Pro00046473

Discontinuation From Chronic Opioid Therapy For Pain Using a Buprenorphine Taper

Protocol v14

NCT02737826

Protocol v14

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1.0 Study Synopsis and Schema

1.1 Study Objectives

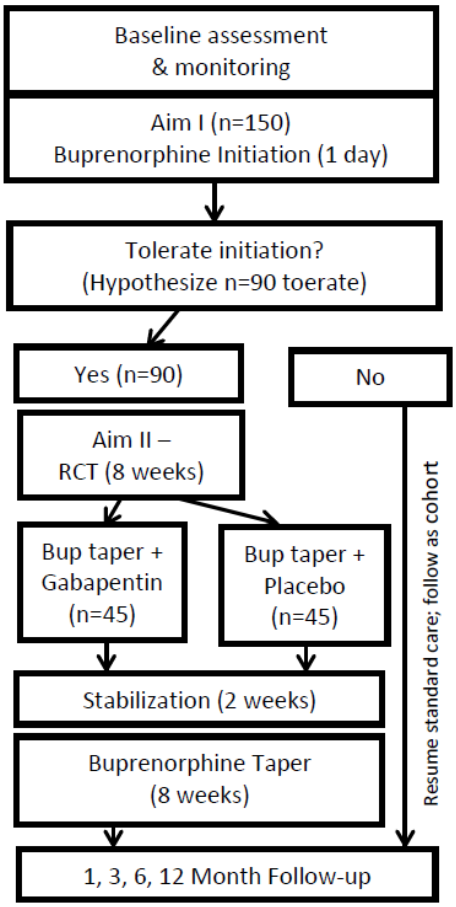
The primary objective of this proposal is to evaluate the feasibility and effectiveness of buprenorphine-assisted discontinuation from chronic opioid therapy for pain (COT-P) and to determine the role of gabapentin, an N-type calcium channel blocker, as an adjunctive agent to assist with opioid cessation. Secondary objectives are to identify patient characteristics (biological, psychological, and pharmacological) that predict (1) successful transition to buprenorphine, (2) successful buprenorphine taper, and (3) opioid cessation.

The central hypothesis of this study is that COT-P patients undergoing a buprenorphine taper with adjunctive gabapentin will have higher rates of opioid cessation when compared with those on buprenorphine/placebo. Secondary hypotheses are that patients will have decreased pain after buprenorphine initiation, and that those on adjunctive gabapentin will have lower withdrawal and pain scores when compared with placebo.

1.2 Study Design

This study will be conducted over four years to evaluate buprenorphine-assisted opioid taper in 150 individuals on COT-P who are (1) seeking assistance with opioid cessation and (2) willing to attempt buprenorphine-assisted taper. Because the fundamental question of how COT-P patients tolerate buprenorphine initiation is unanswered, we have divided this pilot proposal into two aims.

Figure 1. Study Design



1.2.1 Aim 1

1.2.1.1 Research Questions - Aim 1

The primary research question for Aim 1 is, "What is the base rate of COT-P patients who can transition to buprenorphine?" The secondary research question is, "Which patient characteristics (biological, psychological, and pharmacological) predict successful transition to buprenorphine?"

1.2.1.2 Hypothesis Aim 1

Aim 1 Main Hypothesis: It is expected 50% of the subjects transitioned to buprenorphine will tolerate buprenorphine.

1.2.1.3 Primary Outcome Measures – Aim 1

For Aim 1, the primary outcome measure is the **percentage of patients who tolerate buprenorphine initiation** within an 8-hour initiation period, as evidenced by (1) moderate-good level of pain control (same or improved rating on a 0-10 visual analogue scale for pain), (2) mild to no withdrawal symptoms (≤10 on the Clinical Opioid Withdrawal Scale), and (3) willingness to continue to the stabilization and tapering phase of the study.

1.2.2 Aim 2

1.2.2.1 Research Questions – Aim 2

Aim 2 will involve preliminary evaluation of buprenorphine tapering and opioid discontinuation for those on COT-P as well as the efficacy of gabapentin in assisting with discontinuation. The primary research questions for Aim 2 are: "What is the base rate of successful taper from buprenorphine?" and "What is the efficacy of gabapentin in improving completion outcomes during buprenorphine taper?" The secondary research questions are "Do subjects have more/less pain after transition and taper from buprenorphine?" and "Which

patient characteristics (biological, psychological, and pharmacological) predict successful taper from buprenorphine?"

1.2.2.2 Hypothesis – Aim 2

The primary hypothesis of Aim 2 is that COT-P patients undergoing a buprenorphine taper with adjunctive gabapentin will have higher rates of opioid cessation when compared with those on buprenorphine/ placebo. Secondary hypotheses are that patients will have decreased pain after buprenorphine initiation and that those on adjunctive gabapentin will have lower withdrawal and pain scores when compared with placebo.

1.2.2.3 Primary Outcome Measures – Aim 2

For Aim 2, the primary outcome measure will be **opioid cessation at 8 weeks**, measured through self-report, prescription drug monitoring data, and confirmatory UDS for a full panel of opioids.

1.2.3 Study Design Aims 1 and 2

During the screening/baseline phase, all subjects will be assessed to determine eligibility. These assessments may occur over one or more visits and include medical exams, mental health and pain assessments, collection of biological specimens and opioid withdrawal assessments.

Following the screening/baseline procedures, a 1-day induction visit will be conducted during which subjects will receive an initial 4mg dose of buprenorphine and will be observed. The observation periods will include assessment of opioid withdrawal symptoms and pain. Additional doses of buprenorphine will be administered as clinically indicated up to a cumulative dose of up to 16mg. If the subject does not tolerate buprenorphine after 16mg, they will be transitioned back to the prescribing physician. If the subject tolerates the buprenorphine and agrees to continue with the study, they will move into the stabilization/tapering phase of the study (Phase II).

The stabilization/tapering phase of the study will begin with a 2 week stabilization phase during which subjects will be randomized to receive either gabapentin or placebo titration in conjunction with the buprenorphine. Doses will continue to be closely monitored and adjusted as clinically indicated to determine the stabilizing dose of buprenorphine and the appropriately titrated dose of gabapentin/placebo. Subjects will attend weekly study visits and study staff will conduct additional phone visits as needed.

Following the stabilization phase, subjects will begin the tapering phase of the study. The dose of buprenorphine will be tapered over a period of 8 weeks to 0mg, during which subjects will continue to take gabapentin or placebo. Once the buprenorphine dose has been tapered to 0mg, subjects will go through a 1 week taper of the gabapentin/placebo. Subjects will continue to attend weekly study visits throughout the tapering phase and additional phone visits will be conducted as needed throughout the study.

The final phase of the study is the follow-up phase. Subjects will be monitored for opioid cessation which will be measured at 1, 3, 6, and 12-months post-study discontinuation/completion.

1.3 Study Population

150 males and females who are treatment-seeking for opioid discontinuation will be recruited. Subjects must be between 18 - 70 years of age, currently taking COT-P and voluntarily seeking opioid discontinuation. They must be willing to attempt buprenorphine-assisted opioid discontinuation and be randomized to gabapentin or placebo. Subjects must also have a current physician who is actively prescribing COT-P and who will collaborate with the research team as the patient enters the study.

Subjects must not have previous intolerance or allergy to buprenorphine or gabapentin and must not currently be treated with gabapentin, carbamazepine, phenytoin, MAO-inhibitors, fentanyl or methadone. Subjects must not currently use benzodiazepines, illicit drugs or certain sedating medications or QTc-prolonging

medications. Subjects must not meet DSM-V criteria for substance use disorder or have a concurrent medical or psychiatric condition that, in the study team's opinion, would preclude safe or meaningful participation.

2.0 Introduction and Specific Aims

The United States is in the midst of a prescription drug overdose epidemic, and one of the main populations at risk are the 9 million individuals maintained on chronic opioid therapy for pain (COT-P). While the benefits of COT-P continue to be debated, research indicates that a significant number of COT-P patients demonstrate improvement in pain and functional outcomes after opioid discontinuation. Reducing the number of individuals maintained unnecessarily on COT-P would significantly reduce the risk of developing opioid use disorders. Despite this, major barriers to opioid tapering exist (e.g., continued pain, fear of disabling withdrawal symptoms) and empirical evidence regarding optimal opioid discontinuation is critically needed. The overall goal of this study is to expand the evidence regarding opioid discontinuation when indicated for COT-P. In the *opioid addiction* population, evidence suggests that buprenorphine-assisted opioid cessation is the preferred method of detoxification, and gabapentin has been shown to improve outcomes in buprenorphine-assisted opioid detoxification. However, these interventions have not been well-studied in individuals on COT-P without addiction. The primary objectives of the current study are to: (1) evaluate the tolerability of buprenorphine initiation in patients on COT-P, (2) evaluate the efficacy of gabapentin up to 1600mg/day in improving outcomes for patients undergoing buprenorphine-assisted taper from COT-P using a placebo-controlled randomized design, and (3) identify potential predictors of opioid cessation. In order to accomplish this, we will conduct an intent-to-treat, double-blind, randomized controlled trial (8 weeks) of buprenorphine-assisted opioid discontinuation in 150 COT-P patients with an indication for opioid cessation. We will examine standardized, repeated dependent measures of clinical outcomes at pre-, mid- and post-treatment, as well as 1-, 3-, 6-, and 12- month follow up. The following specific aims are proposed:

Specific Aim 1: To determine the base rate of buprenorphine tolerability among COT-P subjects (N=150) with an indication for opioid cessation.

We will determine buprenorphine tolerability among patients on COT-P using a one-day, outpatient medically-supervised buprenorphine initiation protocol. Relevant baseline factors will be measured to identify predictors of buprenorphine tolerability (e.g., gender, opioid dose/duration, pain measures/characteristics). COT-P patients who tolerate buprenorphine initiation (defined by level of pain, opioid withdrawal, and willingness to continue with taper) will then proceed to Phase 2 (stabilization/tapering phase).

Specific Aim 2: To compare the efficacy of the N-type calcium-channel blocker, gabapentin, versus placebo in improving treatment outcomes (i.e., pain, opioid cessation) during an 8-week buprenorphine-assisted taper from COT-P.

After a 2-week stabilization period during which buprenorphine dose is stabilized and gabapentin or placebo is titrated, subjects will then complete a medically-supervised, 8-week buprenorphine taper. We hypothesize that gabapentin will result in significantly higher rates of opioid cessation at the end of treatment, as well as improved measures of pain and functioning. In addition, we hypothesize that patient pain phenotypes and opioid use characteristics at baseline will predict successful opioid cessation at 1-, 3-, 6- and 12-months post taper.

