Protocol

Study Title: Improving Treatment Outcomes for Prescription Opioid Dependence

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2. Title and Abstract: Improving treatment outcomes for prescription opioid dependence

Opioid dependence is a serious public health problem, particularly with the dramatic rise in prescription opioid abuse, but long-term opioid agonist maintenance with methadone or buprenorphine (BUP) may not be optimal for many prescription opioid abusers. Yet current opioid detoxification strategies are limited by high relapse rates and/or lack of efficacy in relieving subjective symptoms. In addition, antagonist maintenance with naltrexone (NTX), which may be an optimal longer-term strategy for this population, requires prior opioid detoxification and has been associated with relatively poor outcomes in heroin abusers. This application takes a novel, broad approach to address the problem of prescription opioid dependence by determining the 1) utility of adjunct gabapentin (GBP) during outpatient BUP detoxification to improve initial outcomes and 2) feasibility of transitioning prescription opioid -dependent patients to depot NTX following detoxification, which may improve longer-term outcomes. GBP, an N-type calcium channel blocker with low abuse potential, potentiates opioid analgesia, decreases both postoperative morphine consumption and movement-related pain, and reverses tolerance to the antinociceptive effects of morphine. GBP is also well tolerated and effective in reducing craving and illicit opioid use in pilot detoxification trials. We propose to assess the efficacy and tolerability of adjunct GBP during BUP-assisted detoxification and the feasibility of subsequent transition to depot NTX therapy in prescription opioid -dependent participants. This 12-week, randomized, placebo-controlled clinical trial will determine the potential utility of adjunct GBP in 150 prescription opioid -dependent individuals undergoing outpatient BUP detoxification and whether transition to short-term depot NTX therapy is feasible. Our three specific aims are to determine **(1)** the efficacy and tolerability of GBP to reduce craving and illicit use of opioids in prescription opioid -dependent individuals undergoing outpatient BUP detoxification; **(2)** acceptability and feasibility of transition to, and short-term maintenance on, depot NTX following detoxification; and **(3)** prognosticators of completion of the BUP taper, successful induction onto depot NTX, symptomatology, and longer-term outcomes. Currently, the only FDA-approved medications for the treatment of opioid withdrawal are the opioid agonists methadone and BUP, both of which have abuse liability, and NTX, which can produce low levels of withdrawal-like symptoms, especially early in treatment. Our findings, if positive, will support further development of GBP as an adjunct medication as well as provide an integrated, seamless approach to outpatient prescription opioid -dependence treatment. Ultimately, this work could impact the addiction field by providing both procedural and pharmacological tools for treating prescription opioid dependence that significantly improve outpatient detoxification outcomes and markedly enhance access and transition to NTX therapy. This would shift clinical practice, establishing an effective adjunct regimen for BUP detoxification and an integrated approach f or transition to NTX therapy. GBP may also be clinically useful for other situations where opioid withdrawal is a concern.

3. Purpose:

The specific aims are the following:

Specific Aim 1. Determine the tolerability and efficacy of GBP (1600 mg/day) to reduce withdrawal symptoms, craving, and illicit use of opioids in prescription opioid -dependent individuals undergoing BUP detox. Our hypothesis is that GBP will be well tolerated and reduce, relative to placebo, illicit use of opioids during and immediately following the BUP detox. Gabapentin may also reduce secondary outcomes of withdrawal symptoms and craving relative to placebo during and/or immediately following the BUP detox.

Specific Aim 2. Determine the acceptability and feasibility of transitioning patients completing detox to depot NTX. Our hypothesis is that the majority of those abstinent immediately post-detox will be successfully transitioned to depot NTX.

Specific Aim 3. Determine prognosticators of completion of the BUP taper, successful induction onto depot NTX, symptomatology, and longer-term outcomes at the 16-week follow-up. Mediators (e.g., changes in ratings over time) associated with outcomes will also be explored.

4. Background:

Opioid dependence continues to be a serious public health problem, particularly with the dramatic rise in abuse of prescription opioids [1]. Prescription pain relievers were second to marijuana in terms of prevalence of dependence or abuse in 2009 [1]. Moreover, the number of emergency department visits in 2009 involving narcotic pain relievers was 137% higher than the 2004 level of 144,644 visits [2]. Prescription-opioid abuse is associated with serious negative consequences that include physiological dependence, high-risk behaviors [3, 4], overdose [5, 6], and death [7-9]. Particularly concerning, the rate of current nonmedical use of prescription opioids increased 17% from 2002 to 2009 among young adults aged 18–25 [1]. This project seeks to address the problem of opioid dependence by improving upon detoxification strategies for opioid dependence.

The three existing FDA-approved treatments for opioid dependence were developed in trials with heroin users and include agonist maintenance with methadone or buprenorphine (BUP), methadone- or BUP-assisted detox, and maintenance on the opioid antagonist naltrexone (NTX) in post-opioid dependent patients. Each of the three approaches has significant drawbacks for prescription opioid abusers.

Opioid Agonist Maintenance. A major factor involved in relapse among chronic opioid abusers is the experience of a particular set of “flu-like” symptoms indicative of opioid withdrawal upon stopping opioids or taking an opioid antagonist (e.g., naloxone). Longer-term maintenance with the opioid agonist methadone or BUP has shown efficacy for treating prescription opioid dependence [10], with prescription opioid users generally showing better outcomes than heroin users [11, 12]. However, given that prescription opioid abusers tend to be younger, have shorter treatment histories and have less severe dependence than heroin users [13, 14], longer-term maintenance may not always be appropriate or feasible. Prescription opioid abusers may also find opioid agonist treatments unacceptable due to the related stigma [14, 15]. The use of longer-term opioid agonist treatment is especially undesirable in the growing population of adolescents and young adults using prescription opioids [16]. Opioid agonist treatment is also considered suboptimal in certain other populations, including criminal justice and professionals [17, 18]. In addition, opioid agonist maintenance treatments may not be accessible in rural regions, which is ironically where prescription opioid use is highly prevalent [19, 20]. In addition to all those disadvantages, the most commonly cited concern of opioid maintained patients regarding coming off opioid agonist treatment is withdrawal symptoms [21]. Thus, alternate treatment options need to be uncovered to enhance accessibility, acceptability, and treatment outcomes.

Detoxification. Traditional opioid detox methods, including methadone taper and supportive treatment of symptoms with the alpha^2-adrenergic receptor agonists, are limited by high relapse rates and lack of efficacy in relieving subjective symptoms [22-28]. Although BUP appears similar to methadone in relieving withdrawal symptoms and may resolve withdrawal symptoms faster than methadone, symptoms are still moderate [29] and highly variable among patients [30]. BUP detox is also complicated by the emergence of withdrawal symptoms post-taper [31, 32]. To our knowledge, only three studies have specifically recruited prescription opioid users to determine outcomes with BUP detox [10, 33, 34]. In a multi-site trial of BUP-naloxone (NX) treatment for prescription opioid dependence, patients who failed a 2-week BUP taper reduced opioid use during extended BUP-NX, but still had high rates of relapse following a 4-week BUP taper similar to those without extended BUP-NX treatment [10]. A feasibility study showed that 14 prescription opioid users undergoing a brief BUP taper had high rates of opioid abstinence during, but not following, the taper, with a subset having high rates of abstinence during the taper and subsequent oral NTX therapy [33]. A small randomized, double-blind trial that included a strong behavioral intervention showed that a 4-, relative to 2- or 1-, week BUP taper resulted in greater opioid abstinence during the taper and subsequent oral NTX therapy in prescription opioid abusers, although response was not complete [34]. These findings highlight the need to identify subpopulations of prescription opioid users most likely to

respond to detox versus opioid agonist maintenance [33]. Thus, improving treatments for opioid withdrawal and identifying those most likely to benefit from this strategy are of great importance for optimizing opioid detox strategies in prescription opioid-dependent patients.

NTX Maintenance. Given the more positive prognosis for prescription opioid users relative to heroin users [11, 13], NTX may be a good long-term approach to maintaining abstinence from opioids. NTX is used to prevent reinstatement of drug use and dependence by blocking the effects of opioid agonists. Evidence suggests that NTX therapy does not worsen depression [35, 36] and may help reduce craving for opioids [37] among medication-compliant patients. However, NTX is limited by the need for patients to undergo detox from opioids and remain abstinent prior to NTX therapy, which reduces acceptability of NTX and success rates [38]. Oral NTX therapy also has been associated with high rates of dropout, medication noncompliance, and relapse associated with noncompliance [39-41] as well as risk of overdose [42]. Although new, sustained-release formulations of NTX have helped to mitigate issues of medication noncompliance, illicit opioid use, retention [38, 43, 44] and overdose [45-47], and the strategic use of contingency management procedures has enhanced outcomes [48, 49], treatment improvements are still necessary to help reduce symptoms, which would bolster outcomes and success rates. For instance, patients have reported experiencing opioid withdrawal-like symptoms of mild to moderate severity during the first few weeks after beginning NTX therapy [50].

Relative Lack of Treatment Research Specific to the Prescription Opioid User Population. Importantly, the vast majority of NTX studies have recruited almost exclusively heroin users [40, 50-52]. Given that acceptability of receiving a second NTX implant has been associated with pretreatment employment length, less drug use, less criminality, and concern about family problems [53], prescription opioid users may be better candidates for this treatment option. However, to our knowledge, two studies have examined BUP detox and transition to oral NTX in prescription opioid users [33, 34]. One uncontrolled study examined the feasibility of a brief BUP detox and transition to oral NTX [33]. Of the 14 who entered the taper phase, all 14 transitioned to oral NTX, but only 5 (36%) individuals seemed to benefit with minimal, if any, opioid use during NTX maintenance. Moreover, only 36% of participants had opioid-negative urines the day following the taper [33]. In another randomized, double blind trial combined with a strong behavioral intervention, greater opioid abstinence occurred during the BUP taper and subsequent NTX therapy among those undergoing a longer versus shorter BUP taper [34]. These findings highlight the need to examine various strategies for optimal transition to, and maintenance on, NTX therapy, particularly sustained-release formulations, in this population to optimize treatment outcomes.

The mechanisms of opioid withdrawal are not well understood, but there is evidence to suggest that the expression of opioid withdrawal is mediated, in part, by mu opioid and other neurotransmitter systems acting through the locus coeruleus, which is the largest noradrenergic nucleus in the brain [54-57] (for exception, see [58]). The locus coeruleus also receives a major excitatory amino acid input from the nucleus paragigantocellularis [59, 60], and excitatory amino acids play a role in opiate dependence and withdrawal [59, 61, 62]. One site where excitatory amino acid neurotransmission occurs is the N-methyl-D-aspartic acid (NMDA) receptor, part of a receptor/ion channel complex with multiple regulatory sites, including sites on cationic channels permeable to potassium, sodium, and calcium [63]. Activation of the NMDA receptor is associated with increased intracellular calcium levels, and calcium channel blockers (CCBs) have been shown to alleviate opioid withdrawal [64-68]. Thus, CCBs may have utility for improving treatment for opioid withdrawal.

