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Protocol

Safety and efficacy of high dose buprenorphine initiation in fentanyl positive emergency department patients

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ABSTRACT

Background: The safety and efficacy of high dose buprenorphine (BUP) induction in fentanyl positive emergency department patients (high dose BUP) study includes two clinical trials funded through the helping to end addiction long-term[SM] initiative. The study tests whether initiation and continuation of BUP at higher doses and over a shorter time period than currently recommended is safe, tolerable and effective.
Methods: Trial 1 is a head-to-head comparison of the safety, tolerability and feasibility of high dose BUP initiation (32 mg) and continuation (24 mg) as compared to standard dose BUP initiation (12 mg) and continuation (16 mg). Trial 2 is a small pilot multicenter randomized, double blind clinical trial in 80 participants, randomized 1:1, that will provide preliminary efficacy data. The primary outcome measure for trial 1 is the frequency of dose treatment-emergent adverse events (TEAEs) grade 3 (per common terminology criteria for adverse events v5.0 (CTCAE v5.0)), including but not limited to bradypnea <8, oxygen saturation<88% on room air and/or rescue naloxone administration. The primary outcome measure for trial 2 is the proportion of participants engaged in comprehensive addiction treatment at 7-days post ED initiation.
Conclusions: The results of these trials will provide crucial data on the safety, feasibility and efficacy of high-dose ED BUP initiation and continuation in fentanyl positive ED patients and inform incorporation of high-dose BUP initiation into ED care for patients with OUD.
Trial registration: ClinicalTrials.gov ID: NCT05589181

Keywords: BUP, Fentanyl, Precipitated withdrawal

INTRODUCTION

Once only responsible for 14% of opioid overdose (OD) deaths, synthetic opioids now account for more deaths than heroin and prescription opioids.[1-3] Currently, three medications targeting the mu-opioid receptor are approved by the US Food and Drug Administration (FDA) for the treatment of opioid use disorder (OUD): methadone, a pure receptor agonist, BUP a partial receptor agonist, and naltrexone, a receptor antagonist.[4-7] High quality evidence demonstrates that all three medications for OUD (MOUD) reduce mortality.[8]

Among the agonists, only BUP can be prescribed for the treatment of OUD outside of registered opioid treatment programs, making it ideal for OUD treatment in office based practices and emergency departments (EDs).

BUP is a partial mu-opioid receptor agonist available alone or combined with naloxone. As a partial agonist, BUP possesses a "ceiling effect" which limits its capacity for severe clinical toxicity, including respiratory and CNS depression.[9-11] Because of BUP's partial agonist action, if initiated while the patient is maintained on opioids, precipitated withdrawal can occur. To prevent this, initiation with BUP should occur when the patient is experiencing opioid withdrawal symptoms.[12] To assess the degree of opioid withdrawal, the clinician can utilize various scoring systems including the clinical opiate withdrawal scale (COWS).[13] Guidelines recommend different COWS scores to initiate BUP. Protocols also differ widely in their initial BUP dose, time between repeat dosing for continued withdrawal symptoms, maximum first day dose and prescribed maintenance dose.[14]

Several commentaries, case reports and case series have reported individuals using fentanyl experience delayed emergence of withdrawal symptoms and more frequent instances of precipitated withdrawal.[15-17] Animal studies have demonstrated that the effects of higher efficacy agonists, like fentanyl, are more difficult to block with BUP.[18] This has been extrapolated to humans to suggest that BUP may be of reduced benefits in patients using fentanyl as a result of persistent euphoria in response to fentanyl despite therapeutic doses of BUP. Additionally, due to fentanyl's high lipophilicity and storage in adipocytes, chronic fentanyl use likely follows a prolonged clearance pharmacokinetic model. While pharmacokinetic studies in patients using illicitly manufactured fentanyl do not exist, data suggests that patients with OUD may have prolonged fentanyl clearance beyond 2-4 days.[19] Consequently, treatment with a high-binding affinity opioid like BUP may contribute to precipitated withdrawal due to prolonged fentanyl clearance from opioid receptors and the total body compartment. While high quality evidence is lacking, these concerns have led to changes in both initiation practices and beliefs among providers and people who use illicit opioids.[17,18,20]

