DOCUMENT COVER PAGE

Buprenorphine as Adjunct to Outpatient Induction onto XR-naltrexone (Vivitrol)

Study Protocol

NYS PI IRB #7456

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Protocol Title:
Buprenorphine as Adjunct to Outpatient Induction onto Vivitrol

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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 proposing an amendment only to an existing protocol

Division & Personnel

Division

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

Unaffiliated Personnel

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

Amendment

Describe the change(s) being made
1. Add the Risk Assessment Battery (RAB) to the list of self-reports that participants will complete.

2. Add a optional short, semi-structured interview at the end of treatment exploring the risk factors described by the RAB with a greater emphasis on the motivation behind risky behaviors—and lack of motivation behind others—especially in relation to naltrexone treatment. This interview will be audio recorded with the participant's written consent. Participants who choose to participate in the interview will receive $40 compensation.

3. A consent for audio recording has been added to the Consent form.

4. The compensation for the optional interview has been added to the consent form and the compensation section of the PSF.

Provide the rationale for the change(s)
Additional assessments.
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
None
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
1. A consent for audio recording has been added to the Consent form.

2. The compensation for the optional interview has been added to the consent form

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

Population

Indicate which of the following populations will be included in this research
✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Adults over 50
✓ Individuals with HIV/AIDS

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
Gift account at RFMH
Is the project externally funded or is external funding planned?
No

Study Location

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

Lay Summary of Proposed Research

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We will enroll 30 opioid-dependent participants into an open-label pilot outpatient study of methods to facilitate induction and stabilization onto XR-NTX. There will be three different methods of XR-NTX induction.

Procedure 1: 5-day induction with 1 day of BUP (8 mg) followed by washout day and 3 days of oral NTX titration. Participants will receive XR-NTX on day five together with BUP 4 mg, and will continue receiving BUP for 4 weeks until they receive 2nd XR-NTX dose.

Procedure 2: 10-day induction with BUP 8 mg administered on Day 1 and 4 mg administered starting day 2 and increasing daily doses of NTX beginning on day 2 (0.25, 0.5, 1, 2, 3, 6, 12, 25). On day 10 participants will receive XR-NTX dose, and another one 4 weeks later. No BUP will be given beyond day 10.

Procedure 3: 10-day induction with BUP 8 mg administered on day 1 and 4 mg administered starting day 2 and increasing doses of NTX beginning on day 2 (0.25, 0.5, 1, 2, 3, 6, 12, 25). On day 10 participants will receive XR-NTX dose, and another one 4 weeks later. BUP 4 mg/d will continue for 4 weeks until the 2nd XR-NTX dose.

All participants will receive weekly therapy with a study psychiatrist. All participants will receive open-label medication.

We will first enroll all participants into Procedure1 followed by Procedure 2 and Procedure 3.

The primary outcome of this study will be percentage of patients who receive the second injection of XR-NTX, Secondary outcomes will include measure of opioid withdrawal and illicit opioid use.

Background, Significance and Rationale

Background, Significance and Rationale

Agonist-based strategies (methadone and buprenorphine) have dominated the treatment of opioid dependence in the US for the last 40 years. However, agonists are not effective for all patients, as many individuals continue abusing opioids or other drugs during agonist maintenance and drop out of treatment (Reece, 2009). As compared to methadone, treatment using buprenorphine is safer and more feasible, although effectiveness and limitations of both medications are generally comparable with treatment retention rates of 35-40% at 6 months (Hser et al., 2015).

The main alternative to agonist-based approach is treatment with the opioid antagonist naltrexone, which has been used in its oral form for the treatment of opioid dependence since 1984. The approval of long-acting (XR) injectable naltrexone (XR-NTX) in 2010 represents a substantial advance, circumventing the need for daily medication adherence, a major challenge with oral preparations. Naltrexone blocks the effects of opioids, while producing no agonist effects itself. Since naltrexone acts by a different mechanism it may be helpful to patients who are not suitable or interested in agonist maintenance, or have failed prior trials of agonist due to side effects or continuing use. However widespread implementation of naltrexone treatment has been limited by: 1) difficulties transitioning patients at the outset of treatment from opioid use onto naltrexone, and 2) persisting withdrawal-like symptoms that some patients experience which may contribute to the dropout prior to the second monthly injection.

Naltrexone can only be started after the completion of opioid withdrawal, which itself is uncomfortable and many patients relapse before achieving long-enough abstinence. Procedures for rapid transition to naltrexone by combining detoxification with oral naltrexone induction may decrease the wait time before the first injection but are labor intensive because of the need to frequently adjust adjunctive medications in response to precipitated withdrawal. As a result, the dropout rate in the first few days is high, and burden on staff is substantial, both factors limiting the clinical feasibility of this approach (Gowing et al., 2009). Decreasing the severity of withdrawal patients experience during the first days in treatment may allow more patients to receive the first injection.

We propose to test a new method of transitioning patients from opioid agonist onto antagonist that may have higher tolerability. It involves maintaining patients on a dose of BUP that will block craving and withdrawal while gradually increasing dose of naltrexone until a final blocking dose is reached. Slow increase of naltrexone will likely minimize the severity of withdrawal.

Some patients continue experiencing withdrawal-like symptoms during the first few weeks after receiving XR-NTX. The common strategy to manage them involves administering adjunctive medications such as clonazepam, clonidine, zolpidem trazodone etc. It has been observed that adding buprenorphine after the patient received a full blocking dose of naltrexone will not produce mu opioid agonist effect (as it is blocked

by naltrexone) but kappa antagonist effects of buprenorphine will remain which may decrease craving and residual withdrawal symptoms and therefore will help patients to stabilize on XR-NTX.

