

Protocol: Buspirone for Opioid Tapering

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JHM IRB - eForm A – Protocol

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1. Abstract

- a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Compelling preclinical evidence has implicated the dopamine (DA) system in the opioid withdrawal syndrome, however this has not yet been prospectively examined in humans. Bupirone (Buspar) is an FDA-approved medication that binds to the D2 family of receptors that has shown initial efficacy in reducing symptoms of opioid withdrawal in animals and in two small human studies of patients undergoing a taper with the opioid agonist methadone. We believe that bupirone may have pharmacologic activity in the receptors of interest and that utilizing it during an opioid taper may improve outcomes. The goal of this study is to collect preliminary feasibility and efficacy data from a sample of patients who are undergoing clinically-indicated opioid tapering, to support a larger R01 grant application. Participants will be enrolled at the beginning of their residential stay on the Pain Treatment Unit at Johns Hopkins Hospital and will be randomly assigned to receive bupirone (15mg, TID for total 45mg daily) or placebo. Withdrawal ratings will be measured each day and withdrawal, time to first request for additional concomitant medications, and willingness to recommend the study to a family or friend will be evaluated as evidence of initial efficacy. Willingness to participate in the study and retention in the study will be evaluated as measures of feasibility. Results may be used to support an R01 grant application to more closely examine this hypothesis.

2. Objectives (include all primary and secondary objectives)

The primary objectives of this study are:

- a) Collect feasibility data regarding the ability to recruit participants into this study
- b) Collect pilot study data regarding the ability of an FDA-approved and generically available medication to suppress symptoms of opioid withdrawal during a clinically-indicated opioid taper program, relative to double-blind administration of placebo

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Scope of the Problem: In 2013, more than 13 million people in the United States had abused an opioid pain reliever or heroin, and more than 2 million people were believed to require treatment for opioid use disorder (OUD) ¹. Treatment admissions for opioid pain relievers and heroin numbered more than 2.4 million in 2013 ^{1,2}. Effectively treating opioid use disorder (OUD) would reduce the substantial societal

economic burden it imposes, which is estimated to exceed \$8 billion annually^{3,4}. Successful treatment of OUD has also been associated with decreases in the risk of opioid-related overdose deaths, which have increased by 137% in the past 10 years and are reaching endemic proportions⁵. The medical community is not generally able to adequately manage symptoms of opioid withdrawal. Patients regularly cite withdrawal symptoms as a primary reason for not stopping opioid use, with higher magnitude symptoms result in poorer treatment retention^{6,7}. The most effective pharmacotherapies for OUD, methadone and buprenorphine, are themselves opioid agonists that confer a withdrawal syndrome similar to that of abused opioids. These medications were only selected for use because they are long-acting opioids that can suppress withdrawal through the known cross-tolerance that exists among opioids, not based upon a mechanistic understanding of the opioid withdrawal syndrome. The mechanisms underlying the human opioid withdrawal syndrome have not been empirically evaluated in humans and are therefore not understood well enough to support development of non-opioid pharmacotherapies that function at a central level. All current non-opioid adjunctive pharmacotherapies are provided to treat individual symptoms (e.g., ibuprofen for aches/pains, hydroxyzine for sleep impairment). This is true also of the adrenergic agonists clonidine and lofexidine, which are hypothesized to minimize the severity of some opioid withdrawal symptoms based upon their peripheral activity in the autonomic nervous system. None of these adjunctive medications have been shown to produce high magnitude effects and confer substantial clinical benefit in terms of retention and withdrawal management.

Dopamine May Modulate the Opioid Withdrawal Syndrome: Compelling preclinical evidence suggests dopamine (DA) plays an important modulatory role in the opioid withdrawal syndrome⁸, and that this modulation only occurs following development of physical dependence upon opioids⁹⁻¹¹. If true in humans, this would suggest that dopaminergic antagonists (many of which have been already FDA-approved for use as antipsychotics) may- in conjunction with opioid agonists- help reduce symptoms of opioid withdrawal at a central level. The DA hypothesis of opioid withdrawal has not yet been examined in humans.

