Dextromethorphan as a novel non-opioid adjunctive agent for pain control in medication abortion: a randomized controlled trial

(Clinicaltrials.gov: NCT03480009)

University of Pittsburgh

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Project Summary

Justification of project

Medication abortion accounts for approximately one-third of first trimester abortions and commonly causes severe pain that women experience and manage at home [1-6]. Currently there are no evidence-based recommendations for a medication abortion analgesic regimen. Surveys and literature reviews show that most medication abortion providers recommend a combination of non-steroidal anti-inflammatory drugs and narcotics for pain control [7, 8].

Given the current epidemic of opioid addiction and the frequency of medication abortion in the United States, it is imperative that we seek alternatives to opioid medications to manage pain. By providing outpatient opioid medications to medication abortion patients, we may be contributing to the opioid abuse problem. This study evaluates dextromethorphan, an over-the-counter cough suppressant, as a non-opioid medication adjuvant for pain control in medication abortion.

Proposed research

This is a four-arm, double-blinded, randomized controlled trial. Our primary outcomes are maximum pain scores and total analgesia usage, and our secondary outcomes are differences in mean pain score between interventions as well as patient satisfaction with their pain control during medication abortion. We hypothesize that dextromethorphan administration in conjunction with the current standard regimen (ibuprofen, narcotic by request) will decrease patient pain scores and total analgesic usage compared to placebo in conjunction with the current regimen. Our study will be conducted at Planned Parenthood of Western Pennsylvania, coordinated by the Center for Family Planning Research of the University of Pittsburgh Medical Center.

New features

This study will be the first to evaluate dextromethorphan for pain control in medication abortion, and one of few to evaluate use of this medication for gynecologic pain control. Dextromethorphan is a promising medication given its long safety record, easy administration and affordability [9].

Problems anticipated

We anticipate that there could be difficulty with enrollment, as women presenting for medication abortion may not be receptive to additional information regarding a research study or to the extra burden of time related to enrollment in a research study. However, with this potential challenge in mind, we plan to succinctly inform patients of the potential for direct benefit to them with the goal to overcome their hesitation about participation and allow us to provide them with more detailed information. We also have planned this study to minimize the duration of engagement and burden on participants to enhance feasibility.

The medication administration schedule may prove difficult for patient compliance. Participants will be prompted by text message as to when they should use their study medications based on their projected misoprostol administration schedule discussed in clinic. This will allow us to support and encourage medication administration at the correct times relative to misoprostol administration. This active engagement is also designed to support participants with timely data reporting.

1. Description of Project

1.1 Rationale and objectives of the study

1.1.1 Rationale

Medication abortion using mifepristone and misoprostol is common, accounting for nearly one-third of first trimester abortions in the United States in 2014 [6]. Although women generally tolerate medication abortion well, pain and bleeding are common and expected with medication abortion [10]. Pain management for medication abortion is challenging since the most acute pain occurs at home rather than under the supervision of medical professionals.

Pain experienced with medication abortion can be severe. In a randomized controlled trial utilizing a mifepristone/misoprostol regimen without premedication, women reported mean pain scores of 8/10 one hour after misoprostol administration [1]. Wiebe et al. monitored pain after premedication with ibuprofen or acetaminophen with codeine in a methotrexate/misoprostol regimen and found that 23.4% of patients reported severe pain (9-10/10) in the first 24 hours after misoprostol administration [2]. Raymond et al. compared different analgesic regimens of ibuprofen in medication abortion with mifepristone and misoprostol and found mean maximum pain scores of 7.1 and 7.3 for prophylactic versus as-needed ibuprofen dosing. [5] In trials varying the timing of administration of vaginal misoprostol after mifepristone administration, median pain scores during the abortions ranged from 57-64 mm on a Visual Analogue Scale (VAS) [3, 4]. A structured literature review from 2006 of first trimester medication abortions found that approximately three-quarters of patients use narcotics on the day of prostaglandin administration to manage their pain [7]. A survey of National Abortion Federation clinics in 2008 found that 95% of providers routinely prescribed analgesics for medication abortion: 51% prescribed acetaminophen with codeine and 44% prescribed non-steroidal anti-inflammatory drugs [8].

The pain experienced by women during medication abortion is a function of uterine cramping and passage of pregnancy tissue through the cervix. However, the experience of pain is complex and a subjective multifactorial phenomenon. Prior studies have found that younger age, nulliparity and increasing gestational age are predictors for higher reported pain scores during medication abortion [10, 11]. Asian race and higher education have been associated with decreased narcotic use during medication abortion [12]. Individual pain history can also be predictive, as women who report more pain during menses consistently also report higher pain scores during medication abortion [10]. Women who suffer from chronic pain syndromes and substance abuse also struggle with acute pain control [13]; however, this has not been specifically studied for medication abortion.

Currently there is insufficient evidence to recommend an optimal regimen for pain control in medication abortion and there are concerns surrounding narcotic prescribing and the opiate abuse epidemic. From 1999-2010, opioid overdoses have risen steadily in parallel with opioid prescriptions. In 2015, there were 33,091 opioid-use related deaths, half of which involved prescribed narcotics [14]. A mixed-methods study of patients with a diagnosis of substance use disorder found that approximately half had their first narcotic exposures through use of prescribed medication and this may have contributed to their ultimate addiction [15]. The Society of Family Planning Clinical Guideline on medication abortion recommends “instructions for analgesia with over-the-counter medications” and “oral narcotics to use as needed” [16]. Given the current epidemic of opioid addiction and the frequency of medication abortion in the United States, it is imperative that we seek alternatives to opioid medications to manage

pain. By providing outpatient opioid medications to medication abortion patients, we may be contributing to the opioid abuse problem.