The proposed project is directly responsive to the mission of the National Institute on Drug Abuse in that it seeks to evaluate preventative interventions to decrease the risk of abuse, addiction, and related mortality among a group of high-risk individuals. The findings from this study will answer critical questions regarding successful buprenorphine initiation, the utility of gabapentin in assisting with buprenorphine-assisted taper from COT-P, and elucidate possible predictors of treatment outcome. Furthermore, the findings will provide effect size estimates to inform the submission of a larger, R01-series trial in the future. We have assembled a multidisciplinary team of experts who have successfully collaborated in the past and are uniquely qualified to implement this type of investigation. The results are expected to have a positive impact by addressing a major

clinical need in the area of chronic pain management, ultimately leading to decreased risk of prescription opioid misuse, addiction and overdose in this population.

2.1 Background

2.1.1 Significance and Rationale

A significant proportion of patients maintained on chronic opioid therapy for pain (COT-P) have suboptimal pain relief and/or poor functioning despite the appreciable risk of opioid treatment. Americans represent less than 5% of the world's population, but consume 80% of the global opioid supply[31] with 9 million users of medical long-term opioid analgesics in the United States[19]. The studies evaluating the effectiveness of opioid analgesic for chronic pain are mixed, with most studies reporting that less than half of patients experience a decrease in chronic pain with opioid analgesics and the degree of pain relief is modest[20]. Systematic reviews report that functional outcomes in COT-P are mixed with no conclusive evidence for improved physical, emotional or cognitive functioning in patients on COT-P[21-26]. Even in the absence of addiction or misuse, physiologic tolerance to opioid analgesics is common[27-29]. These factors, in combination with the alarming increase in the rates of accidental overdose on prescription opioids in the United States[30], lead to a situation where many patients on COT-P become physiologically dependent on a medication from which they are gaining suboptimal benefits and possibly incurring harm.

Opioid cessation is problematic and there are major gaps in clinical knowledge regarding how to manage individuals on COT-P who are in need of opioid cessation. In particular, questions remain with regard to optimal approaches to opioid discontinuation in COT-P patients and how opioid discontinuation affects pain and functional outcomes. Discontinuation of opioid therapy may be considered in patients who fail to experience adequate efficacy, experience improvement in the underlying pain condition (e.g. after surgery or other interventions), exhibit aberrant drug-related behaviors or addiction, and in patients who wish to discontinue therapy for other reasons (e.g., for work, patient preference). Among patients who are functioning poorly on COT-P, decreasing or tapering the opioids would likely improve their functioning and decrease the risk of remaining on a medication with appreciable risks and limited benefit. However, opioid tapering for those on COT-P can cause disabling withdrawal symptoms in a substantial proportion of patients[31-33]. The few studies evaluating opioid cessation in COT-P show dismal rates of both reduction and cessation of opioids with many returning to opioid use shortly after taper[33-36]. Treatment guidelines and tapering protocols vary widely among institutions and specialty societies[37] and there has been little systematic investigation or progress towards optimizing tapering protocols, making it unclear which opioid tapering strategies are effective for which populations. This project will begin to systematically address the gaps in this important area of clinical research.

Buprenorphine is an agent well-suited to assist with opioid discontinuation because of its safety and efficacy, but questions remain regarding optimal length of taper. Buprenorphine, a partial mu-opioid receptor agonist, produces a more limited withdrawal syndrome as compared to other full opioid agonists like methadone[38-40], which may be related to its long plasma half-life and slow dissociation from the receptor[38-42]. Also, buprenorphine has a ceiling on its agonist effects that reduces risk of overdose, making it a good candidate for use in outpatient settings[40-47]. Recent preliminary evidence confirms an advantage of buprenorphine over full agonists, like methadone, in detoxification settings[48]. Longer buprenorphine tapers may be related to improved detoxification outcomes (consistent with methadone literature), but studies are highly variable in methodology and duration (ranging from 1-120 days), thus, investigations in COT-P patients applying more rigorous methodology are needed[49]. Clinical pain rehabilitation programs that incorporate opioid discontinuation allow 3 - 8 weeks on average for taper[50-51], therefore the proposed study will allow the maximum taper time used in current practice, up to 8 weeks based on stabilizing dose, for taper completion (Please see Approach section).

Preliminary studies show that buprenorphine initiation and taper is tolerated in approximately 50% of those on COT-P, which leaves room for significant improvement. In a pilot study, Dr. Eric Strain (Co-Mentor) and colleagues transitioned non-addicted COT-P patients to buprenorphine with the purpose of developing a protocol for the use of buprenorphine in this population[52]. This pilot trial involved a small and diverse sample of patients (n=12) and found that 7 of 12 subjects (58%) on COT-P tolerated initial buprenorphine induction and of the 7, 42% responded favorably to buprenorphine taper. Other trials evaluating the transition rate for those on COT-P to buprenorphine (in those with and without addiction) also show that approximately 50% tolerate transition from COT-P to buprenorphine (taking into account both side effects and efficacy)[53]. Based on these trials, it is recommendation to target COT-P candidates on total opioid baseline doses of ≥19mg and <200mg of oral morphine equivalents for transition to buprenorphine and to not use buprenorphine use in patients receiving methadone or transdermal fentanyl, and these recommendations are followed in the current protocol.

Because COT-P patients who tolerate buprenorphine taper show a significant decrease in pain, patients and clinicians would benefit from an improved response rate to buprenorphine taper. Data from our group and others have shown that even when indications for opioid discontinuation exist, patients' fear of pain and withdrawal symptoms makes the decision to taper off COT-P daunting[54]. Because those who tolerate buprenorphine initiation, taper and opioid cessation show a significant decrease in average and worst daily pain[52], buprenorphine is a promising agent that can address the fears of pain and withdrawal in this population. However, based the existing data above, clinicians only have an approximately 50% chance of identifying COT-P patients who would respond well to transitioning to buprenorphine, and less than 50% chance of identifying those able to tolerate taper. Examining predictors of successful transition from COT-P to buprenorphine as well as ways improve the taper response rate (i.e. adjunctive medication) could have profound clinical implications in this population.

Gabapentin is an ideal adjunctive agent to improve outcomes in those tapering off COT-P, as it is a safe and effective agent that can address both chronic pain and opioid withdrawal symptoms.

Gabapentin, an N-type calcium channel blocker[55-57] and GABA analogue that promotes release of GABA[58-59] is indicated for treatment of neuralgia and epilepsy and used as an adjunctive agent to treat pain. Although it is most efficacious in treating neuropathic pain conditions[60-61], it also has modest efficacy in a variety of pain etiologies, including nociceptive pain[62-65], central pain[66-67], post-operative pain[64], mixed pain syndromes[63], and central sensitization[68]. Gabapentin has also been shown to ameliorate opioid withdrawal symptoms during opioid detoxification, including in subjects undergoing buprenorphine tapers[69]. Gabapentin is well-tolerated, relatively free from serious adverse effects, lacks interaction with other drugs, and lacks addictive potential[60], which makes it an ideal adjunctive agent to evaluate during opioid detoxification. Studies suggest that adjunct gabapentin administration of 1,600 mg/day during a methadone-assisted detoxification in those with opioid use disorders significantly reduced several opioid withdrawal symptoms[70]. Because gabapentin has a proven safety and efficacy history in those with chronic pain and in those on opioids, including buprenorphine, it is an ideal adjunctive agent to study in this proposal. Thus, Phase 2 of this study will evaluate the effects of gabapentin at up to 1,600 mg/day vs. placebo on completion of buprenorphine taper, opioid withdrawal symptoms and pain in those on COT-P undergoing a buprenorphine taper.

2.1.2 Innovation

This innovative study will be the first to systematically explore buprenorphine initiation/tapering with adjunctive gabapentin treatment as an approach to opioid discontinuation from COT-P. Dr. Strain's (Co-Mentor) pilot study of buprenorphine in COT-P showed that a significant proportion of COT-P patients tolerate transition to buprenorphine with a subsequent decrease in pain. This study will expand these findings by exploring buprenorphine transition in a larger sample to allow for the first time: (1) Determination of the base rate of COT-P individuals who can tolerate buprenorphine initiation, (2) Determination of the base rate of successful taper from buprenorphine, and (3) Examine the efficacy of gabapentin in improving completion

outcomes during buprenorphine taper. This data will inform larger, definitive trials that will be critical in developing best practices for the management of one of the largest public health problems that faces our nation today.

Comprehensively evaluating predictors of buprenorphine tolerance and successful opioid discontinuation from COT-P is novel. To date, pain phenotyping, including self-report measures of pain and pain laboratory testing in those tapering from COT-P has not been studied. Exploring pain characteristics and pathways in relationship to treatment outcomes can (1) elucidate the mechanism of change in pain level (descending pain pathways, wind-up pain pathways, nociceptive pain pathways), (2) provide information about predicting opioid discontinuation outcomes, and (3) inform future studies targeting therapeutic development. Thus, this application represents a highly innovative and novel proposal that will yield extremely valuable data pertaining to a significant health concern in the US.

3.0 Study Objectives

The primary objective of this proposal is to evaluate the feasibility and effectiveness of buprenorphine-assisted discontinuation from chronic opioid therapy for pain (COT-P) and to determine the role of gabapentin, an N-type calcium channel blocker, as an adjunctive agent to assist with opioid cessation. Secondary objectives are to identify patient characteristics (biological, psychological, and pharmacological) that predict (1) successful transition to buprenorphine, (2) successful buprenorphine taper, and (3) opioid cessation.

4.0 Study Design

4.1 Overview of Study Design

This study is to be conducted over four years to evaluate buprenorphine-assisted opioid taper in 150 individuals on COT-P who are (1) seeking assistance with opioid cessation and (2) willing to attempt buprenorphine-assisted taper. Because the fundamental question of how COT-P patients tolerate buprenorphine initiation is unanswered, we have divided this pilot proposal into two phases.

4.2 Prescreening and Consent

Subjects will be pre-screened for general inclusion/exclusion criteria. Potentially eligible subjects will be given a full description of the study procedures and will be asked to read and sign an IRB-approved informed consent form.

4.3 Screening and Baseline Assessments

During the screening/baseline phase, subjects will be assessed with a clinical interview and self-report forms to confirm their eligibility. These assessments may occur over one or more visits and will also include medical exams, mental health and pain assessments, collection of biological specimens and opioid withdrawal assessments. Subjects will be required to allow communication with their prescribing physicians and will be on no other opioids other than buprenorphine prescribed through the study. Subjects' prescribing physicians will be informed of patient participation and outcome as part of the study to protect against duplication of opioid therapy. The state prescription drug monitoring database will also be checked weekly throughout the study period and during the follow-up period at 1-, 3-, 6- and 12-months.