Improved strategies of naltrexone induction and stabilization will permit expansion of its use to populations that currently opt for psychosocial-only approaches or those who chose to terminate treatment with agonists.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

The goal of this pilot study is to test three new outpatient procedures to facilitate transition onto a long-acting, injectable form of naltrexone 380 mg (XR-NTX) in opioid-dependent individuals who are actively using opioids and are seking treatment with naltrexone.

We are proposing to enroll 30 opioid-dependence participants, 10 into each of three procedures, for an open-label study of relapse prevention. We will enroll the first 10 participants in Procedure 1, the next 10 in Procedure 2, and the last 10 in Procedure 3. Treatment will be delivered in an outpatient setting including a phase of outpatient opioid withdrawal, followed by XR-NTX injection and another XR-NTX injection 4 weeks later. In addition, patients will receive a psychosocial intervention that will include elements of motivational interviewing and cognitive-behavioral relapse prevention therapy.

The primary aim is to test the the feasibility, safety and efficacy of the new methods to improve tolerability of naltrexone induction and reducing attrition during detoxification and the first month of naltrexone treatment.

Primary Hypothesis 1: Adjunctive treatment with buprenorphine 4 mg during the first 5 weeks of naltrexone maintenance will improve opioid abstinence and treatment retention, defined as receiving the second XR-NTX injection.

Primary Hypothesis 2: Providing buprenorphine 4 mg daily during gradual 9-day titration of oral naltrexone will improve tolarability and success of XR-NTX induction, defined as receiving the first XR-NTX injection.

Primary Hypothesis 3: Providing buprenorphine 4 mg daily during gradual 9-day titration of oral naltrexone and adjunctive treatment with buprenorphine 4 mg during the first 5 weeks of naltrexone maintenance will significantly improve opioid abstinence and treatment retention, defined as receiving the second XR-NTX injection.

Primary Aim 4: To examine in biofluid-derived extracellular vesicle content for the existence of biomarkers related to naltrexone treatment.

Description of Subject Population

Sample #1

Specify subject population
Adults with current Opioid Use Disorder
Number of completers required to accomplish study aims
15
Projected number of subjects who will be enrolled to obtain required number of completers
30
Age range of subject population
18-60

Gender, Racial and Ethnic Breakdown
Both genders and all ethnic groups are eligible. It is estimated that the sample will be 60% male, 40% female, 50% Caucasian, 30% Hispanic-American,15% African-American, and 5% other minorities based on data from previous trials.
Description of subject population
Prospective participants must be adult (18 to 60 years of age) and meet criteria for current opioid use disorder by history and urine toxicology. Other substance use diagnoses are not exclusionary since multiple substance abuse is common in this population, and such an exclusion would rule out a large proportion of the population and limit the generalizability of the study. However, physiological dependence on alcohol or sedative-hypnotics with impending withdrawal is exclusionary. Maintenance on methadone or other long-acting agonist (e.g. buprenorphine) or regular use of illicit methadone (> 30 mg per week) is exclusionary. Prospective participants cannot have concurrent psychiatric or medical conditions that would interfere with

participation (e.g. mania, psychosis, suicidality, pregnancy or failure to use adequate contraception).

Recruitment Procedures

Describe settings where recruitment will occur
All potential participants will be evaluated at the **BSU** 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 Master's level therapist for a screening evaluation and mental status examination as part of routine admission procedures or BSU clinic . Patients who 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, 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
Please provide the NCT Registration Number
NCT03113409

Concurrent Research Studies

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

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Adults with current Opioid Use Disorder ages 18-60
Create or insert table to describe the inclusion criteria and methods to ascertain them

1) Age 18-60. (Clinical interview)

2) Meets DSM-5 criteria for current opioid use disorder (moderate-severe) of at least six months duration, supported by urine toxicology OR COWS score > or =6 OR Naloxone Challenge . (Clinical & MINI Interview; urine toxicology or COWS score > or = 6 OR Naloxone Challenge (see Procedures))

3) Voluntarily seeking treatment for opioid dependence. (Clinical interview)

4) In otherwise good health based on complete medical history and physical examination (Clinical interview and physical examination; vital signs, ECG, laboratory tests (hematology, blood chemistry, urinalysis) within normal ranges (AST or ALT < 3 times normal).)

5) Able to give written informed consent. (Clinical interview and mental status exam)
Create or insert table to describe the exclusion criteria and methods to ascertain them

1) Methadone maintenance treatment or regular use of illicit methadone (> 30 mg per week). (Clinical interview; urine toxicology)

2) Maintenance on, or regular use of buprenorphine or other long-acting narcotic agonists. (Clinical interview; urine toxicology)

3) Pregnancy, lactation, or failure in a sexually active woman to use adequate contraceptive methods. (Clinical Interview, physical examination, urine pregnancy test during screening, serum pregnancy test at screening, and urine test on day of administration of XR-NTX)

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

5) Active psychiatric disorder which might interfere with participation or make participation hazardous, including DSM-5 Schizophrenia or any psychotic disorder, severe Major Depressive Disorder, or suicide risk or 1 or more suicide attempts within the past year. (Clinical and MINI interview, clinical mental status examination, discussions with previous psychiatrist or treatment provider if formerly in treatment.)