Dextromethorphan (DM) has potential to be a safe and effective option for pain control in medication abortion. As a N-methyl-D-aspartate (NMDA) antagonist, dextromethorphan functions by blocking the transmission of pain signals from peripheral nociceptors to the central nervous system. It is not directly anti-nociceptive, but instead modifies the perception of pain and is largely dependent on the concomitant use of another analgesic. Dextromethorphan has demonstrated synergy with both opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) [9], and therefore may be useful in optimizing pain control and minimizing or eliminating opioid use. Dextromethorphan may also be an effective preemptive analgesic, reducing pain sensation when administered prior to the insult. This principle has been demonstrated with ketamine administration, another NMDA antagonist, in "Expedited Recovery After Surgery (ERAS)" protocols [17]. Preemptive administration has been shown to decrease both intraoperative and postoperative opioid needs. Dextromethorphan has been studied in acute post-operative pain as well as in chronic and neuropathic pain management [9]. Oral, orthopedic and gynecologic surgery studies have all shown attenuation of pain or opioid use by using preoperative dextromethorphan in doses varying from 27 mg-120 mg [18-21]. However, several negative studies also exist, though these studies are limited by concerns about adequate dosing or possible confounding by administration with other central pain modifying drugs [22, 23].

Dextromethorphan, the most frequently used cough suppressant in the United States, has a long track record of safety associated with over-the-counter use in adults and children since receiving FDA approval in 1958. It is not considered habit-forming, although there is potential for abuse as large doses cause hallucinations and a dissociative state and has primarily been abused by adolescents aged 13-15 years. Dextromethorphan toxicity can result in hyperthermia and metabolic acidosis at its most extreme, however the more common toxicities arise from overdosing of other agents included in cough medications such as pseudoephedrine or acetaminophen [24]. A rare adverse effect of dextromethorphan is serotonin syndrome when taken with selective serotonin reuptake inhibitors or monoamine oxidase inhibitors [25].

Society of Family Planning guidelines recommend a combination of NSAIDs and opioid analgesia for home pain control associated with medication abortion. Attempting to limit or withhold narcotics because of the opioid abuse epidemic in the absence of an alternative analgesic diminishes our acknowledgement of patient suffering during medication abortion. However, prescribing narcotics also contributes to the epidemic. Ideally, a non-opioid adjunct to NSAIDs or narcotics could be used to control pain and significantly curtail or eliminate opioid use. We seek to test the efficacy and safety of dextromethorphan as a non-narcotic adjuvant analgesic for medication abortion.

1.1.2 Objectives and hypothesis

Study hypothesis: We hypothesize that dextromethorphan administration in conjunction with the current standard regimen (ibuprofen, narcotic by request) will decrease patient pain scores and total analgesic usage compared to placebo in conjunction with the current regimen.

Primary objectives:

- To assess worst pain score as measured by an eleven-point Numeric Rating Scale (NRS-11) for women who receive dextromethorphan vs. placebo as an adjunct to a standardized pain regimen for medication abortion
- To evaluate analgesic usage during medication abortion for women who receive dextromethorphan vs. placebo as an adjunct to a standardized pain regimen for medication abortion

Secondary objectives:

- To evaluate differences in mean pain score between women who receive dextromethorphan vs. placebo as an adjunct to a standardized pain regimen for medication abortion
- To assess patient satisfaction with pain control

1.2 Previous similar studies

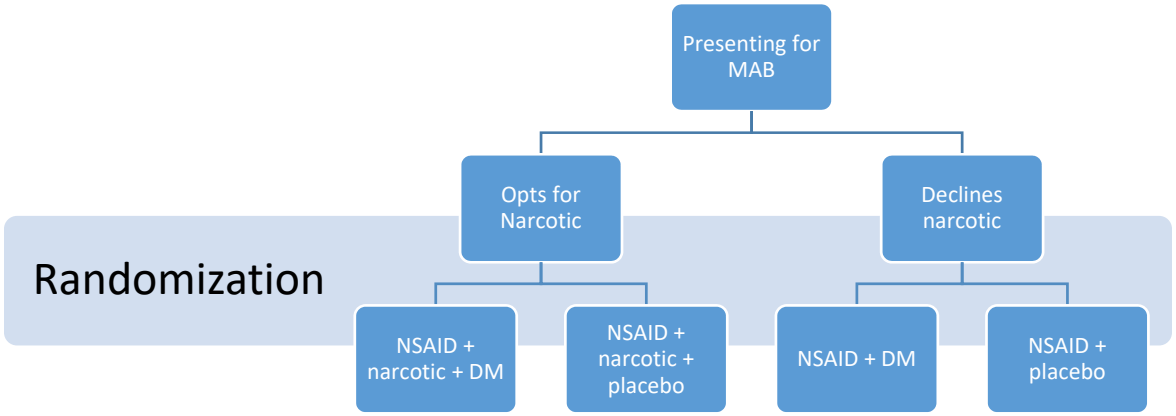
Four studies have evaluated methods of analgesia for first trimester medication abortion. In a randomized double blinded exploratory trial with mifepristone and sulprostone, Weber and Fontan demonstrated that acetaminophen seemed to increase pain scores and pain duration in multiparous women undergoing medication abortion [26]. In their prospective cohort study looking at management of adverse effects during abortion with vaginal misoprostol only, Jain et al. showed that acetaminophen and loperamide administration decreased opioid medication use and diarrhea; however, they did not collect information on pain severity [27]. Wiebe et al. conducted a double-blinded randomized controlled trial with a methotrexate and misoprostol regimen that compared placebo versus acetaminophen and codeine versus ibuprofen alone that demonstrated statistically similar pain scores and analgesic consumption except for a significant decrease in narcotic use in the codeine intervention. [2] Finally, Livshits et al. conducted a double blinded randomized controlled trial using a mifepristone and misoprostol regimen that showed ibuprofen to be superior to acetaminophen for pain relief after onset of abortion symptoms [1].