CCBs have been shown to alleviate opioid withdrawal in opioid-treated nonhumans [67]. Moreover, the L-type CCBs verapamil, nimodipine, and nifedipine have been shown to alleviate withdrawal in clinical trials of opioid detoxification [69, 70]. In a human model of opioid withdrawal, isradipine, which is an L-type CCB, was most effective among the CCBs tested for their efficacy to block naloxone-induced behavioral effects [71-73]. Importantly, isradipine showed greater dose-related efficacy than the alpha2-adrenergic agonist clonidine or tizanidine [72-74]. For instance, clonidine partially attenuated naloxone-occasioned responding in a manner not related to dose and somewhat attenuated naloxone-induced changes in self-report measures, including opioid-antagonist ratings [74]. When combined with naloxone, isradipine significantly attenuated naloxone-occasioned responding without increasing novel-appropriate responding occasioned

when given alone, and significantly attenuated naloxone-induced increases in ratings of opioid-receptor antagonist and in ratings measuring sedation (data not shown) [72]. These results suggest that isradipine may be more effective than clonidine as a nonopioid pharmacotherapy for treating opioid withdrawal. Thus, the proposed project will determine the preliminary efficacy and tolerability of isradipine in opioid-dependent participants undergoing 10-day BUP detoxification.

Evidence suggests that BUP is among the most effective detox agents, but relapse rates are still high post-taper [30] and ancillary medications are ineffective in improving outcomes [75]. Thus, adjunct treatment with a pharmacologically relevant medication is needed. Our pilot studies and those of others suggest that agents acting on non-opioid pharmacological targets implicated in the expression of opioid withdrawal may have utility (see Rationale section below). Given that calcium channel blockers (CCBs) have been shown to alleviate opioid withdrawal [64-68], we will examine the efficacy of a CCB to improve outcomes during BUP detox.

Various calcium channel subtypes have been identified and are grouped according to their distinct electrophysiological and pharmacological properties into T-, N-, L-, P/Q, and R-types (see [76]), of which the L-type CCBs have been the most commonly studied for opioid withdrawal. Yet these agents may have limited utility for outpatient detox due to the potential for hypotensive effects [70, 72], as in the case of the alpha^2-adrenergic agonist clonidine [27, 77], and the feasibility and preliminary efficacy of the L-type CCB isradipine is currently being studied in a pilot trial (R21DA035325; Oliveto, PI). This application focuses on an N-type CCB, due to the fact that N-type CCBs have less impact on blood pressure while alleviating certain pain conditions (see [78]). GBP, an N-type CCB [79, e.g., 80, 81] and gamma-aminobutyric acid (GABA) analogue that promotes release of GABA [82, 83], has been shown to attenuate morphine-induced conditioned place preference in rats [84]; enhance the analgesic effect of morphine in rats [85] and healthy volunteers [86]; decrease postoperative morphine consumption and movement-related pain after radical mastectomy [87]; and block, as well as reverse, tolerance to the anti-nociceptive effects of morphine in the rat paw-pressure and tail-flick tests [88]. These findings indicate a relationship between GBP and the opioid system that is similar to that observed with L-type CCBs [e.g., 89] and should be explored further.

Given that the GABA system has been implicated in the expression of withdrawal [e.g. 90, 91-93], the GABA-ergic actions of GBP may also contribute to its efficacy in attenuating withdrawal. GBP has low abuse liability [94], a favorable side effect profile, minimal drug interactions, and a relatively short elimination half-life (5-9 hours) [95]. GBP has also been shown to decrease naloxone-induced ratings of drug strength in opioid-maintained humans [96]. In addition, GBP at 1200-1800 mg/day, but not 900 mg/day [97], has been shown to alleviate withdrawal symptoms in both uncontrolled [98-100] and placebo-controlled [31] opioid agonist-assisted detox trials. Thus, GBP may be a promising adjunct medication for opioid withdrawal.

Despite the scope of the prescription opioid problem, a paucity of data still exists regarding characteristics of the prescription opioid dependent population as well as those subpopulations of prescription opioid abusers most likely to benefit from a particular treatment [13, 14, 33, 101]. Moreover, results of medications development trials have shown that potential treatment agents such as NTX [102, 103] or alpha-adrenergic agents [22, 104] have modest efficacy in the whole sample, indicating the need to identify potential factors that may impact treatment response. Yet few studies have examined predictors, mediators, and moderators of outcomes in medication treatment for opioid dependence [34, 101, 105-107]. To determine whether we can identify subpopulations of prescription opioid -dependent patients who are most likely to benefit from GBP and transition to NTX, we will assess several types of measures at baseline and/or during the course of the trial, including demographic, drug dependence severity, level of opioid use, treatment history, retention, and comorbid psychiatric and substance use disorders. Other major prognosticators we will examine are gender, distress tolerance, readiness to change, and anxiety: 1) Gender: Women are as likely as men to misuse prescription opioids [108], and almost half of treatment admissions with opioids other than heroin as the primary drug of abuse are women [109]. To our knowledge, one large clinical trial for prescription opioid dependence showed sex differences in baseline characteristics but not treatment outcomes [107]. Given that sex differences have been observed in response to other pharmacological

interventions during medication trials [110, 111] and laboratory studies [112, 113], we will examine whether sex differences in response to GBP versus placebo occur. 2) Distress tolerance: Psychological distress tolerance is defined as the ability to persist in goal-directed activity while experiencing psychological distress [114, 115]. Distress tolerance has been shown to be negatively associated with a range of problematic behaviors, including drug and alcohol use [116, 117]. Moreover, drug or alcohol treatment outcomes are poorer in individuals with low distress tolerance [118, 119]. Because detox and NTX therapy can produce symptoms that are uncomfortable or "distressing," we will examine whether baseline objective and subjective measures of distress tolerance predict subsequent treatment response. We will also measure distress tolerance at several time points to determine whether distress tolerance changes as a function of study phase. 3) Readiness to change: Motivation to change drug-using behaviors has been associated with treatment retention and outcomes [120, 121] and is thought to predict patient behaviors during treatment. We will assess whether "readiness to change," measured by a validated instrument [122], will predict treatment response during the detox as well as successful transition to and maintenance on NTX therapy. We will also reassess this construct at several time points to determine whether motivation changes during participation, as has occurred previously [48]. 4) Anxiety: Anxiety is prevalent in opioid-dependent populations [106] and is associated with craving for opioids during opioid withdrawal [123]. Higher anxiety and craving ratings also occur during early abstinence in former heroin users [124]. In addition, anxiety sensitivity (i.e., fear of anxiety-related bodily sensations, arising from a belief that such sensations have harmful personal consequences) is associated with greater likelihood of dropping out of residential treatment programs [125] as well as greater sedative use among methadone-maintained women [126]. On the other hand, severe anxiety symptoms at baseline doubled the likelihood of treatment success during medically supervised opioid withdrawal procedures [106]. Meanwhile, impaired decision-making in opioid-dependent patients has been shown to be influenced by current levels of anxiety and by the personality markers trait anxiety and self-directedness rather than drug use per se [127]. Given the dearth of data on the prevalence and prognostic relevance of anxiety in prescription opioid abusers, we will obtain several measures of anxiety at baseline and during the study.

5. Significance or Importance of Proposed Research:

The clinical significance of this research is clear. Despite current treatments that are available to date, prescription opioid dependence is a chronic, often relapsing, disorder with medical, social, and legal complications and opioid withdrawal is implicated in relapse to opioid use. This study will help shed light on whether the N-type CCB gabapentin may be a useful adjunct medication during detoxification from BUP as well as the feasibility of transition to injection NTX. The results of this study, if positive, will support further examination of the utility of N-type CCB's like gabapentin as adjunct medications during BUP detoxification, transition to NTX and other situations where opioid withdrawal may be of concern.

6. Experimental Subjects:

Up to 200 individuals (18-64 yrs old) who are seeking treatment for prescription opioid dependence will be recruited until 150 eligible participants have enrolled into the study proper.

A. Inclusion criteria

1) be between the ages of 18-64
2) be available to attend clinic 3 - 6 days a week for approximately 30-120 minutes per day during the first 3 weeks
3) fulfill DSM-5 criteria for moderate to severe Opioid Use Disorder. These criteria will be ascertained in the following manner: the physician will determine whether the individual is appropriate based on several clinical assessments that are routinely employed by methadone program physicians, including history and severity of opioid use, presence of track marks, prior treatment history, self-reported and/or observed signs and symptoms of opioid withdrawal. If any individual's severity of opioid use disorder is

questionable, that person will be excluded from further consideration as a participant.
4) submit a urine sample negative for benzodiazepines or barbiturates prior to starting the study.

B. Exclusion criteria

1) report having had a severe adverse reaction to study medications
2) have an unstable medical condition or stable medical condition that would interact with study medications or participation, including a current chronic pain or other medical condition that requires ongoing opioid agonist treatment (determined by physician assessment)
3) conditions such as chronic obstructive pulmonary disease (COPD) that reduce lung function
4) have a major psychiatric disorder (psychosis, schizophrenia, bipolar)
5) current suicidal ideation or suicidal attempt in the past 12 months
6) have a seizure disorder
7) physiological dependence on alcohol or drugs other than opioids, tobacco or marijuana (as determined by physician assessment)
8) are pregnant, plan to become pregnant, have inadequate birth control, if relevant, or lactating
9) report ongoing use of OTC or prescription drug (including Maalox) that would have major interaction with study drugs, including CNS depressants (e.g., anxiolytics, antidepressants, antihistamines).
10) have any of the following: liver function tests >3 times normal, BUN and Creatinine outside normal range; ECG abnormalities including but not limited to: bradycardia (<50 bpm); prolonged QTc interval (>450 msec); Wolff-Parkinson White syndrome; wide complex tachycardia; 2nd degree, Mobitz type II heart block; 3rd degree heart block; left or right bundle branch block; pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic).

Individuals with anxiety or depression and not taking exclusionary medications will be included unless findings during screening indicate a need for immediate treatment determined by the study physician and/or the Columbia–Suicide Severity Rating Scale [128].