Buspirone May Reduce Opioid Withdrawal Symptom Severity:

Buspirone has shown initial efficacy in treating opioid withdrawal symptoms: Preliminary data collected from two small double-blind, placebo-controlled trials in OUD subjects undergoing methadone suggests buspirone may reduce the magnitude of some opioid withdrawal symptoms^{27,28}. Though these studies had small sample sizes (n=20 across 2 groups, n=29 across 4 groups) and were conducted only in men, they did show a positive signal for buspirone in reducing the overall severity of withdrawal when it was co-administered with methadone and maintained after methadone discontinuation. Individual item analysis reported in one of these studies²⁷ reported significant differences in patients who received adjunctive buspirone (45mg) or placebo in the following symptoms: “I feel like yawning”, “my nose is running”, “I have gooseflesh”, “I have cold flashes”, “my bones and muscles ache”, “I feel restless”, “my muscles twitch”, “I have cramps in my stomach”, and “I feel like shooting up right now”, which suggests that buspirone may have potential to impact a wide-range of opioid withdrawal symptoms.

Conclusion: Compelling preclinical data suggests DA modulates the opioid withdrawal syndrome in a manner that could increase symptom severity and symptom severity is a primary reason for which patients continue abusing opioids. There are no human empirical studies that investigate whether a DA-medication can reduce the severity of the opioid withdrawal syndrome in humans.

4. Study Procedures

- a. Study design, including the sequence and timing of study procedures

Participants: Participants who are undergoing clinically-indicated tapering off their prescribed opioid medications for pain treatment will be invited to participate in this double-blinded pilot study within the

first week of entering the Pain Treatment Unit located in the Johns Hopkins Hospital. The goals of the study are to collect initial feasibility and efficacy data to support a NIH grant application.

Study Enrollment: During the first week of their residential stay, patients who meet initial eligibility criteria will be informed of the study by their attending physician or other clinic staff member. Patients who are interested in the study will review and sign the informed consent with a trained study staff member before completing the Screening. To increase generalizability, the Screening process will be very limited and restricted to collecting baseline data regarding opioid withdrawal severity and information to characterize the sample. Participants will also be asked to provide authorization for the study to access their medical records to allow documentation of additional concurrent medications and retention in treatment.

Standard of Care Taper Procedures:

- This study will be run concurrent with the standard taper that is administered in the Pain Treatment Unit. The study will not dictate the terms of the taper, however (if our hypothesis is correct) it is possible that the taper may occur more quickly in patients who are treated with buspirone. Information regarding the taper will be retrieved from the medical records and evaluated as outcome data.
- The tapering protocol is individualized to the patient but follows the same standard rationale. Patients are generally stabilized on their admitting medications to ensure they have informed the staff their correct usage. They are then converted to a long-acting formulation such as Oxycontin (if not already on one) and a standing schedule of dosing is implemented (e.g., q6 hours). In most cases, the opioid dose is decreased by 10-20% every 3 days, and withdrawal symptoms and pain are monitored. The speed and magnitude decrease of the taper is adjusted based upon the results of those ongoing assessments in order to optimize patient participation in the treatment plan. The goal is to completely taper the patient off opioids by the end of 28 days, though this may vary depending on the individual circumstances of the patient. Additional PRN concomitant medications are also made available via standing orders to help manage symptoms of withdrawal (e.g., nausea, diarrhea, muscle aches and pains). Medications are available upon patient request.
- Study medication will be prescribed for thrice-daily administration and will be managed independent of PRN medications.