A rapid high-dose BUP initiation and continuation strategy could have several advantages. In contrast to "standard" dosing, a rapid high-dose initiation could reduce initiation time and the need for frequent re-evaluations of withdrawal severity. In observed initiations, this could reduce length of stay, which is important to ED providers faced with unprecedented ED crowding.[21] If a simpler protocol using a rapidly administered large BUP initiation dose is shown to be safe, it may have increased acceptance among patients and providers. Further, from a neuropharmacological standpoint, it has been proposed that high-dose BUP may be better tolerated in patients using fentanyl with a lower likelihood of precipitated withdrawal than with standard dose BUP initiation.[22] Additionally, a higher maintenance dose following ED discharge may encourage treatment retention by providing improved withdrawal symptom relief. However, as described above, the safety and efficacy of this approach in patients using fentanyl has not been prospectively established and requires further evaluation.

This manuscript describes the protocol for two clinical trials testing high-dose ED BUP initiation and continuation versus standard-dose ED BUP initiation and continuation on the primary outcome of grade 3 treatment emergent adverse events (TEAEs) (Trial 1) and the proportion of participants engaged in comprehensive addiction treatment at 7 days post-ED BUP initiation (Trial 2).

METHODS

Overview

This study is funded as part of the NIH HEAL initiative[SM] efforts to increase access to medications for OUD. The study has two discrete clinical trials. Trial 1 is a single site prospective test of the safety and tolerability of 32 mg of BUP as an initiation dose (split dosing over 30-60 minutes with 4 hours of post-initiation monitoring) and 24 mg as a continuation dose compared with the currently recommended BUP initiation dose of 12 mg and continuation dose of 16 mg.[23] Dosing for the 12 mg initiation cohort is 8 mg at time=0 and 4 mg at time=30-60 min. The dosing for the 32 mg initiation cohort is 16 mg at time=0 and 16 mg at time=30-60 min. Trial 1 Timeline is summarized in Figure 1.

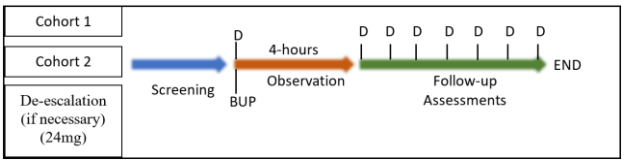

Figure 1: Trial 1 timeline.
BUP=Buprenorphine; D=day.

The dose escalation pathway for trial 1 is summarized in Figure 2. The frequency of unacceptable dose limiting toxicities (DLT) is set at 10%. The study will compare two cohorts of 10 participants, with the potential for 5 additional participants per cohort if 1 DLT is observed in the first 10 subjects in a cohort.

If the 12 mg (control) cohort has 2 DLTs, at n=15 the data safety and monitoring board (DSMB) will be consulted about enlarging the cohort size. If there are two DLTs in the 32 mg cohort, de-escalation to 24 mg will take place. If the 24 mg cohort has 2 DLTs it will be concluded that no safe/tolerable high initiation dose has been identified and trial 2 will not occur.