C. Initial Diagnostic Evaluation

1) Medical—Care will be taken to exclude medically ill participants from the clinical trial by having participants undergo a comprehensive evaluation, including physical, psychiatric, and neurological examinations. Routine laboratory studies will ensure that participants are medically acceptable for participation (CBC, BUN/creatinine, electrolytes, liver-function tests, pregnancy test for women, urinalysis, ECG). Liver function tests will be repeated at week 4. A physician will review laboratory data and ECG prior to study entry. Women of childbearing potential will have a pregnancy test before starting the study and prior to oral NTX. If a woman suspects she has conceived during the study a pregnancy test will be done at her request.
2) Psychiatric/Behavioral—Care will be taken to assure that participants meet diagnostic criteria by means of a screening interview by one of the physician investigators.

7. Experimental Methods:

A. Entry into Treatment. If we are recruiting for more than one study at a time, then screening procedures will be done under screening protocol # 204167. If a person is eligible to participate, then all screening materials will be transferred to this protocol. Participants will be recruited by word-of-mouth, public service announcements through local radio and TV stations, internet ads, flyers, newspaper advertisements, social media, and AR Research. Otherwise, triage will be done by a staff member and take about 60 minutes. It will cover the basic inclusion and exclusion criteria, as well as a brief description of the study, to determine if the participant is interested in participating. Treatment alternatives as described below will also be offered to the prospective participant. If (s)he is appropriate and agrees to the study, full screening will be completed typically within that week.

Intake will be done by a research staff member and take about 2-4 hours to cover explanation of the study, evaluation of exclusion criteria, screening for opioid or other drug dependence, and obtaining informed consent. A physical exam will be completed by a study physician and laboratory examination

will include urinalysis, urine toxicology screen, ECG (which will be completed by a research assistant or research nurse), and blood evaluation (SMA-20, CBC—these and any other laboratory test mentioned in this protocol will be outsourced to Quest Diagnostics and/or Redwood Laboratories). TB test status will be assessed during the physical exam; individuals who report a history of positive TB test results will be required to provide documentation from the Arkansas Department of Health verifying a negative chest x-ray in the past year. HIV testing is available if requested by the participant. A study physician will then interview the participant for psychiatric diagnosis and review of medical data for starting medication. This screening would typically be complete within one week; however, this process may take longer in cases where a person needs to submit documentation about a medical issue that requires resolution prior to study entry, etc. Those who present for screening in severe withdrawal will be referred to the Emergency Department. Also, if a physician determines that abnormal screening results may be linked to withdrawal, the tests will be redone. Then participants undergo our intake procedure, which can take up to 4 hours to complete, including obtaining informed consent for the specific study (if participants was screened under IRB#204167) and intake assessments (see assessment section).

B. Experimental Procedures. During the detox phase (weeks 1-3), participants will attend the Center for Addiction Services and Treatment on the 4th floor of PRI 3-6 days per week to receive study medication, attend a weekly therapy session, and complete assessments (**Table 1**). During the NTX induction (week 4), participants will attend clinic 4-5 days. On day 1 (either Monday or Tuesday) of week 4, participants will submit a urine sample that may need to be opioid-negative in order to start NTX induction. (If the urine sample is positive for opioids then the decision to start NTX induction will be made by a study physician). Upon daily confirmation of an opioid-negative urine sample or determination by study physician to proceed with NTX induction, participants will be administered clonidine, followed by oral NTX (6.25 mg). Participant's orthostatic vital signs and symptoms will be monitored prior to and 20 minutes following clonidine administration as well as 2 hours after initial oral naltrexone administration. If the participant experiences lightheadedness or dizziness and has evidence of orthostatic hypotension with BP drop of > 20 mm Hg for systolic or >10 mg Hg for diastolic, accompanied by an increase in pulse of more than 20 beats per minute, then the vitals will be repeated in 30 minutes. If the orthostatic changes persist at the time of the second measurement prior to naltrexone administration, then naltrexone will not be administered and vitals will be repeated every 30 min until they are within study parameters for release.

If participants receive naltrexone 6.25 mg on day 1 (either Monday or Tuesday depending on clinic closures and scheduling), they return the following day and several of the procedures from the previous day will be repeated, including a drug screen for recent opioid use and vitals to include orthostatic measurements. If the drug screen is negative for opioids and no orthostasis is present, then the participant will be administered clonidine, followed 20-40 min later by oral NTX (6.25 mg if Tuesday or 12.5 mg if Wednesday). Participant's orthostatic vital signs and symptoms will be monitored prior to and 20 minutes following clonidine administration as well as 2 hours after oral naltrexone administration. Procedures for release from the clinic will occur as in day 1. Participants will return on two subsequent days to undergo several procedures as before and receive clonidine followed 20-30 min later by increasing doses of oral NTX under observation, and receive the NTX injection on day 5. Participants then attend clinic once per week for up to 8 weeks (weeks 5-12).

If participants do not receive naltrexone on day 1 of week 4 (e.g., Monday was a holiday so did not attend clinic) then the following will occur: Participants will attend clinic on day 2 of week 4 and submit a urine sample that may need to be opioid-negative in order to start NTX induction. (If the urine sample is positive for opioids then the decision to start NTX induction will be made by a study physician; participants have up to day 3 to be inducted onto NTX). Upon confirmation of an opioid-negative urine sample or determination by study physician to proceed with NTX induction, participants will be administered clonidine, followed by oral NTX (6.25 mg). If the sample is negative or regular use is not indicated, participant's orthostatic vital signs and symptoms will be monitored prior to and 20 minutes following clonidine administration as well as 2 hours after initial oral naltrexone administration. If the participant experiences lightheadedness or dizziness and has evidence of orthostatic hypotension with

BP drop of > 20 mm Hg for systolic or >10 mg Hg for diastolic, accompanied by an increase in pulse of more than 20 beats per minute, then the vitals will be repeated in 30 minutes. If the orthostatic changes persist at the time of the second measurement, then the transition to NTX will be halted on that day. The participant will be invited to return on day 3 and the procedures from the previous day will be repeated including a drug screen for opioids and vitals to include orthostatic measurements. If drug screen is negative for opioids and no orthostasis is present, then the participant will resume the process that was attempted on day 1 or 2, except that they receive 12.5 mg of NTX on day 3 and proceed with the dose escalation above on subsequent days. If orthostatic changes recur, then the participant will not be transitioned to NTX, and his/her study participation may be ended and s/he will be referred to alternative treatment, if desired. Those participants that are opioid abstinent but choose not to receive the NTX injection, may otherwise proceed in the study through week 8, attending weekly clinic visits for individual psychotherapy and assessment completion. If there is no evidence of opioid relapse at week 8 as determined by a study physician, these individuals may proceed in the study through week 12.

Participants who successfully transition to NTX injection in week 4 will be offered the opportunity to receive one additional NTX injection in week 8. In order to be eligible for the second NTX injection, participants submit a urine sample that may need to be opioid-negative to receive NTX injection during week 8. If the urine sample is positive for opioids then the decision to give the second NTX injection will be made by a study physician. If the study physician determines that the participant will not receive the second NTX injection, they will be referred to appropriate alternative treatment, if desired. Otherwise, participants continue in the study as before, attending weekly clinic visits for individual psychotherapy and completion of assessments. All participants will attend their last clinic visit during week 12 to complete final assessments, terminate therapy, and receive aftercare referrals as determined during the course of treatment. A follow-up interview will be conducted during week 16 (+/- 1 week). Participants will receive an appointment reminder at least one day prior to each appointment during the NTX phase to increase attendance. Participants will be asked to supply names and phone numbers of at least two stable contact people whom staff can call if the participant can't be reached post-participation. Staff will maintain at least monthly contact with participants who have been discharged from the trial to enhance follow-up rates. In advance of the scheduled follow-up appointment, a reminder letter will be sent to each participant's most recently recorded address.

Assessments will typically be obtained once or thrice weekly (more often during week 4). A supervised urine sample will be obtained and self- and observer-ratings completed. Blood samples will also be drawn during week 4 to determine buprenorphine and gabapentin levels.

C. Drugs. The UAMS Research Pharmacy will prepare medications during the study. BUP mono tablets (sublingual), oral NTX tablets, clonidine tablets, depot NTX (Vivitrol), GBP and placebo (microcrystalline cellulose) will be purchased through the UAMS Hospital and a bulk supply of gabapentin and placebo capsules will be prepared by the UAMS Research Pharmacy. Study medications for Phase I (buprenorphine detox) will be brought to the CAST Pharmacy and stored in the research vault of the CAST dispensary for dispensing through the CAST medication window. Study medications for phase II (naltrexone induction) will be stored in a refrigerator and/or wall-mounted narcotics lock box in the NTX induction room on the 4th floor of PRI.

Detox procedures are similar to those performed previously by our group [31]. The 12 mg dose of BUP has been used successfully in our prior trial and has been shown to be associated with minimal withdrawal symptoms [31]. We have shortened the BUP maintenance prior to GBP induction in order to start the 10-day detox on Wednesday of week 2. This allows us to better characterize symptomology during the second half of the detox as well as end the taper on Friday of the following week, thereby providing a 3-day window over the weekend before initiating NTX induction on Monday (see below). During the detox phase, participants will typically attend the clinic either 6 days per week (Monday–Saturday) per current protocol or thrice weekly truncated study visits due to COVID-19. Buprenorphine dosing will begin Monday or Tuesday of Week 1. During Week 1, all participants will receive 4 mg of buprenorphine on Monday (or Tuesday), followed by another 4 mg dose 30 minutes later, and 12 mg (maintenance dose) per day on Tuesday (Wednesday)–Friday; on Saturday, participants will receive a

double dose (24 mg) of BUP. Participants with truncated study visits due to COVID-19 will receive a lockbox for medications taken on days when they do not attend clinic (Tuesday, Thursday, and weekends) during the detox phase. Staff will ensure that participants sign medication accountability logs. Participants receive 12 mg of BUP on days 1 and 2 of week 2. Beginning on day 3 (Wed) of week 2, all participants will begin a 10-day BUP detox schedule [129], such that they receive 8 mg for two days, 6 mg for 1 day, 12 mg dose on Sat (double dose to cover Sun, or 6 mg doses on Saturday and Sunday if they are receiving take –home medications due to COVID-19), 4 mg on day 1 of week 3, 2 mg on days 2 and 3, and 1 mg on days 4 and 5 (Thur-Fri) of week 3. Participants may receive take-home dose(s) of buprenorphine to ensure participants are receiving the medication according to the dosing regimen on holidays and holiday weekends when the clinic is closed. This may also occur when inclement weather is forecast and the decision is made to have the clinic close on a given day. If a participant initially experiences side effects (e.g., feeling high) on the 8 mg dose of buprenorphine (which does occur during the first day or two of buprenorphine induction in a subset of opioid dependent patients), the physician may delay the increase to 12 mg depending on symptoms severity and duration; however, the participants will typically be on a stable dose of buprenorphine before day 3 of week 2. If a participant cannot tolerate the 12 mg dose of buprenorphine their dose will be reduced to no less than 8 mg/day and the detox schedule will be adjusted accordingly. If the participant cannot tolerate 8 mg of buprenorphine they will be discharged from the study. In the event that a participant is quarantined due to COVID-19 during phase I BUP detox, they will be discharged from the protocol and the study physician will provide them with take-home BUP taper individually tailored according to where in phase 1 the participant was at the time of quarantine.

