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Randomised clinical trial of a 16 mg vs 24 mg maintenance daily dose of buprenorphine to increase retention in treatment among people with an opioid use disorder in Rhode Island: study protocol paper

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ABSTRACT

Introduction Buprenorphine is a highly effective treatment for opioid use disorder (OUD). However, provider observations and preliminary research suggest that the current standard maintenance dose may be insufficient for suppressing withdrawal and preventing cravings among people who use or have used fentanyl. Buprenorphine dosing guidelines were based on studies among people who use heroin and have not been formally re-evaluated since fentanyl became predominant in the unregulated drug supply. We aim to compare the effectiveness of a high (24 mg) vs standard (16 mg) maintenance daily dose of buprenorphine for improving retention in treatment, decreasing the use of non-prescribed opioids, preventing cravings and reducing opioid overdose risk in patients.

Methods and analysis Adults who are initiating or continuing buprenorphine for moderate to severe OUD and have a recent history of fentanyl use (n=250) will be recruited at four outpatient substance use treatment clinics in Rhode Island. Patients continuing buprenorphine must be on doses of 16 mg or less and have ongoing fentanyl use to be eligible. Participants will be randomly assigned 1:1 to receive either a high (24 mg) or standard (16 mg) maintenance daily dose, each with usual care, and followed for 12 months to evaluate outcomes. Providers will determine the buprenorphine initiation strategy, with the requirement that participants reach the study maintenance dose within 7 days of randomisation. Providers may adjust the maintenance dose, if clinically needed, for participant safety. The primary study outcome is retention in buprenorphine treatment at 6 months postrandomisation, measured using clinical and statewide administrative data. Other outcomes include non-prescribed opioid use and opioid cravings (secondary), as well as non-fatal or fatal opioid overdose (exploratory).

Ethics and dissemination This protocol was approved by the Brown Institutional Review Board (STUDY00000075). Results will be presented at conferences and published in peer-reviewed journals.

Trial registration number NCT06316830.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This randomised trial will use an allocation method designed to minimise imbalance of prognostic covariates (eg, sex, race/ethnicity, age) between treatment arms to avoid confounding that may have biased prior observational studies.
⇒ The trial will use a pre-established statewide data sharing framework to assess the primary outcome (retention in treatment) and an exploratory outcome (non-fatal or fatal overdose) with administrative data, allowing for near-complete outcome ascertainment including among participants who are no longer receiving care at an enrolment site.
⇒ This trial focuses on English-speaking populations, a limitation of the study that may impact generalisability of findings to other populations.

INTRODUCTION

Background and rationale

Unintentional overdose deaths have drastically increased in the past decade in the USA due to increasing amounts of fentanyl and other highly potent synthetic opioids in the unregulated drug supply, among other social and economic factors.[1] In 2022, approximately 110 000 people died due to drug overdose in the USA, with more than two-thirds (68%) involving synthetic opioids other than methadone, mainly fentanyl.[2] Buprenorphine is a highly effective medication treatment for opioid use disorder (OUD), and prescribing has more than doubled since 2009.[3] Compared with non-medication treatment for OUD, buprenorphine reduces overdose mortality by 50% and improves retention in care.[4–7] Additionally,

buprenorphine and other medications for OUD confer numerous other personal health and social benefits, including maintenance of employment and improved birth outcomes.[5 6 8 9] However, fentanyl is changing the calculation of treatment, and optimal buprenorphine dosing for people who use fentanyl is unknown.[7 10]

Mounting preclinical and clinical data demonstrate that the pharmacological profile of fentanyl is fundamentally different from other 'short-acting' opioids, such as heroin.[11] Fentanyl is a more efficacious agonist of mu-opioid receptors than heroin or morphine, suggesting that buprenorphine at standard doses may be less effective in treating patients with a history of fentanyl use than heroin use.[12 13] Buprenorphine dose guidelines for OUD treatment were determined by clinical trials conducted in populations with a history of heroin use. Trial doses were selected based on opioid receptor blockade studies with buprenorphine in the context of morphine, hydromorphone and heroin challenge doses.[14] Unfortunately, the early receptor blockade studies did not assess opioid blockade with buprenorphine using fentanyl as a challenging drug, which limits application to populations who use fentanyl.[15] In studies that assessed higher doses of more potent opioids, higher buprenorphine doses were required to maximise opioid receptor blockade.[16–19] This is supported by animal studies demonstrating that, for both methadone and buprenorphine, higher efficacy agonists are more difficult to block than lower efficacy agonists.[12 13]

Clinician observations, case reports and observational studies also suggest that higher than standard doses of buprenorphine may be needed for people who use fentanyl. Physicians have observed that higher daily doses of buprenorphine are needed to suppress withdrawal and prevent cravings among patients who use fentanyl.[20–24] Some providers have already started increasing from the standard 16 mg daily dose to 24 mg or more,[25] and case studies suggest that higher doses of buprenorphine may benefit patients with a history of fentanyl use.[20 25 26] Prior work from our research team found that, among a retrospective cohort of patients initiating buprenorphine treatment in the fentanyl era, those prescribed the standard 16 mg dose were 20% more likely to discontinue treatment than those prescribed 24 mg.[27] Higher-dose treatment protocols may be necessary to provide adequate control of withdrawal symptoms and cravings, improve treatment retention and prevent ongoing non-prescribed opioid use and overdose among patients who use fentanyl. However, existing evidence regarding the effectiveness of higher doses of buprenorphine is based on preclinical studies, clinician anecdotes, case reports and retrospective analyses, which have substantial limitations and may be subject to important biases.