Study Procedures:

- Participants who are enrolled into the study will be randomized (stratified by sex, current morphine equivalent dose ($>100\text{mg}/\leq 100\text{mg}$), and Brief Pain Inventory Severity Scale ratings ($<7/\geq 7$)) to receive double-blind dose of buspirone (15mg, TID) or placebo. Buspirone will be purchased commercially and over-encapsulated to support blinding. In the event a participant leaves the unit prematurely (e.g., before completing the buspirone taper) he or she will be abruptly discontinued from buspirone.
- Participants will be asked to complete daily self-report ratings of opioid withdrawal severity (such as the Subjective Opioid Withdrawal Scale; SOWS) and to complete an exit survey that indicates whether they would recommend the medication to another person and the degree to which they believe the study medication helped them to successfully taper down on opioids and to which it suppressed their withdrawal symptoms.
- Participants will be permitted to stop taking the study medication at any time period and adherence will be collected and analyzed as a measure of acceptability.

- We will ask participants to refrain from requesting additional concomitant medications to help manage withdrawal symptoms until absolutely necessary. However, participants' requests for additional concomitant medication will be honored, and the day on which additional medication was requested will be recorded as a measure of efficacy (with the hypothesis that buspirone may delay the need for additional medications). Concomitant medications will be administered as part of the standard clinical practice and will not be provided by the study, though data regarding medication use will be collected for study outcome analyses. We believe this is the best approach for this initial study, as we cannot yet be certain that buspirone will reduce the severity of the withdrawal syndrome.

b. Study duration and number of study visits required of research participants.

Participants will be enrolled for the duration of their residential stay or 28 days, whichever comes first.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants in this study will be blinded to their study medication condition. This will provide the most rigorous test of this hypothesis and allow us to collect the strongest data with the smallest possible sample size. Since buspirone is not regularly administered for the treatment of opioid withdrawal, this blinding will not prevent participants from receiving their general standard-of-care treatment. We will also allow participants to request additional concomitant medications, consistent with standard care, and will track use of concomitant medications as an outcome measure.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

A placebo control will be used to rigorously assess the study hypotheses, however buspirone is not currently used as a treatment for opioid withdrawal symptoms, therefore this placebo control will not prevent patients from otherwise receiving their standard of care treatment.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they withdraw consent, are unable to tolerate the medication, begin another medication that is contraindicated with buspirone, or are diagnosed with another condition for which buspirone treatment may be contraindicated.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants can choose to participate and withdraw consent later with no consequences; any participant who withdraws consent will continue to receive standard-of-care opioid tapering resources as part of their primary treatment. Participants who wish to continue buspirone treatment following study completion will be referred to their physician for continued care.

5. Inclusion/Exclusion Criteria

Inclusion Criteria: Be 18 years or older and undergoing a taper from their opioid medications

Exclusion Criteria: Being pregnant or breastfeeding, past 7-day use of grapefruit juice or other strong CYP P450 inhibitors, have no clinically significant chronic medical or surgical disorders or conditions that are judged by the investigators to be contraindicated with buspirone administration, or have current suicidality as assessed by clinic staff or the Columbia Suicide Severity Rating Scale (C-SSRS).

6. **Drugs/ Substances/ Devices**

- a. The rationale for choosing the drug and dose or for choosing the device to be used.

Oral buspirone (Buspar) will be tapered up to a total daily dose of 45mg. This dose has shown previous efficacy in reducing opioid withdrawal symptoms in patients being tapered off the long-acting opioid methadone²⁷ and will be replicated here as pilot data to support an NIH grant application. Participants in this study may request to not take a dose and the reason for this will be documented and treated as primary outcome data.

Buspirone is generally administered twice daily, based upon early reports indicating multiple daily dosing was effective for reducing anxiety (relative to diazepam) and based upon cited but not published open-range dose finding study⁴⁵. A meta-analysis subsequently reported equivalent anxiety treatment outcomes and adverse events profiles with BID vs. TID dosing⁴⁶. Early studies reported a greater incidence of dysphoria and dizziness following 20mg buspirone dosing relative to smaller doses^{45,47,48}. Though the incidence of adverse events was lower with 20mg buspirone than the diazepam comparison, this result appears to have shaped the current practice of multiple daily dosing. A subsequent evaluation of side effects among 700 patients receiving a mean 20mg buspirone reported no difference in the rate of side effects as compared to placebo and fewer side effects relative to diazepam and clorazepate⁴⁹.