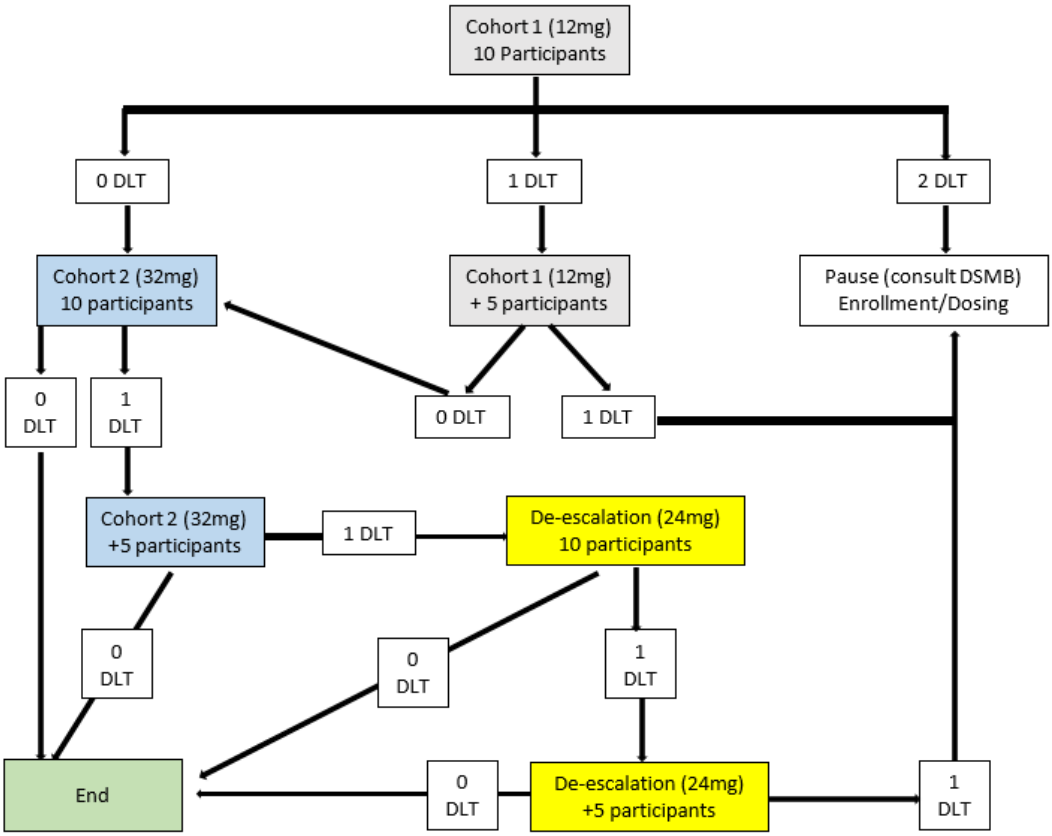

Figure 2: Trial 1 dose escalation pathway.

In trial 1, any participants who choose not to take their full assigned dose will be replaced to ensure the full cohort size. No more than 20% of participants who choose not to take their full assigned dose can be replaced.

Trial 2 is a four-site double blind pilot randomized controlled trial RCT study (n=20×4) conducted in the ED, that will test the efficacy of the high BUP dose (selected in trial 1) as an initiation dose (split dosing over 30-60 min) compared to a standard BUP initiation dose (12 mg, split dosing over 30-60 min) as assessed by the proportion of participants engaged in comprehensive addiction treatment 7-days post treatment initiation.

Primary aims

Trial 1 primary aims

To determine the safety, tolerability and feasibility of high dose BUP initiation and continuation in ED patients with OUD using fentanyl who are in moderate to severe opioid withdrawal (minimum COWS of 8).

Safety

The initiation protocol will be considered safe if: There are no more than two occurrences of grade 3 or above CTCAE v5.0 events, no more than two precipitated withdrawal events defined as an increase in COWS ≥12 within 90 minutes of BUP administration. No more than one respiratory depression events defined as bradypnea <8 and/or 02 saturation <88% on room air, requiring the use of supplemental oxygen or naloxone rescue.

Tolerability

The initiation protocol will be considered tolerable if: The participant can be safely discharge from the ED 4-hours post-medication administration as determined by their primary treating provider. Less than 10% of participants experience the following 4-hours after BUP administration: Persistent nausea/vomiting requiring treatment, a Pasero opioid-induced sedation scale (POSS) of 3 or higher, mini mental status exam (MMSE) indicating severe cognitive impairment, precipitated or worsening withdrawal requiring continued treatment with ancillary medication.[24]

Feasibility

The initiation protocol will be considered feasible if: Less than 20% of participants fail to achieve the targeted initiation dose of BUP.

Trial 2 primary aims

To determine if high dose BUP initiation and continuation improves engagement in comprehensive addiction care at 7-days post BUP treatment initiation.