Objectives

We aim to test the effectiveness of a high maintenance daily dose of buprenorphine (24 mg) for improving outcomes among patients who use fentanyl compared with the standard maintenance daily dose (16 mg). We hypothesise that patients who are randomly assigned to the high 24 mg maintenance dose, as compared with patients randomly assigned to the standard 16 mg maintenance dose, will have improved retention in buprenorphine treatment (primary outcome), improved treatment response based on use of non-prescribed opioids (secondary outcome), decreased opioid cravings (secondary outcome) and decreased risk of non-fatal or fatal opioid overdose (exploratory outcome).

Trial design

The trial will use a parallel design in which patients with a history of fentanyl use who are initiating or continuing buprenorphine at a substance use treatment clinic are randomly assigned 1:1 to receive a high maintenance daily dose (24 mg) with usual care or a standard maintenance daily dose (16 mg) with usual care.

METHODS: PARTICIPANTS, INTERVENTIONS OUTCOMES

Study setting

The trial will take place in Rhode Island, a state with historically high rates of non-prescribed opioid use and unintentional overdose death which have increased in the fentanyl era. In 2021, nearly 4% of adult Rhode Islanders reported misusing opioids and more than 2% met criteria for OUD in the past year.[28 29] Rhode Island ranked 17th in the nation for opioid overdose mortality in 2022,[30] and the number of overdose deaths in Rhode Island increased by 40% between 2014 (n=240) and 2023 (n=404).[31] Fentanyl has been the main driver of overdose deaths in the state for years, accounting for over 70% of unintentional drug overdose deaths since 2016.[31–33]

Buprenorphine treatment for OUD is widely accessible in Rhode Island in a number of clinical settings including the emergency department, a statewide 24/7 bridge hotline, outpatient treatment providers in specialised behavioural health and primary care and opioid treatment programmes (OTPs). Buprenorphine for OUD is covered by private and public insurance. However, some insurers require prior authorisation for doses above the standard 16 mg daily dose, and disparities remain in access to buprenorphine by race/ethnicity, socioeconomic status and geography.[34–36]

Eligibility criteria

To be eligible for the trial, patients must (1) be identified by the treating provider as having moderate to severe OUD (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition), (2) be initiating or continuing buprenorphine for treatment of OUD and (3) have a recent history of fentanyl use. A recent history of fentanyl use will be confirmed through a fentanyl-positive urine drug screen (UDS) at intake or within the last month or based on self-reported ongoing fentanyl use during treatment at the time of study enrolment. Participants who are continuing buprenorphine must be on doses of

16 mg or lower and willing to be randomly assigned to a trial intervention arm. This decision was based on ethical concerns with lowering the daily buprenorphine dose of a patient with ongoing fentanyl use during active treatment for study participation. This determination was made to align with (1) standard clinical practice that ongoing fentanyl use during buprenorphine treatment should result in additional support for the patient and dose maintenance or, if clinically appropriate, a dose increase in the case that use is due to ongoing cravings or withdrawal at the prescribed dose, not dose reduction and (2) strong preliminary retrospective evidence of improved treatment retention for patients on 24 mg compared with 16 mg of buprenorphine.[27] Participants must also be age 18 years or older, live in Rhode Island and speak English. Patients who are on concomitant medications deemed to present the potential for serious medication interaction by the treating clinician (eg, site principal investigator (PI)) will be excluded. Pregnant people will be ineligible, and a pregnancy test will be conducted as a part of study screening for pregnancy-capable potential participants. Pregnant people are excluded because physiological changes in pregnancy can impact drug pharamacokinetics and pharmacodynamics, which may result in the need for dosing adjustments throughout different stages of pregnancy. For this reason, participants who become pregnant during the trial will be withdrawn from the study.

Patient and public involvement

The motivation to conduct the trial was based on clinical experience of the study PIs and patient feedback regarding the need for higher doses of buprenorphine in the context of fentanyl use. This trial incorporated feedback from clinical providers at the study enrolment sites into the design of the protocol. Additionally, an expert panel of physicians in addiction medicine informed the dose considered in each trial arm.