In preparation for buprenorphine initiation, subjects will be advised by the study physician (board-certified addiction psychiatrist) how to taper and stop their full agonist opioids the day before initiation so that subjects present in mild withdrawal on the day of buprenorphine initiation; they will also be prescribed supportive medications to take as needed for withdrawal the day/night prior to buprenorphine initiation. Long-acting opioids will be discontinued 24 hours prior to buprenorphine initiation, but short-acting opioids be will allowed up until 8 hours prior to induction. Subjects will have a phone or in-person session with the study physician the day prior to the induction and a phone call with research staff at least 2 days prior to induction.

4.4 Buprenorphine Initiation

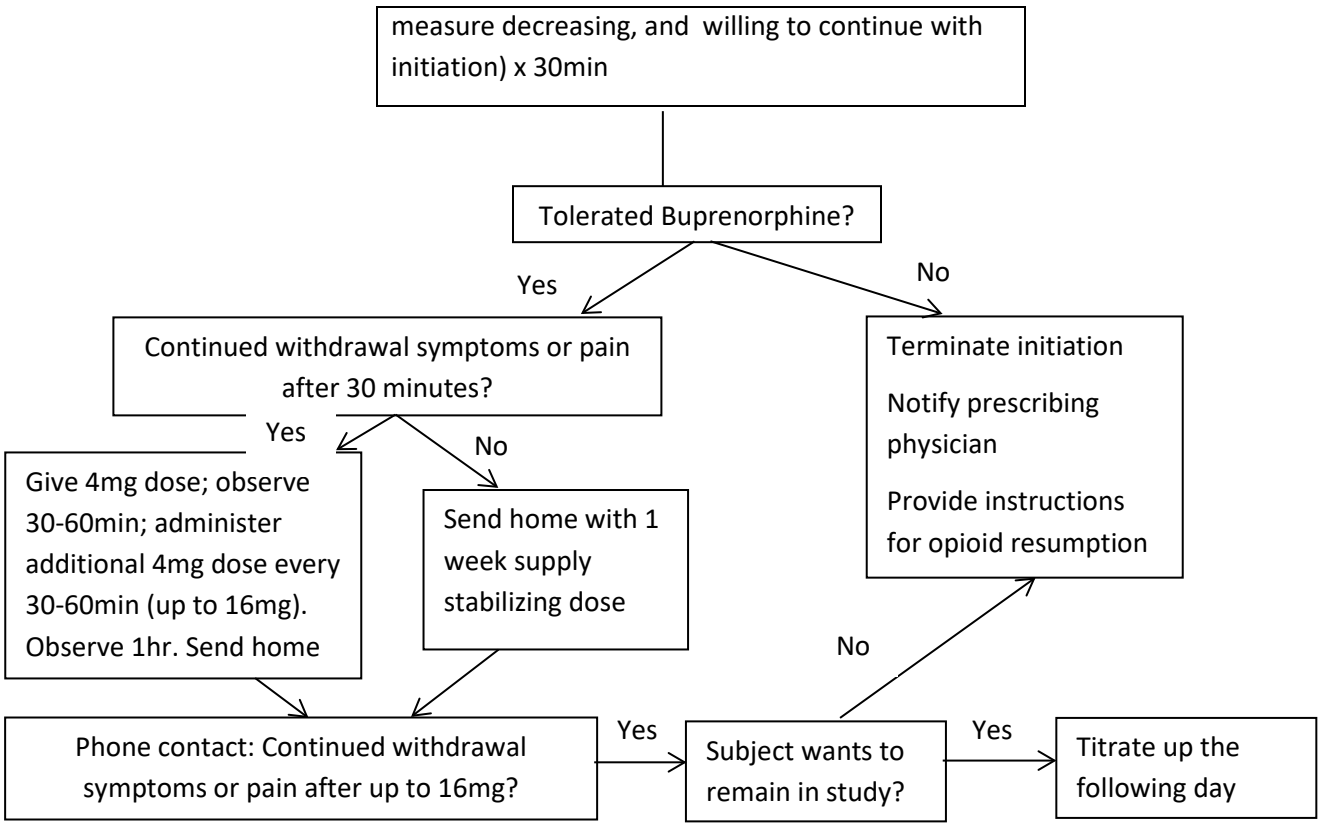
Following the screening/baseline procedures, the buprenorphine induction visit will be conducted. On buprenorphine initiation day, subjects will spend up to 5 hours in the Research Nexus or clinical office. On arrival, vital signs, subjective pain levels, and opioid withdrawal measures will be obtained, and buprenorphine induction will begin with 4mg once the COWS is ≥8. If the 4mg induction dose is tolerated and withdrawal symptoms remain, repeated doses of buprenorphine 4 mg (up to 16mg on day 1) will be given every 30-60 minutes until withdrawal symptoms are mild or resolved, monitoring for sedation. The following induction algorithm is proposed:

1. Participants should refrain from any opioid use for at least 8 hours prior to induction.
2. Pre-dose baseline score on COWS should be ≥8 (with no signs of intoxication).
3. An initial 2 mg sublingual dose should be given and the participant observed for 30 minutes. If symptoms do not improve, an additional 2-4 mg (total cumulative dose 6mg) can be given and the participant observed for 30-60min. If withdrawal or pain symptoms persist, another 2-4mg (total cumulative dose 10mg) can be given, and patient will be observed for 30-60 min. If withdrawal or pain symptoms persist, the study medical clinician believes it is necessary, and participant wants to continue in study, a final 4mg dose can be given in the office and patient observed for 1 hour (total cumulative dose 14mg).
4. Participants can leave once the assessment suggests that withdrawal phenomena and pain are both tolerable and stable or improving. If the patient does not tolerate buprenorphine after 16mg, they will be transitioned back to prescribing physician (see details below).
5. The study medical clinician or a designated staff member should contact the participant by phone later on the first day.

This induction scheme is relatively conservative and aims to limit the first day dose to 16mg. Alternative induction schedules can be used if the study medical clinician believes it is necessary.

Self-report measures of pain, withdrawal and sedation will be obtained every 30 minutes during the induction period. Once the subject has achieved self-reported satisfactory levels of pain relief and decreased withdrawal with the least amount of side effects (stabilizing dose), he or she will be observed for 30 min-1 hour and pain measures will be repeated. If the subject (1) does not tolerate the initial or subsequent doses of buprenorphine; (2) experiences an increase in pre-buprenorphine measures of pain; (3) fails to have a decrease in withdrawal symptoms to the mild range (COWS≥8); or (4) does not want to continue with buprenorphine for any reason, the patient will be instructed to resume their previous opioid medications at approximately 1/2 the previous dose for one day, then as tolerated, slowly titrate back up to previous dose (in collaboration with their prescribing physician). The prescribing physician will also be provided with general guidelines for outpatient opioid tapering, should that be pursued. If the patient has any serious adverse reaction to buprenorphine, they will be escorted to the emergency room.

Initiation Day
Subject arrives in mild withdrawal
Vital signs and baseline measures obtained
Once withdrawal scale COWS is >8, initiate 2mg buprenorphine; monitor for withdrawal
Record vital signs, monitor "tolerance" (pain level less than or equal to pre-bup level, withdrawal



4.5 Randomization and Blind Maintenance Procedures

All subjects who tolerate buprenorphine initiation during the induction visit will be enrolled in the study and randomized to adjunctive gabapentin or placebo (labeled A or B by study pharmacist to maintain blinding) performed by the study physician per protocol set up by study statisticians (stratified random block design with block sizes of 2, 4 and 6 through RedCap), balancing groups on sex. Based on the randomizations sequence generated by RedCap at the time the subject enters Phase II, the study physician will dispense the correct medication to the subject (labeled "A" or "B" from the supply). Only the research pharmacist and data manager will be aware of medication condition. After each study visit, the clinician and subject will complete a questionnaire asking them to guess the study condition (real vs. placebo) along with a confidence rating on a Likert scale (0=complete guess; 10=absolutely sure). Any scores of 10 on the confidence scale will be investigated. If a problem is detected, it will be corrected under the advisement of the Medical Monitor. Blinding will be broken for any emergencies or with any recommendation from the Medical Monitor after review of adverse events or serious adverse events.

4.6 Buprenorphine stabilization and gabapentin induction (2 weeks)

Subjects who tolerate buprenorphine induction and choose to continue in the study will be randomized in a double-blind fashion to gabapentin or placebo and enter a 2-week buprenorphine stabilization/gabapentin titration period.

Suggested Gabapentin Titration (mg)							
Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	100 bid	100 bid	200 bid	200 bid	300 bid	300 bid	300 bid
2	400 bid	400 bid	400 bid	400 tid	400 tid	800 bid	800 bid

Subjects will have phone contact with research staff once/week, and will be seen by the study physician once/week for medication management (15min) and cognitive behavioral therapy (CBT) for pain (45 min).

Buprenorphine dose may be adjusted in increments of up to 8mg (to maximum 24mg/day; split doses allowed) to balance pain relief, withdrawal relief and sedation to set a buprenorphine "stabilizing dose." Dose changes are to be determined after the study staff obtains vital signs, evaluation of opioid use (urine and self-report), craving, signs and symptoms of opiate withdrawal or over-medication, adverse events and current buprenorphine and other medication taken since the last visit. Subjects will also be titrated on gabapentin/placebo according to the suggested titration schedule (split doses), which can be adjusted by the study clinician based on tolerance. Subjects will be provided with a 7 day take-home supply of buprenorphine and gabapentin, and receive weekly urine toxicology. Compliance with medication doses will be assessed via pill counts, UDS, and self-report. Buprenorphine and gabapentin will be dispensed and monitored throughout the study.

4.7 Buprenorphine Tapering Phase (8 weeks)

An 8-week buprenorphine taper will be assigned based on stabilizing dose determined in the 2 week stabilization period. All subjects will be maintained on gabapentin during the buprenorphine taper. Subjects will be provided with a 7 day take-home supply of buprenorphine and gabapentin, and receive a weekly urine toxicology (and at completion). During the taper, subjects will continue weekly medication management (15 min) and CBT for pain (45 min) with the study physician for support and to review critical issues or problem areas. If the participant wants to taper more rapidly or slowly, they will discuss with study physician. If in agreement, the taper change will be noted and dose adjustments can be made, but all tapers must complete by day 4 of week 8. If subjects are unable to come in for an in-person visit, subjects can be scheduled for phone medication management and phone CBT with the study physician in place of in-person meeting (medications would need to be distributed in advance or taper adjusted accordingly). Prescription Drug Monitoring Data will be checked weekly. The following standard supportive medications for opioid withdrawal symptoms will be allowed (and assessed for self-reported use and pill counts weekly): (1) clonidine 0.1mg every 8 hours as needed for withdrawal; (2) cyclobenzaprine 5mg every 8 hours as needed for pain; (3) dicyclomine 20mg every 8 hours as needed for GI upset. All supportive medications will be tracked (type and dose utilized) to allow for statistical control and to track as an ancillary outcome measure.

