A Prospective, Randomized Trial of the Effect of Buprenorphine Continuation versus Dose reduction on Pain Control and Post-Operative Opioid Use

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Introduction

Buprenorphine is a high-affinity, partial mu opioid receptor agonist that is effective, life-saving opioid maintenance treatment (OMT) for individuals with opioid use disorder (OUD). Due to the pharmacokinetics of buprenorphine, managing acute post-surgical pain can be challenging, especially when full mu opioid receptor agonists are used concomitantly. Currently, the Substance Abuse and Mental Health Services Administration (SAMHSA)- the national organization that provides guidance on the management of substance use disorder treatment- recommends discontinuation of buprenorphine prior to surgery, replacing it with full opioid agonists for withdrawal prevention, to facilitate postoperative analgesia.[1] However, SAMHSA states as an advisory warning that this can introduce significant risks to an individual's substance use recovery, including cravings and relapse. Conversely, SAMHSA also recommends full dose buprenorphine continuation perioperatively; however, they also warn that the risks associated with this management strategy include ineffective analgesia necessitating escalating opioid administration.

Preliminary clinical observations support that buprenorphine continuation at low analgesic doses (8mg) can adequately facilitate postoperative pain management without interrupting OUD treatment.[2,3] Over the past couple of years, there has been growing support for perioperative continuation of buprenorphine.[4-6] At our institution, providers are currently more willing to recommend low dose buprenorphine continuation, a significant practice shift from a year prior when buprenorphine discontinuation was the accepted standard. Furthermore, there are recent reviews- based on professional opinion as opposed to prospective studies- that contend buprenorphine should be continued without dose adjustment perioperatively.[4,7] This is paradoxical to the reports saturating the literature up until recently asserting that patients had poorly controlled postoperative pain when maintained on high doses of

buprenorphine, leading to increased opioid utilization and disruption of hospital courses.[8,9]

To date, no prospective trial has investigated low dose buprenorphine continuation in comparison to buprenorphine discontinuation and SAMHSA has not endorsed low dose buprenorphine continuation as a management strategy. Similarly, no study has compared full dose buprenorphine continuation to buprenorphine dose reduction perioperatively. Because of this, there has been a call for prospective studies to investigate an optimal perioperative buprenorphine dosing strategy.[3,5,7] Since there is growing acceptance that the risks of OUD relapse with buprenorphine discontinuation overshadow the risks of increased opioid utilization and potentially difficult pain control with buprenorphine continuation, our next course of action is to determine whether full dose buprenorphine continuation is superior to reducing buprenorphine to analgesic doses in individuals with OUD presenting for elective surgery. For this study, we propose to compare postoperative pain scores, opioid consumption, outpatient opioid dispensing, and OUD related symptoms between these two treatment strategies. The goal of our study is to inform the development of guidelines for the perioperative management of patients on buprenorphine that are based on science as opposed to expert opinion.

Background

Opioid use disorder (OUD) is a chronic neurobehavioral disease characterized by continued opioid use despite the desire to quit, often punctuated by cycles of remission and opioid use relapse. OUD is associated with high rates of medical co-morbidity and life expectancy is two decades shorter when compared to those without OUD.[10] In the past 20 years, opioid related deaths have risen exponentially.[11,12] Maine has been especially devastated by this trend and, although OUD mortality rates declined in 2018, they are beginning to re-ascend. It is projected that the overdose death rates for 2020 will be the highest on record, as the first quarter of this year has seen a 23% increase in opioid related mortality.[13] Unfortunately, despite our national crisis, opioids remain prominent in perioperative

analgesic regimens for the millions of surgeries and procedures performed each year in the United States.

Opioid maintenance therapy (OMT) with buprenorphine has reduced hospitalization rates and mortality for those with OUD.[14] The optimal duration of OMT has not been established and relapse rates can be high when OMT is discontinued. A multi-site study sponsored by the National Institute on Drug Abuse (NIDA) reported relapse rates approaching 90% following the premature discontinuation of OMT.[15]

Clinical opinion is mixed on whether buprenorphine should be held, continued at full dose, or reduced in the perioperative period as it is limited to case reports, case series and provider opinion. Acute post-surgical pain management can be challenging in these patients when standard pain regimens, including full mu opioid receptor agonists, are needed for post-operative pain management.[16] Buprenorphine has high receptor binding affinity, a long half-life, and displays partial mu opioid receptor agonism- all properties which can prevent effective analgesia from full mu opioid agonists used in conjunction for pain control. Therapeutic doses of buprenorphine for OUD treatment (16-32mg) are thought to saturate opioid receptors, rendering further opioid use for analgesia ineffective. There are published reports of patients with poorly controlled postoperative pain when buprenorphine was continued and some providers recommend buprenorphine discontinuation at about 72 hours prior to elective surgery and replacement with low dose opioid agonists to reduce the risk of opioid withdrawal. One report describes a 50 year-old man with acute limb compartment syndrome on buprenorphine for OUD requiring escalating doses of hydromorphone without pain control until buprenorphine had been discontinued for 48 hours. Similarly, a 47 year-old female with OUD on buprenorphine had poor pain control with escalating doses of hydromorphone after thoracic surgery that did not resolve until her buprenorphine was discontinued.[9]

However, case reports also describe difficult perioperative pain control regardless of buprenorphine discontinuation. In one report, a 37 year-old woman on buprenorphine underwent two separate uro-gynecologic procedures where

buprenorphine was continued for the first procedure and discontinued for the subsequent one. Pain management was challenging for this patient in both instances.[9]