The literature regarding the use of dextromethorphan in acute postoperative pain management from a variety of procedures suggests improved pain control or reduced analgesia usage in a majority of reviewed papers [9]. In gynecology, there have been few trials looking at dextromethorphan for acute pain control. Four studies have administered preoperative dextromethorphan prior to non-malignant elective total abdominal hysterectomy and three out of the four found decreased postoperative narcotic use [20, 21, 23, 28]. Ilkjaer also tested dextromethorphan in a double blinded randomized control trial for postoperative pain after dilation and curettage for first trimester surgical abortion [29]. They did not find any difference in post procedure analgesia usage or pain scores. Notably in this study, patients underwent D+C with propofol sedation rendering the patient asleep during the most painful portion of the procedure. Most of the immediate post-operative VAS scores were below 40mm, and after the first 30 minutes, most were below 20mm, representing minimal pain. Such low intensity post-operative pain is difficult to study because large numbers of participants would be needed to discern such small differences in pain control. Additionally, pain after D+C is typically short-lived, also contributing to the difficultly in discerning differences in outcomes.

1.3 Design and methodology

1.3.1 Research design and General Methodological Approach

This is a four-arm, double-blind, randomized controlled trial.



MAB= medical abortion, NSAID= non-steroidal anti-inflammatory drug, DM= dextromethorphan

Women seeking medication abortion independent of this study will present to Planned Parenthood of Western Pennsylvania (PPWP). Their eligibility for medication abortion per Planned Parenthood Federation of America medical guidelines will be assessed. They will then be asked if they would like to receive narcotics for pain control per routine clinical care and then subsequently offered participation in this study to avoid any influence over their decision regarding narcotics.

All women who choose to participate will receive standardized counseling about how to take pain medications during their abortion and will be given written instructions regarding expectations about pain control and how to take both their study medication and routine pain medications. They will undergo their medication abortion as per the current PPWP protocol in effect at the time of their visit.

The intervention arms are first participant-determined as they self-select into opioid-receiving and non-opioid-receiving groups. Within each of those two groups, patients will be randomized to receive either dextromethorphan or placebo as adjunctive pain medication. It is expected that the non-opioid receiving group will only use NSAIDs and randomized study medication for pain control, and that the opioid-receiving group will use NSAIDs, their clinically prescribed narcotic medication and randomized study medication.

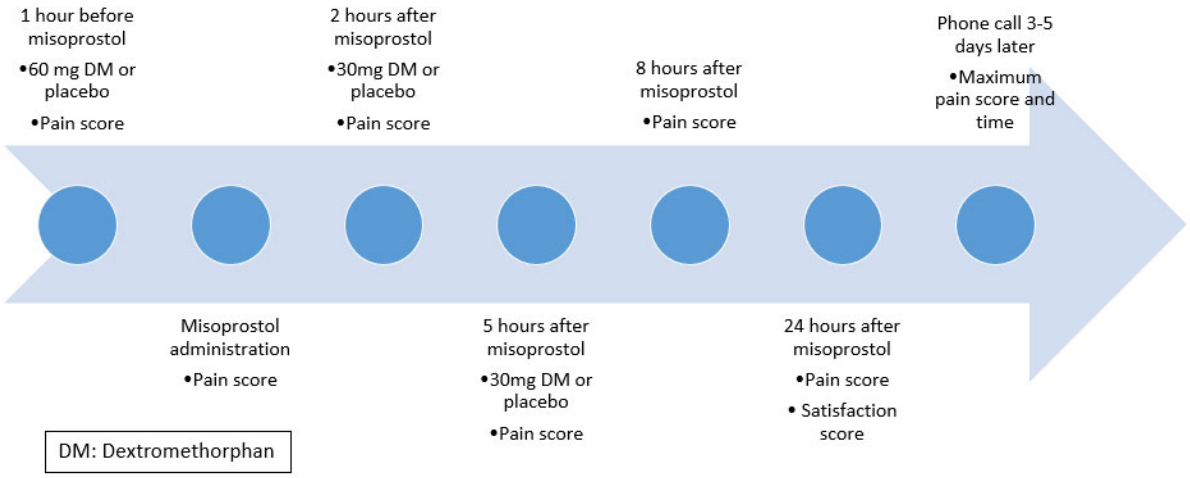
The active study drug is dextromethorphan. The FDA maximum daily dosing as an anti-tussive is 120 mg daily in divided doses. One study looking at dextromethorphan for acute analgesia demonstrated that a single dose at 120 mg resulted in increased adverse effects of the drug without any improvement in pain scores compared to a dose of 60 mg [30]. A study that dosed at 27 mg TID did not demonstrate any effect on pain scores [23]. Consistent with the potential ability for dextromethorphan to be used as a preemptive analgesic and with known pharmacokinetics, we have scheduled the first dose to be administered prior to misoprostol use followed by two additional subsequent doses, for a total of three

doses spaced to optimize analgesia [31]. Pre-emptive dosing of the study medications also permits absorption prior to potential nausea and vomiting associated with misoprostol administration.