6) Physiologically dependent on alcohol or sedative- hypnotics with impending withdrawal. Other substance use diagnoses are not exclusionary. (Clinical & MINI interview; urine toxicology)

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

8) Chronic organic mental disorder (e.g. AIDS (CD4 count under 200 currently or medically ill with an opportunistic infection) dementia). (Clinical interview, mental status, physical and laboratory examination)

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

10) Painful medical condition that requires ongoing opioid analgesia or anticipated surgery necessitating opioid medications. (Clinical interview, physical examination)

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
Potential participants will sign a 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. Pregnancy tests will be conducted for women.
Describe Study Consent Procedures
After the screening evaluation, the study physician will review the study inclusion/exclusion criteria to determine if the participant is eligible for the study based on the screening materials. If the participant is eligible for the study, they will be given the consent form to read, and review with the consenting physician. The study consent will only be signed after all of the participant's questions are asked, and after all the risks and benefits are explained to and understood by the participant. Study related procedures will only be initiated after the consent form is signed by both the participant and consenting physician.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Bisaga, Adam, MD
Brezing, Christina, MD
Evans, Elizabeth, MD
Kidd, Jeremy
Levin, Frances, MD
Luo, Sean, MD
Mariani, John, MD
Naqvi, Nasir, MD
Nunes, Edward, MD
Shulman, Matisyahu, MD
Vaezazizi, Leila
Williams, Arthur
Type in the name(s) not found in the above list
Derek Blevins, MD
Jonathan Wai, MD

Study Procedures

Describe the procedures required for this study

All three procedures will be conducted under similar conditions. During the first study visit (Day-1), study inclusion/exclusion criteria will be reviewed and participants will be consented into the study. Participants will be instructed to remain abstinent from opioids for at least 16 hours, until the next morning. Adjunctive medications (clonidine, clonazepam, trazodone/zolpidem) as well as behavioral strategies to minimize withdrawal symptoms during opiate deprivation will be offered.

During the 5-day induction (Procedure 1) or the 10-day induction (Procedures 2 and 3) participants will be assessed daily Monday to Friday for opioids and other substance use (urine toxicology and self-report), vital signs, opioid withdrawal symptoms, and opioid craving. Study medications (buprenorphine and naltrexone) as well as adjuvant medications to alleviate opioid withdrawal (clonidine, prochlorperazine, and clonazepam) will be administered on site during the weekdays and taken by the patient at home during weekend days. All medications will be administered in an open-label manner and dispensed to take home as needed on a daily basis during the detoxification week.
Patients will be required to visit the clinic daily and remain there for at least 1.5-2 hours to permit close monitoring, with an option to stay as long as necessary to achieve relief of symptoms and medical stability prior to being discharged home. During study visits, participants will be evaluated clinically by a research nurse and physician prior to dose administration and monitored on site for up to 8 hours. Transportation home will be provided by car service for patients experiencing drowsiness or medication side effects. During evenings and weekends, participants will have access to a 24-hour physician coverage service, staffed by research psychiatrists familiar with this protocol.

Patients will have their vital signs checked at the beginning of the induction visit (prior to medication dosing) and again at the end of the visit. At the start of each visit and prior to administration of medication, a baseline COWS and SOWS assessment will be obtained. COWS and SOWS assessments will be repeated at approximately 30 minutes after administration of buprenorphine 4mg (prior to administration of naltrexone), and 60 minutes after administration of naltrexone.

Procedure 1:

Design
Patients will undergo an outpatient buprenorphine-clonidine-naltrexone procedure to initiate treatment with XR-naltrexone (XR-NTX) as developed at STARS (Sullivan et al., in print). At the end of the procedure, after the injection of XR-NTX participants will begin treatment with buprenorphine 4 mg/d for 4 weeks, after which they will receive another injection of XR-NTX and will continue with buprenorphine for additional 4 days up to the total of 5 weeks of buprenorphine.
Rationale
Adding buprenorphine after the transition onto XR-naltrexone will not produce any significant opioid agonist effect (as it will be blocked by naltrexone) but will add an additional kappa antagonist effect which may help alleviate residual/protracted withdrawal symptoms. This is a replication study of the method previously published by Gerra et al. (2006) with oral naltrexone.
Study Medications Dosing
On the morning of Day 1, participants will receive 2 mg of buprenorphine, to be followed by a second dose after 1-2 hours. Participants will receive a total of 8mg of buprenorphine on Day 1. One washout day follows which includes administration of adjuvant medications. On Day 3, after pre-treatment with prochlorperazine 10mg for nausea, the first dose of naltrexone 1 mg is given, followed by ascending doses titrated gradually, as tolerated, to 25 mg on Day 5. Adherence will be supported by observed ingestion of powdered doses of naltrexone as suspension in water. Participants will receive XR-NTX on Day 5 together with buprenorphine 4mg, and will continue to receive BUP 4 mg/d for 4 weeks until they receive the 2nd XR-NTX dose. Participants will receive the total of two doses of XR-NTX.

Participants will receive 8mg buprenorphine on Day 1 of the detoxification, and following administration of XR-NTX will receive 4mg buprenorphine daily for four weeks of outpatient treatment. All participants will be receiving a sublingual tablet once daily. Buprenorphine will be discontinued the day after the 2nd injection of XR-NTX. Buprenorphine will be given once daily, starting after administration of 25mg of naltrexone. The dose of 4 mg will be continued at the 4mg until administration of 2nd XR-NTX dose. Following the second XR-NTX injection buprenorphine dose will be decreased to 2 mg for 4 days after which it will be stopped.

Adjuvant medications for Procedure 1 include: Clonidine 0.1 mg QID (MDD=0.4 mg), clonazepam 0.5 mg QID (MDD=2.0 mg), prochlorperazine 10 mg QD, trazodone 100 mg HS, and zolpidem 10 mg HS. Clonidine will be held if blood pressure falls below 90/60 mm Hg at any visit's vitals check. Adjuvant medications will be offered for one week following administration of XR-NTX as needed for persistent withdrawal symptoms.
If opioid use occurs in combination with missed doses of naltrexone, a naloxone challenge will be administered to confirm that the next dose of 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, more severe dependence (> 6 bags per day), or a strong reaction to the first dose of naltrexone), the procedure may be slowed down by 1 or 2 days. Once a patient has tolerated a first daily dose of naltrexone 25 mg, he/she is eligible to receive XR-NTX 380 mg IM on Day 5.