Conversely, case series have reported effective pain management with full mu-opioid agonists in patients maintained on buprenorphine perioperatively. In one report, five patients undergoing major surgery continued buprenorphine and their pain control was adequately treated with supplemental opioids given as needed. In a retrospective cohort study of 22 surgical patients taking buprenorphine, there was no difference in pain control on postoperative day one in the half for whom buprenorphine was continued vs the half for whom buprenorphine was discontinued.[9]

There are preclinical data and evidence from patients taking buprenorphine for chronic pain at analgesic doses that the addition of opioid agonists is effective in treating breakthrough pain.[9] Neuroimaging of opioid receptor availability in heroin dependent patients receiving buprenorphine suggest that 8mg of buprenorphine is the ideal dose where receptors are available for additional opioid agonists to bind and facilitate analgesia. We compiled this evidence to establish institutional guidelines to continue buprenorphine at an 8mg analgesic dose. We subsequently published a retrospective observational study about our experience with analgesic dosed buprenorphine continuation compared to discontinuation.[3] We identified that outpatient opioid dispensing and PACU pain scores were significantly higher in the cohort where buprenorphine was discontinued compared to when it was continued. A recent retrospective study from Stanford University published similar findings, reporting that patients continued on buprenorphine perioperatively at varied tapered doses received significantly less opioid prescriptions without changes in pain scores when compared to patients where buprenorphine was discontinued.[17] These clinical observations challenge previous assumptions that, due to its pharmacology, buprenorphine interferes with opioid based pain management. However, these studies are limited by their retrospective, non-randomized design, and their absence of controlled clinical conditions; also, they do not address relapse rates and postoperative OUD-related symptoms. Most importantly, current established

national guidelines are to continue buprenorphine without dose adjustment or to discontinue buprenorphine perioperatively, without evidence to support either strategy. The current national guidelines disclose that full dose buprenorphine continuation can lead to inability to treat pain with opioid agonists and discontinuation can lead to withdrawal, however, they do not include recommendation for adjusting buprenorphine to an analgesic dose to facilitate opioid based analgesia, while preventing withdrawal.

Even though no prospective trial has been conducted to identify if buprenorphine continuation or discontinuation should be the preferred strategy for perioperative pain management, in the past couple of years there has been a paradigm shift where many contend that the risks of OUD relapse with buprenorphine discontinuation outweigh the risks of increased opioid utilization and potentially difficult pain control with buprenorphine continuation. This is evident from our initial study, designed as a head-to-head comparison of buprenorphine continuation to discontinuation. In our two months of active recruitment for this study, we found a significant number of patients that were reluctant to enroll in the study. When given the option to stop versus continue their buprenorphine at a lowered dose, patients were understandably inclined to continue their buprenorphine at the lowered dose due to their concerns and fears of relapse. Also, many of the patients stated that their doctor told them to continue their buprenorphine- in line with the current MaineHealth guidelines of low dose continuation that the authors of this study proposal helped establish in 2020.

An outstanding question still remains regarding the optimal dosing of buprenorphine perioperatively. As stated previously, there is evidence to support that low dose buprenorphine continuation may be ideal, because when buprenorphine is at a lowered, analgesic dose, there would still be availability for full opioid agonists to work for pain control given increased opioid receptor availability. However, it is quite possible that even at elevated doses of buprenorphine and corresponding low opioid receptor availability, pain control is still possible and dose reduction is not required. Thus, we propose to compare full dose buprenorphine continuation to low dose buprenorphine continuation in

patients scheduled for elective surgery. It is worth noting that this revised proposal was intended to be our follow-up study upon completion of our prior study comparing buprenorphine continuation to discontinuation.

Our proposed study will provide data to improve acute pain management delivery for the growing population of individuals receiving buprenorphine as OUD therapy. Not only will our study address a considerable gap in care delivery, but it will help establish consensus for a topic that currently has mixed opinion. If this clinical trial identifies that buprenorphine dose reduction is no different than full dose buprenorphine continuation, than we can change our MaineHealth guidelines to recommend continuation without having to make any adjustments to patient's OUD treatment. If, however, we identify that patients with full buprenorphine continuation use more opioids and have prolonged hospital courses, it will confirm the need for our current guidelines, confirming our preliminary findings of adequate pain control with buprenorphine continuation at analgesic dosing. Additionally, it could help establish treatment plans where patients are provided with less opioids both as inpatients and outpatients decreasing opportunities for diversion and opioid related relapse. We will further explore the comprehensive effect of buprenorphine management strategies through engaging representatives from the substance use disorder community and the providers involved in the various phases of their care. Convening this group of stakeholders together as members of our Data Safety and Monitoring Review Board will help us identify the key concerns for patients with OUD. It will also allow us to tailor our study to address these issues, with the ultimate goal of reducing perioperative OUD severity and the risks associated with relapse.

Hypothesis

There is limited guidance on the optimal management of buprenorphine perioperatively and both buprenorphine discontinuation and continuation are acceptable standards of care.[1] Buprenorphine continuation at low analgesic dosing is also accepted, however is not provided as a potential treatment strategy by SAMHSA.[1] There is the risk of inadequate pain control necessitating opioid

escalation when buprenorphine is continued. Preliminary clinical observations support buprenorphine continuation at low analgesic doses (8mg) as it adequately facilitates postoperative pain management without interrupting OUD treatment, however to date, no prospective trial has investigated this treatment strategy in comparison to low dose buprenorphine continuation. Since optimal perioperative dosing strategies remain unknown, the purpose of this study is to investigate if buprenorphine continuation at analgesic dosing is superior to buprenorphine continuation in individuals presenting for elective surgery.

