urine drug tests and collecting use episodes each time they attend the clinic. If relapse occurs participants will be given referrals for methadone, buprenorphine maintenance, or inpatient detoxification and follow-up treatment if deemed necessary.

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 intoxication and potential for medication misuse. 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. At clinic visits, a physician will assess participants for signs and symptoms of adverse effects of buprenorphine, noting which if any symptoms are present, the severity of the symptoms, make adjustments to study medication dose, discontinue study medication, or withdraw participant(s) 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, she will be withdrawn from the study, and offered clinical referrals in a community-based setting.

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 such as cannabis by keeping reimbursements at a low monetary value. 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 any time. If participants become upset during the interviews/assessments, assistance will be made available to them.

Participants will be notified that there may be a delay of up to 2 weeks after screening before treatment begins.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
A Certificate of Confidentiality has been acquired 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 have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There are no direct benefits to the participants. The participant 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 BXR treatment in combination with medical management. 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 $10 in cash per visit for transportation costs for attending study visits for the study period of 12 weeks. The maximum amount over the 12 weeks they may potentially earn for attending all study visits is $270.

References

References
upon request

Uploads

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