Procedure 2:

Design
Patients will undergo a modified outpatient buprenorphine-clonidine-naltrexone procedure to initiate treatment with XR-naltrexone (XR-NTX). During a 10-day procedure, oral naltrexone will be very slowly titrated upwards to the full dose of oral naltrexone but buprenorphine will remain at the same dose of 4 mg a day starting on Day 2. At the end of the procedure, participants will receive the injection of XR-NTX, and the second XR-NTX injection will be administered 4 weeks later. No buprenorphine will be given beyond Day 10.

Rationale
We hypothesize that a gradual titration of naltrexone while maintaining stable does of buprenorphine will allow for a transition from an opioid agonist to an opioid antagonist state with minimal withdrawal severity. Based on our extensive experience administering low-doses of naltrexone we believe that repeated administration of very low-doses of naltrexone with 1-day dosing interval should not precipitate severe withdrawal. Because of the long-duration of receptor binding naltrexone will accumulate at the receptor and over time it will replace the buprenorphine at the receptor.
This is a variation of the methods decribed by Resnick et al., (1977) and Hammig et al., (2016). Resnick gave increasing doses of naloxone over 1-2 days to participants who stopped methadone maintenance (and presumably still had methadone present in their brain when naloxone was given). The severity of precipitated withdrawal was decreasing with each subsequent naloxone dose and at the end of the procedure participants had negative naloxone challenge and received oral naltrexone 100 mg. This method was further elaborated by Charney et al., (1982) who administered increasing doses of naltrexone over 4-day period to participants who were maintained on methadone (20-30 mg/d) prior to this procedure.

Hammig described a "Bernese Method" where small doses of buprenorphine are titrated upward while the subject continues taking full agonist (Hammig et al., 2016). While in the Bernese method, opioid agonist is stopped once the therapeutic dose of buprenorphine is reached we will continue administering buprenorphine even after the full blocking doses of naltrexone is reached as it is known that buprenorphine can be safely administered in combination with naltrexone in participants who were first treated with naltrexone.

We have experience (30 participants) administering buprenorphine 8 mg for 1 day followed by a day of washout and increasing doses of naltrexone for 2 days with a full blocking dose of naltrexone reached on day 3

We hypothesize that with a very slow and gradual upwards titration of naltrexone while the participant receives overlapping buprenorphine we will avoid the precipitation of severe withdrawal and will be able to arrive at the blocking dose of naltrexone 25 mg/d followed by an injection of XR-naltrexone.

Study Medications Dosing

On the morning of Day 1, participants will receive 2 mg of buprenorphine, to be followed by a second dose after 1-2 hours. Participants will receive a total of 8mg of buprenorphine on Day 1. Patients will then receive 4mg of buprenorphine on Days 2-10. Beginning on Day 2 participants will receive increasing doses of naltrexone 30 minutes after the dose of buprenorphine 4 mg has been administered, starting with 0.25mg titrating up to 25mg on Day 10 (Day 2:0.25mg; Day 3: 0.5mg; Day 4: 1mg; Day 5: 2mg; Day 6: 3mg; Day 7: 6mg; Day 8: 12mg; Day 9: 25mg; Day 10: 25mg. On Day 10 participants will receive a dose of XR-NTX, and a 2nd dose 4 weeks later. No buprenorphine will be given beyond Day 10.

Procedure 3:

Design
Procedure 3 is a combination of procedure 1 (BUP 4 mg/d given in combination with XR-NTX) and procedure 2 (slow titration of oral naltrexone while maintaining stable BUP dose).

Rationale
This is a combination of Procedure 1 and 3
Study Medications Dosing
On the morning of Day 1, participants will receive 2 mg of buprenorphine, to be followed by a second dose after 1-2 hours. Participants will receive a total of 8mg of buprenorphine on Day 1. Patients will then receive 4mg of buprenorphine on Days 2-10. Beginning on Day 2 participants will receive increasing doses of naltrexone 30 minutes after the dose of buprenorphine 4mg has been administered, starting with 0.25mg titrating up to 25mg on Day 10 (Day 2:0.25mg; Day 3: 0.5mg; Day 4: 1mg; Day 5: 2mg; Day 6: 3mg; Day 7: 6mg; Day 8: 12mg; Day 9: 25mg; Day 10: 25mg. Participants will receive XR-NTX on Day 10 together with buprenorphine 4mg, and will continue to receive buprenorphine 4mg for 4 weeks until they receive the 2nd XR-NTX dose. Following the second XR-NTX injection, the buprenorphine dose will be decreased in Study Week 5 to 2 mg for 4 days after which it will be stopped.
If a significant withdrawal symptoms emerge during the naltrexone titration, the next dose of naltrexone will be repeated (rather than doubled) and therefore the procedure may be slowed by 1-3 days. Once a patient has tolerated a first daily dose of naltrexone 25 mg, he/she is eligible to receive XR-NTX 380 mg IM.
Adjuvant medications (Procedures 2 & 3)
We believe that there will be less withdrawal symptoms in participants receiving buprenorphine therefore we will us lower standing doses of medications with the option to administer additional doses as needed for breakthrough withdrawal. We will administer Clonidine 0.1 mg BID and clonazepam 0.5 mg BID daily. Additional doses of clonidine 0.1 mg (MDD=0.4 mg), clonazepam 0.5 mg (MDD=2.0 mg), prochlorperazine 10 mg QD, trazodone 100 mg HS, and zolpidem 10 mg HS will be administered as needed. Clonidine will be held if blood pressure falls below 90/60 mm Hg at any visit's vitals check. Adjuvant medications will be offered for one week following administration of XR-NTX as needed for persistent withdrawal symptoms.