Specific Aims

Aim 1: To compare the efficacy of perioperative standard of care low dose buprenorphine continuation (STD-BUP) to full dose continuation (FULL-BUP) in adults maintained on buprenorphine for OUD. *Hypothesis 1: Postoperative pain scores at postoperative day (POD) 1 will be higher in FULL–BUP patients compared to STD-BUP patients and this difference will be clinically significant (defined as a > 20% difference in pain scores between groups).* We will measure pain using a numeric rating scale (NRS) of 0 to 10, a standard tool used in comparing analgesic efficacy between distinct treatment interventions.

Aim 2: To compare postoperative opioid consumption (excluding buprenorphine formulations) in adults maintained on buprenorphine for OUD, measured as morphine milligram equivalents (MME) at 24, 48 and 72 hours postoperatively. *Hypothesis 2: FULL-BUP patients will have higher opioid consumption at 24, 48 and 72-hours postoperatively compared to STD-BUP patients.*

Aim 3: To compare OUD symptom severity and depressive symptoms; measured preoperatively and 30 days postoperatively using the Patient Health Questionnaire-9 (PHQ-9), Current Opioid Misuse Measure (COMM), and Opioid Craving Scale (OCS) instruments. *Hypothesis 3: There will be no difference in OUD symptom severity and depressive scores FULL-BUP patients compared to STD-BUP patients, both on day of surgery and at 30 days postoperatively.*

Aim 4: To compare the number of opioid prescriptions and quantity (in MME) of opioid medications dispensed, up to 30 days following surgery. *Hypothesis 4: The number of opioid prescriptions and the quantity of MMEs dispensed will be higher*

for FULL-BUP patients than for STD-BUP patients during the 30 day period following surgery.

Significance

Greater than two million Americans are estimated to currently suffer from opioid use disorder (OUD), and over the past two decades, opioid related mortality has exponentially increased. Buprenorphine is a Food and Drug Administration (FDA) approved treatment for OUD management. Reflective of its long-term, life-saving benefits, buprenorphine is currently the most frequently prescribed medication in the state of Maine, with the blood pressure medication, hydralazine, being the second most commonly prescribed.[18] Buprenorphine works by binding strongly to opioid receptors- targets for drugs of abuse - for relatively extended periods of time, attenuating the cravings and withdrawal symptoms that fuel opioid addiction and relapse. When individuals on buprenorphine present for surgery, their acute post-surgical pain can be challenging, as the opioid medications commonly given to provide analgesia are unable to easily displace buprenorphine. Currently, both buprenorphine discontinuation and continuation are recognized as acceptable standards of care. The Substance Abuse and Mental Health Services Administration (SAMHSA), the organization that manages the federal approval of buprenorphine prescribers, recommends either perioperative buprenorphine continuation or discontinuation, based upon patient and provider preference, with consideration of the inherent risks for each management strategy.[1] However, there is limited specific guidance on the optimal perioperative management of buprenorphine in this patient population and low dose buprenorphine continuation is not currently described as a treatment option by SAMHSA .

Preliminary clinical observations support that buprenorphine continuation at low analgesic doses can adequately facilitate postoperative pain management without interrupting OUD treatment.[3,17] However, no prospective trial has investigated this treatment strategy. The purpose of this study is to investigate whether buprenorphine continuation at analgesic dosing is superior to buprenorphine continuation in individuals presenting for elective surgery. Adults scheduled for

elective surgery who are taking ≥12mg buprenorphine for OUD treatment will be eligible for this study. Enrolled participants will be randomized to receive either a reduced analgesic dose of buprenorphine (8mg) or to continue buprenorphine on the day of surgery without dose reduction. Our primary outcome of interest is postoperative pain scores. Our secondary outcomes of interest are opioid consumption, opioid dispensing up to 30 days following the surgical procedure and OUD related symptoms, including opioid withdrawal, cravings and relapse. We hypothesize there will be a clinically significant increase in pain scores when buprenorphine is continued in full compared to when it is continued at a lower analgesic dose. We will define clinical significance as a difference in composite pain scores of greater than 20% between groups. We also hypothesize that opioid consumption and opioid dispensing will be greater with full dose buprenorphine continuation compared to low-dose continuation. This will be the first randomized trial comparing competing perioperative buprenorphine treatment strategies and will yield critical preliminary data for larger, confirmatory studies. Additionally, we envision that this study will lay groundwork for follow-up investigations in this patient population, focused on preventing opioid cravings and relapse perioperatively, along with other clinical scenarios where acute pain is anticipated, such as intensive care unit settings.

Successful execution of this prospective trial will provide Dr. Quaye with the tools and critical experience necessary to pursue her aspirations of becoming a successful clinical investigator. Aurora Quaye has a mentorship team that is committed to her success and is led by her department chair, Dave Warters. Her mentorship team also includes Wendy Craig, Cliff Rosen, Kathleen Fairfield, Irwin Brodsky, Kinna Thakarar and Liz Jacobs. Her mentorship team will help provide guidance as she mentors residents, including Yussr Ibrahim, that have expressed interest in engaging in clinical research. They will meet with her periodically and provide her with any feedback that is required, based upon the trial phase, to help promote successful trial completion.