In this protocol, the a-priori definition of improved engagement is a 15% increase in engagement in comprehensive addiction treatment at 7-days in the high dose BUP initiation cohort compared to the standard dose BUP initiation cohort.

Secondary aims

Secondary aims include, 1) determining the tolerability of rapid BUP dose titration, 2) determining if there is a signal of superiority of high dose BUP initiation with regard to time to relief of symptoms, 3) assessing the need for ancillary medications, and 3) examining patient and operational outcomes (Table 1).

Site selection

For trial 2, site selection will be based on a sites prevalence of ED patients with International Classification of Diseases, 10th revision codes related to OD, OUD and other opioid-related diagnoses in the preceding 12 months; existing relationship with a site PI who has experience with OUD research with capacity to oversee the proposed research; presence of the necessary clinical infrastructure to perform a high-dose ED BUP initiation and adequate community health resources in order to link patients to outpatient care following ED BUP initiation. All sites have to agree to single IRB oversight.

Table 1: Secondary aims and outcome assessments.

Secondary objectives	Secondary outcomes
Determine the tolerability of a rapid titration of BUP administered to patients with untreated OUD presenting to the ED in moderate to severe opioid withdrawal with fentanyl positive UDSs	Frequency of persistent nausea/vomiting requiring treatment. Frequency of A POSS of 3 or higher Frequency of a MMSE indicating severe cognitive impairment Frequency of precipitated or worsening withdrawal requiring continued treatment with ancillary medications
Determine if there is a signal of superiority of high dose BUP initiation in regard to 1) relief of symptoms, 2) worsening withdrawal with COWS≥5 over the 4-hour observation period and 3) precipitated withdrawal with COWS increase ≥12 within 90 minutes of medication administration.	Difference in proportions of individuals having a worsening/precipitated withdrawal
Assess the need for ancillary medications for the treatment of opioid withdrawal in patients initiated on BUP in the ED	Difference in proportions of total number individuals requiring ancillary medications
Assess patient related and operational outcomes of high versus standard ED BUP induction	Patient satisfaction Time to withdrawal symptom relief ED length of stay Adverse events Self-reported days of illicit opioid use (past 7) as measured by timeline follow-back (TLFB) Healthcare utilization Overdose

Participants

The target population is comprised of adult ED (age 18+) patients with untreated OUD who have a urine drug screen (UDS) positive for fentanyl. Patients are eligible to be included if all of the following inclusion criteria are met: treated in the ED during screening hours, meet DSM-5 diagnostic criteria for moderate to severe OUD, COWS score ≥8, able to speak and read English sufficiently to understand study procedures and signed informed consent.

Patients are ineligible if they have UDS positive for methadone, are pregnant as determined by HCG testing, have an unstable medical or psychiatric condition including suicidality requiring hospitalization, have arequirement of ongoing opioids for pain management, or have been enrolled in formal addition treatment within the last 30 days. Additional exclusion criteria include anyone who is a prisoner or in custody at the time of the index visit, have pending legal status or pending legal action that could prohibit full participation in or compliance with study procedures, are unable to provide one additional point of contact other than themselves, are unwilling to follow study procedures, have prior enrollment in the current study, have a known allergy or hypersensitivity to BUP, received naloxone in the 60-minutes prior to the anticipated first BUP administration or undergoing concurrent treatment with another investigational agent/enrolment in another clinical study.

Screening

Research assistants (RAs) will identify patients seen in the ED by reviewing electronic tracking boards and by provider referral. The RA will keep a log of all patients screened and excluded and the reasons for exclusion.

Patients will be asked for verbal consent to complete a set of screening assessments starting with a screener that includes questions about illicit opioid use in the past 30 days embedded in a general health and substance use screener that also includes questions about safety, tobacco and alcohol and opioid use.[25] Potential study patients who report any opioid use in the past month will complete a 7-day recall of such use. If opioid use is reported during the past 7 days a brief structured diagnostic interview with questions on the DSM-5 criteria will be used to evaluate the presence of moderate/severe opioid use. Patients who do not meet inclusion criteria will be given instructions, referrals and access to naloxone and medication for OUD as per the ED's existing protocols. Those who meet study inclusion criteria will provide a urine sample for toxicology testing. If the UDS is positive for fentanyl the informed consent document will be reviewed with the patient. Once participant signs the consent form, the patient will be considered enrolled into the study. Screening assessments are shown in Table 2.