Treatment Period

Adherence to oral naltrexone
All doses of buprenorphine and oral naltrexone will be directly observed when possible. If a significant withdrawal symptoms emerge during the naltrexone titration, the next dose of naltrexone will be repeated

(rather than doubled) and therefore the procedure may be slowed by 1-3 days.

XR-NTX Injections
XR-NTX will be administered on either Day 5 (Procedure 1), or Day 10 (Procedures 2 & 3), as an intramuscular injection (380 mg) in one buttock by one of the research psychiatrists or research nurses of the clinic, who are currently trained and administer XR-NTX in other protocols. All participants will be required to remain at the clinic for 1 hour of observation following the first injection, to monitor vital signs and to observe for any increased withdrawal symptoms or side effects. At the beginning of Week 4 (4 weeks post-XR-NTX injection) participants will receive a second injection of XR-NTX.

Procedures for Missed Doses of XR-NTX
If the patient misses a scheduled second injection and takes an opioid during at least two of the seven days following the date of the scheduled injection, relapse will be suspected, and we will perform a naloxone challenge, if appropriate, using 0.8 mg naloxone, administered intramuscularly. The patient is followed clinically and withdrawal symptoms are assessed over the next hour. If the challenge is negative, the administration of XR-naltrexone will be resumed. If fully positive, the patient will have relapsed as XR-naltrexone may precipitate significant withdrawal so it cannot be resumed. However, because there are blood levels and partial blockade beyond 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 72 hours, or escalating doses of oral naltrexone over 3 days will be attempted, and if tolerated, the next injections can be given. Patients who fail two consecutive naloxone challenges are considered to have relapsed and are referred for inpatient detoxification or agonist maintenance, as deemed clinically appropriate and in accordance with the patient's wishes.

Missing a scheduled second XR-NTX injection is the most important threat to the success of XR-naltrexone maintenance. In the event of a patient missing a scheduled injection, the clinic staff will immediately attempt to contact the patient to re-establish commitment to the naltrexone treatment and reschedule the injection within a 24-48-hour period. If the patient cannot attend the treatment clinic within that two-day 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.
Use of opiates presents concerns in the management of patients receiving XR-naltrexone. Failure mode with XR-naltrexone is that a patient misses a scheduled injection, resumes heroin, and becomes re-dependent. However, because of the long duration of action of XR-NTX (full blockade lasts up to 5 weeks after the last injection) a grace period of at least 7 days can be expected during which the inection can be rescheduled without risk of relapse.

Study Visits
Participants will be seen in the clinic daily on weekdays during the induction phase (Days -1- 10) and two times per week during weeks 1-8. Once XR-NTX has been administered, outpatient Week 1 will start. At each visit the patient will meet with the research assistant to complete research ratings. Research nurse collects safety measures, inquires about side effects, and obtains a urine sample under observation. Side effects of study medications are reviewed weekly during the visit with a research psychiatrist, or more frequently if clinically indicated, and study psychiatrist will adjust medication dose if necessary. At the completion of all activities for the visit, a $15 voucher is offered to the patient to reimburse the costs of transportation and the time taken to complete study-related assessments.

At each visit to the clinic the patient meets with the research assistant to complete research ratings, including self-report of withdrawal, mood, and drug use. Blood samples are drawn according to the protocol for liver enzymes. The patient provides a urine sample under observation by a staff member at each visit. Our clinic is staffed by both male and female research assistants so that all urines can be appropriately monitored. The sample is tested immediately for opiates with the iScreen system (Instant Technologies, Inc.). Vital signs are also taken. All data are then brought to the therapist and therapy session is held. Liver function tests will be drawn before the second XR-NTX injection.
Participants may come to the clinic to be seen as frequently as needed. In particular, any participant who is experiencing protracted opioid withdrawal will be offered clinical contact on a frequent, even daily, basis if needed. For clinical matters arising in the evenings or on weekends, participants will have access to the 24-hour emergency telephone service, staffed by physicians familiar with this protocol who can address patients' concerns.
We will collect 4ml of saliva, 50ml of urine, and 4, 6-7ml blood from subjects at baseline and at the end of study. From these we will isolate extracellular vesicle-containing pellets and evaluate their contents using advanced -OMICs analyses, in order to identify molecular signatures that differ across subjects before and after naltrexone treatment.

Behavioral Therapy
Participants will receive counseling focused on medication adherence, education about management of withdrawal symptoms, on correct medication usage and the importance of adherence to study procedures and abstinence from any substance use outside of the protocol. All participants will receive behavioral therapy daily (Mon-Fri) during the induction phase. Physician will meet with participants during each clinic visit during the induction process and weekly afterwards. In addition therapists will meet with individuals for 30 minutes at each weekly visit offering patients support and education about the recovery process. The goals of these counseling sessions are to: educate and support the patient as he or she stabilizes on XR-NTX, provide a motivational platform to discuss pharmacological and nonpharmacological strategies for the management of opioid withdrawal symptoms, provide education regarding any medication side effects, and increase patient's motivation to adhere to the XR-naltrexone and to remain on it with the provider in the community after the completion of the study.

Transitioning to Follow-up care
Once the participant has received the first injection of XR-NTX, therapists will begin discussing the participant's plans for treatment at the end of the study. If the participant plans to continue with XR-NTX, therapists will inquire about the participant's current insurance coverage, or help the participant apply for insurance if needed. At study end, participants who have successfully completed the trial and wish to continue injectable naltrexone maintenance will be offered second XR-NTX. If the patient has difficulty transitioning to an outside provider in time for the 3rd injection, it will be offered if samples have been obtained from the manufacturer (Alkermes). Participants will be encouraged to attend 12-step and other self-help groups, as well as other treatment providers, according to the selected follow-up plan they have developed with their research therapist and Study MD by Week 7.