Buspirone has only 4% bioavailability and is eliminated quickly and primarily by first-pass metabolism-with less than 1% of an oral dose being excreted as unchanged drug and 60% of metabolites being excreted in urine⁵⁰. The elimination half-life of an oral dose is 2.5 hours and this does not change as a function of the dose administered⁵⁰. Buspirone serum levels increase in a linear manner with dosing. Plasma levels of buspirone increase quickly after ingestion, achieving Cmax within an hour of dosing and Tmax within 60-84 minutes^{50,51}. Human laboratory studies indicate that buspirone doses and area-under-the-curve values are linear up to QD 40mg dose (which was the highest dose tested)⁵¹ indicating that bioavailability is proportional to the dose administered. A multi-dose administration study that provided healthy volunteers with 10mg doses every 12 hours for 10 days reported no accumulation of buspirone or its metabolites⁵².

- b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Buspirone is FDA-approved for the treatment of anxiety disorder and can be prescribed off-label for other indications. Consistent with our study procedures, the FDA permits a maximum of 60mg to be administered per day in divided doses.

- c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics (Partially Blinded)

a) Primary outcome variable.

i. Feasibility

- a. Participant retention in treatment, evaluated as a) last day in the study and b) being present on the final day of the study

ii. Initial Efficacy

- a. Withdrawal symptom suppression, measured through daily self-report ratings of withdrawal on the Subjective Opiate Withdrawal Scale (SOWS)

b) Statistical plan including sample size justification and interim data analysis.

- a) Sample size: This is a pilot study to support an R01 trial. A power analysis using G-power, evaluating an independent groups t-test of area-under-the-curve (AUC) values from the SOWS, with alpha set to 0.05, revealed that 12 participants per group would yield 60% (moderate) power to detect a large (0.80) effect. We believe this will provide sufficient data to support an R01 study evaluation.

- b) Statistical Plan. Given the small sample size and low perceived risk, no interim data analyses will be conducted.

1. Feasibility

- i. Patient retention in treatment will be compared across groups using independent groups t-tests for continuous and chi-squares for dichotomous outcomes. Regressions factoring group, baseline opioid dose in morphine equivalents, pain severity ratings from the Brief Pain Inventory, and number of concomitant medications, and study medication adherence (% prescribed doses) will be used to determine the degree to which group assignment predicted being retained on the final scheduled day (Logistic) and final day in treatment (Linear).

2. Initial Efficacy

- i. Withdrawal symptom suppression will be compared across groups using area-under-the-curve (AUC) analyses.

c) Early stopping rules.

Participants will be discharged from the study if they leave the residential unit against medical advice, request to be removed from the study, begin taking a medication that is contraindicated with participation, are diagnosed with a contraindicated condition, express suicidal thoughts, or if new information becomes available to suggest this study may cause them more than minor harm.

8. Risks

- a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Buspirone (Buspar) is an oral tablet that is FDA-approved for the treatment of anxiety and prescribed off-label for the treatment of depression. It has been prescribed at doses up to 90mg/day for depression. The maximum dose provided to participants in this study (45mg/day) is well within the range of approved doses and is below the maximum dose recommended for the treatment of anxiety (60mg/day). Buspirone is rated as pregnancy category B, indicating that animal studies have not indicated a unique risk of buspirone on the

developing fetus but that controlled human studies have not yet been conducted. We will exclude all women who are pregnant or breastfeeding from participating. When administered orally (as proposed here) buspirone effects peaks in 40-90 minutes. It has 90% bioavailability and 86% protein binding. It is subject to extensive first-pass metabolism by the P450 CYP3A4 enzymes, and produces active metabolites. The elimination half-life is 2-3 hours, and this is prolonged in patients with impaired hepatic or renal function.