Timing of drug administration will be linked to misoprostol administration. Participants will be instructed to take their first dose of study medication (dextromethorphan 60 mg vs. placebo) one hour before misoprostol administration. Study medications are encapsulated and can be taken either as a capsule or as capsule contents mixed in a liquid if the patient is unable to swallow pills. Based on the known half-life of three hours, participants will take a second dose of study medication (dextromethorphan 30 mg vs. placebo) two hours post misoprostol administration and a final, 3rd dose of study medication (dextromethorphan 30 mg vs. placebo) five hours post misoprostol administration to facilitate three hour intervals between doses and with the aim of maintaining continuous dosing over 9 hours, during which the majority of pain would be anticipated.

A texting application (textit.in) will be used to communicate with participants after they leave the clinic. Kew demonstrated that participants find texting to be an acceptable method of reporting data in research, and in fact, find that it is more private than pen and paper [32]. Christie et al. showed that text message reporting of pain with a NRS-11 correlates well with pen and paper logs [33]. Both studies had very high (97-100%) response rates. All participants will be asked to report their pain scores at the following times: at the time of misoprostol administration, every time study drug is taken (1-hr before and 2 and 5-hrs after misoprostol use) and at eight and twenty-four hours after misoprostol administration. At each interval, they will report their maximum pain since their last report, any adverse effects and any other pain medications taken (ibuprofen, acetaminophen and narcotics). We will also encourage participants to report breakthrough pain at any time. All calls made to the emergency PPWP line will be noted in their charts as well as any additional interventions required.

The data received by text on drug administration and pain scores will be reviewed with the participant during a follow-up phone call conducted by research study staff approximately three days (window 3-5 days) after taking misoprostol. Participants will additionally be asked to retrospectively report their most severe pain score (NRS-11) and the approximate time that their pain peaked. Participants will be reminded to complete the routine medication abortion follow-up care with PPWP to confirm the medication abortion outcome.



1.3.2 Criteria for selection of subjects

Recruitment for this study will occur at PPWP. Research activities will be coordinated through the Center for Family Planning Research (CFPR) at Magee-Womens Hospital.

Inclusion Criteria

- Willing and able to provide informed consent
- Women aged 18 and over
- English-speaking
- Eligible for medication abortion per PPWP protocol
- Self-reported reliable cellular phone access for the duration of study participation
- Able to receive and reply to a "test" text at time of consent
- Willing to comply with the study protocol

Exclusion criteria

- Use of selective serotonin reuptake inhibitors or monoamine oxidase inhibitors in the prior 14 days, or anticipated use in the subsequent 14 days
- Allergy to any component of the medication abortion regimen or study drug
- Dextromethorphan use within twenty-four hours of study medication, current or anticipated
- Currently on opioid maintenance therapy or chronic opioid medication use for pain control
- Has any other condition that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, complicate the interpretation of the study outcome data, or otherwise interfere with achieving the study objectives

1.3.3 Subject recruitment and allocation

Participants will be recruited from seeking medication abortion at PPWP. There will be no external advertising to recruit for this study to avoid undue influence in decision-making about pregnancy termination. Patients will be informed of the study and given the option of participation after they have otherwise completed their routine abortion counseling and consenting. Study recruitment may be performed by the Principal Investigator (PI), co-investigators or research assistants from the CFPR. For a complete description of these roles and other staff at the CFPR, please see section 3.2.1, Personnel.

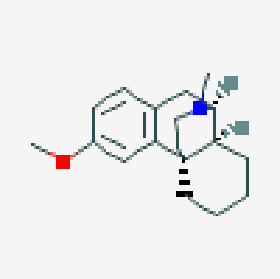
A biostatistician not associated with recruitment for the study will prepare the randomization sequences with Stata statistical software, release 14.2. The opioid-receiving arm and non-opioid receiving arm will each have independent randomization schemes with random block sizes of 2, 4 and 6 and a 1:1 allocation sequence. After the block randomization keys are generated, they will be given to the research pharmacist who will prepare packets to consist of four 30 mg capsules of dextromethorphan or placebo. Study staff dispensing medication will not have access to randomization sequences and will only have access to the sequentially numbered, opaque, sealed packets. This trial is double-blind; both study staff and participants will be blinded to medication assignment. The blind may be broken if deemed to be clinically necessary in the event of a serious adverse event, please see Section 1.3.7, Criteria for discontinuation. PPWP staff will not be given information about arm assignment when the patient presents for their routine medication abortion follow up.

1.3.4 Description of the drugs and devices to be studied

Dextromethorphan is an NMDA receptor antagonist commonly used as an over-the-counter anti-tussive. As an anti-tussive, standard adult dosing is 20-30 mg every 6-8 hours or 60 mg twice daily with a maximum dose of 120 mg in 24 hours. We will stay within these dosing guidelines for this study.