During the detox phase, morning GBP/placebo ingestion will occur under supervision 6 days per week, and a take-home dose will be given each day for evening ingestion (3 take-home doses on Sat to also cover Sun). For participants on the truncated schedule due to COVID-19 (thrice weekly), lockboxes with BUP and GBP/Placebo will be given on the same schedule to be taken on days when not presenting to clinic (Tues, Thurs, weekends) with specific instructions provided by CAST nurse, in addition to drug accountability logs signed by the participant. Additional take-home doses of GBP/placebo will be given to take on holidays, days when clinic is closed due to inclement weather and holidays to ensure adequate blood levels of GBP are maintained. The initial dose of GBP at 100 mg will be given on day 3 of week 1, and a 100 mg dose provided to take home. The GBP dose will increase to 200 mg BID on day 4, 400 mg BID on day 5, 600 mg BID on day 6, and 800 mg BID (1,600 mg/day) on day 7 of week 1. Participants will remain on 1600 mg/day through day 2 of week 5 (during NTX therapy, GBP/placebo capsules will be given in weekly blister packs). Then GBP will be reduced to 1200 mg/day on day 3, 800 mg/day on day 4, 600 mg on day 5, 400 mg on day 6, and 200 mg on day 7. On days 1 and 2 of week 6, all participants will receive placebo. If GBP side effects are too severe at the 800-mg BID dose, GBP will be decreased to no less than 1200 mg/day, given data that 900 mg/day of GBP is ineffective [97]. If GBP side effects are too severe at 1200 mg/day, GBP will be discontinued and the participant will be discharged from the study and referred to local treatment agencies. During transition to NTX (week 4), if a) the participant's urine sample is opioid-negative and/or regular opioid use is not indicated, *and* b) orthostatic vital signs and symptoms are within limits specified below (Section 14, Protection of Participants, B. Protections Against Risk): On day 1 of week 4, participants will receive 0.1 mg of clonidine followed 20-30 min later by 6.25 mg of oral NTX. If tolerated, the person will return on day 2, receive 0.1 mg of clonidine followed 20-30 min later by 6.25 mg of oral NTX. On day 3, participants will receive 12.5 mg of NTX 20-30 min after clonidine. (For those who do not start induction until day 2 or 3: Starting on day 2, NTX will be given at the 6.25 mg dose 20-30 min after clonidine. On day 3, NTX will be given at the 12.5 mg dose 20-30 min after clonidine.) On day 4, 25 mg of NTX will be given 20-30 min after clonidine. If 25 mg is tolerated, then on the morning of day 5, participants will receive the depot NTX injection. (Participants have up to day 3 of week 4 to start the transition to NTX. For those who do not start induction until day 2 or 3: Starting on day 2, NTX will be given at the 6.25 mg dose 20-30 min after clonidine. Starting on day 3, NTX will be given at the 12.5 mg dose 20-30 min after clonidine. In such cases, dosing/administration on subsequent days will be as specified above.) Those

who received the first NTX injection, and who have been determined to be eligible for the second NTX injection and choose to receive a second NTX injection, will do so during their week 8 clinic visit. If a participant is required to quarantine due to COVID-19 during phase II, they may remain on protocol and complete assessments and therapy sessions remotely (by phone or teleconference). If this occurs, urine drug screens and the COWS assessment will be recorded as missed until they are no longer required to quarantine. If a participant is unable to provide a urine drug screen at week 8 due to quarantine, they will not be eligible for the second Vivitrol injection and will be discharged from protocol and offered referrals to treatment as necessary.

D. Medication Compliance. During the detox phase/week 4 oral NTX phase, compliance with BUP, oral NTX, and GBP/placebo (AM dose) will be assured by observing participants as they ingest the medication and/or providing lockboxes and accountability logs signed by participants that are in the protocol on the truncated schedule due to COVID-19. Compliance with take-home doses of GBP during the detox and weekly blister packs of GBP during/immediately following week 4 depot NTX will be monitored by pill counts, self-report, and/or week-4 blood levels of GBP. Riboflavin will be added to capsules and weekly urine samples will be stored for back-up quantitative urinalysis of riboflavin levels, especially if GBP blood levels are disparate. The research nurse will perform depot NTX injections.
E. Randomization of sample. To increase the likelihood that treatment groups are balanced with respect to key baseline variables (opioid-withdrawal symptom severity, marijuana-use status, anxiety ratings and tobacco-use status), males and females (with and without prescribed psychoactive medication) will be separately assigned to treatment groups with “urn” randomization, using a Microsoft Access program developed and used in previous studies [130, 131]. In urn randomization, an algorithm modifies ongoing randomization probabilities based on prior composition of treatment groups, maximizing multivariate equivalence of treatment groups [132]. Thus, urn randomization balances allocation of important prognostic variables in treatment groups, while retaining other benefits of random assignment [133, 134].
F. Maintenance of the Double Blind - A code will be kept in a locked cabinet, in a special file in the data manager’s or PI’s office, and pharmacy matching participants with the active/placebo study medications. This code will be available 24 hours a day and will be broken at the request of outside health professionals in the event of a medical emergency. To prevent any of the investigators from inadvertently discovering the medication assignments of other participants in the special file needs to be opened, a psychiatrist not directly involved with the study participants will open the special file. Once the code is broken, that participant will be dropped from the study. Although we do not anticipate difficulties maintaining the double blind, we will evaluate the adequacy of the double blind by having each participant and a research staff member report the medication (placebo or gabapentin) they believe is being administered.
G. Counseling Guidelines - Several components of Behavioral NTX therapy [135] will be employed in the present study. During the BUP/GBP induction and detox phase, all participants will be scheduled to meet weekly, either in person, via telephone or video conference, with a research therapist typically for 60 minutes. Content of these sessions will include education and support, medication management, techniques to enhance motivation for abstinence or NTX therapy, and review of contingency management procedures. The session also provides an opportunity to review critical issues and problem areas. During NTX treatment, weekly sessions with the research therapist will include Cognitive Behavioral Treatment, manual-driven [136, 137] as a controlled element of the study. Modules will focus on relapse prevention and engagement in community support groups (e.g., Narcotics Anonymous). Although the involvement of a significant other in the treatment process will be encouraged, it will not be required for participation. The research therapist will monitor number and duration of scheduled treatment sessions, including frequency and reason for extra-session telephone calls, subjects' involvement in any ancillary treatments, and other clinically significant events and formal treatment concurrent with their study treatment (including self-help meetings). At the end of the study, participants will be given treatment referrals.

H. Program Termination - Any participant choosing not to take the study medication will be discharged from the study with appropriate referrals. During the detox phase and NTX transition week, participants missing medications on three successive days (or any two days during week 1) or do not complete assessments will be administratively discharged. If participating under the truncated schedule due to COVID-19, participants will be discharged if they miss any clinic visits during week 1 and miss 1 clinic day during weeks 2 and 3 due to the take-home medication schedule, therefore, they cannot miss Friday visits. Participants will be discharged if they do not receive their take-home medication blister packs by day 5 of week 4. Participants who cannot provide an opioid-free urine on either day 1, 2, or 3 of week 4 during oral NTX induction may be deemed ineligible to continue onto depot NTX therapy as determined by the study physician. Similarly, if participants are unable to provide an opioid-free urine at the week 8 visit, a study physician will determine if participants will be eligible to continue in the study with or without the second NTX injection. A participant will be discharged if PIs believe a subject's health or wellbeing may be threatened by continuation in the study. If a participant is required to quarantine due to COVID-19 during the phase I BUP detox, they will be discharged from the protocol, and the study physician will provide take-home BUP taper for detox. If a participant is required to quarantine due to COVID-19 during phase II, they may remain on protocol and complete assessments and therapy sessions remotely (by phone or teleconference). If this occurs, they will be unable to provide urine drug screens or complete the COWS assessment until they are no longer required to quarantine. If a participant is unable to provide a urine drug screen at week 8 due to quarantine, they will not be eligible for the second Vivitrol injection and will be discharged from protocol and offered referrals to treatment as necessary. If a pregnancy test becomes positive, the participant will be withdrawn from the study and referred to an appropriate treatment program. Participants who relapse following BUP detox or NTX therapy, as determined by physician assessment, will be offered referrals to the UAMS Center for Addiction Services and Treatment, a residential therapeutic community, an inpatient treatment program, or others, as appropriate. Participants administratively discharged will also be referred to local treatment programs, if desired.

I. Dependent Measures. The purpose and timing of assessments are shown in **Table 1**. Assessments will be presented via computer whenever possible with responses entered directly into the computer (with paper copies as backup in case of computer malfunction or unavailability). If an assessment is missed at any time point, whether due to participants missing appointments, glitches with computer or staff error, the assessments will be completed at the next earliest visit as possible and appropriate. If not, the assessment will be considered missed.

The primary outcome measure is illicit opioid use (typically obtained thrice weekly during weeks 1-4, weekly during weeks 5-12, and once at the week 16 follow-up interview, biologically verified by the Redwood Toxicology Laboratory and/or Lochness Medical Supplies dipstick and/or EMIT assay). Secondary outcomes include craving ratings, retention, self- and observer-rated opioid withdrawal symptoms, adverse events, sleep quality, withdrawal signs (blood pressure, body temperature), mood, heart rate variability (HRV), decision making, and prescription opioid and other drug use, including alcohol, tobacco and caffeine. We chose assessment techniques as recommended in NIDA's A Diagnostic Source-book for Drug Abuse Treatment and Research to use comparable assessments by different investigators in substance abuse [138]. Our set of screening instruments will provide general patient information, including demographic data; medical history; and history of substance use, family substance abuse, and psychiatric treatment [130, 131]. Other assessments include the following: **1)** *Weekly Drug Use* (done weekly), which uses a timeline recall method that we developed in previous studies to assess self-reported use of opioids and other drugs [130, 131]; **2)** *PRISM 5* (done at intake or during week 1), a computerized structured clinical interview (software package will be purchase) from completed to determine several DSM-V psychiatric diagnoses [139, 140]; **3)** *Medication Side Effects Checklist* (done weekly), consisting of multiple items describing side effects specific to GBP, BUP or NTX [141] rated on a scale from 0 (not at all) to 4 (very much); **4)** *Subjective Opiate Withdrawal Scale* (SOWS) (done thrice weekly during weeks 1-3, daily (5 days) during week 4, and weekly thereafter), consisting of 16 items describing possible opioid withdrawal symptoms that are rated on a scale from 0

(not at all) to 4 (extremely) [142]; **5)** *Clinical Opiate Withdrawal Scale* (COWS) (done thrice weekly during weeks 1-3, daily (5 days) during week 4, and weekly thereafter), an observer-rated opioid withdrawal scale that consists of 11 items describing withdrawal symptoms [142]; **6)** the *Stages of Change Readiness and Treatment Eagerness Scale* (SOCRATES) [122]; **7)** measures of distress tolerance, including *Breath Holding Endurance* [143], in which the length of time (seconds) that participants can hold their breath is measured, and the *Distress Tolerance Scale* [144]; **8)** measures of anxiety/depression, including the *State Trait Anxiety Inventory* (purchased through Mind Garden, Inc) [145], the *Anxiety Sensitivity Index* (purchased at anxietysensitivityindex.com from IDS Corporation, Inc.), a reliable and valid 16-item self-report questionnaire that assesses the degree to which an individual is concerned about the possible negative consequences of arousal-based anxiety symptoms [146], and the *Hamilton Anxiety and Depression Scales* [147, 148]; **9)** measures of sleep quality, including the *Pittsburgh Insomnia Rating Scale* [149] and *Pittsburgh Sleep Quality Index* [150]; **10)** measures of known physiological indicators of withdrawal (vital signs, body temperature); and **11)** the *Endpoint Rating Form*, which assesses functional level at termination and reason for termination. To assess potential adverse effects of the study medication, participants will be asked at every visit whether they are experiencing any symptoms, which will be recorded on a Symptoms Form.