Table 2: Screening assessments.

Procedure/assessment	Screening	Notes
Screen verbal consent	X	Patients will be asked for verbal consent to complete a set of screening assessments starting with a screener that includes questions about illicit opioid use in past 30 days embedded in a general health and substance use screener that also includes questions about safety, tobacco and alcohol use. Potential study patients who report any opioid use in the past month will complete a structured DSM-5 interview to assess severity of OUD. Those with moderate to severe OUD will provide a urine sample. If the urine tests are positive for Fentanyl and negative for methadone; he/she is able to provide contract information for 1 separate reliable contacts (in addition to their own); meets all eligibility criteria written informed consent informed consent will be obtained. Once participant signs the consent form, the patient will be considered into the study per IRB regulations. Study participants who do not complete all screening assessments or who are otherwise found to be ineligible for participation in the study will be considered screen failures.
ED health quiz	X	
COWS	X	
DSM-5 quiz	X	
UDS	X	
Urine pregnancy test	X	
Patient eligibility summary	X	
Written informed consent	X	

ED=Emergency department, COWS=Clinical opioid withdrawal scale, DSM-5=Diagnostic and statistical manual of mental disorders version 5, UDS=Urine drug screen.

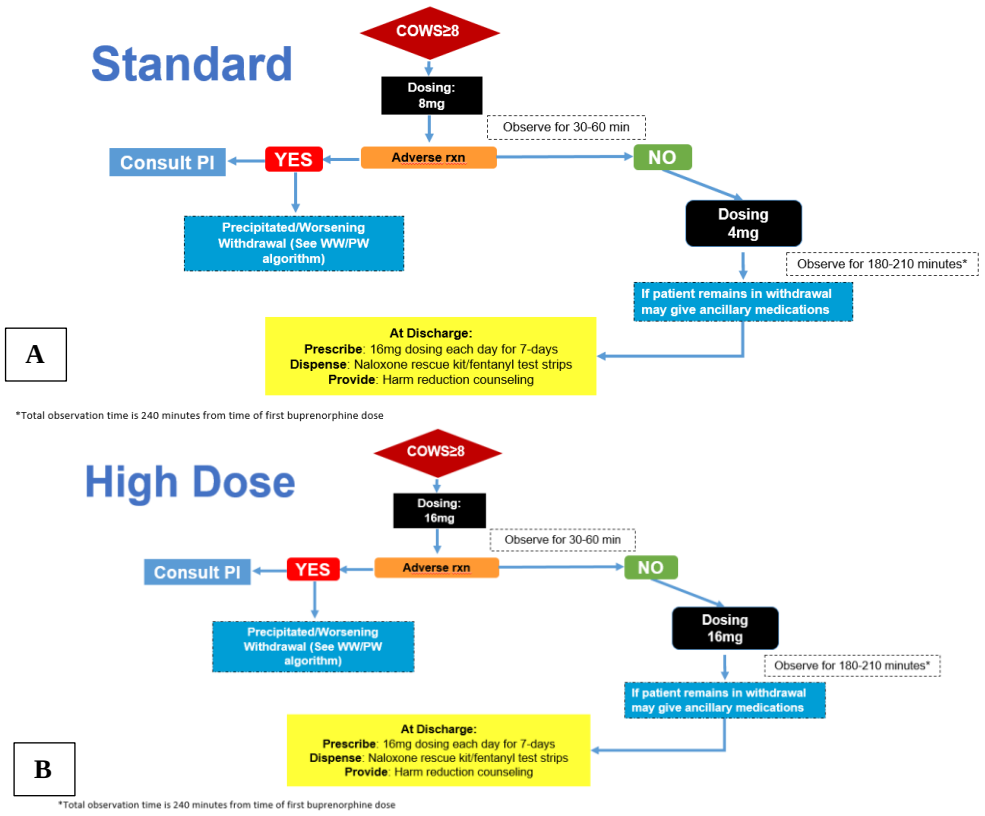

Figure 3: (A) Standard-dose BUP initiation pathway and (B) high-dose BUP initiation pathway.