STUDY DESIGN AND RESEARCH PROCEDURES

This is a prospective, randomized, unblinded clinical trial comparing full dose buprenorphine continuation to buprenorphine continuation at analgesic dosing in adults with OUD maintained on 12mg or greater sublingual equivalent buprenorphine, who are scheduled for elective surgery.

Randomization Plan

Enrolled participants will be randomized 1:1 into one of two groups (defined below). The randomization scheme will be developed using NQuery Software (Statistical Solutions, Boston, MA).and will use permuted blocks of 4 and 6 patients to ensure balance between study arms. The analyst will provide the research coordinator with randomization assignments in sequentially-numbered opaque envelopes (one series of envelopes for each stratum of anticipated post-surgical pain) . The study coordinator will pass the next envelope in sequence to another member of the study team when it is time to assign a subject to a group. Gerbershagen et. al. documented the distribution of pain scores for 179 different surgical procedures and we will use these data to establish randomization strata.[19] For true practice generalizability on the association between buprenorphine management and postsurgical pain control, we will include surgical procedures based on average pain intensity on postoperative day (POD) 1, as opposed to limiting our criteria to a particular surgical type (see Appendix 1).

Patients will be stratified according to their anticipated pain score on POD 1 (4-6/10 range vs >6/10 range) and those within each stratum will be randomized to one of two groups as follows:

- FULL-BUP group: buprenorphine formulation continued throughout the perioperative period
- STD-BUP group: buprenorphine formulation reduced to 16mg the day prior to surgery and then 8mg on the day of surgery onwards. Participants in this group taking 12-16mg buprenorphine at baseline will have no change to their buprenorphine dose on the day prior to surgery.

All participants will be transitioned back to their regular dose of buprenorphine when postoperative surgical pain has subsided as determined by their

buprenorphine provider following hospital discharge. This transition will be coordinated with their buprenorphine provider, which is our current standard practice when buprenorphine is reduced perioperatively.

As the study is unblinded, both patients and providers will be aware of the randomization assignment. To help mitigate bias, the team members collecting and entering data will be masked regarding the patient's assignment. The REDCap database has the randomization assignments in an instrument separate from the study data collection instruments, allowing for data entry without seeing which group the subject is in.

Study Procedures

On the day of surgery, prior to the procedure, participants will be asked to complete a series of questionnaires to obtain baseline self-assessments for opioid cravings, opioid misuse, and opioid withdrawal symptoms (see protocol schema and Measures for Aim 3 section for details). Patients will be asked to report early for their procedure to complete the study questionnaires in a private space.

Both groups will receive identical preoperative, intraoperative and postoperative multimodal opioid sparing strategies, coordinated with the surgical, anesthetic, and psychiatric clinical care teams directly involved in the study participant's care. Multimodal analgesia, or the administration of two or more drugs that act by different mechanisms, provides more effective analgesia compared to medications used individually. Multimodal analgesia has been well established at achieving early recovery after surgery and reducing pain scores. According to the American Society of Anesthesiologists (ASA) task force for acute pain management, multimodal pain management therapies should be used for the treatment of surgical pain whenever possible however it is not mandatory to use these methods routinely for all surgical procedures and they are utilized at the discretion of the anesthesiologist taking care of the patient. As such, we will adopt this standard of care practice for the treatment of post-surgical pain in both randomized groups. Our multimodal analgesic strategy will consist of gabapentin, acetaminophen and Celebrex preoperatively and postoperative ketorolac, acetaminophen, opioids, nerve blocks infusions/epidural catheters, alpha agonists,

ketamine and lidocaine infusions as indicated. Postoperatively, opioid medications will be given IV or PO as second line analgesic agents. If a participant has an allergy or aversion to any of these medications, they will not receive the medication, but will be able to participate in the study with alternative medications. All analgesic medication administered will be documented by study staff. In the event of poorly controlled pain at any point during the study, we will provide the patient with appropriate analgesic rescue agents to ensure that post-surgical pain is adequately controlled.

Intraoperative opioid consumption, type of anesthesia, total PACU opioid consumption, normalized for time spent in PACU, and 24, 48 up to 72-hour opioid consumption will be extracted from the patients' charts. All opioid consumption will be converted into MME. One month postoperatively, participants will receive virtually- administered questionnaires, including: a substance use evaluation, where they will be asked to complete self-assessments identical to those administered on the day of surgery for comparison analysis. Patients will be encouraged to record postoperative pain and opioid consumption on the Timeline website regularly and reminded that compensation is tied to completion. Reminder phone calls will be made by study staff during this time period.

We will contact each participant's buprenorphine provider to collect data for buprenorphine treatment retention following surgery and will assess each patient's Maine Prescription Awareness Tool (MainePAT) record to collect data for outpatient opioid utilization during the 30 days following surgery. Buprenorphine formulations will not be included in our MME total.

Measures for Aim 1 (Pain scores)

The primary outcome of this study will be composite pain scores 24 hours after surgery. Others have shown that composite pain scores quantify pain with greater accuracy than a single measurement. Jensen et. al. concluded in their study that composite pain intensity scores from two or more individual ratings of pain are valid for detecting treatment effects.[20,21] Pain scores will be measured using a numeric rating scale (NRS) (0=no pain; 10= worst possible pain). "Worst," "average," and

"least" pain scores will be assessed for the preceding time interval at 24, 48, and 72 hours following surgery. Inpatient pain scores will be collected as part of routine post-operative care and will be extracted from the medical record; there is no set protocol for routine pain score collection but typically it is done every 4-8 hours. To collect pain scores, nursing staff asks patients to rate their current pain on a scale from 0-10. If a participant is discharged prior to 72 hours after surgery, NRS scores will be assessed at the remaining time points via telephone. Prior to discharge, study staff will provide patients with a log to keep a record of their pain scores, at least once every 8 hours, in order to mitigate recall bias in anticipation of being contacted by research staff. Study staff will call discharged patients and ask them to report their pain scores for each 24 hour period between discharge and 72 hours postoperatively as recorded on the forms they were given at time of discharge.