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 a federal

DEA research license. 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).

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Criteria for Study Dropout during Detoxification

We have operationalized the criteria for study dropout during the detoxification procedure as follows:
1. Participant is unable to tolerate oral naltrexone induction on 3 consecutive visits, as demonstrated by continued opioid use and/or failed naloxone challenge.
2. Participant refuses XR-NTX injection or demonstrates moderate or severe opioid withdrawal in response to 25 mg oral naltrexone (COWS score 13-36)
3. Participant requests withdrawal from study to receive agonist maintenance or to pursue other treatment options.
4. Participant experiences medical or psychiatric worsening of a condition deemed to make further study participation hazardous
5. Participant is absent from study visits for 5 days during the detoxification period

Criteria for Study Dropout following Detoxification

Participants who have completed the detoxification phase of the study will be withdrawn for the following reasons:
1. Relapse to opioid dependence; patient misses scheduled XR-NTX injection and resumes opioid use for more than 3 days and is unable to provide an opioid-negative urine or to pass a naloxone challenge.
2. Binges of opioid use resulting in overdose or severe somnolence, or in attempts to override the blockade.
3. Clinical deterioration rendering further study participation hazardous (e.g. significant worsening of medical or psychiatric condition, elevation of liver enzymes to >5 times normal, dangerous escalation of non-opioid drug or alcohol use).
4. Absent from study visits for 14 days or 6 consecutive visits post-XR-NTX induction, unless patient has remained blocked from opiates (i.e. within 28 days of last XR-NTX injection) and in regular telephone contact with staff.
5. If a participant has a Global or Opiate CGI improvement score of 6 or greater at any time, the participant will meet with an MD for a clinical evaluation of serious psychiatric symptoms or continued opiate use that puts the participant at harm for self-destructive behavior. Clinical judgement of continued study participation or discontinuation following the evaluation will be documented in patient's clinical chart.

Relapse is the major clinical endpoint in naltrexone studies, since the usual failure mode with naltrexone is that a patient stops taking the medicine, resumes heroin, and rapidly becomes re-dependent. In the present

trial we will adopt procedures that we implemented in other studies in **our division** that use XR-NTX (IRB # 5307, #4847) (see above for handling of lapse or relapse involving XR-NTX).

Patients who fail two consecutive naloxone challenges are considered to have relapsed and are referred for inpatient detoxification or agonist maintenance, as deemed clinically appropriate and in accordance with the patient's wishes. The Principal Investigator may also decide to administratively withdraw participants who show other clinically significant worsening of medical or psychiatric symptoms, evidence of significant discomfort related to the withholding of rescue medication, any behavior which suggests significant risk from attempts to over-ride blockade, subject request, and noncompliance with study procedures (missing at least 6 consecutive visits or 2 weeks).

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
Approximately 10 cc of blood is drawn at baseline for blood chemistries , CBC, and pregnancy(females). Since naltrexone occasionally produces reversible liver toxicity, liver enzymes (approx 5 cc) will be followed to monitor safety. Liver function tests will be drawn at baseline and and the end of the study. We will also draw 4 x 6-7 ml tubes at consent and the end of study to examine in biofluid-derived extracellular vesicle content for the existence of biomarkers related to naltrexone treatment. Additionally 50 ml of urine and 4 ml of saliva will be collected at baseline and end of study.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
MINI- International Neuropsychiatric Interview (MINI) (30 minutes) (Screening Visit)
Urine sample for toxicology (5 min) (Daily during induction phase; bi-weekly during post induction)
Clinical Global Impression Scale- Observer (CGI-O) (5 min) (Weekly)
Hamilton Depression Scale (HAM-D) (5 min) (Weekly)
Clinical Opiate Withdrawal Scale (COWS) (2 minutes) (Daily during induction phase; bi-weekly during post induction)
Subjective Opioid Withdrawal Scale (SOWS)(2 minutes)(Daily during induction phase; bi-weekly during post induction)
Systematic Assessment for Treatment Emergent Effects (SAFTEE) (3 min) (Weekly)
Concomitant Medications Form (3 min) (Weekly)
Locator Form (5 minutes) (Baseline)
Craving Scale (2 min) (Daily during induction phase; bi-weekly during post induction)
Vital Signs Nursing Form (3 min) (Daily during induction phase; bi-weekly during post induction)
End Study Form (5 min)(End of Study)
Risk Assessment Battery (RAB) (5 min) Baseline & End of study
Risk Interview (30 minutes) End of Study

Please attach copies, unless standard instruments are used

RISK INTERVIEW.pdf

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
2 weeks.
Maximum duration of delay to standard care or treatment of known efficacy
Screening, diagnostic and medical evaluation to determine eligibility are generally completed within 3 to 5 days. It may take another week to complete a longer evaluation (for example if input is needed from another treating physician), or for patients to arrange to be absent from work or family responsibilities. Clinical staff are in regular contact with patients during this time, and patients are informed of other treatment options available in the community.
Treatment to be provided at the end of the study

All participants who remain active in treatment will have an End-of-Study visit, within a week of the final study day (28 days after second XR-NTX injection), during which final ratings measures, and toxicology will be obtained. At the conclusion of the protocol, the participants will be offered supportive therapy for at least one additional month or until an appropriate referral for on-going treatment is made. If the patient is interested to continue on XR-NTX, we will try to work with the patient's insurance to provide coverage to continue XR-NTX. Most insurance plans cover Vivitrol, and we have devloped a network of providers who we have referred patients to. If the patient is unable to find a provider to administer injection but we were able to secure the medication through patient's insurance and the patient is at risk to become unblocked we will administer the injection.

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

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

maximum of 2 weeks.