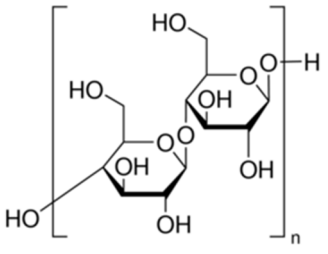
Our study drug will be compounded by an outside pharmacy working in close conjunction with our Investigational Drug Service to ensure quality and purity for participant safety.

Our study drugs are Avicel (a hypo-allergenic cellulose base) for placebo, and dextromethorphan hydrobromide for active drug. The chemical structure of dextromethorphan is shown below:



[34]

Our placebo consists of Avicel (microcrystalline cellulose.) The chemical structure of Avicel is shown below:



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1.3.5 Admission procedure

Pre-screening and consent (Timepoint 1- Eligibility and Consent):

1) The potential participant will present for her scheduled appointment for medication abortion at PPWP.
2) After undergoing routine counseling and consent for her medication abortion, including counseling about pain management and deciding whether she would like an opioid analgesic prescribed, the potential participant will be offered an opportunity to participate in this study and given study information (please see Appendix).
3) If interested, the potential participant will meet with a research assistant who will provide an overview of the study; a pre-screen will be administered to assess eligibility (please see script in Appendix).
4) If the participant is eligible per the pre-screen and interested in participation, the participant and research staff will discuss study protocol, risks, and benefits. She will be given ample opportunity to ask questions. She will be reminded that participation is voluntary and that if she declines participation, her refusal will not affect her subsequent care.
5) A research physician will confirm understanding of the study and obtain informed consent for study participation. An unsigned copy of the consent will be given to the participant.

Counseling (Timepoint 2- Medication Abortion)

1) The physician can then proceed with routine medication administration for the medication abortion. The participant will be assessed again for her certainty regarding her medication abortion. Any questions will be answered. She will then take her mifepristone for her medication abortion. We anticipate that informed consent and the medication abortion can occur in the same encounter, however this may be subject to clinic patient flow and the medication abortion administration may occur after additional study screening procedures are completed prior to final eligibility confirmation.

Counseling (Timepoint 3- Screening and Counseling)

1) Screening starts when the participant signs the informed consent document. A research clinician will obtain the participant's pertinent medical history.
2) A short baseline demographics survey including an assessment for pain will be administered by research staff.
3) A test text will be sent to the participant's cellular phone to confirm her ability to receive and send text messages with the messaging system (textit.in).

4) The participant will be counseled about the study protocol and medication management. She will also be given a handout for home use with frequently asked questions. She will be informed that she can take routine pain medications throughout the medication abortion as needed for pain, in addition to the study medications as directed per protocol.
5) Additionally, the participant will be asked when she anticipates self-administering misoprostol within the clinical protocols in effect at the time of the visit. Study medication timelines will be reviewed with the participant and she will be given a handout outlining her timeline of anticipated medication administration that will correspond to her text message reminders.

Randomization (Timepoint 4- Randomization and Dispensation)

1) The participant's eligibility will be confirmed by the study physician prior to randomization.
2) The participant will then be randomized by obtaining the next sequentially numbered, opaque, sealed envelope, which will contain a package with either the study medication or placebo. Medication dispensation will be recorded in a study drug accountability log. Medication dispensation will be recorded in a study drug accountability log. Medication dispensation will be carried by a listed physician-investigator.
3) The participant will be compensated for her participation after dispensation of the study drugs.
4) The participant will be discharged home after all questions are answered.

Medication administration (Timepoint 5- Medication administration)

1) One hour prior to the participant’s planned misoprostol administration time, a reminder text will be sent to take her first two tablets of study drug. A pain score, any pain medication taken, and any side effects experienced will also be reported. The types of pain medication the participant has available at home will be collected at this time.
2) The participant will self-administer her misoprostol at the pre-determined time, unless she has previously responded to change her scheduled time via the texting system. She will receive a text reminding her to take her misoprostol at this time and can also reschedule her misoprostol time as needed. This loop repeats until the participant indicates that she has taken her misoprostol. At the time of the reminder text, information about her maximum pain since the last text, all side effects experienced, and all non-study pain medications used will be collected.
3) Two hours after misoprostol administration, the participant will be prompted to take her next dose of study medication and to report her maximum pain over the preceding 2 hours, all side effects experienced, and all non-study pain medications used.
4) Five hours after misoprostol administration, the participant will be prompted to take her next dose of study medication and to report her maximum pain over the preceding 3 hours, all side effects experienced and all non-study pain medications used.
5) Eight hours after misoprostol administration, the participant will be prompted to report her maximum pain over the preceding 3 hours, all side effects experienced, and all non-study pain medications used.
6) Twenty-four hours after misoprostol administration, the participant will be prompted to report her maximum pain over the preceding 16 hours, all side effects experienced, and all non-study pain medications used. She will be asked to report her satisfaction with her pain control on a Likert scale of 1-4, with 4 being most satisfied and 1 being least satisfied.

7) The patient will be prompted via text message to take her medication in concordance with the projected time discussed at her MD visit. The patient can adjust her planned time of misoprostol administration by replying to text prompts, and if so, the subsequent medication reminder text messages will be adjusted to reflect the new time of misoprostol administration. Misoprostol administration timing can be adjusted to any degree if the window remains consistent with the PPWP clinical protocol.

1.3.6 Follow-up procedure

A research assistant will call the participant 3-5 days after misoprostol administration to assess maximum pain and timing of maximum pain during the entire medication abortion experience. The participant will also be asked whether she experienced any adverse events or sought additional emergent or non-emergent care. She will be reminded and encouraged to keep her follow-up as scheduled with Planned Parenthood to confirm completion of her medication abortion, as well as reminded to avoid SSRI and MAOi medication for the two weeks following her medication administration.