Buprenorphine Tapering Phase (8 weeks)							
Preliminary Buprenorphine Tapering Schedule (mg)							
Stabilizing Dose	24	20	16	12	8	4	2
Week 1	16	16	12	8	6	4	2
Week 2	12	12	8	6	4	2	2
Week 3	8	8	6	4	4	2	2
Week 4	6	6	4	2	2	2	2*
Week 5	4	4	2	2	2	2*	2*
Week 6	2	2	2	2*	2*	2*	2*
Week 7	2*	2*	2*	2*	2*	2*	2*
Week 8	2*	2*	2*	2*	2*	2*	2*
Completion	0	0	0	0	0	0	0
2*=every other day							

4.7 Gabapentin taper

All subjects will be maintained on gabapentin or placebo throughout the buprenorphine tapering period and receive a 7-day gabapentin or placebo taper starting after buprenorphine has been tapered to 0mg or upon study termination.

Gabapentin Taper (mg)							
Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	400 tid	400 bid	400 bid	200 bid	200 bid	100 bid	0

4.8 Follow-up Visits

At the end of 8 weeks, subjects will be monitored for opioid cessation via urine toxicology (including full panel of opioids and buprenorphine), self-report, and Prescription Drug Monitoring Program (PDMP) data. Those who have buprenorphine present on final urine toxicology will have a repeat urine toxicology 1 week after cessation. Opioid cessation will be measured at 1, 3, 6 and 12 months post-study discontinuation/completion via in-person and/or phone assessment of self-report opioid use, urine toxicology (if visit is conducted in office), and PDMP data. Pain levels will also be assessed using a Brief Pain Inventory.

4.9 Termination

Should the subject terminate from the study at any point during the buprenorphine taper, they will be provided with instructions and medication for a one-week taper of gabapentin, and post-study pain treatment will be decided by the patient, study physician, and prescribing physician, including (1) restarting an opioid or non-opioid pain medication by the prescribing physician or (2) completing buprenorphine taper in MUSC's Comprehensive Pain Management Clinic. Copies of all decided post-study recommendations will be provided to the patient and prescribing physician with appropriate follow-up appointments. Although subjects meeting criteria for opioid addiction will be excluded from study, and we do not anticipate that this study would increase risk for addiction, if opioid addiction becomes suspected or diagnosed during the study, the subject will be discontinued from the study and referred/arranged for addiction treatment. Because each of these subjects will have had at least one indication for opioid cessation, the prescribing physician will be provided with general information about opioid tapers.

4.10 Duration of study and visit schedule

Participation in the study will last approximately 12 months in total. The screening/baseline and buprenorphine induction visits will occur over a period of 1-2 weeks. The treatment phase will include a 2 week stabilization period, followed by an 8 week taper, for a total of 10 weeks. There will also be a 1 week gabapentin/placebo taper period. There will then be follow-up appointments at 1-, 3-, 6- and 12-months post-taper.

4.10.1 Visit Schedule

Screening/Baseline Visits: approx. 2 hours
Induction Visit: up to 5 hours; within 1 week of (final) baseline visit
Treatment Phase: weekly visits; up to 2 hours
Week 1-2 (Stabilization) within 6 (+/-3) days of induction
Weeks 3-11 (Tapering Phase): weekly
Follow-Up Visits (Months 1, 3, 6 and 12 post-taper): up to 1 hour

4.11 Data Collection

Baseline self-report measures, pain laboratory measures, and follow-up data will be collected on paper questionnaires and entered into MUSC's REDCap database by research staff. REDCap data will be exported directly into SPSS with study IDs only, and data security, patient privacy, and HIPAA requirements will be followed. The codes that link the name of the participant and the study ID will be kept confidential by the PI (through only allowing PI and essential research staff access to that portion of the REDCap Database). Data quality will be monitored by random inspection of the completed forms by research staff, and any irregularities or problems detected will be discussed with the PI. Interim analysis is not indicated in this study.

5.0 Study Population

5.1 Subject Recruitment

We will recruit 150 subjects on COT-P who are treatment-seeking for opioid discontinuation. Participants will be recruited through flyers at the Ralph H. Johnson VA Medical Center, MUSC campus, and community forums in the tri-county area (e.g. coffee shops, waiting rooms, bulletin boards in community areas). We will also seek recruitment via flyers from physicians within and outside of MUSC, including area medical offices in the tri-county area (including but not limited to physician, chiropractic, physical therapy, urgent care, and independent Nurse Practitioner offices). We will also recruit from the community by means of chronic pain support groups, social media, and craigslist. Utilizing MUSC's system that identifies patients who have agreed to be contacted for research purposes (by indicating such in the MUSC Research Permissions preferences in MyChart), we will conduct targeted database reviews to identify patients who would qualify for this study. These patients will then be contacted according to their preferred method (phone, email) and invited to participate in the study using a phone script.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

Subjects between 18 - 70 years of age will meet the following inclusion criteria: (1) have the ability to speak and read in English; (2) currently taking COT-P for at least 6 months; (3) be on a reported daily opioid dose of ≥19mg and <200mg oral morphine equivalents/day (calculated at:http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm); (4) be voluntarily seeking opioid discontinuation, (5) be willing to attempt buprenorphine-assisted opioid discontinuation; (5) be willing to be randomized to gabapentin or placebo; and (6) have a current physician who is actively prescribing COT-P and who will be notified by the research team of the patient's entry into the study.

5.2.2 Exclusion criteria

Subjects will not have the following exclusion criteria: (1) previous intolerance or allergy to buprenorphine or gabapentin, (2) meeting DSM-V criteria for substance use disorder currently (except nicotine), (3) concurrent medical or psychiatric condition that, in the study team's opinion, would preclude safe or meaningful participation (e.g. sedation; pregnancy; traumatic brain injury; severe mental illness; severe cardiac, renal, pulmonary, or liver disease), (4) current use of benzodiazepines (except prescribed dose of benzodiazepines for 6 months duration or more at same dose and without evidence of sedation) , or illicit drugs other than THC, (5) current use of the following sedating medications: barbiturates, "z-drugs" (zolpidem, eszopiclone, zaleplon, zopiclone), baclofen, carisoprodol, chloral hydrate, marinol, sodium oxybate (Xyrem), (6) current use of the following QTc-prolonging medications: amiodarone; anagrelide; artemether; asenapine; astemizole; aepridil; cisapride; disopyramide; dofetilide; domperidone; dosulepin; dronedarone; Eeiglustat; flupentixol; halofantrine; ibutilide; iloperidone; lopinavir; lumefantrine; mifepristone; nilotinib; paliperidone; pimozide; pipamperone; procainamide; quetiapine; quinidine; quinine; sotalol; sparfloxacin; sulpiride; terfenadine; tetrabenazine; thioridazine; toremifene; vandetanib; vemurafenib; ziprasidone; zuclopenthixol (5) current treatment with fentanyl or methadone, (6) current treatment with gabapentin, carbamazepine, phenytoin, MAO-inhibitors.

6.0 Study Drug Management

6.1 Dosing During Taper

Taper guidelines are provided in Section 4.7. The study medical clinician may deviate from the guidelines and individualize the taper to the extent indicated by clinical considerations (missed doses, emergent withdrawal signs, etc.) but the taper must be completed within the specified timeframe, and the dosing schedule recorded on the appropriate form.

6.2 Dispensing of Study Medication

Buprenorphine will be dispensed for the first day of dosing by a medical clinician in accordance with state and federal regulations. Subjects will be evaluated in-person or by phone at least once again in Week 1 and then once weekly thereafter for dispensing of buprenorphine, medication management and education, cognitive behavioral therapy, and study drug and clinical assessments. Take-home doses of buprenorphine will be provided to participants to self-administer at home on days between clinic visits. An additional visit may be occasionally required to adjust a participant's dose, or dispense additional medication to accommodate an increased dosage. Participants receiving buprenorphine will be instructed to hold the tablet(s) under their tongue until the tablet(s) have completely dissolved. This may take several minutes. The tablet(s) should not be swallowed.

6.3 Drug Packaging/Handling/Storage/Accountability

Buprenorphine is available as a sublingual tablet in two doses: 2 mg and 8 mg. Buprenorphine will be obtained through MUSCs Narcotic Vault (narcotic-vault@musc.edu) by submitting the following items when placing an order for a C-III: copy of DEA registration, copy of DHEC registration, Authorization Signature Sheet, MUSC Controlled Substance Purchase Requisition Form. Accurate recording of all buprenorphine received, dispensed, administered, returned, or destroyed will be made. Buprenorphine will be stored in the PIs locked narcotic cabinet at MUSCs Institute of Psychiatry, room 104H in accordance with the PIs registered research DEA and stored at 25ºC (77ºF), with excursions permitted to 15-30ºC. The PI will prepare individual prescriptions for each participant visit. These prescriptions will be provided in participant-numbered, child resistant packaging and clearly labeled with local regulatory requirements. Unused drug supply will be destroyed under the direction of Ernest Thomas, MUSCs Controlled Substance Investigator.

Gabapentin/placebo will be obtained and dispensed through Pitt Street Pharmacy in Mount Pleasant, SC. The study pharmacist will prepare the gabapentin and placebo and will dispense pre-ordered batches labeled as "A" and "B" to the study physician, with the assignment of med vs placebo to either A or B blind to the study physician. The pharmacist will retain the assignment and also give it to the study statistician in a sealed envelope in the event that the blind needs to be broken. Only the study pharmacist and study statistician will know the assignment of the gabapentin or placebo. Each participant who is enrolled in Phase II of the study will be dispensed gabapentin or placebo.

Non-controlled withdrawal medications (clonidine, dicyclomine, cyclobenzaprine) will be obtained through MUSCs Pharmacy Procurement Center (pharm-dc@musc.edu).

6.4 Training Procedures

Cognitive behavioral therapy will be provided weekly by the PI, a board-certified psychiatrist, who will complete and document training through completion of the Professional Guide of "Managing Chronic Pain – A Cognitive-Behavioral Therapy Approach." In the event the PI is not available for a CBT session, a trained and IRB-approved back-up provider will provide CBT, and this will be noted accordingly.

7.0 Concomitant Therapy

7.1 General Considerations

Most participants entering this trial will have pain, and many will be receiving other medications (e.g., non-steroidal anti-inflammatory drugs, antidepressants) and/or nonpharmacologic treatments (e.g., acupuncture, physical therapy, hypnosis) to assist them with their pain. This trial will not restrict the use of concomitant medications used by a participant's outside physician for pain management with the exception of gabapentin or opioids. Concomitant treatments will be assessed at each scheduled visit and recorded.