Patient who meets all eligibility criteria and are interested in study participation but have a COWS score <8 may be asked to remain in the ED with permission of the treating physician and be rescreened at a later time.

Cohort assignment

Cohort assignment trial 1

The first 10 consecutively enrolled participants will be assigned to the 12 mg initiation cohort with split dosing with 8mg at time=0 and 4mg at time 30-60 minutes. If any of the first 10 participants experiences an unacceptable dose limiting toxicity (DLT), 5 additional participants will be recruited for a total of 15 participants. If two or more DLTs occur the DSMB will be consulted about enlarging the cohort size. The standard dose 12 mg BUP initiation pathway is shown in Figure 3 A.

In cohort two, 10 consecutively enrolled participants will be will be assigned to the 32 mg initiation cohort with split dosing with 16 mg at time=0 and 16mg at time=30-60 minutes. The high-dose 32 mg BUP initiation pathway is shown in Figure 3 B. If any of the first 10 participants experiences an unacceptable DLT, 5 additional participants will be recruited for a total of 15 participants. If there are two DLTs in the 32 mg cohort, that cohort will no longer recruit and the dose will be de-escalated to 24 mg. If the 24 mg cohort has 2 DLTs in either 1st 10 patients or when expanded to n=15, it will be concluded that no safe/tolerable high initiation dose has been identified and trial 2 will not occur.

Cohort assignment trial 2

Randomization (Trial 2)

Eligible participants will be randomized in a 1:1 ratio to high or standard dose BUP initiation. A permuted block randomization procedure with random block sizes will be implemented to balance randomization by site. A randomization slot, once used, will not be re-allocated.

Blinding

Trial 1 blinding

In trial 1 neither the investigator nor the participant will be blinded to group assignment.

Trial 2 blinding

In trial 2, participants, investigators and site personnel with the exception of the investigational drug pharmacist will be blinded to group assignment.

Discharge and post-discharge care

Trial 1 discharge and post-discharge care

At discharge all participants will receive a prescription for BUP for 7-day (16 mg/day for those receiving standard dose initiation and 24 mg/day for those receiving high dose initiation), harm reduction counseling that includes the provision of a naloxone rescue kit and fentanyl test strips and a referral for out-patient addiction treatment within 7-days of the ED visit. After discharge, research associate will conduct daily follow-up assessments of study participants for 7 days via phone/text to assess daily drug use and opioid craving. At 7 days, all participants will be asked to return to provide a UDS and be assessed for engagement in comprehensive addiction treatment and healthcare utilization.

Trial 2 discharge and post-discharge care

At discharge, all participants will receive a prescription for BUP for 7-day (16 mg/day for those receiving standard dose initiation and 24 mg/day for those receiving high dose initiation), harm reduction counseling that includes provision of a naloxone rescue kit and fentanyl test strips and a referral for out-patient addiction treatment within 7-days of ED visit.

Participants have a phone follow-up at 7 and 30-days to assess primary and secondary outcomes.

Study assessments

Index visit assessments

For both trial 1 and 2, initiation assessments (assessments conducted upon trial enrollment during index visit for BUP initiation) are presented in Table 3. Included in the initiation assessments are serial measures of opioid withdrawal, drug effects, vital signs, sedation scale and mental status exams.

Table 3: Index visit assessments.

Assessment	Baseline (Time 0)	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	150 min	180 min	210 min	240 min
Vital signs	X		X		X		X		X	X	X	X	X
Demographics	X												
TLFB	X												
Physical exam	X												
COWS	X	X	X	X	X		X		X	X	X	X	X
OOWS	X				X				X		X		X
Withdrawal VAS	X				X				X		X		X

Continued.