Decision Making Assessment. Delay discounting will be assessed via paper survey at intake and at the end of detoxification (week 3, day 5) [151, 152]. Participants will complete 27 fixed-choice options between immediate, smaller and delayed, larger hypothetical amounts of money (e.g., “Would you prefer (a) $54 today or (b) $80 in 30 days?”). Delayed amounts of money range from small ($25-$35), medium ($50-$60), to large ($75-$85). Rates of delay discounting will be characterized by calculating *k* values based on Mazur’s hyperbolic discounting function [153] for choices in each of the three delayed monetary categories. For this study, *k* values will be averaged across the three monetary categories and log transformed. Higher average *k* values indicate increased delay discounting.

Heart Rate Variability (HRV). On day 2 or 3 of weeks 1-2 and day 5 of week 3, participants undergo a 10 min assessment of Heart Rate Variability (as a noninvasive measure of relative autonomic nervous system imbalance such as stress versus relaxation) while sitting, standing and sitting while performing measured breathing prior to receiving that day’s medication. Participants will be asked to secure a belt with sensors around their torso as well as place another sensor on their finger and to refrain from talking during the assessment. After approximately 30 seconds after settling down, participants will be given instructions to sit quietly and their HRV will be recorded for 2 minutes. Then the participant is instructed to stand quietly and their HRV will be recorded for 2 minutes. Finally, the participant will be instructed to sit quietly and follow a measured breathing indicator (i.e., inhaling and exhaling) on the computer screen while their HRV is recorded for 2 minutes. HRV will be measured using the HRV System - ProComp2 with Biograph 2,069.10 2,069.10 Infiniti & HRV Suite Software with 1 BVP Sensor/1 Respiration Sensor.

Objective Distress Tolerance Tasks. On day 3 of week 1 prior to receiving active/placebo study medication, participants will be invited to complete two computerized games. The purpose of this preliminary testing is to test the relevance of a quantitative measure of affective distress tolerance (mirror tracing task) and effortful performance (EffRT) with Opioid Use Disorder severity, to self-report measures of distress tolerance, and treatment outcomes.

1) Mirror Tracing Task. This task measures distress tolerance as persistence on the task. In this task, participants use a computer mouse to move a cursor around a monitor to trace over a star shape without leaving the shape’s lines. The mouse is programmed to move the red dot in the reverse direction. If the participant moves the red dot outside of the lines of the star, or stalls for more than 2 sec, the red dot returns to the starting position and there is a loud buzzing noise. There is a simple

practice task before the experimental task. In the experimental task, participants can end the task at any time, but the longer they persist in the task the more points they earn. This task lasts up to 20 min.

2) Effort Expenditure for Reward Task (EffRT). This task measures effort-based decision making. On each trial, participants choose between two different task difficulty levels to obtain monetary rewards. For all trials, participants make repeated manual button presses within a short amount of time. Each button press raises the level of a "bar" viewed onscreen. If the bar is raised to the top within the allotted time period, the participants wins the points for that trial. Each trial offers a choice between two levels of difficulty: a "hard" task and an "easy" task. Hard task trials required the subject to make 100 button presses using the non-dominant little finger within 21 seconds, while easy task trials require the subject to make 30 button presses using the dominant index finger within 7 seconds. Completion of easy task trials will earn 1 point. Hard task trials could earn between 1.24 and 4.30 points. However, the probability of earning the points for successful task completion is 88%, 50%, or 12%. The probability of earning points is indicated onscreen at the start of each trial. At the end of each trial, participants are shown whether they completed the task on time or not, and earned the points or not. Participants have 20 min to play as many trials as they are able.

For completing these optional tasks, participants will be compensated $20 plus they can earn up to an additional $5 per task ($30 total) based on their performance.

Table 1. Summary of the Schedule and Purpose of Assessments.

PURPOSE/INSTRUMENT	Rater	TIME OF ADMINISTRAION							
		Phase I BUP/GBP				Phase II GBP/NTX			
		Pre-TX	3 X Weekly	Weekly (typically Day 3)	Day 5 Week 3	Days 1 and/or 2 NTX transition	Days 4 and/or 5 NTX transition	Weekly (typically Day 3)	Week 16 (+/- 1 week)
Screening Variables and Predictors of Outcomes									
Demographics Form	**RS**	**X**							
Medical History	**RS**	**X**							
Substance Use History	**RS**	**X**							
PRISM-5	**RS**	**X^**							
Distress Tolerance Scale	**P**	**X^**			**X**			**X****	**X**
Breath-holding Endurance	**RS**	**X^**			**X**			**X****	**X**
Mirror tracing task	**RS**	**X^**							
EffRT task	**RS**	**X^**							
State Trait Anxiety Inventory	**P**	**X^**			**X**			**X****	**X**
Anxiety Sensitivity Index	**P**	**X**			**X**			**X****	**X**
SOCRATES	**P**	**X^**			**X**				
Columbia Suicide Severity Rating Scale	**P**	**X+**							
Assessment of Outcome: Substance Use									
Urine Drug Screens (12 panel)	**P**	**X**	**X**			**X**	**X**	**X**	**X**
Weekly Drug Use	**RS**	**X**		**X**				**X**	**X**
Weekly Craving	**RS**			**X**				**X**	**X**
Physical/Psychological Symptoms									
Subjective Opiate Withdrawal Scale (SOWS)	**RS**	**X**	**X**			**X**	**X**	**X**	**X**
Medication Side Effects Checklist	**RS**			**X**		**X**	**X**	**X**	
Clinical Opiate Withdrawal Scale (COWS)	**RS**		**X**			**X**	**X**	**X**	**X**
Vitals (BP, HR, RR, T)	**RS**	**X**		**X**		**X+***	**X+***	**X+***	
Symptoms Form	**RS**		**X+**			**X**	**X**	**X**	
Pittsburg Insomnia Rating Scale	**RS**			**X**				**X**	**X**
Pittsburg Sleep Quality Index	**RS**	**X^**			**X**			**X****	**X**
Hamilton Anxiety Scale	**RS**			**X**				**X**	**X**
Hamilton Depression Scale	**RS**			**X**				**X**	**X**

Other									
Blood Chemistries (CBC, Chem 20 to include LFT's) and Urinalysis	**P**	**X**				**X***			
Pregnancy Test (women)	**P**	**X**				**X**			
Breath sample to test alcohol levels	**P**		+						
Buprenorphine blood level	**RS**					**X**			
Gabapentin blood level	**RS**					**X**			
ECG	**RS**	**X**							
Heart Rate Variability Assessment	**RS**			**X**					
Employment Assessment	**RS**	**X**							**X**
Endpoint Rating Form	**RS**							**X**++	
Monetary Choice Questionnaire	**RS**	**X**			**X**				

RS—Research Staff; **P**—Participant. **X**=assessment performed (at specified time point). [^ = during intake or week 1] [*=Liver function tests, bup and GBP levels only]
[** = only at week 8 and 12] [+*=orthostatic vitals, week 4 only] [+=completed during the trial as clinically necessary] [++=Completed after discharge from active treatment protocol]

An *Employment Assessment* form consisting of up to 3 questions regarding employment activities during the past 7 and/or 30 days will be administered at intake and at the 16-week follow-up. The *Columbia–Suicide Severity Rating Scale* [128] will be done at either screening or intake as well as during the study if clinically indicated. Breath analysis for alcohol will be performed as clinically indicated at any time point, although current alcohol physiological dependence is among the exclusion criteria. One of the coded urine samples obtained each week during weeks 2- 5 will be frozen, and those from individuals in the GBP group will be sent to the core laboratory of Dr. Hendrickson to determine quantitative urine riboflavin levels, especially if GBP blood levels are disparate. Blood chemistries (SMA 20, CBC, which will be done using Quest Diagnostics) and ECG as well as a general physical examination (completed by the study physician) will be performed during screening. A blood sample for liver function tests will also be drawn and results obtained from Quest Diagnostics prior to week 4 NTX injection. Blood samples obtained during week 4 will be processed, frozen and stored until sent to Dr. Hendrickson's laboratory for analysis of BUP and GBP levels.

At every visit, participants are asked whether they are experiencing any symptoms. The onset, duration, quality, and severity of any symptoms are recorded on the *Symptoms Form* and tracked to resolution. If symptoms are severe, then the medical staff is notified immediately. These symptoms are also discussed at weekly team meetings to ascertain whether the symptoms meet criteria for an adverse event. If so, attribution and severity are also determined.

The hypothesis posed under **Specific Aim 1** (regarding efficacy and tolerability of GBP during and immediately following BUP detox) will be tested by comparing drug-screen results, withdrawal measures, craving, sleep quality and adverse events between GBP and placebo groups during weeks 2-3 and day 1 of week 4. The hypothesis posed under **Specific Aim 2** (regarding acceptability/feasibility of transition to NTX therapy) will be tested by determining retention, reasons for dropout, drug-screen results and side effects during the oral NTX induction (week 4) and depot NTX therapy (weeks 4-8). Queries posed under **Specific Aim 3** (regarding prognosticators) will determine whether salient factors such as sex, other drug use, dependence diagnoses, distress tolerance measures, caffeine use, etc.: **a)** differentially impact response to GBP vs. placebo on outcomes during detox, **b)** are associated with differential outcomes during transition to NTX and **c)** are associated with differential longer-term outcomes at week 16.