7.2 Medications Allowed During the Trial

Prior to study initiation (induction) participants should not have taken or been administered any opioid medications for at least 8 hours and must not be on gabapentin.

7.2.1 Ancillary Withdrawal Comfort Medications

All participants will have the option to receive ancillary withdrawal comfort medications before the induction and during the tapering portion of the protocol. Use of any medications will be recorded. Each participant will be instructed on the use of each medication prescribed and told they can self-administer the medication in accordance with the instructions. The use of ancillary medications will be closely monitored for the duration of the study. Prescribing of ancillary medications will be at the physician's discretion in accordance with clinical need to assist with the management of withdrawal signs and symptoms during taper but should be limited only to those medications listed below. All supportive medications will be tracked (type and dose utilized) to allow for statistical control and to track as an ancillary outcome measure. The following list provides the dose, schedule and indication for withdrawal ancillary medication use:

For general withdrawal: clonidine 0.1mg every 8 hours as needed

For muscle pain: cyclobenzaprine 5mg every 8 hours as needed

For GI upset: dicyclomine 20mg every 8 hours as needed

If the physician feels additional medications are needed for symptoms related to withdrawal, the following medications can be prescribed (but they will not be provided through the study):

- For anxiety and restlessness: hydroxyzine hydrochloride 50 mg, po q6 hrs prn; not to exceed 200 mg per 24 hrs
- For bone pain and arthralgia: non-steroidal anti-inflammatory agent (NSAID) such as ibuprofen (Advil, Motrin and others-use within current guidelines) 800 mg po q8 hrs with food, not to exceed 2400 mg per 24 hrs; if an NSAID is not appropriate, acetaminophen – not to exceed 3 gm/day
- For nausea: trimethobenzamide (Tigan) 250 mg po q8 hrs prn, not to exceed 750 mg per 24hrs or 100/200 mg suppositories, not to exceed 400 mg per 24 hrs
- For insomnia: trazodone hydrochloride 50 mg, 1-3 tabs, po qhs prn OR doxepin hydrochloride 50 mg, 1-3 tabs, po qhs prn OR diphenhydramine 25-50 mg q 4-6 hrs prn, not to exceed 300 mg per 24 hrs

8.0 Outcome Measures

8.1 Primary Outcome Measures – Aim 1

For Aim I, the primary outcome measure is the **percentage of patients who tolerate buprenorphine initiation** within an 8-hour initiation period, as evidenced by (1) moderate-good level of pain control (same or improved rating a 0-10 visual analogue scale for pain), (2) mild to no withdrawal symptoms (≤8 on the Clinical Opioid Withdrawal Scale), and (3) willingness to continue to the stabilization and tapering phase of the study.

8.2 Primary Outcome Measures – Aim 2

For Aim 2, the primary outcome measure will be opioid cessation at 8 weeks, measured through self-report, prescription drug monitoring data, and confirmatory UDS for a full panel of opioids.

8.3 Secondary Outcome Measures

1. Opioid cessation post taper: 1 month, 3 months, 6 months, 12 months
2. Pain self-report: Brief Pain Inventory, Pain Catastrophizing Scale
3. Pain laboratory testing: Mechanical, wind-up/temporal summation, descending pathways

4. Opioid misuse risk: Current Opioid Misuse Measure

5. Physical Function: PROMIS Physical Function Short Form (PROMIS SF 10)

6. Sleep: Pittsburgh Sleep Quality Index

7. Opioid Withdrawal: Subjective Opioid Withdrawal Scale

8. Psychiatric co-morbidity: Structured Clinical Interview (SCID)

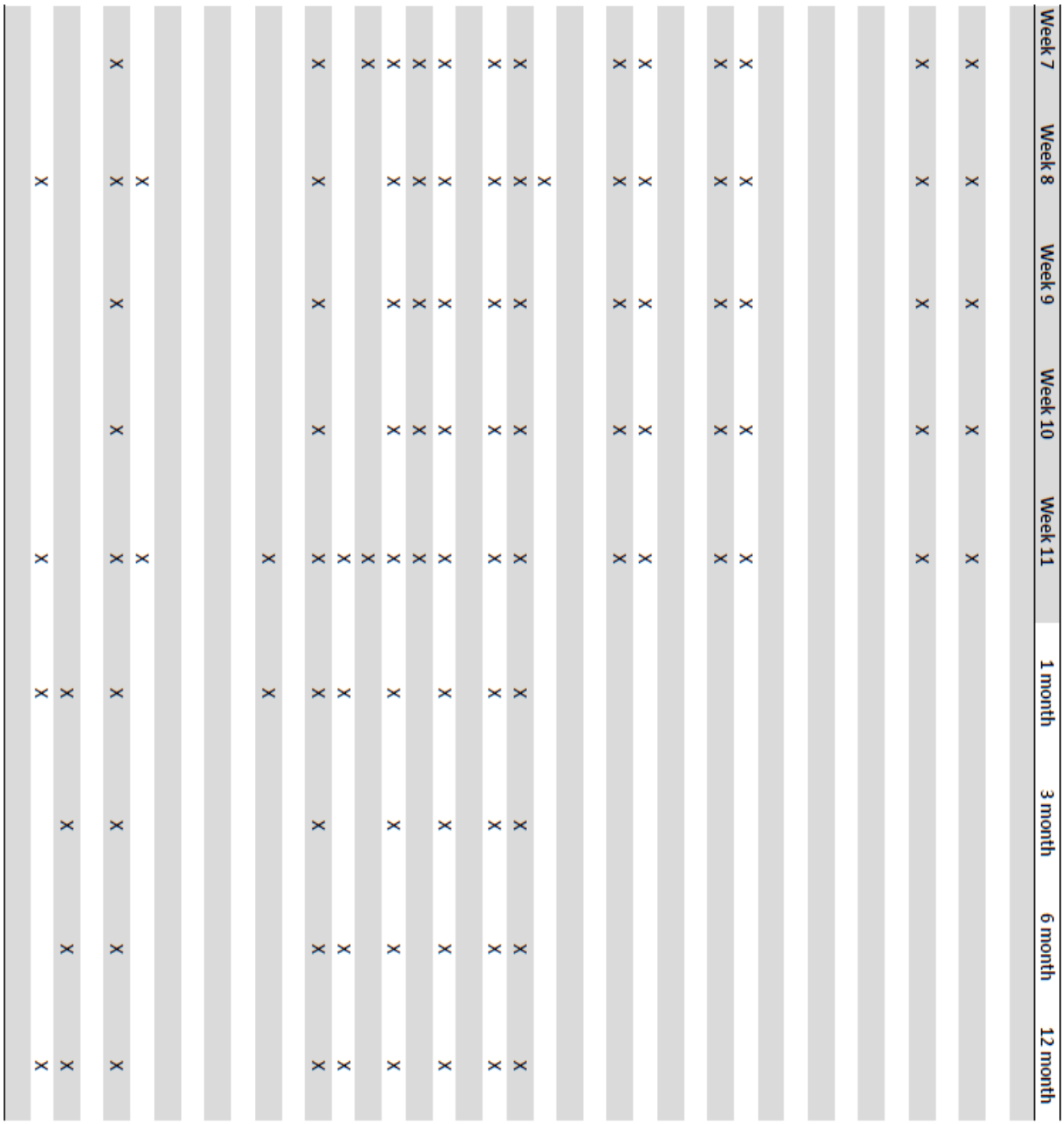
9. Patient characteristics: Standard demographic information; Pain diagnosis and history; Opioid history and characteristics; Other medications (including analgesics); Medical co-morbidities

9.0 Study Assessments

9.1 Study Timetable

Schedule of Assessments

Activity	Screening/BL	Induction	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Informed Consent	X							
Inclusion/Exclusion	X	X						
Phone Contact	X	X	X	X	X	X	X	X
Randomization		X						
Physical Exam	X	X(pre and postB)	X	X	X	X	X	X
Demographics	X							
Buprepenorphine Orientation	X							
Dispensation of Withdrawal medications	X							
Clearance for Pain Participants Progress Note	X							
Concomitant Treatment Form	X							
Prescribing Doctor Collaboration Form	X							
Blinding Assessment Form			X	X	X	X	X	X
Pill Count Form			X	X	X	X	X	X
Medical & Psychiatric Evaluation (SCID)	X							
Pain & Opioid Analgesic Use History	X							
Cognitive Behavioral Therapy (CBT)		X	X	X	X	X	X	X
Vital Signs	X	X(pre and postB)	X	X	X	X	X	X
CMP	X							
Genetic testing	X							
Urine Pregnancy Test	X	X(preB)				X		
Adverse Events		X(postB)	X	X	X	X	X	X
Opioid Use Report		X(preB)	X	X	X	X	X	X
Buprenorphine Tolerance Form		X(postB)						
State Prescription Monitoring Data	X	X	X	X	X	X	X	X
Clinical Opioid Withdrawal Scale (COWS)		X(pre and postB)	X	X	X	X	X	X
Urine Drug Screen (full panel)	X	X(preB)	X	X	X	X	X	X
Pain Laboratory Testing (QST)	X		X	X	X		X	
PROMIS SF 10	X		X	X	X			X
Brief Pain Inventory (BPI)	X	X(pre and postB)	X	X	X	X	X	X
Vas-Pain		X(pre and postB)						
Beck Depression Inventory II (BDI)	X			X				X
Current Opioid Misuse Measure (COMM)	X							
Pain Catastrophizing Scale (PCS)	X							
Controlled Preference Scale (CPS)	X							
Adverse Childhood Experience Form (ACE)	X							
Pittsburgh Sleep Quality Index (PSQI)	X			X				
Subjective Opiate Withdrawal Scale (SOWS)	X	X(pre and postB)	X	X	X	X	X	X
PHQ-15	X							
Locator Form	X	X(preB)						
SF-36	X						X	
Buprenorphine Tolerance Testing (Induction)		X						



9.2 Laboratory Tests (e.g., Pregnancy Test, CMP, genetic test)

9.2.1 Pregnancy Testing

Female participants of child-bearing potential will be required to have a negative pregnancy test (urine hCG,) prior to induction on buprenorphine, and every 4 weeks thereafter while receiving buprenorphine. Buprenorphine is a Pregnancy Category C Drug. Female participants of childbearing potential will also be expected to practice acceptable birth control. Women who become pregnant will be withdrawn from the study and the decision to taper off buprenorphine, remain on buprenorphine, or transition back to opioid analgesic treatment will be decided with patient, study physician and prescribing physician.