Measures for Aim 2 (Opioid consumption)

For our opioid consumption assessments, data will be collected intraoperatively, in the PACU and at the 24hr, 48hr and 72hr timepoints following surgery. Information on opioid type and dose will be obtained through review of the participant's electronic medical record or through phone assessment, depending on point of hospital discharge. Opioid amounts will be converted into MMEs. Patients who are discharged prior to 72 hours after surgery will be given a log to record the pain medications they consume during that period. Study staff will call patients to collect this data.

Measures for Aim 3 (Depression and OUD severity)

To evaluate depression severity, we will use the patient health questionnaire (PHQ-9), a validated screening tool used to monitor depressive symptoms. For our OUD severity assessments, we will administer the Desires for Drug questionnaire (DDQ) and the opioid craving scale (OCS) to determine level of opioid cravings, the current opioid misuse measure (COMMS) to detect opioid misuse, and a 30-day Timeline Follow-Back questionnaire (https://www.smashlabs.org/timeline[22]) to obtain a quantitative estimate of substance use in the month prior to surgery. Timeline Follow-Back is a commonly used, validated tool in behavioral research; it is a calendar based method of collecting self-reported use of illicit substances.[23] We will compare the pre-operative and 30-day postoperative participant responses

to the above instruments to assess differences between the +BUP and –BUP groups. On the day of surgery, we will also administer the clinical opioid withdrawal scale (COWS) to detect opioid withdrawal.

Measures for Aim 4 (Opioid Dispensing)

For our assessments on outpatient opioid utilization during the 30 days following surgery, we will review each participant's Maine Prescription Awareness Tool (MainePAT). MainePAT is part of the monitoring program that tracks all schedule II-V medications prescribed in Maine, Massachusetts and Rhode Island. Using this resource, we will collect data on the number of opioid agonist prescriptions filled and the total amounts of opioids (in MME) dispensed. Buprenorphine formulations will not be included in our MME totals.

Subject Selection

Inclusion Criteria: Male or female; aged 18-75 years; American Society of Anesthesia (ASA) health class I-III; currently taking buprenorphine formulations equivalent to 12mg or greater for at least the prior 30 days for treatment of OUD (as defined by the Diagnostic and Statistical Manual of Mental Disorders- 5 (DSM-V) criteria); scheduled for surgery at MMC or SSC where a procedure with a greater than 4/10 intensity is expected on POD 1 (see Gerbershagen et.al. and appendix 1 for list of surgeries).

Exclusion Criteria: Unable to consent to the study; currently pregnant; current major medical illness that could limit the ability to utilize medications within our protocol driven multimodal analgesic plan (e.g. cancer, severe end-stage organ disease, or dementia).

Inclusion of women and minorities. We will not exclude any adults on the basis of age, gender or ethnicity and our projected enrollment is based on most recent Maine census. See appendix 2 for projected enrollment table.

Inclusion of individuals across the lifespan. We will exclude individuals under the age of 18 years from enrollment in this trial. These patients require personalized treatment strategies often coordinated by multiple providers therefore we will not alter these treatments decisions for study purposes.

Source of subjects, recruitment and retention methods:

Participants will be recruited when they attend their pre-surgery appointment at the MMC Pre-Operative Readiness Education Program (PREP) clinic. Currently, the majority of patients scheduled for surgery receive consultation from the PREP Clinic, within two months prior to their procedure. Patients who are potentially eligible for the study will be identified by the PREP nurse practitioner or the physician provider who conducts the preoperative evaluation. As part of an IRB reviewed quality improvement project (IRBNet #15892224-1) there is a dashboard in Epic that identifies patients scheduled for surgery who are on buprenorphine. Study staff will review this dashboard to identify potential candidates for this study. The standard practice at MMC is when a patient is identified taking buprenorphine/naloxone through the preoperative chart review, the patient is referred to an anesthesiologist for instructions on the management of buprenorphine/naloxone prior to surgery. Our recruitment method for study participants, therefore, does not differ from this current established practice. A member of study staff will then contact patients by calling the number obtained from the Epic Dashboard. We will introduce the study, and any patient who is interested in learning more about the study and potentially participating will have a consent form sent to them. The informed consent form will be provided electronically, or by mail, for the patient to review. If patient requests the consent be mailed, a follow up phone call will be scheduled. During this phone call, further questions will be answered. Because consent needs to be given prior to day of surgery in order to randomize patients for this trial, we will use Docusign to obtain consent electronically for patients who would like to participate in the trial.

Patients who choose to participate in the study will receive a phone call within one week prior to their surgery to confirm the buprenorphine management plan that they were assigned (see randomization plan, above). Participant confidentiality will be maintained throughout the consent process.

Participants will be reminded that their involvement in the study is completely voluntary and that they can choose to withdraw from the study at any point. They will also be advised that withdrawing from the study would not affect the care they

receive at MMC. All conversations about their history of OUD and the medications they are taking for treatment will be kept confidential and participating in this study would not cause any additional exposure to their health history outside of standard of care.