If emergency care is sought, no interventions or post-abortion care will not be limited due to study participation. The University of Pittsburgh Medical Center will provide for emergency care directly related to participation in research; however patients of PPWP have all their non-emergent follow-up care included in the cost of the medication abortion.

Patients who do not reply to text-messaging prompts will be contacted twice in the week following their misoprostol administration to elicit reasons for their non-participation and appropriately categorize these patients in terms of follow up. If they took their study medication, the routine follow up phone call will be used to confirm their medication administration and ask for their worst pain score. If they did not take, or did not complete, their study medication follow-up data will still be collected. If they did not complete their medication abortion, no further information will be elicited. Participants who withdraw their consent or are discontinued from the study prior to randomization will not be contacted for any follow-up information.

1.3.7 Criteria for discontinuation

Participants may withdraw from the study at any time. No further interventions or prospective data will be collected after a participant withdraws consent. In the event a participant experiences a serious adverse event, whether to discontinue the participant from the study immediately secondary to safety concerns will be at the discretion of the primary investigator and may involve breaking the blind if deemed requisite to care for the participant. To break the blind, the PI will reference a secure database connecting the patient's medication packet number to their drug assignment.

However, there are almost no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. Dextromethorphan has a wide margin of safety and study dosing has been selected such that risk of overdose is minimal, even if all study drug were taken at once. In the event that a participant might be put at undue risk by continuing product use, the Investigator may discontinue study product use by this participant; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment.

Participants will be discontinued from further study participation if:

- The participant will not undergo a medication abortion for any reason
- Participant is found to meet exclusion criteria after informed consent has been signed

Participants who are discontinued after randomization will be kept in the trial and included in an intention-to-treat analysis. A per-protocol analysis will also be performed to better assess efficacy of the intervention while acknowledging the risks of attrition bias [36].

All protocol deviations will be documented and when possible, discussed with a study clinician in advance except when necessary to prevent harm to a subject. All protocol deviations will be reported to the Institutional Review Board (IRB) as per IRB policies.

1.3.8 Laboratory and other investigations

There will be no laboratory tests required for this study.

1.3.9 Data Management

The CFPR staff, with assistance from the principal investigator, will create electronic data collection forms in REDCap. Each study variable will be named and coded electronically and data entered directly into a REDCap database and will be backed up on the hospital server. REDCap is a web-based application for building and managing online surveys and databases and provides automated export procedures for data downloads to statistical packages, such as STATA. Collection of questionnaire and text messaging data will be entered in a secure database by research staff. Contact information will be kept on our secure server to prevent transportation of participant identifiers. Before the completion of the study visit or phone call, charts will be reviewed by study staff to ensure completeness and quality of data.

Paper files will be locked and secured, and transported from PPWP to CFPR at the end of each recruitment day. A linkage log will be maintained on our secure server and directly entered from PPWP on each recruitment day. The linkage log will never be transported alongside participant charts to maintain data security. Our participant data security plan has been preliminarily approved by our institutional Policy Risk and Compliance team.

Access to the study data will be restricted to research staff and study investigators. Monitoring of data will be performed by the principal investigator and research coordinator to assure that the clinical staff adheres to the protocol and that data is entered completely and accurately into the database. Research data is maintained for a minimum of seven years. Only members of the CFPR are authorized to access the computer database and final trial datasets. Appropriate firewall and virus scanning software are installed and updated routinely by the hospital support staff.

Complications and side effects will be continuously monitored by research staff and investigators (on site and available during normal business hours, on call 24 hours per day outside of business hours). All participants reporting an adverse event will be followed clinically until the occurrence resolves (returns to baseline), stabilizes, until the adverse event is otherwise explained, or the participant is lost to follow-up. Per the University of Pittsburgh IRB Policy and Procedures Manual Section XVII, the University of Pittsburgh IRB will be notified of any serious adverse events. If any severe adverse events or complications occur, one of the investigators will notify the IRB within 24 hours.

The daily monitoring of participant safety, data collection, recruitment, and confidentiality will be the primary responsibility of the principal investigator and the research coordinator. These individuals, therefore, will serve as the foundation of the data and safety monitoring plan. Enrollment, outcomes, and adverse events will also be reviewed in biweekly meetings with the CFPR staff. At the time of annual review, the regulatory coordinator and principal investigator will be responsible for providing summaries of monitoring reports to the University of Pittsburgh IRB. Severe complications or side effects will be managed with evaluation and treatment as indicated at the discretion of the evaluating clinician. A study investigator will be available by pager 24 hours a day to direct care should a study participant have a problem or question.

1.3.10 Data Analysis

Analysis will be performed using statistical software, such as STATA release 14.2 (StataCorp LP, College Station, TX) or similar. Analyses will be performed using an intention-to-treat approach with respect to patient self-selection into opioid and non-opioid arms, as well as an as-treated analysis by querying the Pennsylvania Prescription Drug Monitoring Program (PA PDMP) to see if participants are filling their prescriptions and secondly, by pain medications taken (opioid vs non-opioid) self-reported via text message. For missing data in participants who discontinue after randomization, pain scores will be assumed to be the worst (10/10) for conservative analysis and to avoid magnifying any drug effect. Analgesia usage assessment for patients with missing data will carry forward their last usage report. If there was no analgesia usage reported, then that data will be blank.