Assessment	Baseline (Time 0)	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	150 min	180 min	210 min	240 min
POSS	X								X				X
Nausea and vomiting	X		X		X		X		X		X		X
Drug effect	X		X		X		X		X		X		X
OC-VAS	X		X		X		X		X		X		X
MME	X												X
12-lead EKG	X												
LFTs	X												
Transmucosal BUP[14]	X		X										
Satisfaction survey													X
BUP prescription													X
Referral to addiction care													X
Narcan rescue kit, fentanyl test strip distribution; harm reduction education													X

AE=adverse event, BUP=BUP, COWS=Clinical opioid withdrawal scale, ECG=electrocardiogram, MME=mini mental status exam, OC-VAS=Opioid craving visual analog scale, OOWS=objective opioid withdrawal scale, POSS=Pasero Opioid-induced sedation scale, TLFB=timeline follow back.

Follow-up assessments

Follow-up assessments and timeline for Trial 1 are: opioid craving visual analog scale (day 1-7), Other drug use (day 1-7), healthcare utilization (day 7), engagement in treatment as confirmed by participant and facility (day 7). Trial 2 follow-up assessments include: locator form (day 7 and 30), timeline follow back (day 7 and 30), other substance use (day 30), overdose (day 30), health services utilization (day 30), satisfaction scale (day 7 and 30), engagement in treatment as confirmed by participant and facility (day 7 and 30). These include assessments of engagement in treatment confirmed by the treating site or provider, healthcare utilization, other drug use and an assessment of withdrawal.

Laboratory assessments

In trial 1, urine samples will be collected from all participants at enrollment and on day 7 for the determination of BUP and norBUP urine concentration as well as fentanyl and fentanyl analogue testing. Plasma concentrations will be quantified using a specific and validated liquid chromatography tandem mass spectroscopy method.

Precipitated/worsening withdrawal definitions

All participants will receive the full TM BUP dose for their assigned cohort regardless of their repeat COWS score unless they develop precipitated withdrawal. Precipitated withdrawal will be defined as an increase in the clinical opioid withdrawal scale (COWS) by ≥12 within 90 minutes of BUP administration.

Treatment for precipitated withdrawal with ancillary medications is protocolized in both trial 1 and trial 2 and is as follows: muscle aches and pain: Acetaminophen 650 mg, NSAIDS (Ibuprofen 200-800 mg or ketorolac 30-60 mg); abdominal cramps and diarrhea: Dicyclomine (Bentyl) 20 mg, loperamide (Imodium) 2 mg; nausea: Ondansetron (Zofran) 8 mg, prochlorperazine (Compazine) 5-10 mg or promethazine (Phenergan) 12.5-25 mg; elevated BP and tachycardia: clonidine 0.1-0.3 mg, q 4-6 hrs, not to exceed 0.6 mg in 24 hrs, (hold for systolic blood pressure <100 mmHg, or heart rate <56 bpm) and agitation/anxiety: Lorazepam 2 mg PO.

Participant compensation

For trial 1, participants will receive $100 for completion of the initial ED initiation, $10 each day for each day 1-7 follow-up completed, $50 if all day 1-7 follow-ups completed and $50 for completion of the day 7 follow-up visit for a maximum possible compensation of $270 for trial 1. For trial 2, participants will receive $100 for completion of the initial ED initiation, $50 for completion of the day 7 follow-up visit and $50 for completion of the day 30 follow-up visit for a maximum possible compensation of $200 for trial 2.

Justification for sample size

Trial 1 sample size

Trial 1 sample size will be a minimum of 20 and maximum of 45 participants based on the number of DLTs as described in section 2.7.1.

Trial 2 sample size

Trial 2 will not be powered to provide evidence of efficacy of one initiation strategy over the other with

regard to 7-day engagement in comprehensive addiction treatment. However, in collaboration with the funder, a pre-requisite Go/no go criteria of a 15% higher 7-day follow-up in comprehensive addiction treatment in the high-dose BUP initiation group was chosen to a sufficient effect size to justify moving onto a subsequent larger trial. Accordingly, for trial 2, we will target a sample size of 80 participants (20 per site×4 sites).

Statistical analysis

Study outcomes and statistical analysis plans for each outcome are described below.