To retain participants in this study, they will be reimbursed $10 for each combined postoperative pain and opioid consumption assessment at POD 0, 1, and 2, and $60 for completion of the one-month follow-up virtual session. The maximum compensation for participating in this study is $90 in the form of a reloadable reimbursement card. The appropriate amounts will be loaded at each milestone encounter.

Safety

We will ensure that appropriate plans are in place to guarantee the safety of enrolled subjects. All patients will be made aware of the possible risks associated with treatment group to which they are randomly assigned, as well as the risks inherent in experiencing postoperative pain. For instance, both groups are at risk of experiencing OUD symptom exacerbation. The use of opioid agonists and perioperative pain itself may be risks for OUD symptom exacerbation and relapse. Reduction of buprenorphine to 8 mg before surgery as well as full dose buprenorphine continuation can potentially lead to OUD relapse since exposing patients to opioids with similar properties to the agents they abused in the past as management of their acute post-surgical pain can serve as a trigger for relapse. However, this risk is inherent in the current MMC standard of care.
Another potential risk is difficult post-operative pain control due to buprenorphine continuation since the pharmacokinetics of buprenorphine may interfere with the effectiveness of full opioid agonists used for pain control. However, this risk is not greater than the current risk to patients, since full dose buprenorphine continuation is a practice endorsed by SAMHSA. If patients experience poorly controlled pain, they will receive opioid and non-opioid rescue analgesic agents such as nerve blocks or epidurals when indicated, ketamine infusions, and alpha agonist medications, as determined necessary by the treatment providers caring for the

patient. All participants will be transitioned back to their regular dose of buprenorphine when postoperative surgical pain has subsided as determined by their buprenorphine provider following hospital discharge. This transition will be coordinated with their buprenorphine provider, which is our current standard practice when buprenorphine is discontinued, or the dose is reduced, perioperatively.

Data Integrity and Privacy Protection

Our study will use a data safety monitoring board (DMSB) that will be scheduled to meet once the study reaches 50% enrollment and in response to any adverse event. The DSMB will review the progress of the study, monitor data, identify any inconsistencies or errors in data collection, and review patient safety. Any errors in data collection that are identified will be reconciled immediately to ensure the validity of our findings. The DSMB will also ensure that this study will not continue to enroll patients if one treatment modality shows early and significant superiority. Below is a table of major and minor adverse outcomes (AEs) that will be reported to the DSMB during the study period and the actions that will be taken. Any unanticipated adverse events will be reported within 7 days. For patients who experience AEs related to substance use in the outpatient setting, Dr. Silvia will provide patients with information regarding community resources available to patients- such as support groups and harm reduction resources. Study staff will contact the patient's buprenorphine provider on record, as well.

Table 1: Major and Minor Adverse Events

	Item	Action	Regulatory Reporting
Major AE	1. ED admission due to severe pain 2. Intractable Pain	Alert acute pain service (APMS) for management recommendations	Immediate to DSMB; Within 7 days to IRB
	3. Opioid misuse/relapse 4. Opioid overdose 5. Opioid Withdrawal	Alert buprenorphine provider on record immediately; provide patients with community resources to seek help as needed	
Minor AE	1. Hospital discharge delay due to poor pain control 2. Pain worse than anticipated 3. Cravings	Alert integrated medication assistance treatment (iMAT) team and APMS as needed	Within 30 days of event to DSMB; DSMB reports to IRB within 7 days

The DSMB will determine study stop rules; however, we will recommend to them that when 10 patients have been enrolled in each group (25% enrollment), if >7 in either group have intractable pain interfering with hospital discharge or opioid overdose within 2 weeks of discharge, the study should be terminated. The DSMB members are Dr. Galina Korsunsky (Dept. of Anesthesiology); Dr. Issac Chemmanam (Dept. of Anesthesiology); Amy McAuliffe, NP (Psychiatric Nurse

Practitioner); Maya Bulman, MD (Inpatient Psychiatry Consultation-Liaison Team) ; Christine Lary, PhD (Senior Biostatistician, MMCRI/CORE); and Dr. Marc Kimball (Family Medicine, Maine Medical Partners, graduate of MMC Addiction Medicine Fellowship). David Gagnon, PharmD (Faculty Scientist, Critical Care Pharmacy) will be the medical monitor for this study.

All phases of this study will comply with Health Insurance Portability and Accountability Act (HIPAA) regulations. Data will be collected and stored in a REDCap database to preserve privacy and confidentiality. The 30-Day Timeline Followback will be completed on Timeline, a website (https://www.smashlabs.org/timeline) developed and supported by Brown University.[22] Please also refer to the PDF copies of this data collection tool included in the IRBNet package. The responses on the Timeline website will be identified by study numbers only, no PHI will be collected or stored on this site. Information regarding substance abuse history, including illicit narcotic use, will remain confidential and personal identifiers will be removed during data storage. Only members of the research team will have access to the data that participants have consented to provide. Participants will be informed that they have the right to not answer any question that makes them feel uncomfortable.

Biostatistical Analysis

Sample Size:

We estimated study size based on postoperative pain scores in a recent study of surgical patients at our institution (manuscript submitted); mean NRS was 50±28. Our estimate for effect size is based on published data showing that a difference in NRS of 20/100 points is clinically significant.[24] A sample size of 32 per group will have 80% power to detect a difference in means of 20 (the difference between a Group 1 mean, m1, of 50 and a Group 2 mean, m 2, of 30) assuming the common standard deviation is 28 using a two group t-test with a 0.05 significance level. To account for dropout, we will enroll an additional 8 patients for each group for a total sample size of 80 patients.