Buspirone is excreted in both fecal (18-38%) and renal (29-63%) waste, though renal excretion is primarily as metabolites. Buspirone is contraindicated with severe hepatic or renal impairment, and has several severe drug interactions with alcohol, MAOIs, and grapefruit juice (all of which will be excluded).

Recognized side effects include nausea (8%), dizziness (12%), headache (6%), somnolence (10%), and feeling nervous (5%). Potential serious side effects include congestive heart failure (less than 0.1%), myocardial infarction (less than 0.1%), and cerebrovascular accident (less than 0.1%).

Review of the literature on buspirone suggests that reported buspirone discontinuation effects pertain to the reemergence of depression and/or anxiety for which the buspirone was prescribed. We can find no published evidence of a buspirone-specific withdrawal syndrome aside from this effect. Further, the majority of research regarding reemergence effects refers to extended buspirone exposure (>6 weeks), which is significantly longer than what is proposed here. Since we cannot find evidence of a buspirone-specific withdrawal syndrome, are not prescribing buspirone for anxiety or depression, and are administering it for a relatively short period of time, we do not believe this study puts participants at undue risk of experiencing buspirone-specific withdrawal symptoms.

b. Steps taken to minimize the risks.

The biggest risk incurred by buspirone administration is that it is consumed with contraindicated medication and/or alcohol, and this risk is mitigated in this study because participants will only be consuming buspirone under staff observation while residing on a closed clinical unit. We will also exclude or wait to enroll any participant who has consumed any contraindicated medications (including CYP3A4 inhibitors or inducers) or grapefruit juice in the previous 7 days to further prevent any drug interactions from occurring. Any participant who experiences adverse effects of the study medication will be permitted to stop taking the medication or to remain at the dose at which they felt comfortable and this decision will be made jointly with the study physician and participant. Finally, there is a risk that participants who decide to discharge themselves from treatment will abruptly discontinue their buspirone dosing without benefit of a dose taper period. There is a chance that participants could experience a mild and transient dysphoria following abrupt discontinuation. We will inform all patients about the risk associated with abrupt discontinuation of the study medication prior to study enrollment, so they will be able to make an informed choice regarding whether they want to participate in the study. Given the very brief duration for which participants will receive buspirone, we expect that any discontinuation syndrome that is experienced will be mild and of short duration.

c. Plan for reporting unanticipated problems or study deviations.

All study events will be monitored during weekly meetings between the study investigators and we will follow all IRB guidance and recommendations regarding the reporting of unanticipated problems of study deviations. All such problems and deviations will be documented and if they do not meet the criteria for immediate reporting, they will be submitted to the IRB as part of the continuing review (or when otherwise requested).

- d. Legal risks such as the risks that would be associated with breach of confidentiality.

We do not believe this study poses any legal risks associated with breach of confidentiality.

- e. Financial risks to the participants.

Participants will not incur any cost for study participation. All study medications will be provided to them at no cost.

9. Benefits

- a. Description of the probable benefits for the participant and for society.

This study will collect pilot data to support an NIH grant application to evaluate bupirone as an adjunctive medication to help suppress and/or manage symptoms of opioid withdrawal during clinically-indicated tapering. This approach is grounded in sound preclinical mechanistic data and results from this line of research has the ability to make a new medication immediately available for wide-spread use to help combat and address the opioid use disorder epidemic and need to taper patients down from high doses of opioid medications for pain control.

10. Payment and Remuneration

- a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be paid \$10 a day and a \$120 completion bonus at the end of the study, for a total potential earning of \$400. Payments will be made contingent upon completion of withdrawal rating measures only and not medication adherence, to prevent patients from continuing to take the medication for the compensation even if they experience untoward effects from doing so. All payments will be made via check to the participant or on a reloadable credit card that will be provided to patients upon discharge from the unit.

11. Costs

- a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

All study-related costs, including bupirone, will be paid for by the study. All costs related to tapering (including concomitant medications) will be paid for by the patient's insurance, as per standard care treatment, and the study will not interfere with the tapering schedule in any way.