Trial 1 statistical analysis

The primary objective of this trial is the assessment of safety/tolerability. The secondary objectives are exploratory and include patient satisfaction, drug effect and opioid craving, engagement in formal addition treatment, substance use and healthcare utilization. There is no formal hypothesis to be tested. Continuous endpoints will be summarized using parametric descriptive statistics by dose cohort, which will include the number of participants (n), mean, standard deviation, median, minimum, and maximum. Categorical endpoints will be summarized using non-parametric statistics such as frequency distributions and proportions. 95% CI will be computed where appropriate.

TEAEs will be defined as events that occur on or after the first dose of study medication. TEAEs, serious or CTCAE will be summarized overall and by medical dictionary for regulatory activities (MedDRA) primary system organ class.

Frequency of dose limited toxicities (DLTs) will be summarized by dose cohort. Serial vital sign (blood pressure, heart rate, pulse oximetry) and withdrawal severity (COWS, OOWS, withdrawal VAS) measurements will be reported as numeric summaries of all observed findings and changes from baseline/screening by time point and dose cohort. Proportion of binary exploratory endpoint will be summarized using frequencies and percentages. Number and percentage of participants with protocol deviations will be summarized by dose cohort and overall. Interim analyses are not planned.

Trial 2 statistical analysis

Tolerability outcome

The tolerability outcome of precipitated withdrawal, dichotomized (yes/no), will be assessed in all patients randomized. Differences between the arms will be examined using generalized estimating equations (GEE) although weighted GEE may be used based on the amount of missing data for the primary outcome which we expect to be minimal.

Fidelity/feasibility outcome

Protocols will be compared descriptively by a relative risk of non-compliance ratio for each component. The study team, in consultation with DSMB members and the funder will determine the thresholds of acceptable protocol fidelity to determine whether a larger RCT is feasible.

Analysis of baseline characteristics

Distribution of baseline demographic and clinical characteristics will be summarized. Comparability for continuous variables will be examined graphically and by summary statistics. Categorical variables will be examined by calculating frequency distributions.

Analysis of secondary outcomes

ANCOVA will be used to assess the relationship between craving and satisfaction by time periods (baseline, 7 and 30-days). Counts of self-reported opioid use, health service utilization and overdose events will be compared between groups at 7 and 30 days using negative binomial regression. All of the models will include covariates for outcomes measured at baseline as well as site, age, sex, ethnicity/race. Linear contrasts will be used to estimate differences between the groups along with 95% confidence intervals.

Analysis of adverse events and serious adverse events

Listings and tabulations of counts of AEs and SAEs will be summarized as frequencies and percentages by type, severity and relation to study drug.

RESULTS

In this study involving two distinct clinical trials, we first will compare safety, tolerability and feasibility of a high-dose ED BUP initiation (32 mg or 24 mg if 32 mg found to be unsafe or intolerable) and continuation (24 mg) approach with a standard-dose initiation (12 mg) and continuation (16 mg) approach.

If safety, tolerability and feasibility of the high-dose approach is established, we will subsequently compare 7-day engagement in comprehensive addiction treatment between the high-dose and standard-dose initiation and continuation approach through a multi-center randomized controlled trial conducted at 4 sites.

CONCLUSION

As the opioid crisis continues to worsen and fentanyl and fentanyl analogs are increasingly implicated in ODs and deaths, removing barriers to ED BUP initiation and establishing safe, tolerable, feasible and effective initiation and continuation practices in patients with fentanyl/fentanyl analog use is of paramount importance.

A high-dose ED BUP initiation and continuation approach has the potential to reduce patient, provider and logistical/resource barriers to ED BUP initiation and improve post-ED patient treatment retention, but currently, the safety, tolerability, feasibility and efficacy of high-dose BUP initiation and continuation in patients with fentanyl and fentanyl analog use is unknown.

This study has the potential to overcome existing barriers to ED BUP initiation and decrease ODs and deaths through potentially establishing the safety, tolerability and feasibility of a high-dose ED BUP initiation and continuation approach and through providing preliminary data on efficacy of this high-dose approach.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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