Participants who did not come for a clinic visit for 14 consecutive days will be removed from the study, and the next day after their last visit will be a point of dropout.

At the End Study, or the point of dropout, the research psychiatrist will complete the End-of-Study Form indicating:
1) trial completer/noncompleter status,
2) opioid abstinent/non-abstinent status (confirmed by the urine toxicology) during the last four weeks in the trial
3) number of weeks completed
4) the reasons for early removal (if applicable)

Study Discharge/Aftercare Plan
Discharge and aftercare planning and implementation will be incorporated into the study. A formal Discharge Plan will be completed by a clinician and approved by a study physician prior to the End of Study visit. A Study Discharge Checklist (SDC; see attached) will be used to assist clinicians in planning the most appropriate disposition and to monitor patients' transition out of the research protocol and overlap of care with the subsequent provider. SDC consists of treatment response summary, pre-discharge assessment, discharge plan, and post-discharge follow-up.

Treatment response status will be operationalized as one of the following:
a. Full response: Abstinent for the duration of study, no craving
b. Delayed full response: isolated use episodes early in treatment, no craving
c. Partial response: abstinent at the end of study but with intermittent use throughout treatment, including the preceding month
d. Non-response: use and craving throughout treatment period
e. Relapse: stopping naltrexone and resumption of opioid use
Participants who are full responders (a or b) are candidates for continuing naltrexone maintenance. Partial and non-responders are candidates for agonist treatment. Participants who relapsed are candidates for inpatient detoxification or agonist treatment. Pre-discharge assessment will be used to recognize risk factors for relapse to identify patients who, in the absence of STARS-level of intensive care, are unlikely to do well on antagonist and may need to be referred to standard format of continuing treatment such as agonist maintenance.

Discussion of treatment recommendations as well as risks and benefits of accepting and refusing referrals will take place and will be documented. Such a plan will be formalized and approved by a study physician no later than 4 weeks prior to planned treatment termination (by study week 4). If a patient misses discharge-planning visits, the discharge plan will be sent to the patient in the mail .

If a patient has not made a successful transfer of care by the end of follow-up period, despite full compliance with recommendations, additional visits may be offered to enable appropriate placement. If patient is interested to continue on XR-NTX, we will try to secure medication samples from the manufacturer (Alkermes) and work with the patient's insurance to provide coverage to continue on XR-NTX.

For participants who are unable to secure follow-up treatment with another provider by Study Week 8 or before the end of the blockade of the last naltrexone injection (4 weeks after the injection), we will discuss alternative treatment options such as treatment with buprenorphine/naloxone or oral naltrexone, with a strong recommendation for treatment with buprenorphine/naloxone as the safest treatment option. If participants chose buprenorphine they will be inducted and stabilized for 1-2 weeks after which they will be referred to a provider in the community to continue treatment. If participant prefer to be treated with naltrexone, we will initiate treatment using 3 times per week dosing (100 mg on Mon, 100 mg on Wed, and 150 mg on Friday) with onsite monitoring if possible or we will involve and train a significant other for monitoring at home. During oral naltrexone maintenance we will continue efforts to transition patient onto injection naltrexone. If we have available spare doses of XR-NTX, we will offer an additional injection of XR-NTX to participants who intend to continue treatment with XR-NTX but are unable to secure a follow-up injection in time due to a delay with the participant's insurance, or scheduling with the follow-up treatment provider.

Clinical Treatment Alternatives

Clinical treatment alternatives
Naltrexone maintenance and Relapse Prevention Therapy are effective and accepted treatments for opioid dependence. The major alternatives for outpatients with opioid dependence would be either methadone or buprenorphine/naloxone maintenance, which has a high success rate for patients willing to take it; injection naltrexone maintenance without research procedures; or inpatient detoxification followed by residential treatment. Detoxification is associated with high relapse rates in the absence of antagonist maintenance.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
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 trazodone or 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 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

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.

The risks associated with buprenorphine administered to participants stabilized on naltrexone are relatively low. Naltrexone will block the majority of mu-opioid effects (Gerra et al., 2006) and therefore: 1) risk of sedation and other adverse effects related to mu-opioid receptor-mediated effects is low, and 2) it is unlikely that physiological dependence will be produced.
Buprenorphine will be dispensed daily during the induction phase, and weekly after administration of the first XR-NTX injection. Buprenorphine will be dispensed by medical staff trained in the use of opioids, and in the management of adverse effects of opioids. The doses proposed for use in the current application are rather low as compared to doses used in the treatment of opioid addiction.
The use of buprenorphine in opioid-abusing, opioid-dependent volunteers is also associated with the risk of using the medication for the purposes of achieving euphoria. If sublingual buprenorphine is crushed and used parenterally, there is an increased risk of adverse effects but, again, all acute effects should be blocked by naltrexone. Participants will be warned of this risk and advised not to use the medication in this manner. Such an event, if it were to occur, would be short-lived and not life threatening. If it is determined that patients have been abusing their buprenorphine in such a manner, they will be removed from the study and transferred to methadone maintenance. Deaths have occurred in patients who were either injecting, or taking massive oral sublingual doses of buprenorphine in combination with benzodiazepines. It is also likely that the benzodiazepines were injected in those cases. We will monitor participants for evidence of benzodiazepine abuse and remove from the study if clinically indicated.

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

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. Liver enzymes will be repeated at regular intervals over the 8-week treatment course. LA naltrexone achieves higher blood levels than oral naltrexone initially, but these should remain lower than levels associated with hepatitis.
If naltrexone-induced hepatitis were to occur in the setting of depot, 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 depot 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 **the clinic**. 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. They will be told that the reaction could resemble that experienced during the initial buprenorphine-clonidine-naltrexone procedure. Patients will be advised to report to **the clinic** 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 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 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. During the screening period, a serum (quantitative) pregnancy test will be obtained prior to administration of XR-naltrexone. 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. In addition, urine pregnancy will be tested on Day 5 or Day 10, prior to administration of XR-NTX. Patients who become pregnant during the trial will be removed from the trial and treated as clinically indicated.