9.2.2 Comprehensive Metabolic Profile (Blood Chemistry and Liver Function Test)

Blood will be collected for quantitative analysis, which will be performed for a standard chemistry and liver function profile. The following analytes will be recorded on the appropriate case report form: sodium, potassium, chloride, bicarbonate, glucose, creatinine, albumin, total protein, calcium, alanine aminotransferase

(ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, alkaline phosphatase (ALP), and blood urea nitrogen (BUN). Subjects with LFTs > 5X upper limit of normal range or glomerular filtration rate <60 at screening will be ineligible for the study.

9.2.3 Genetic Tests

Blood will be collected and stored for variants of opioid system genes and dopamine system genes that may predict buprenorphine response and successful taper in a future study. This is explained in the Informed Consent.

9.2.4 Urine Drug Testing

Screening/baseline, induction, weekly treatment phase and 1, 3, 6, 12 month follow-up urine samples will be collected and analyzed for drugs of abuse. The sample collected at baseline will be to determine eligibility and the samples collected during the treatment phase will be prior to dispensing medication. If the subject's buprenorphine screen is positive at completion of the taper, they will be asked to return in 1 week for repeat testing.

9.3 Clinical Assessments (e.g. Medical History and Physical/Psychiatric Exam)

The study medical clinician (or other qualified medical study staff) will complete a physical/psychiatric examination to help determine eligibility. The physical exam will also ensure that there are no medical concerns regarding participation and to gather baseline information about the participant's health. The physical examination will be repeated at the end of buprenorphine induction visit and weekly during the buprenorphine taper phase. Pertinent laboratory tests (CMP, UPT) will be reviewed. Participants with abnormal laboratory values will be notified and counseled to seek medical evaluation and care. For participants receiving opioids for chronic pain, the study medical clinician will consult with the participant's prescribing physician to ensure that the participant is appropriate to participate in this protocol; e.g., that the participant's pain is not due to an underlying malignancy or that further diagnostic testing is not needed to determine the source of the pain.

9.4 Efficacy Assessments

9.4.1 Urine Drug Testing

Urine samples will be collected and analyzed for drugs of abuse at baseline to determine eligibility and prior to dispensing medication. All urine specimens will be analyzed by staff using drug test cups with temperature-controlled monitoring. Drug test cups with immunoassay drug screen cards will be used to identify the following substances: oxycodone, benzodiazepines, THC, buprenorphine, methadone, cocaine, amphetamine, methamphetamine, propoxyphene, PCP, barbiturates, MDMA, TCAs and the Opiate 300 group analytes (morphine, heroin, and codeine). Other drugs may be detected by these analytes at high concentrations. For example, hydrocodone may be detected under the oxycodone test at high concentration levels. The cups also include adulterant testing for creatinine, nitrite, pH, bleach and specific gravity. The results will be recorded on the appropriate CRF. If the subject's buprenorphine screen is positive at completion of the taper, they will be asked to return in 1 week for repeat testing.

9.4.2 Opioid Use Report

Self-reported opioid use data will be collected in conjunction with weekly medical management visits. A calendar technique similar to the Timeline Followback will be used to fill in each day since the last visit, which helps to fill in missing data in case of missed visits. Baseline data collection will review past 30 days of opioid use. The use of opioids, other drugs of abuse, and alcohol will be recorded. A urine drug screen will be performed at each of these visits as well as week 11 (if necessary) and all follow-up visits.

9.4.3 Buprenorphine Tolerance Form

During the induction onto buprenorphine, the physician will fill out the Buprenorphine Tolerance form to determine outcome and eligibility for Phase II.

9.4.4 State Prescription Drug Monitoring Program (PDMP) Data

At baseline, at each study visit, and at months 1,3, 6, and 12, the study physician will check the subject's PDMP data and record results on the appropriate CRF.

9.4.5 Clinical Opioid Withdrawal Scale (COWS)

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item scale designed to be administered by a clinician. This tool can be used in both inpatient and outpatient settings to reproducibly rate common signs and symptoms of opiate withdrawal and monitor these symptoms over time. The summed score for the complete scale can be used to help clinicians determine the stage or severity of opiate withdrawal and assess the level of physical dependence on opioids. This will be administered before and during buprenorphine induction and weekly during Phase II.

9.5 Safety Assessments

Safety assessments will consist of physical examination, vital signs, laboratory tests, pregnancy tests, adverse event reporting, and concomitant medications use.

9.5.1 Adverse events (AEs) and Serious adverse events (SAEs)

Adverse events will be monitored during the study. An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication- or study-related or clinically significant. For this study AEs will include events reported by the participant. A new illness, symptom, sign, or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF (Case Report Form). The AE CRF is also used to record follow-up information for unresolved events reported on previous visits. Each AE will be classified by the study investigator as serious or non-serious and appropriate reporting procedures followed.

Serious adverse events (SAEs) are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs hospitalization, any congenital anomaly, or any event that required intervention to prevent one of the above outcomes.

9.5.2 Unexpected Events

An unexpected event is one that is not described with respect to nature, severity or frequency in the current Investigator Brochure, or is standard symptomatology for opioid withdrawal.

9.5.3 Pain and Opioid Analgesics Use History

Information will be collected at the Phase 1 baseline visit to determine a variety of pain-associated issues (body region(s) affected by pain, participant description of pain diagnosis, duration of pain, number of days in past 30 days and past 6 months with pain, past history of pain if not currently experiencing pain; pain treatment history) and opioid analgesics use issues [initial reason for initiating opiate use (e.g. pain relief versus illicit use), current and past sources of opiate analgesics, current and past types of opioid analgesics].

9.5.4 Structured Clinical Interview for the DSM-V (SCID)

A SCID will be used during the initial medical and psychiatric exam to measure psychiatric co-morbidity and confirm no exclusion criteria are present (e.g. substance abuse diagnosis, severe mental illness).

9.5.5 Prescribing Physician Collaboration Form

This form will be used to document coordination with prescribing physician and document education and expectations for the study.

9.6 Blinding Assessment

This is a double-blinded study. For Phase II, the participant and the study physician will complete a Blinding Assessment Form to document their respective guesses as to which condition the subject is under.

9.7 Pain and Other Assessments

9.7.1 Brief Pain Inventory

The Brief Pain Inventory-SF (BPI; Cleeland & Ryan, 1994) is a 9-item assessment of intensity of pain and interference of pain in life. Originally developed for cancer pain, it is widely used to assess nonmalignant acute and chronic pain (Tan, Jensen, Thornby & Shanti, 2004). The complete BPI-SF will be collected at baseline, pre- and post-induction, during each visit in Phase 2 and follow-up. In addition to verbal patient report of pain, these items will permit study clinicians to monitor for any clinical deterioration in pain status that may require collaboration with prescribing physician, follow-up and/or referral.

9.7.2 VAS-Pain

Before and after buprenorphine induction, subjects will be asked to rate their pain on a scale of 0-10.

9.7.3 Pain Laboratory Testing Procedures

Laboratory Pain Procedures (Quantitative Sensory Testing; QST) will be performed at baseline and at visits week 1, 2, 3, 5, 7, 11 and month 1, 6, and 12 in Phase II.

1. Mechanical (Pressure) Pain Threshold Assessment (PPTh): A digital anesthesiometer (IITC Life Sciences ElectroVonFrey) will be used to assess mechanical pain perception. Pain threshold to static mechanical stimuli will be determined by applying the rigid monofilament to the dorsum of each subject's right hand with increasing pressure (10 grams per second) until the participant indicates verbally that the pain threshold has been reached. Participants will rate the intensity and unpleasantness using a computerized visual analog scale (CVAS).

2. Diffuse Noxious Inhibitory Controls (DNIC): Baseline mechanical pain threshold will be assessed on the right brachioradialis or right trapezius in random order as above. Immediately following this "baseline" assessment, participants will undergo a cold pressor task. During the cold pressor task, each participant will immerse his or her contralateral hand up to the wrist in a circulating ice water bath maintained at 4.5 degrees C (40 degrees Fahrenheit). Ten seconds after starting hand immersion, PPTh will be reassessed at the same site of baseline assessment. During each pain assessment session, a total of 4 DNIC tasks will be performed: 2 trials at each anatomical site with 2 minute intervals between cold pressor tasks. Participants will be directed to keep their hand in the water for the duration of the PPTh assessment. DNIC will be measured as the percent change in PPTh during the cold pressor tasks relative to baseline. An increase in PPTh during cold pressor reflects normal functioning of pain-inhibitory processes.

3. Controlling for General Physiological Arousal: During the laboratory pain procedures, subjects will be hooked-up to an Avant 2120 Pulse Oximeter with non-invasive blood-pressure measurement capabilities. Heart rate, pulse oximetry readings and blood pressure will be recorded during the procedure to determine if effects on pain are associated with any changes in cardiovascular activity. These are important processes to track in order to rule-out potential confounds of general physiological arousal and changes in pain perception.

9.7.4 Beck Depression Inventory II

This 21-item scale (Beck et al., 1961) assesses common features of depression on a 4-point severity scale, with a focus on cognitions. It is widely used in both drug and psychosocial treatment studies of depression, and

is commonly used in studies of pain (Dworkin et al., 2005). The BDI will be collected at baseline and weeks 2, 6, 11 and Month 1 follow-up.

9.7.5 SF-36

The SF-36 version 2 is a 36-item, participant administered instrument examining health-related quality of life changes as a function of treatment (Ware and Sherbourne, 1992). Most items are rated on a 5-point scale. The SF-36 v. 2 will be completed at baseline and Weeks 4, 8, 11 and Months 1 and 12 during Phase II.

9.7.6 Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a 19 item self-report questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, creating 7 components that produce one global score, and takes 5-10 minutes to complete. This will be administered at baseline and Weeks 2, 8 and 11 of Phase II.

9.7.7 Patient Health Questionnaire – 15 (PHQ-15)

The PHQ-15 is a brief, self-administered questionnaire that may be useful in screening for somatization and in monitoring somatic symptom severity in clinical practice and research. This will be performed at baseline.

9.7.8 PROMIS SF 10

The PROMIS SF 10 is a 10-item scale that evaluates self-report of general health, mental health, physical activity and quality of life. This will be performed at baseline, and Weeks 1, 2, 3, 6, 11, and Months 1, 6, and 12.

9.8 Treatment Compliance

Medication compliance will be measured using pill counts done at the weekly visits. Treatment participation will be measured in the follow-up treatment visit CRF.

Participation in medical and psychosocial treatment and self-help outside of the study will be captured on a concomitant treatment CRF.

9.9 Common Assessment Battery (CAB)

9.9.1 Brief Demographics Form

Basic demographic information assessing for age, ethnicity/race, and gender will be collected at baseline.