Baseline clinical characteristics will be compared between the opioid-receiving and non-opioid-receiving groups, as well as the aforementioned medication usage groups, using Fisher's exact, Student's t tests, and Mann Whitney U tests where appropriate. Similar analysis will also be carried out within the opioid-receiving and non-opioid-receiving arm to evaluate the comparability of the groups after randomization. The primary outcome of maximum pain score and analgesia usage will be compared using Student's t- or Mann Whitney U tests, where appropriate. Linear mixed effects models will be used to assess the impact of the intervention on pain scores over time and to evaluate whether any baseline demographic or clinical variables are associated with pain. Likert results for satisfaction with pain control will be compared with the Mann-Whitney U test. Frequency of adverse events will be assessed for significance with the Mann-Whitney U test. Statistical analysis will be performed by the Principal Investigator in conjunction with a staff biostatistician.

1.3.11 Number of participants and statistical power

A study using an NRS-11 to evaluate pain during medication abortion found mean pain scores for the two arms that were 8.35 (standard deviation (SD) 1.6) and 8.2 (SD 1.7) [1]. Another study using an NRS-11 sought to detect a difference of 1.3/10 with a SD of 3 based on other studies evaluating pain [2, 37]. Our own clinical experience suggests that a difference of 2.0 would be meaningful. Based on these studies and our experience, we would need a sample size of 34 participants per arm to detect a difference of 2.0 on a NRS-11 with 80% power, or a total of 136 participants. With an estimated 15% dropout and loss to follow-up rate, we plan to randomize a total of 156 participants across four arms and with a screen fail rate of 15% we plan to screen up to 192 participants.

During an interim analysis, we have found that although 74% of patients have opted for an opioid prescription, far fewer (47%) filled the prescription as per review of the PA PDMP. Thus, they may have requested an opioid prescription in order to have one available in the event that they needed a narcotic pain medication without intending to take the medication. Due to this medication use pattern, we have revised our recruitment plan so that we will recruit to a total of 156 randomized participants but will not limit recruitment per treatment arm.

1.3.12 Study limitations

Potential weaknesses in the internal validity of this study are addressed through the study design of a double-blinded, randomized controlled trial. Through randomization, the two study groups (treatment and control) should have similar participant characteristics. The placebo medication will be of similar color, size, shape and consistency to the study medication, helping to ensure that both investigators and participants are blinded to the intervention.

National standards for pain control for medication abortion are varied. The best pain management regimen for medication abortion is uncertain. We seek to increase the generalizability of this study by allowing patients to take pain medication as needed, with the study drug as a synergistic adjunct. However, if patients do not take any pain medicine, we would not be able to assess the drug's efficacy as an adjunct medication. Additionally, we are assessing patient satisfaction with pain control during medication abortion. Despite asking specific questions, it is possible other facets of their abortion experience may impact their responses regarding satisfaction with pain control.

We are enrolling women from a Planned Parenthood clinic and we have minimized exclusion criteria to increase the external validity of this study to other Planned Parenthood sites as they all share clinical care standards. We are also including women with substance abuse histories to increase generalizability of this study. Due to limitations in timeline for recruitment, it was not feasible to add another arm exclusively of women with histories of opioid-use disorder, though that may be considered for future study.

1.3.13 Duration of project

Expected length of study: We initially anticipated that recruitment would take 9-12 months. At PPWP, we perform approximately 100 medication abortions a month. During protocol development, we found that ~40% opted for narcotics. We estimated that between one-fifth to one-quarter of patients will opt for study participation. Each participant will be followed for approximately five to eight days, from initiation of medication abortion to her follow-up phone call. Due to the nature of recruitment for clinical trials, we allotted more time for recruitment [38]. On interim analyses, we found that 74% opted for narcotics, but only 47% filled their prescriptions for narcotics. Our experience with recruitment thus far demonstrates about 15% of medication abortion patients are opting for participation in the study, although there is significant day-to-day variation in this estimate. As previously discussed, we have revised the recruitment plan to recruit to 156 randomized participants but will not restrict recruitment per treatment arm.