Statistical Analysis:

Data will be summarized using descriptive statistics and will be presented as means (SD), medians [IQR] or frequency counts (%), as appropriate. Data will be analyzed on an intention to treat basis. We will first examine the success of randomization by comparing covariates demographic and clinical covariate measurements between the FULL-BUP and STD-BUP groups; to conserve study power, no formal statistical comparison will be performed and the data will be reviewed visually. Next we will perform univariate analyses to compare outcome measures between the FULL-BUP and STD-BUP groups, using a two-sided t-test or Mann Whitney U test for continuous variables and chi square or Fisher exact tests for categorical data, as appropriate. For paired analysis of pre/post surgery instruments, we will use McNemar's test or the Wilcoxon test, as appropriate. We will then explore the relationships between demographic and clinical variables and outcome measures in bivariate analyses, using the above methods or Pearson's and/or Spearman's correlation, ANOVA or Kruskal-Wallis test, as appropriate. Finally, we will explore further any observed differences in outcome measures between study arms by adjusting for covariates using analysis of covariance or (in the event of missing data), mixed models regression. Covariates will be entered into the model if they demonstrate a significant ($p \leq 0.1$) association with outcome measures in bivariate analyses.

We will perform an interim analysis at 50% enrollment and will terminate the study if a significant pain score difference is detected. Significance for the interim analysis will be accepted at $p<0.003$, based on 2 sequential tests and using an O'Brien-Fleming spending function to determine test boundaries. Significance overall will be accepted at $p<0.047$ to account for interim analysis. All statistical analyses will be performed by the Navigation team at CORE using SPSS Statistical Software version 27 (IBM SPSS Inc., Armonk, NY).

Study Team

Our team consists of providers from the departments of Anesthesia, Perioperative Pain Medicine, and Addiction psychiatry. We also include researchers with a strong

history of completing clinical trials successfully, utilizing the resources available at MMC. We are uniquely suited for executing this study because we are directly responsible for providing care for patients with Opioid Use Disorder as well as those experiencing complex acute pain conditions. Aurora Quaye, MD Principal Investigator, is a board-certified Anesthesiologist with expertise in Regional Anesthesia and Acute Pain Management. She currently leads the MaineHealth perioperative opioid task force, which manages the acute pain guidelines for patients with history of OUD. Her responsibilities also include directly educating providers on current best practice procedures for treating pain in opioid tolerant patients. Dr. Quaye will be responsible for IRB preparation, study design, implementation, and dissemination of the research plan, coordination of data collection, data management, data analysis and overseeing manuscript preparation.

Kristen Silvia MD is co-Investigator and Director of the Division of Addiction Medicine at Maine Medical Center. Dr. Silvia chairs the MMC Substance Use Disorder steering committee and is a member of the Opioid Clinical Advisory Committee. These committees, respectively, review the institutional and community resources available to individuals with OUD, while identifying barriers related to care delivery. Dr. Silvia's strong connections to both the OUD patient and provider communities, as well as her extensive expertise in treating patients on buprenorphine, will help support patient recruitment and retention, while ensuring this study reflects the needs of this patient group.

Dave Warters MD, FASA is chair of the Department of Anesthesia and Perioperative Pain Medicine at Maine Medical Center. Dr. Warters has an extensive career in academic medicine, engaging in and supporting clinical research trials. As co-investigator and department leader, Dr. Warters will ensure staff and space resource support, department and institutional adherence to protocol driven management plans, and administrative oversight. He will act as a mentor to Dr. Quaye and also assist with data interpretation and manuscript preparation.

Wendy Craig, PhD is a Research Navigator for MaineHealth and Assistant Research Professor at Tufts University. As co-collaborator, Dr Craig will provide her extensive expertise in clinical research to ensure successful study completion, while providing mentoring to Dr. Quaye. She will assist with study design, data analysis- including conducting the statistical analyses- reviewing data integrity and manuscript preparation.

Janelle Richard, BA and Yussr Ibrahim, MD will serve as study staff for this trial. They will create the data capture platform, will be involved in implementation of the research plan, including obtaining consent, administering study instruments both virtually and in-person, data collection, and manuscript preparation.