J. Timeline. We estimate that we will develop standard operating procedures during months 1–3 and enroll 2-4 participants/month during months 4–53, allowing for major holidays and staff vacations. All study procedures will be completed by month 55 and follow-up interviews by Month 58. We will complete data analyses and manuscript preparation by Month 60. These data, if positive, will be used to support further research on adjunct GBP during BUP detox as well as provide preliminary feasibility data for outpatient transition to NTX therapy.

8. Data Analysis Methods:

We will compare baseline characteristics of the two groups using the intent-to-treat sample with analyses of variance for continuous variables (e.g., age) and Chi^2 analyses for categorical variables (e.g., sex, race) to determine whether any significant baseline differences have accrued despite randomization. In addition, given that later phases (i.e., transition, depot NTX therapy) may have different sample configurations due to anticipated dropout, we will similarly compare the two groups on participant characteristics. If we find significant baseline differences in variables within a phase or at each subsequent phase relative to the one prior, these differences will be informative of factors associated with treatment outcomes. For those variables found to affect outcome, we will use contingency tables with stratification or add these factors to the appropriate random regression models to adjust for these differences.

Specific Aim 1: Efficacy and tolerability of GBP versus Placebo during and immediately following BUP detox. For data during the BUP taper (weeks 2-3), dependent variables obtained at several time points (e.g., urine sample results for opioids, opioid withdrawal symptoms scores) will be entered into random regression models, also known as hierarchical linear models (HLMs), to determine whether scores change differentially across treatment groups [154, 155]. Continuous data will be analyzed longitudinally with MIXREG, an HLM modeling program for continuous measures [156]. Dichotomous urine results (i.e., negative or positive) will be analyzed longitudinally using the SAS procedure GLIMMIX, which allows an HLM modeling program for ordinal outcome measures [157]. We will use all available data in our analyses and will make no attempt to interpolate missing data. HLM methodologies fit a regression line for each participant, effectively interpolating missing data, before deriving final estimates. This approach of modeling repeated measures is specifically designed for use in repeated measures designs with missing data, allowing for intra-participant serial correlation and unequal variance and covariance structures over time. These problems, common to clinical trial data, are solved by incorporating available trend data for each individual with information on the behavior of the group from which the participant is drawn. If there are any significant baseline differences, the variable will be added as a cofactor in the HLM analyses. We will examine differences in retention using Kaplan-Meier Survival Analysis. Analyses will be done on those who participated long enough to start the BUP taper, as well as during GBP induction to detect possible differential dropout before the taper. To determine whether treatment group differences occurred in 1) success of retention from the BUP detox to the NTX transition and 2) eligibility to undergo oral NTX induction, we will build 2 X 2 contingency tables using percentages of participants in the GBP vs. placebo groups who 1) return on day 1 of week 4 versus drop out after completing the taper, and 2) test negative versus positive for opioids. The type, severity, and frequency of adverse events will be compared across groups. All analyses will employ a significance level of $\alpha = 0.05$, and all tests are two-tailed.

Specific Aim 2: Acceptability and feasibility of outpatient transition to and maintenance on depot NTX therapy. Because there are two phases to NTX therapy transition (i.e., 4-day oral induction and up to 8-week depot NTX), data obtained during these phases will be analyzed separately. For the oral NTX induction, descriptive statistics will be used to report the percentage of abstinent participants who receive the 4-day oral dosing. Urine data collected each day during the 4-day induction will be entered into random regression models similar to those above to determine whether changes in illicit opioid or other drug use occurred over time. To obtain pilot data on the association between treatment group (GBP vs. placebo) and successful induction, data regarding the percentage of those receiving oral NTX and the NTX injection or not in the GBP vs. placebo groups will be entered into a 2 X 2 contingency table. The type, severity, and frequency of opioid withdrawal and/or adverse events will be compared across groups. Reasons for not receiving the NTX injection will be summarized.

For the NTX phase (weeks 4-12), dependent variables obtained at weekly time points (e.g., urine sample results for opioids and other drugs, side effect scores, opioid withdrawal scores, etc.) will be entered into random regression models (HLMs) to determine whether scores change differentially over time [154, 155]. Continuous data will be analyzed longitudinally with MIXREG [156]. Dichotomous urine results (i.e., negative or positive) will be analyzed longitudinally using the SAS procedure GLIMMIX [157]. We will examine differences in study dropout during this phase using Kaplan-Meier Survival Analysis. Our principal

analyses will be done on those who participated long enough to start the depot NTX therapy. The type, severity, and frequency of adverse events will be recorded and summarized.

Specific Aim 3: Identify prognosticators of treatment outcomes. Predictors of treatment efficacy during each phase will be examined using baseline assessments (e.g., sex, level of opioid use, distress tolerance scores, etc.). We will evaluate general predictors of successful outcomes (with success as defined above) regardless of treatment type and predictors of differential response to treatments. Depending on the distribution of participants with moderate versus severe opioid dependence, severity of opioid dependence will also be examined as a prognosticator. Our basic analytic strategy will be to dichotomize groups into the presence and absence of a dichotomous predictor variable (e.g., female or alcohol dependence diagnosis) and then to examine the relative predictive values on treatment outcomes by adding each factor to the log linear analyses for single time point outcomes and HLM for longitudinal measures such as frequency of self-reported drug use, opioid-negative urines and craving measures. Each continuous measure (e.g., HAM-A, distress tolerance scores) will be entered as a covariate in the above analyses.

Longer-Term Outcomes. Continuous data from the 16-week follow-up interview will be initially entered into repeated measures ANOVA's with group (GBP vs. placebo), successful completion of detox (yes vs. no), successful induction onto oral NTX therapy (yes vs. no), and successful transition to depot NTX therapy (yes vs. no) as factors. Dichotomous follow-up data will be entered into Chi^2 tables for each phase. Longitudinal data captured during each phase of the study and at follow-up will be entered into random regression models as above, and piece-wise comparisons will be made between each phase. For all analyses, a p value <0.05 will be used to infer statistical significance.

Sample Size. PASS (Power Analysis & Sample Size) Software was used to estimate power. Sample size for the intent-to-treat sample was determined based on having enough power during and immediately following the BUP taper to detect group differences in the primary outcome of illicit drug use and identify potential prognosticators. Based on the proportion of participants in the GBP versus placebo groups having opioid-free urines on the last day of the BUP taper from our pilot trial with GBP [31, 129], treating the one missing value as positive, a difference in the percentage of participants with opioid-free urines at the end of detox as well as immediately prior to initiating NTX therapy will be detected with >90% power with an analysis sample size of 106 total participants anticipated to remain for NTX transition. Thus, our sample size is adequate to detect differences for our primary outcome during and immediately following the detoxification. Meanwhile, there has been minimal, if any, study of sex (or other bivariate prognosticator) differences for the effect of an adjunct medication for opioid dependence, much less for prescription opioid dependence. This study will provide unique data to quantify a potential difference. Given our expected sample size of 150 participants entering the BUP detox phase, the study will have >80% power for an effect size of 0.29 (small effect size), and 106 participants eligible for NTX transition will have >80% power to detect an effect size of 0.35 (considered a "medium" effect size).

9. Location of Study:

The study will be located on the fourth floor of the Psychiatric Research Institute at UAMS.

10. Payment to Participant:

Participant retention can be challenging for detox and NTX therapy studies. To facilitate attendance and offset inconvenience, participants in our study will have the opportunity to earn both fixed monetary payments (for attendance at longer visits and study medication container returns) and compensation based on a low-cost "fishbowl" contingency management procedure (for clinic visits) that has been shown to enhance retention and attendance [158, 159]. Contingency management is increasingly used in community treatment settings for this purpose [160-164]. In the fishbowl procedure, participants will have the opportunity to draw chips, according to an escalating ratio schedule. Chips have varying dollar amounts from $1.00-$100.00 (or "Good Job!") written on them. Participants can receive, on average, up to $35 for participating in the screening, $90 for bottle returns and attendance at all required appointments during the

detox phase, $150 for attendance at all required appointments during the transition to NTX injection, $480 for returning blister packs and attendance at all required appointments during NTX therapy, and $50 for attending the week 16 follow-up interview. In our previous studies at Yale University and UAMS, we have developed and implemented procedures to successfully recruit, enroll, and ensure the safety of participant populations. To help ensure good follow-up rates, staff will check in with participants or their contacts monthly post-participation to make certain contact information is up-to-date.

11. Source of funds:

NIDA

12. Probable Duration:

Up to Five Years

13. Risks and Benefits:

1. Buprenorphine. Buprenorphine is approved by the Food and Drug Administration (FDA) to treat opioid dependence. Common side effects of buprenorphine include sedation, nausea, dizziness/vertigo, sweating, hypotension, vomiting, miosis, hypoventilation, confusion, blurred vision, euphoria, gastrointestinal distress, headache, weakness/fatigue, dry mouth, nervousness, depression, slurred speech, paresthesia, hypertension, tachycardia, bradycardia, constipation, pruritus, diplopia, visual abnormalities, urinary retention, dreaming, flushing/warmth, chills/cold, tinnitus, conjunctivitis, Wenckebach block, psychosis [141] and sleep disturbances.

2. Detoxification with Buprenorphine. In an opioid-dependent individual, slowly decreasing the buprenorphine dose over time can produce temporary signs and symptoms of opioid withdrawal such as malaise, nausea, nasal congestion, abdominal symptoms, anxiety, myalgia, insomnia, sweating, diarrhea, tremor, body ache, muscle spasms, rhinorrhea, and piloerection. These symptoms can be unpleasant, but are not medically dangerous [141].

3. Gabapentin. The most commonly reported side effects of gabapentin include somnolence, nausea/vomiting, gastrointestinal distress, ataxia, and vertigo [165]. Other side effects include asthenia, peripheral edema, infection, fever, confusion, accidental injury (due to a fall, for instance), worsening of depression, suicidal thoughts, peripheral edema, diarrhea, dry mouth, constipation, clumsiness, loss of muscle coordination, abnormal gait, conjunctivitis, abnormal thinking, abnormal vision[165], and possibly vivid and disturbing dreams. The dose of gabapentin (1600 mg/day) chosen for this study was based on 1) results of our prior study showing that this dose was well tolerated and alleviated craving and opioid use in prescription opioid-dependent patients stabilized on BUP [31, 129]; 2) results of other studies showing that gabapentin at 1200-1800 mg/day, but not 900 mg/day, appeared to improve outcomes during opioid detoxification [97-100]; and 3) a review by Ho et al. [166] that showed a typical dose of gabapentin that was used adjunctively with opiates to treat postoperative pain was 1200 mg, while some studies did use doses as high as 1800 mg.
   According to a safety communication by the Food and Drug Administration (FDA) on 12/19/19, serious breathing difficulties may occur in patients who have respiratory risk factors and using gabapentinoids such as gabapentin. Risk factors include the use of opioid pain medicines and other drugs that depress the central nervous system, and conditions such as chronic obstructive pulmonary disease (COPD) that reduce lung function. The elderly are also at higher risk.