1.4 References

1. Livshits, A., et al., *Ibuprofen and paracetamol for pain relief during medical abortion: a double-blind randomized controlled study.* Fertility and sterility, 2009. **91**(5): p. 1877-1880.
2. Wiebe, E., *Pain control in medical abortion.* International Journal of Gynecology & Obstetrics, 2001. **74**(3): p. 275-280.
3. Creinin, M.D., et al., *A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion.* Obstetrics & Gynecology, 2004. **103**(5, Part 1): p. 851-859.
4. Creinin, M.D., et al., *Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial.* Obstetrics & Gynecology, 2007. **109**(4): p. 885-894.
5. Raymond, E.G., et al., *Prophylactic compared with therapeutic ibuprofen analgesia in first-trimester medical abortion: a randomized controlled trial.* Obstetrics & Gynecology, 2013. **122**(3): p. 558-564.
6. Pazol, K., et al., *Abortion surveillance—United States, 2010.* Morbidity and Mortality Weekly Report: Surveillance Summaries, 2013. **62**(8): p. 1-44.
7. Penney, G., *Treatment of pain during medical abortion.* Contraception, 2006. **74**(1): p. 45-47.
8. Wiegerinck, M.M., et al., *Medical abortion practices: a survey of National Abortion Federation members in the United States.* Contraception, 2008. **78**(6): p. 486-491.
9. Weinbroum, A.A., et al., *The role of dextromethorphan in pain control.* Canadian Journal of Anesthesia/Journal canadien d'anesthésie, 2000. **47**(6): p. 585-596.
10. Suhonen, S., et al., *Pain during medical abortion: predicting factors from gynecologic history and medical staff evaluation of severity.* Contraception, 2011. **83**(4): p. 357-361.
11. Westhoff, C., et al., *Predictors of analgesia use during supervised medical abortion.* Contraception, 2000. **61**(3): p. 225-229.
12. Westhoff, C., R. Dasmahapatra, and E. Schaff, *Analgesia during at-home use of misoprostol as part of a medical abortion regimen.* Contraception, 2000. **62**(6): p. 311-314.
13. Alford, D.P., P. Compton, and J.H. Samet, *Acute pain management for patients receiving maintenance methadone or buprenorphine therapy.* Annals of internal medicine, 2006. **144**(2): p. 127.
14. Schuchat, A., D. Houry, and G.P. Guy, *New data on opioid use and prescribing in the United States.* JAMA, 2017. **318**(5): p. 425-426.
15. Cicero, T.J. and M.S. Ellis, *Understanding the demand side of the prescription opioid epidemic: Does the initial source of opioids matter?* Drug and alcohol dependence, 2017. **173**: p. S4-S10.
16. ACOG, *Practice bulletin no. 143: medical management of first-trimester abortion.* Obstetrics and gynecology, 2014. **123**(3): p. 676.
17. Kalogera, E., et al., *Enhanced recovery in gynecologic surgery.* Obstetrics and gynecology, 2013. **122**(2 0 1): p. 319.
18. Grace, R.F., et al., *Preoperative dextromethorphan reduces intraoperative but not postoperative morphine requirements after laparotomy.* Anesthesia & Analgesia, 1998. **87**(5): p. 1135-1138.
19. Kawamata, T., et al., *Premedication with oral dextromethorphan reduces postoperative pain after tonsillectomy.* Anesthesia & Analgesia, 1998. **86**(3): p. 594-597.
20. Henderson, D.J., et al., *Perioperative dextromethorphan reduces postoperative pain after hysterectomy.* Anesthesia & Analgesia, 1999. **89**(2): p. 399-402.
21. Chia, Y.-Y., et al., *The preoperative administration of intravenous dextromethorphan reduces postoperative morphine consumption.* Anesthesia & Analgesia, 1999. **89**(3): p. 748.
22. Rose, J.B., et al., *Preoperative oral dextromethorphan does not reduce pain or analgesic consumption in children after adenotonsillectomy.* Anesthesia & Analgesia, 1999. **88**(4): p. 749-753.

23. McConaghy, P., et al., *Dextromethorphan and pain after total abdominal hysterectomy.* British journal of anaesthesia, 1998. **81**(5): p. 731-736.
24. Boyer, E.W., *Dextromethorphan abuse.* Pediatric emergency care, 2004. **20**(12): p. 858-863.
25. Bem, J.L. and R. Peck, *Dextromethorphan.* Drug safety, 1992. **7**(3): p. 190-199.
26. Weber, B., et al., *Abortion induced by mifepristone and sulprostone combination: attempting analgesia with acetominophen or dipropyline.* Contraception, fertilité, sexualité, 1990. **18**(12): p. 1073.
27. Jain, J.K., et al., *Early pregnancy termination with vaginal misoprostol combined with loperamide and acetaminophen prophylaxis.* Contraception, 2001. **63**(4): p. 217-221.
28. Ilkjaer, S., et al., *Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy.* Pain, 2000. **86**(1): p. 19-24.
29. Ilkjær, S., et al., *The effect of dextromethorphan, alone or in combination with ibuprofen, on postoperative pain after minor gynaecological surgery.* Acta anaesthesiologica scandinavica, 2000. **44**(7): p. 873-877.
30. Mehlisch, D., et al., *Synergistic analgesic interaction of morphine with dextromethorphan, an NMDA receptor antagonist, in oral surgery pain.* Clinical Pharmacology & Therapeutics, 1998. **63**(2): p. 139.
31. Helmy, S.A. and A. Bali, *The effect of the preemptive use of the NMDA receptor antagonist dextromethorphan on postoperative analgesic requirements.* Anesthesia & Analgesia, 2001. **92**(3): p. 739-744.
32. Kew, S., *Text messaging: an innovative method of data collection in medical research.* BMC research notes, 2010. **3**(1): p. 342.
33. Christie, A., et al., *Collection of patient-reported outcomes;-text messages on mobile phones provide valid scores and high response rates.* BMC medical research methodology, 2014. **14**(1): p. 52.
34. Pubchem. *Dextromethorphan* 10/19/2017]; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/dextromethorphan#section=Top.
35. SigmaAldrich. *Avicel PH-101* 2017 [cited 2018 January 2nd]; Available from: http://www.sigmaaldrich.com/catalog/product/sial/11365?lang=en&region=US.
36. Gluud, L.L., *Bias in clinical intervention research.* American journal of epidemiology, 2006. **163**(6): p. 493-501.
37. Todd, K.H., et al., *Clinical significance of reported changes in pain severity.* Annals of emergency medicine, 1996. **27**(4): p. 485-489.
38. van der Wouden, J.C., et al., *Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research.* Journal of clinical epidemiology, 2007. **60**(8): p. 819-824.