Limitations

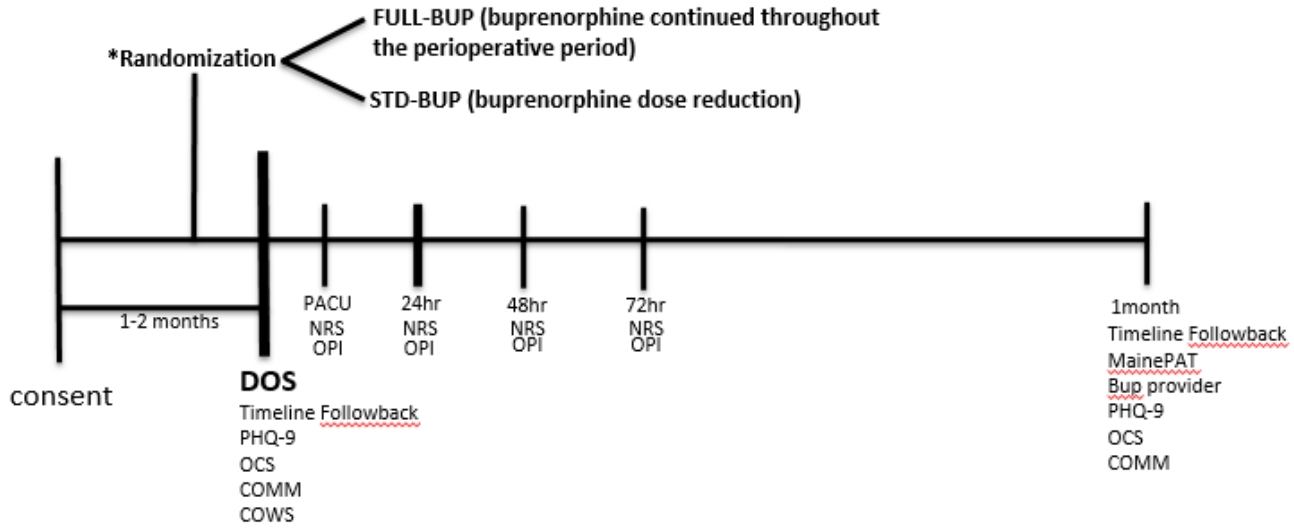
A study limitation is that pain scores, craving scales, and drug use are all self-reported measures, therefore complete accuracy cannot be assured. However, our randomization design should help prevent the introduction of bias, as inaccuracies based on self-report subjectivity would be randomly distributed between the two treatment arms. To encourage accurate drug-use reporting, we will remind participants that information they provide regarding drug use will not be included in their patient record, nor will their providers have access to the information. Another limitation is that our study does not have a placebo arm, however, since randomization occurs prior to hospital admission and physical interaction with study staff, it is impractical to provide patients with placebo medication at the time of study commencement. An additional limitation is that the study is not blinded to patients or treatment providers, however, we attempt to mitigate this limitation by masking the data collection and data entry, as described in the study design and research procedures section.

Study Timeline and Future Plan

We anticipate it will take 11 months to complete the subject recruitment for this trial. Data collection will begin at month 2 of the funding period and will be completed by month 12. Data analysis will begin at month 6 of the funding period and will be completed by month 12.

The findings obtained from this study will provide the framework for investigating strategies to improve postoperative treatment retention and relapse. The perioperative period can be highly stressful and providing patients with analgesic medications abused in the past can be a strong trigger for relapse. We anticipate our research findings will help us identify the major points to focus on in future investigations identifying ways to reduce postoperative OUD symptom severity.

PROTOCOL SCHEMA



*** Randomization based on surgical type**

DOS: Day of Surgery
PACU: Post Anesthesia Care Unit
NRS: Numeric rating scale scores NRS 0-10
PHQ-9: Patient Health Questionnairre-9
OCS: Opioid Craving Scale
OPI: opioid consumption in milligram morphine equivalents (MME)
COMM: current opioid misuse measure
COWS: clinical opioid withdrawal scale
MainePAT: prescription awareness tool tracking opioid prescriptions 30 days post-surgery in MME
Bup provider: Phone call to buprenorphine provider to identify postoperative OUD treatment adherence

APPENDIX 1

Surgical inclusion criteria for elective procedures with greater than 4/10 average pain intensity on postoperative day (POD) 1

MODERATE PAIN SCORE (4-6/10 POD1)

Closed reduction internal fixation-upper and lower extremity procedures
Arthroscopic upper and lower extremity joint procedures (i.e. shoulder arthroscopy)
Clavicle repair/reconstruction
Hip joint replacement
Amputation above and below the knee
Laminectomy
Spinal canal decompression
Laparoscopic abdominal surgical procedures including:
- Appendectomy
- Cholecystectomy
- Bowel resection
- Lysis of adhesions- bowel obstruction
- Gastrectomy
- Nissen Fundoplication

Hernia repair (ventral, inguinal and femoral)
Resections involving the rectum
Thyroidectomy
Nephrectomy (laparoscopic)
Hysterectomy (vaginal)
Laparoscopic gynecologic procedures including:
- Myomectomy
- Hysterectomy
- Oophorectomy
- Endometriosis excision

Kidney transplantation (laparoscopic)
Cystectomy
Prostatectomy
Orchidectomy
Femoral and popliteal bypass graft procedures
Sternotomy procedures
Thorascopic procedures (i.e. lung wedge resection)
Breast reconstruction
Surgical reconstruction nasal septum
Removal, reconstruction teeth

SEVERE PAIN SCORE (>6/10 POD1)

Open Reduction Internal Fixation- upper and lower extremity procedures
Shoulder replacement
Knee joint replacement
Open and arthroscopic foot procedures
Arthrodesis- foot and phalangeal joints
Complex spinal reconstruction, (i.e. scoliosis repair)
Spinal fusion
Open gynecologic procedures including:
- Myomectomy
- Hysterectomy

Open abdominal procedures including:
- Pancreatectomy
- Proctocolectomy
- Splenectomy
- Liver resection
- Bowel resection

Laparoscopic procedures converted to open
Nephrectomy (open)
Open thoracotomy procedures

Adapted from:
Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology. 2013 Apr;118(4):934-44

Appendix 2

Planned Enrollment Table

Racial Categories	Ethnic Categories				
	# of Not Hispanic or Latino		# of Hispanic or Latino		Total #
	Female	Male	Female	Male	
American Indian/Alaska Native	1	1	0	0	2
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	0	2
White	35	35	1	1	72
More than One Race	1	1			2
Total	39	39	1	1	80

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