4. Buprenorphine plus Gabapentin. There have been no reports of interactions or serious adverse reactions between buprenorphine and gabapentin. In our pilot study [31], the following adverse events

occurred during gabapentin induction that were at least possibly study-related and showed a greater incidence in the gabapentin than placebo group: nausea/vomiting (gabapentin: N=2/16; placebo: N=1/14), somnolence (gabapentin: N=2/16; placebo: N=0/14), sleep disturbances (gabapentin: N=2/16; placebo: N=0/14), loss of motor skills (gabapentin: N=1/16; placebo: N=0/14), and lightheadedness (gabapentin: N=1/16; placebo: N=0/14). All events were mild and did not require an intervention, except for the lightheadedness, which occurred on day 4 during induction onto gabapentin. Even though vital signs were within the normal range, because this was a pilot study, a conservative approach was used and the gabapentin induction discontinued for this participant. Thus, we anticipate no pharmacokinetic interactions between these agents. There has also been one case study looking at gabapentin and buprenorphine and there was no adverse reaction. This case study was based on a previous 2006 review that showed that gabapentin produced a decrease in opioids consumed postoperatively [166, 167]. Nevertheless, based on the 12/19/19 safety report by the FDA, serious breathing difficulties may occur as a result of combined use of gabapentin and opioid pain medicines.

5. Clonidine. The use of clonidine to alleviate symptoms of opioid withdrawal is a standard clinical practice. Clonidine produces side effects such as dry mouth, drowsiness, sedation, dizziness, headache, fatigue, and changes in heart rate and blood pressure. The dose employed is within the recommended daily dose range [168].

6. Naltrexone. Both oral and injection formulations of naltrexone are approved by the FDA to treat formerly physiologically dependent opioid abusers. Oral doses of naltrexone may be associated with an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. Other commonly reported side effects include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, low energy, joint and muscle pain, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills. If participants do not keep well hydrated, these symptoms can result in moderate to severe dehydration that can lead to low blood pressure. Patients taking naltrexone may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics [169]. The remaining precautions for oral naltrexone are similar to those for Injectable Naltrexone and are outlined below.

   Naltrexone injectable is contraindicated in patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent of the injection [169]. Other potential risks include eosinophilia pneumonia, unintended precipitation of opioid withdrawal, and opioid overdose following an attempt to overcome opiate blockade. Other precautions include depression and suicidality, injection site reactions, renal impairment, use in patients with thrombocytopenia or any coagulation disorder, and use in patients who are pregnant, plan to become pregnant, or are breastfeeding. Furthermore, the most common side effects associated with the use of injectable naltrexone include injection site reactions, nausea, tiredness, headache, dizziness, vomiting, decreased appetite, and muscle cramps. Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. Other commonly reported side effects include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, low energy, joint and muscle pain, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills. Patients taking naltrexone may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. Naltrexone and its primary metabolite are excreted primarily in the urine, and caution is recommended in administering the drug to patients with renal impairment. The risk of suicide is increased in patients with substance abuse with or without concomitant depression. This risk is not abated by treatment with naltrexone. In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more

prolonged. While naltrexone is a potent antagonist with a prolonged pharmacologic effect, the blockade produced by naltrexone is surmountable. This is useful in patients who may require analgesia, but poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose. Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses. Patients will be warned of the risk of hepatic injury and advised to stop the use of Naltrexone and seek medical attention if they experience symptoms of acute hepatitis. The risk of overdose on opioids is transiently increased as naltrexone's effects diminish due to naltrexone-induced increases in sensitivity to opioids. Patients will also be warned not to use opioids due to the risk of overdose during the first two weeks after the effects of depot NTX (or several days after oral NTX) have worn off.

7. Naltrexone plus Clonidine. Clonidine has been shown to alleviate some of the signs and symptoms of opioid withdrawal associated with very low doses of naltrexone [170]. The most common side effects included dizziness, fatigue and gastrointestinal upset [171].

8. Naltrexone plus Clonidine plus Gabapentin. Gabapentin with clonidine may increase clonidine-induced dizziness and drowsiness as well as produce difficulty thinking. Gabapentin and clonidine have shown a synergistic effect on inhibiting allodynia in a spinal nerve ligation model in the rat [172]. Gabapentin has also been shown to potentiate clonidine-induced anti-nociception in the formalin test [173]. Thus, we expect that gabapentin will potentiate clonidine's impact on alleviating naltrexone-induced withdrawal symptoms. This combination may also produce greater sedation and stomach upset.

9. Naltrexone plus Gabapentin. To our knowledge, no laboratory studies have examined the interaction between gabapentin and naltrexone. However, gabapentin at doses up to 1,200 mg/day was examined concomitantly with oral naltrexone in alcoholic patients [174]. Side effects were mild to moderate in severity and included dizziness (both naltrexone alone and naltrexone plus gabapentin), daytime somnolence, blurred vision and premature ejaculation.

10. Other risks.
    a. Blood Drawing. Participants will have approximately 40 cc of blood drawn as a result of their participation in the study. Blood drawing can cause some pain and result in a hematoma.
    b. Nonspecific Risks. Other risks from the counseling, rating scales and urine collections are not beyond usual clinical procedures in a substance-abuse treatment program. Confidentiality of these results are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the PI or Data Manager.
    c. Riboflavin. The addition of riboflavin to the capsules may turn the participants' urine bright yellow.
    d. Performance Tasks. There may be some affective discomfort during the performance of the Mirror Tracing Tasks. Participants are allowed to end the task at their discretion.

14. Protection of Participants:

A. Participant Recruitment and Consent Procedures.

Opioid-dependent participants seeking detoxification from opioids and short-term NTX therapy will be recruited via newspaper ads, radio ads, flyers, word-of-mouth, online ads, social media, email, and referrals. A research staff member experienced in obtaining informed consent will interview participants to determine interest in participating in this trial. Aspects of the study procedures, risks, and potential benefits will be explained, and any questions will be answered. The participant will be asked questions

to ensure an adequate understanding of the study and encouraged to read through the consent form a second time. The participant is asked to read aloud a section of informed consent to ensure that s/he can read (if the person is illiterate, a witness will be found to be present for the entire informed-consent process). If the participant indicates any hesitation about signing the consent form, s/he will be encouraged to leave with the consent form to consider the matter at leisure. If a participant indicates a desire to sign the consent form, both the participant and staff member will sign the form. The staff member will document that the informed-consent process occurred and whether the person's questions were addressed to his/her satisfaction. If at any time the participant exhibits intoxication, sedation, over-agitation, or some form of inattentiveness, the consenting process will be stopped and the interview rescheduled. After obtaining written informed consent for participation in the study and completing all screening procedures, a study physician will interview the participant and review all medical and psychiatric data prior to admitting the participant and beginning medication.

B. Protections Against Risk.

1. Our inclusion and exclusion criteria will be applied by experienced professionals, who will be carefully trained and monitored in order to accept only appropriate participants into the study. Thus, effective screening will exclude participants who would be placed at a greater risk. Risk level is determined by the medical and psychiatric history, drug use history, the physical examination, and the laboratory studies done prior to beginning this research protocol.

2. The close monitoring of objective and subjective drug effects by direct observation, interviewing, and self-ratings will allow objective evaluation of the effects of gabapentin on detoxification from buprenorphine and transition to depot NTX therapy. If at any point during the trial adverse reactions become excessive, the participant will be removed from the study. If the participant drops out of the study, alternative treatment will be offered. If a person relapses to opioid use following the BUP detox or following NTX therapy as determined by a study physician, he or she will be offered BUP as a rescue medication (2 mg) and referred to the Center for Addiction Services and Treatment opioid agonist maintenance program. Those who do not transition to NTX but are opioid abstinent will be offered alternative treatment as well as the option to continue to participate in the study without NTX therapy.

3. Based on current recommendations by the manufacturer, pregnant women will be excluded by history and urine pregnancy test. They may, however, have the opportunity to enter the UAMS methadone or buprenorphine maintenance program. Women capable of becoming pregnant will be asked to use effective birth control in order to participate and to inform the study physician if their birth control plans change after being accepted into the study. Participants who become pregnant will be transferred to an area program.

4. On each day of transition to oral NTX, participants may need to submit an opioid-negative urine sample in order to receive the medication (if relapse to regular opioid use is indicated as determined by physician assessment, participants will not receive NTX). If positive, the participant may be invited to return the next day. If the sample is negative or regular use is not indicated, on all days that include clonidine administration (days 1-4), participants' orthostatic vital signs and symptoms will be monitored prior to and following clonidine administration as well as 2 hours following initial naltrexone administration, to assure orthostatic hypotension does not occur at severity indicating increased risk. If the participant experiences lightheadedness or dizziness and has evidence of orthostatic hypotension with BP drop of > 20 mm Hg systolic or >10 mg Hg diastolic, accompanied with an increase in pulse >20 beats per minute, then the vitals will be repeated in 30 minutes. If the orthostatic changes persist at the time of the second measurement, then the transition to NTX will be halted on that day. The participant will be invited to return the following day and the procedures from the previous day will be

repeated, including a drug screen for opiates and vitals to include orthostatic measurements. If drug screen is negative for opiates and no orthostasis is present, then the participant will resume the process that was attempted on day one. If orthostatic changes recur, then the participant will not be transitioned to NTX; his/her study participation may be ended, in which case s/he will be referred to alternative treatment, if desired.

5. During the NTX induction week, participants will be reminded to hydrate prior to clinic attendance. Drinks containing electrolytes will be provided to participants each day of the induction and participants will be encouraged to drink at least 20 oz during their 2+ hour visit. Clonidine will be given each day of the oral NTX induction to ease some of the typical discomfort experienced by participants during this time.

6. Breathalyzer readings will be taken if alcohol use is suspected. If a participant has a breath-alcohol concentration of ≥0.08%, they cannot receive study medication until it drops below 0.08%. If the participant wishes, s/he can come back for a repeat alcohol breath analysis reading before the end of clinic dosing hours.