Blood Tests

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

Naloxone Challenge Test

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

Intramuscular Injection of Naltrexone

XR-NTX injections may be followed by pain, tenderness, induration, abscess, sterile abscess, and pruritus. Cases of serious injection site reactions, some of which involved surgical intervention, have been reported. Participants will be evaluated for injection site reaction at each outpatient visit, and will be educated about signs and symptoms of site reaction and will be encouraged to bring it to the attention of medical staff if any of these occurs. Injection with this formulation of depot naltrexone (XR-NTX) was well tolerated in over 400 alcohol-dependent patients treated with monthly injections for 6 months in the pivotal trial leading to FDA approval for alcohol dependence (Garbutt et al 2005, Anton et al. 2006). More recently, XR-NTX has been approved by FDA for the prevention of relapse to opioid dependence, following opioid detoxification.

Risks associated with receiving vouchers or cash equivalents

During outpatient treatment participants will receive vouchers or cash equivalents, which could pose a risk of using the cash to buy drugs. In response, we have developed procedures to minimize and protect against this risk. A voucher incentive system is being used to compensate patients for their time and travel and to encourage compliance with study procedures. For that purpose we have adopted procedures used widely in the context of Contingency Management Therapy. We believe that using low-value incentives is essential to maximize participation in study-related procedures, including nursing and physician visits for safety monitoring, study outcomes collection, and therapy participation. At each visit patients will earn $15 after completing all procedures scheduled for this visit. Risks that participants will attempt to use study payments to purchase drugs, though still present, are rather small with current procedures.
Describe procedures for minimizing risks

Exclusion Criteria: The exclusion criteria of this study are designed to minimize the risks to patientparticipants. Patients are excluded if they have severe psychiatric illness (mood disorder with functional impairment or suicide risk, schizophrenia) which might interfere with their ability to participate in the outpatient therapy. A history of drug overdoses will be exclusionary. Pregnancy, lactation, or failure to practice a reliable birth control method is exclusionary, and patients are instructed to inform their psychiatrist immediately if they suspect they may be pregnant. Urine HCG is tested during screening and monthly throughout the trial. Serum (quantitative) pregnancy test will be obtained during screening. The baseline medical evaluation includes physical examination, blood chemistry profile (including liver function tests), complete blood count, urinalysis (including HCG), and electrocardiogram, urine toxicology, and naloxone challenge if opiate dependence diagnosis is unclear. The evaluating psychiatrist reviews all these and takes a medical history.
Any disorders which might make buprenorphine-clonidine-naltrexone or naltrexone maintenance hazardous, such as uncontrolled hypertension, diabetes, heart disease, hepatitis with transaminase levels greater than three times the upper limit of normal, renal disease, or advanced AIDS are exclusionary. Participants with uncertain hepatitis status and unexplained liver enzyme elevation > 5 times the upper limit of normal will be offered hepatitis panel testing to determine study eligibility. Patients with acute hepatitis infection and increasing liver function tests during screening will be excluded from study participation. The patient will

be assisted in obtaining appropriate medical evaluation and treatment, and may be eligible for the research study once the problem is controlled. History of an allergic reaction to any of the medications used is an exclusion criterion.

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

Patient Monitoring and Removal from Study: The psychiatrist and/or therapist will assess appropriateness for continuation in the research study on a continuous basis, and will remove from the trial patients with significant clinical deterioration or noncompliance of a type which could be dangerous. Criteria for removal from the study will include:
1.) Relapse to opiate dependence: This will be suspected if a patient misses more than three days in a row of naltrexone and resumes opiate use for more than three days during that time and produces an opiate positive urine. It may be confirmed with a naloxone challenge.
2.) Binges of opiate use with the intent to over-ride the blockade produced by naltrexone, or opiate use resulting in severe intoxication or somnolence.
3.) Seven (7) consecutive missed days during detoxification period or 14 consecutive missed days post-XR-NTX induction (unless they are in contact with clinic staff).
4.) Other clinical deterioration which cannot be managed safely in the context of outpatient treatment. This would include a patient who becomes suicidal, or a patient who goes on severe drug binges (including nonopiate drugs), endangering him/herself, or CGI-S>6.
5.) Elevation of liver enzymes In the injectable naltrexone condition, if liver enzyme are elevated > 3 times normal, the next injection will be delayed.

A hepatitis panel will be obtained and liver enzymes repeated; long-acting injectable naltrexone will not be re-administered until liver enzymes fall below 3 times upper limit of normal. If liver enzymes do not improve, the subject will discontinue naltrexone.

If a patient is removed from the research trial for medical reasons, he/she will be retained in open treatment for the remaining of the study period and will be offered a supply of buprenorphine while transitioning to other treatment. Upon removal of a patient from the trial due to clinical deterioration, the patient will be referred for appropriate follow-up treatment, in most instances either inpatient detoxification or residential treatment, or methadone maintenance. The PI, Co-PI, or a study psychiatrist is available 24 hours/day by phone and/or beeper in case of emergency.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
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. Audiotaped psychotherapy sessions and digital CD-ROMS created from these sessions will be stored in locked cabinets without any identifying information, and destroyed after 10 years. 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 may benefit from many of the components of the treatment that they receive, induction onto injection naltrexone, naltrexone maintenance, and components of behavioral therapy.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Participants will receive $15 for each visit for completion of study assessments and reimbursement for travel. **Participants can also earn an additional $40 if they complete an optional interview at the end of the study.** Participants can earn approximately **$430** total over the course of the study.

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