9.9.2 Locator Information

Basic locator data will be collected and kept confidential in the participant's record. Locator information typically includes contact information such as residential street address, or an address of someone who knows where to contact the participant if they are homeless, and a phone number where they can be reached. Additional information includes the names and addresses of two or three individuals who would likely know their whereabouts, particularly relatives or close friends. This information will be obtained at baseline and will be updated as necessary. This information will be used to facilitate contact with the participant during the study and at follow-up.

9.9.3 Current Opioid Misuse Measure (COMM)

The COMM is a 17-item scale validated in chronic pain patients used to identify aberrant behaviors associated with risk for misuse of opioid medications. A cut-off score of 9 or greater identifies 77% of those at high risk for opioid misuse (non-addicted, whereas those with a score of 13 or greater identifies patients with an opioid use disorder (sensitivity 77%, specificity 77%). The COMM will be administered at baseline.

9.9.4 Pain Catastrophizing Scale (PCS)

The PCS is a 13-item scale that was developed to help quantify an individual's pain experience, asking about how they feel and what they think about when they are in pain. Compared to other ways of measuring pain-related thoughts, this questionnaire is unique in that the individual does not need to be in pain while completing it. This will be measured at baseline.

9.9.5 Controlled Preference Scale (CPS)

The CPS is a context domain, card sort instrument that assesses preferences regarding participation in health care decisions for people with life threatening illnesses. This will be administered at baseline.

9.9.6 Adverse Childhood Experiences (ACE) Questionnaire

The ACE Questionnaire is a 10-item self-report measure developed for the ACE study to identify childhood experiences of abuse and neglect. The study posits that childhood trauma and stress early in life, apart from potentially impairing social, emotional, and cognitive development, indicates a higher risk of developing health problems in adulthood. This will be administered at baseline.

10.0 Statistical Analysis

10.1 Statistical analysis

Baseline demographic and clinical characteristics will be tabulated for all screened subjects. Following completion of enrollment, baseline variables will be compared between subjects who tolerated buprenorphine and continued were enrolled in the study and those who did not. Continuous and ordinal characteristics will be compared using a Wilcoxon Rank-Sum test statistic while categorical characteristics will be compared using a Pearson Chi-Square test statistic. Following completion of the study, estimates of the proportions (and associated 95% confidence intervals) of participants that successfully completed opioid cessation at 8 weeks will be calculated for end of treatment, as well as 1, 3, and 6 months post taper. Model based estimates will be compared between those who were randomized to gabapentin vs. placebo using Generalized Estimating Equations for correlated binary outcomes (treatment phase cohort). Additionally, generalized linear models will be used to investigate clinical and demographic correlates of treatment success using baseline and longitudinal study characteristics while controlling for adjunctive medication use. Following the analysis of the treatment phase cohort, a complementary analysis will compare opioid cessation between the treatment phase cohort and with those in the standard care cohort. Secondary outcomes such as medication compliance and withdrawal symptoms will be tracked longitudinally over time. As selection into the treatment phase cohort was not randomized, a full analysis of covariates associated with the cohort assignment will be done and those predictive of assignment will be included in model development and tested for possible effect modification.

10.2 Power and Sample Size

The primary aim of the proposed study is to investigate the proportion of subjects enrolled into a buprenorphine taper who discontinue use of COT-P. The study aims to estimate the precision of the efficacy estimate by calculating the effective proportion abstinent at the end of the taper period, the 95% confidence interval for each study treatment group (gabapentin vs. placebo), and the difference between groups. The lower bound of the 95% confidence interval around each estimate will be used to inform larger randomized trials of efficacy. The induction phase of the proposed study is to determine the proportion of subjects maintained on COT-P who tolerate transition to buprenorphine using a one-day outpatient protocol. Based on a small pilot study of a COT-P participants (n=12), 58% (7/12) tolerated buprenorphine initiation and 71% of those that tolerated the study drug completed the taper (5/7)65. Of a feasible sample of 150 participants screened for tolerance (using target morphine dose equivalents), we anticipate 50-60% (n=75-90) will tolerate the study drug and be randomized into the treatment phase of the study. The detectible margin of error varies with the proportion that succeeds in discontinuation of opioids following the taper, with greater margins associated with proportions near 50% (most conservative). With an estimated base rate of 50% of COT-P subjects who successfully

discontinue opioids following taper, we are powered to detect a margin of error from the overall study proportion and lower 95% confidence interval between 0.09 (n=90) and 0.10 (n=75). Based on pilot data within a similar population, we anticipate 30% attrition in the treatment phase study population65. With attrition, we are powered to detect a slightly wider margin of error of between 0.095 (n=90) and 0.105 (n=75). In the analysis of the effect of gabapentin versus placebo in the treatment phase cohort, assuming an overall rate of 50% of COT-P subjects who successfully discontinue opioids following taper, 45 participant randomized to each drug group, we are powered to detect a margin of error in the difference and lower 95% confidence interval of 0.20 (n=45 per group). When accounting for possibly high attrition, with 70% retention, we will be able to detect a lower limit of the 95% confidence interval of 0.24 below the true proportion of the group difference.

11.0 Protection of Human Subjects and Data Safety Monitoring Plan

11.1 Inclusion of Women and Minorities

This study will include and recruit women and minorities. Based on previous and ongoing research efforts at MUSC within prescription opioid users, we anticipate that approximately 50% of the subjects recruited will be women. We will make every effort to recruit and retain women into the study. Charleston's population is currently 64% Caucasian and 34% African-American, with African Americans representing the only minority group of any large number in South Carolina. However, it is estimated, based on previous and ongoing research efforts in prescription opioid users presenting for research studies at MUSC, that approximately 20% of the subjects will identify themselves in a minority group. Every effort will be made to recruit and retain minority individuals in the study. We will also utilize the South Carolina Clinical and Translational Research Institute's (SCTR) Research Support Services (SUCCESS) Center's Recruitment Core in order to ensure adequate numbers of males, females and minorities.

11.2 Quality Assurance

Data quality will be monitored by random inspection of the completed forms by research staff, and any irregularities or problems detected will be discussed with the PI. Interim analysis is not indicated in this study.

11.3 Trial Safety and Reporting of SAEs

During screening, subjects will undergo a battery of medical tests and physical exam to determine eligibility and safety for participation in the study. Subjects will be excluded if they have any medical or psychiatric condition that would preclude safe or meaningful participation (e.g. traumatic brain injury; severe mental illness; severe cardiac, renal, pulmonary, or liver disease); current use of benzodiazepines or illicit drugs; or maintenance on fentanyl or methadone. During each clinic visit of the treatment phase, subjects will be asked about adverse events and have vital signs taken. Patients will not receive medication if they have any signs or symptoms that may pose a safety issue with either trial medication. All adverse events during the study will be collected, documented and reported to the PI. The occurrence of AEs will be assessed at screening/baseline, and at each clinic visit during the treatment phase of the study and again during any follow-up visits. All AEs are reviewed weekly by the PI (new or continuing), quarterly by the Medical Monitor. All AEs will be assessed to determine if they meet the criteria for an SAE. Any SAE (meeting reporting criteria) will be reported within 48 hours in writing to the MUSC IRB, NIDA (via SAETRS), and the FDA. Initial and follow-up of any SAEs will also be reported to these three agencies. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution or stabilization. A subject may have their medication discontinued or may be withdrawn from the study if the investigator determines it is the best decision in order to protect the safety of a participant. In the event that a subject withdraws or is discontinued from the study due to an SAE, the patient will have appropriate follow-up medical monitoring. Monitoring will continue until the problem has resolved/stabilized with no further change expected, is clearly unrelated to study medication, or results in

death. Outcome of SAEs will be periodically reported to NIDA, and a summary will be included in an annual progress report to NIDA.

11.4 Potential risks for participants

The subjects recruited for this study will have one or more indications for opioid cessation and be suffering with chronic pain, which places them in a higher risk category for adverse events in general. The following are the expected risks in this study:

1. Discomfort from opioid withdrawal: It is necessary to be in moderate opioid withdrawal in order to safely be inducted on buprenorphine. To minimize the discomfort, subjects will be provided with standard symptomatic medications detailed in the protocol to relieve those symptoms of withdrawal. It is expected that withdrawal symptoms will be temporary until buprenorphine is initiated. Subjects will be provided with extensive supportive counseling prior to and while undergoing withdrawal.

2. Precipitated withdrawal: Induction on buprenorphine comes with risk of precipitated opioid withdrawal, and every step will be taken to minimize this risk (by excluding patients on methadone, fentanyl, or on opioid doses greater than 200 morphine equivalents), ensuring patients are in moderate withdrawal before induction, and discontinuing long-acting opioids 24 hours before induction.

3. Side effects to buprenorphine: The following are the expected adverse events (and frequency, over 5%) related to buprenorphine (from package insert for Suboxone, which includes rates for buprenorphine alone): headache (29%), insomnia (21%), pain (18%), withdrawal syndrome (18%), nausea (14%), sweating (13%), pain in abdomen (12%), infection (12%), rhinitis (10%), pain in back (8%), chills (8%), constipation (8%), and vomiting (8%). Expected adverse events will be closely monitored and recorded, and subjects will be able to discontinue the study at any time due to an adverse event. Supportive medications will be used or suggested to assist with treatable adverse events (e.g. bisacodyl for constipation).

4. Side effects to gabapentin: The following are the expected adverse events (and frequency, over 5%) related to gabapentin (from package insert for Neurontin): dizziness (28%), somnolence (21.4%), peripheral edema (8.3%), asthenia (5.7%), diarrhea (5.7%), infection (5.1%). Expected adverse events will be closely monitored and recorded and subjects will be able to discontinue the study at any time due to an adverse event, Supportive medications will be used or suggested to assist with treatable adverse events (e.g. loperamide for diarrhea).

5. Side effects of buprenorphine + gabapentin: In a population that received this dose of gabapentin (vs. placebo) while undergoing a buprenorphine taper (n=30) (Sanders et al 2013), the following adverse events were noted: nausea/vomiting (gabapentin: n=2; placebo: n=1); somnolence (gabapentin: n=2, placebo: n=0); sleep disturbance (gabapentin: n=2, placebo: n=0); loss of motor skills (gabapentin: n=1; placebo: n=0); fatigue (gabapentin: n=1, placebo: n=0), and lightheadedness (gabapentin: n=1, placebo: n=0). All events were mild and did not require intervention, except for lightheadedness. Although vital signs were within the normal range, the gabapentin titration was kept at a lower dose to be conservative.

6. Side effects from buprenorphine + benzodiazepines: The combination of benzodiazepines and opioids, including buprenorphine, can result in respiratory depression and increase risk for overdose death. However, a recent FDA Drug Safety Report (9/20/17) explains that buprenorphine products should not be withheld from patients solely because they are on benzodiazepines. For this reason, we will include subjects who are on prescribed stable doses of benzodiazepines for at least 6 months with no evidence of sedation. Our induction regimen is very conservative with regards to induction dosing, and all subjects will be closely monitored for sedation.