7. Research staff members monitor participant's status on at least a thrice-weekly basis during weeks 1-4 and weekly during weeks 5-12. The research counselor will monitor psychiatric symptoms such as depression and anxiety on a weekly basis. Should symptoms worsen, the study physician will evaluate the participant to determine whether he/she could safely continue in the study. We will evaluate suicidality using the Columbia Suicide Severity Rating Scale during either screening or intake and as clinically indicated thereafter. Those who answer yes to the second question regarding current (meaning last 30 days) suicidal thoughts AND to at least one of questions 3, 4, and 5 about plans or intention to attempt suicide in the past month or answers Yes to question 6 in the past 12 months will be excluded during screening. If current suicidal ideation or a suicide attempt occurs during the study, the physician will be notified, campus police and/or MEMS called (if this occurs on campus) or 911 called (if this occurs off campus) and the participant removed from the study. Participants will be given telephone numbers to call 24 hours a day in case of emergency. An on-call study physician will be available at the after-hours number.

8. Confidentiality will be protected by having all records identified by code number only, with the master file that matches subjects' names with their study doses kept under lock by the data manager and pharmacy. To prevent any of the investigators from inadvertently discovering the medication dose assignments of participants, drug records will be maintained by ID code only in the pharmacy and will be made accessible to research staff only after a participant has completed the study. A Certificate of Confidentiality will be obtained from the Department of Health and Human Services when the protocol is approved by the IRB and will be submitted to the IRB prior to participant enrollment.

9. Participants will be removed from the study if they experience any of the following: loss of consciousness, moderate-to-severe muscle weakness, seizure, or syncope, as determined by study physician. If at any point the participant is found to have orthostatic hypotension after complaining of lightheadedness or dizziness, then the vitals will be repeated within 30 minutes. If orthostatic hypotension has not resolved, then the physician will be notified for further instructions. If a participant is required to quarantine due to COVID-19 during phase I BUP detox, they will be discharged from protocol and study physician will provide a take-home BUP detox taper individually tailored to where in the phase 1 protocol the participant is. If a participant is required to quarantine due to COVID-19 during phase II, they may remain on protocol and complete assessments remotely (by phone or teleconference). If this occurs, urine drug screens and COWS assessments will not be able to be done until participants are no longer required to quarantine. If a participant is unable to provide a urine drug screen at week 8 due to quarantine, they will not be eligible for the second Vivitrol injection, be

discharged from protocol and be offered referrals to treatment as necessary.

10. All participants will be instructed to refrain from opioid use for at least 24–48 hours prior to their first dose of buprenorphine or naltrexone in order to decrease the likelihood of precipitating opioid withdrawal symptoms. If the participant had used within the window, this is discussed with the physician and the decision will be made with the participant to either continue with the induction (with the participant understanding they may experience withdrawal) or reschedule. Participants are monitored after the initial buprenorphine dose to ensure withdrawal symptoms don't emerge (if they do, participants will be supported and a physician will be available to evaluate if symptoms become severe.) If symptoms emerge, the second dose of buprenorphine on day of induction may be held, as determined by physician. Buprenorphine doses will almost always be ingested at the clinic (except during holiday weekends, inclement weather, or if participating under truncated visit schedule due to COVID-19) in order to decrease the likelihood of diversion and/or intravenous use. Participants will also be advised of the increased risk of overdose on opioids should they use opioids during the first two weeks after the effects of depot naltrexone (several days after oral naltrexone if participants did not transition to the depot formulation) have worn off.

11. Participants will be issued a card at admission that states that the holder is in a UAMS research study during a certain time period, is potentially receiving study medications that should not be stopped abruptly and/or may block the effects of opioid medications, and, if, for any reason, the holder cannot make the scheduled appointment, then s/he should call the appropriate phone numbers listed on the card. If a participant notifies us that s/he is incarcerated and will be detained for at least 3 days, we will discharge the person from the study, break the blind, and inform the participant which medication s/he was taking as well as what types of symptoms to be watchful for. The participant also will be told that s/he should notify the prison medical or other authority if symptoms develop. The consent form will provide participants with telephone numbers to call 24 hours a day. Upon injection with Vivitrol, participants will be issued a similar card specific to Vivitrol; name/contact information of the study physician will be recorded on the card in case of medical emergency.

12. The trial will be stopped if investigators discharge 15 participants (10% of total sample) from the study due to study-related adverse effects. The trial will be stopped if 3 participants experience study-related serious adverse events or if 3 participants experience serious gabapentin/opioid-related events of a behavioral or physical nature. This requirement to terminate the study is based on 5 out of 150 active participants (3.0%).

13. All personnel involved in this project will undergo biannual training in protection of human subjects.

Potential Benefits and Risk/Benefit Ratio. The risks associated with this study include the effects of the study medications, detoxification, naltrexone transition and blood sampling. In addition, participants will have the inconvenience of participating in the study. Benefits offsetting these risks include that participants will undergo a medical evaluation, will be tapered off opioids will receive short-term naltrexone therapy and psychotherapy, and may experience abstinence from illicit opioids. The information gained in this study can assist us in developing more effective strategies for treating prescription opioid dependence, which ultimately would be of great benefit to society. We believe that the benefits more than justify the risks of participating in this study.

15. Data and Safety Monitoring Plan

A. Data Acquisition, Collection, Transmission, and Entry

Each research staff member is instructed on the timing of assessments for each individual. Checklists are used to ensure that assessments are obtained at the time indicated and are reviewed by the data manager, therapist and/or principal investigators.

For the computerized assessments, the programs were created in such a way that 1) each participant has his/her own template of questionnaires that are prescheduled based on the timing of assessments outlined in the protocol, 2) each question must be answered in order to go to the next task or question, 3) each answer has a "built in" range of appropriate values such that out-of-range answers will not be accepted. The computer data will be backed up onto a secure server or flash sticks and brought to the data manager's office, who will then export the date to excel or SPSS and check for missing data. The devices(s) used to collect data will be kept in a locked office when not in use.

For paper assessments, the research assistant reviews the assessments for missing/out-of-range values and then brings them immediately to the data manager and/or principal investigator(s) to review as well. If any missing or inaccurate values are found, the participant will be asked to complete those again. Paper data will be entered into the computer independently by two different research staff trained to perform data entry, and the data manager will employ a verification program to determine and correct any discrepancies based on source data. If the data manager notices recurring data entry errors, he/she will inform the person(s) responsible and retrain them as necessary.

For urine data, participants will be observed by a member of the same sex (or nurse) while they provide a urine sample to ensure that the sample truly came from a particular participant. In addition, research assistants check the temperature of the container of the urine sample to discern whether the container is cooler than normal. When a urine sample is suspect, the participant is asked to submit another sample. Urine data will be downloaded from the Redwood Toxicology Laboratory into an excel document. Research staff trained in phlebotomy will obtain blood samples. Riboflavin, gabapentin and buprenorphine assay results will be entered into the computer independently by two different research staff members as before.

Prior to statistical analyses, the data manager and/or principal investigator will check the data for mislabeling, missing data, out-of-range data, etc., and change/correct as appropriate based on source data. The data manager will also assign study condition per study ID for analysis purposes. A master data set will be created with at least two back-ups. One of these back-up disks will be given to the statistician, with a data assessment dictionary, for analysis.

B. Procedures in Place to Ensure the Validity and Integrity of the Data

The research assistant will have at least a Bachelor's level education and the research therapists at least a Masters level education (or relevant experience) and previous experience in clinical rating and/or interviewing. Under the direct supervision of the principal investigators and/or data manager, the rater will receive one month of training on the assessments, including the PRISM CV-V. Training may include viewing videotapes, observation of interviews and ratings, co-rating and interviewing with the supervisor present. In order to conduct interviews for this study, it is required that the rater complete three consecutive conjoint interviews on which DSM V diagnoses are in complete agreement with those of more experienced raters. After training, reliability will be spot-checked on a semi-annual basis.

As for training on the other scales, the investigators and/or data manager first provides a training session on the background of the particular scale and how it is to be completed. Then the staff member observes the completion of the assessment by an experienced rater on at least 3 occasions. Afterwards, the staff member completes the assessment in the presence of an experienced rater on at least 3 occasions, with feedback given each time until the supervisor is confident that the person understands the assessment and completes it properly. Thereafter, assessments are checked on a continuous basis for appropriate completion and constructive criticism is given as necessary. Staff members also undergo a refresher on assessments every 6 months.

C. Collection and Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs).

All adverse events (AEs) occurring during the course of the study must be collected, documented, and reported to the PIs. The occurrence of AEs will be assessed in an ongoing way. Each week study investigators will review the AEs from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs to the point of satisfactory resolution. A list of all AEs will be included in the annual progress report to NIDA.

The PIs and the Co-Investigators will determine whether an event meets the criteria of a serious adverse event (SAE) and/or an unanticipated problem involving risks to subjects or others (UPIRTSO). The PI will report AEs and SAEs on an annual basis and UPIRTSOs to the IRB in a timely fashion. The PI will report all SAEs such as deaths, hospitalizations and unexpected toxicity, whether or not study-related, to NIDA within 72 hours. The procedures for reporting these SAEs to NIDA include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. Outcomes of SAEs will be periodically reported to NIDA. A summary of the AEs, SAEs and UPIRTSOs that occurred during the year will be included in an annual report to NIDA.

The IRB communicates recommendations and decisions to the PI in a timely manner. In the event that the IRB takes an action that impacts the day-to-day operations of the trial (e.g., suspends recruitment, halts the trial), the PI will report those actions to the NIDA officer both verbally and in writing.

D. Data and Safety Monitoring (DSM) Plan

The PIs will be ultimately responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with reporting requirements. The trial also has a study monitor, Michael Mancino, M.D. A Data and Safety Monitoring Board (DSMB) will also monitor this study. Members will be given a copy of the DSM plan prior to study initiation and will have the opportunity to make any recommendations at that time. DSM will occur in an ongoing way throughout the study. In addition, DSM will be formally reviewed when 33%, 67% and 100% of individuals have been enrolled. The PI will provide a summary of the DSM report to NIDA on an annual basis as part of the progress report. The DSM report will include a brief description of the trial, baseline sociodemographic characteristics, retention data, disposition of study participants, Q.A. issues, regulatory issues, AEs and SAEs along with assessments of attribution and severity, any actions or changes with respect to the protocol, and efficacy analyses, if conducted. This report will be given to the members of the DSMB for review when 33%, 67% and 100% of individuals have been enrolled or more frequently as necessary. The DSM Board will meet upon review of the DSM report generated when 33%, 67% and 100% of individuals have been enrolled or more frequently as necessary. Whether risks of participation remain acceptable under the present protocol or modifications to the protocol are necessary while still maintaining scientific integrity of the project will be determined. Interim analyses will not be performed unless clinically indicated. All SAEs, such as death, hospitalization, and unexpected toxicity, will be reported to the IRB, FDA, and NIDA under expedited reporting. The procedures for this reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. We will report major protocol amendments or changes in the informed consent to NIDA, as well as any temporary or permanent suspension of patient accrual.

16. References:

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