7. Suicidal Ideation: Antiepileptic drugs (AEDs), including gabapentin, increase the risk of suicidal thoughts or behavior in patients taking these medications for any indication. In this study, subjects will be assessed three times a week for worsening mood, suicidal thoughts or behavior by the study team. Should depression or

suicidal thoughts/behavior emerge during the study, the subject will be immediately evaluated by the PI, board-certified psychiatrist, to determine appropriate recommendations for treatment (inpatient, outpatient, intensive outpatient) and safety planning. Coordination of care will occur with the referring/prescribing physician to ensure proper follow-up and monitoring.

8. Respiratory depression and sedation: To minimize this risk, current use of illicit or unstable dose of benzodiazepines, alcohol, or active/history of sedative-hypnotic use disorder will be exclusion criteria for the study. Additionally, on the day of buprenorphine initiation, subjects will be monitored for up to 8 hours and subsequently weekly during the study to monitor for risks of sedation and respiratory depression. Subjects will be educated about the risks of using sedatives, hypnotics or alcohol with buprenorphine and will also be monitored weekly with urine toxicology to test for the use of other opioids or any benzodiazepine or barbiturate. Subjects will be terminated from the study if sedation or respiratory depression become evident and will be referred to the emergency room (if symptoms are moderate-severe) or monitored until resolution (if symptoms are mild).

9. Worsening pain/clinical deterioration: Buprenorphine, a partial mu opioid agonist, can provide variable pain relief to those with chronic pain. Although most studies show an improvement in pain with buprenorphine initiation, should the subject's pain worsen after buprenorphine initiation or during taper, subjects will have the opportunity to exit the study and resume their previous treatment. Any effects of buprenorphine in worsening pain control should be temporary and wear-off within 48 hours, after previous medications have been re-initiated.

11.5 Risk mitigation plan, management of SAE and other study risks

Drs. Barth and Brady will meet regularly to discuss study progress, subject participation, and any clinical issues that arise. Drs. Barth and Brady, both of whom are reachable by pager or cell phone, will monitor participants for psychiatric and medical stability. In addition, there will be a Medical Monitor who will review any adverse events occurring during the study on a quarterly basis.

The following safety precautions will be utilized to minimize risks/harms:

Laboratory pain testing: For mechanical stimulation procedures, the range of von Frey Hair weights to be used for stimulation will be incapable of breaking the skin or causing any tissue damage. The study is set up to test for thresholds, so when a subject feels any pain, the stimulus will immediately stop.

Confidentiality: Every effort will be made to ensure that health information will be collected and stored in a manner that ensures the highest level of protection of confidentiality, including coding all study material and keeping all study material behind locked door in locked cabinet. All interviews and procedures will be performed in a private office at MUSC generally used for private medical interviews. Each subject will be assigned a code number which will be used to identify all collected data. The key for the code numbers will be kept in a separate locked cabinet from the study data in a locked office, accessible only by the PI. Data management and statistical analysis will be done with coded material only. This study involves healthy participants who will be entering the Institute of Psychiatry. If they are seen by anyone they know, they will be able to share that they are participating as a healthy control in a research study, if they feel so inclined. Study data collected will be stored in the following locations: in a locked office, in a locked cabinet, in a password protected office computer and password protected network storage.

Buprenorphine Initiation: To minimize the risks of buprenorphine initiation, we will be taking the following precautions: (1) selecting individuals within a certain opioid dosing range to optimize successful transition, (2) selecting subjects without major medical or psychiatric co-morbidities, (3) providing close medical supervision in the week preceding the initiation and up to a full day of medical supervision the day of the initiation, (4) requiring that subjects have transportation available the day of buprenorphine initiation and not be operating any heavy machinery, (5) excluding individuals on illicit or unstable doses of benzodiazepines or other

sedatives as well as those on fentanyl of methadone, (6) conducting the induction in the Research Nexus or physician's office , (7) completing a physical exam and laboratory evaluation prior to buprenorphine initiation, (8) allowing subjects to stop the study at any time and resume their previous level of care, (9) coordinating with the subject's opioid and, if applicable, benzodiazepine prescriber at the initiation and conclusion of the study, (10) providing cognitive behavioral therapy for pain, (11) providing patient education about the risks of buprenorphine overdose, especially in combination with sedatives or alcohol, (12) obtaining weekly urine toxicology for opioids to ensure the subject is abstinent from prescription opioids other than buprenorphine. For those on stable doses of benzodiazepines for at least 6 months duration who are unable or unwilling to safely taper off benzodiazepines to enter the study, it has been shown that buprenorphine can safely be used with stable doses of benzodiazepines, as reported in a recent FDA Drug Safety Communication (attached). Our initiation protocol is very conservative using 2mg buprenorphine induction, we provide education about using caution with benzodiazepines and buprenorphine, and we monitor closely for sedation throughout the study.

Gabapentin initiation/maintenance/taper: To minimize the risk of poor tolerance of initial gabapentin titration, our proposed titration is more gradual than that which was already demonstrated to be well-tolerated in a sample of 30 subjects undergoing buprenorphine taper (Sanders, et al). We will monitor for worsening mood or suicidal thoughts/behavior once a week and review all adverse events with our Medical Monitor. Gabapentin taper has been well-tolerated in durations of less than one week, but we will taper gabapentin over one week to minimize any possible risk and maximize tolerance.

Buprenorphine Taper/Study Termination: To minimize the risks of buprenorphine taper, we will complete the above precautions with the following additions: (1) continue to coordinate with the prescribing physician during and at the conclusion of the taper (or study termination), (2) medical supervision once a week, (3) providing only a 1 week supply of take-home buprenorphine to minimize the risk of diversion, (4) have a phone meeting with the prescribing physician should a patient terminate at which time options for safe pain treatment will be discussed, including education about decreased tolerance and increased risk of overdose should the patient resume opioid therapy immediately at the previously prescribed dose. Education will be provided to patient and prescribing provider regarding safe re-initiation and/or tapering of opioid therapy.

Students and Employees: Students and employees are eligible for this study. It will be clearly discussed that there is no obligation to participate in this study, consequence for not participating, and confidentiality will be maintained.

Use of buprenorphine and gabapentin in elderly populations:

Gabapentin: The total number of patients treated with gabapentin in controlled clinical trials in patients with postherpetic neuralgia was 336, of which 102 (30%) were 65 to 74 years of age, and 168 (50%) were 75 years of age and older. There was a larger treatment effect in patients 75 years of age and older compared with younger patients who received the same dosage. Since gabapentin is almost exclusively eliminated by renal excretion, the larger treatment effect observed in patients ≥75 years may be a consequence of increased gabapentin exposure for a given dose that results from an age-related decrease in renal function. However, other factors cannot be excluded. The types and incidence of adverse reactions were similar across age groups except for peripheral edema and ataxia, which tended to increase in incidence with age. We are following package insert recommendations for cautious dosing for all subjects, starting at the low end of the dosing range. We are also only including subjects with normal renal (GFR>/=60) and hepatic function (LFTs<5x upper limit of normal). Renal dosing for gabapentin for GFR≥60 = 900 to 3600mg/day. In clinical studies, efficacy for neuralgia was demonstrated over a range of doses from 1800 mg/day to 3600 mg/day with comparable effects across the dose range; however, in these clinical studies, the additional benefit of using doses greater than 1800 mg/day was not demonstrated. In this study, we are limiting the max dose to 1600mg/day gabapentin.

Buprenorphine: Clinical studies of SUBOXONE sublingual tablets, SUBOXONE (buprenorphine and naloxone) sublingual film, or SUBUTEX (buprenorphine) sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In this study, we do start buprenorphine dosing at the low end of dosing, and we are excluding patients with renal or liver disease, or any other medical condition or concomitant drug therapy (e.g. unstable or illicit benzodiazepines), that would put them at increased risk with buprenorphine. Given opioid use among the elderly is an important issue and many qualify for opioid discontinuation, it is not warranted to exclude healthy elderly individuals that otherwise qualify for the study based exclusively on age, so the upper limit of age cut-off for this study will be set at 70 years of age.

Unknown Risks: The experimental treatments may have unknown side effects. The researchers will inform subjects immediately if any information learned might cause subjects to reconsider participation in the study. Should it become apparent that the subject has a medical or psychiatric issue, appropriate referrals will be made for treatment. Any adverse events will be reported to the IRB.

Populations vulnerable to coercion/influence: In order to minimize the risk to subjects vulnerable to coercion or undue influence, we are ensuring prior to study entry that all subjects have an active opioid prescriber who is willing to resume their care (including opioids as appropriate) should the initiation/taper not be successful. Dr. Barth currently manages 50 outpatients on chronic opioid therapy for pain as part of a clinical pilot program (Comprehensive Pain Management Program, CPMP) at MUSC (10% effort, Wednesday afternoons)). To eradicate the possibility of conflict of interest, coercion or undue influence, Dr. Barth will not recruit for this study from her CPMP clinical population. All referrals to the study will come from providers other than Dr. Barth, and the subjects can return to that provider's care upon completion of the study.

11.6 Potential Benefits of the Proposed Research to Human Subjects and Others

Acute and chronic pain are very prevalent conditions that cause much suffering. It is hoped that the information gained from the study will help in the treatment of patients with chronic pain conditions. This research can lead to improved interventions and treatment options for those with chronic pain, improved understanding of pain, and potentially decrease risk of opioid overdoses. Previous research with clinical pain populations show that many patients have a decrease in pain after tapering off opioid medications, which would be an individual potential benefit to the participants.

11.7 Trial Stopping Rules

All SAEs will be reviewed regularly. If at any time in the study, it appears that the potential risks to participants outweighs the potential benefits, the PI will ask the governing bodies their recommendations about stopping the trial.

11.8 Conflict of Interest

Dr. Barth (PI) and Dr. Guille (Medical Monitor) have no current conflicts of interest in performing or monitoring this research. Each physician is reviewed yearly by MUSC for potential conflicts of interest. If a potential conflict of interest becomes apparent, this will be addressed under the guidance of MUSC's IRB by either removing the conflict (in the case of the PI or Medical Monitor), or if it cannot be removed (in the case of the Medical Monitor), to change the Medical Monitor.

11.9 Data and Safety Monitoring Plan Administration

Dr. Barth is responsible for monitoring the safety of subjects, executing the DSM plan, and complying with reporting regulations. A DSM report is filed with the IRB and NIDA Program Official on a yearly basis, unless greater than expected problems occur. The report includes a brief description of the trial, subject characteristics, retention and disposition of study subjects, quality assurance issues, reports of AEs, significant/unexpected AEs and serious AEs, and efficacy.