Interventions

Current treatment guidelines

The current dosing guidance for sublingual buprenorphine treatment of OUD is based on the package insert approved by the Food and Drug Administration (FDA).[37–40] It is recommended that medication be titrated over the course of a few days once a patient begins to experience objective withdrawal signs. After buprenorphine initiation and stabilisation, standard maintenance dosing is between 4 and 24 mg, with a target daily dose of 16 mg for most patients. Dosing recommendations depend on the individual's response to the medication, and prescribers adjust accordingly, although the package insert specifically states 'dosages higher than 24 mg have not been demonstrated to provide any clinical advantage'.[39]

In practice, there is variability in titration and maintenance dosing with buprenorphine. The dominance of fentanyl in the illicit opioid supply has introduced new challenges to buprenorphine initiation. In response, some providers have moved away from standard buprenorphine initiation strategies and adopted alternative low or high buprenorphine dosing strategies, based on clinical judgement and patient factors during the initiation period, to lower the risk of precipitated withdrawal in the setting of chronic fentanyl exposure.[41]

Given the variation in clinical practice and lack of consensus guidelines on optimal buprenorphine initiation protocols in the era of fentanyl, we will follow a provider-guided initiation strategy in the trial. Participants will be randomly assigned to receive a high maintenance daily dose (24 mg) or the standard maintenance daily dose (16 mg). Participants will obtain their medication at the clinic or a pharmacy in accordance with standard of care at the clinic. The requirement will be that the participant reach the study maintenance dose within 7 days of study enrolment. Providers may adjust the maintenance dose, as clinically needed, for the safety of participants. Specifically, the maintenance dose may be increased or decreased during the study based on the provider's clinical judgement to maintain patient safety.

Sixteen milligram

The control intervention is the FDA-recommended target daily maintenance dose of buprenorphine (16 mg) plus any usual clinical care the participant receives at the clinic. During the course of treatment, providers may add adjunctive medications outside of the opioid class consistent with usual care, including clonidine, ondansetron, acetaminophen, ibuprofen and metoclopramide.

Twenty-four milligram

The experimental intervention is a high daily maintenance dose of buprenorphine (24 mg) plus any usual clinical care the participant receives at the clinic. This high daily dose is the upper limit of the FDA-approved dose range[37–39] and was selected based on preclinical studies, clinician anecdotes, case reports and retrospective analyses suggesting improved effectiveness of higher buprenorphine doses among patients with a history of fentanyl use.[20 25–27] Specifically, we conducted a retrospective study of Rhode Island residents initiating buprenorphine between 2016 and 2020 to guide the trial's high-dose determination. In this study, those prescribed the standard 16 mg maintenance daily dose were 20% more likely to discontinue treatment compared with those prescribed a high 24 mg daily dose, and very few participants received doses of more than 24 mg.[27] These data were reviewed with an expert panel of addiction medicine specialists to determine the final dosing arms in the trial. Pharmacological and clinical data support that the 24 mg daily dose of buprenorphine is likely to be well-tolerated, safe and better control cravings among people with a history of fentanyl use.[26 42]

Outcomes

The trial has one primary outcome, two secondary outcomes and one exploratory outcome.

Primary outcome

The primary outcome is the percentage of participants retained in buprenorphine treatment at 6 months postrandomisation. Six months was chosen for the primary outcome because this duration of treatment has previously been associated with good long-term prognosis.[43–45] Buprenorphine treatment engagement will be assessed using study records from the enrolment site and, for patients no longer engaged in care at that site, statewide data from the Prescription Drug Monitoring Programme (PDMP) of the Rhode Island Department of Health. The PDMP database includes information on all buprenorphine prescriptions dispensed to Rhode Island residents by retail pharmacies with a controlled substance registration in Rhode Island. Prescriptions for buprenorphine products specifically FDA-approved for pain management will not be considered OUD treatment. Participants will be classified as retained in buprenorphine treatment at 6 months postrandomisation if (1) the study site data indicate that they remained engaged in treatment or (2) the PDMP suggest that they continued treatment elsewhere and have not had a gap of more than 27 days in medication on-hand based on fill dates and days' supply.[27 46] We will also explore potential differences in retention in treatment at 1 month and 3 months postrandomisation.

Secondary outcomes

The secondary outcomes are (1) treatment response based on use of non-prescribed opioids and (2) control of opioid cravings at 6 months postrandomisation. Treatment response will be defined as a composite outcome measure incorporating UDS testing and participant self-report data. UDS will be assessed monthly for 6 months during follow-up visits with a UDS plus immunoassay fentanyl test strip as a part of usual clinical care at the clinic. Self-reported opioid use will be assessed via 2-week timeline follow back (TLFB) on the study questionnaire at the 1, 3 and 6 months study follow-up visits.[47] Based on UDS and self-reported data, participants will be classified as treatment responders if they have (1) no evidence (negative UDS and negative self-report) of non-prescribed opioid use at one or more assessments in months one to three and (2) no evidence of non-prescribed opioid use at two or more assessments in months 4–6.[48]

Participants will not be withdrawn from the trial due to use of non-prescribed opioids during study follow-up. The results of assessments that are conducted as part of routine clinical care for patients with OUD at the study sites (eg, UDS testing) will be available to participants and the treatment provider. The results of study assessments not conducted as a part of routine clinical care (eg, TLFB) will not be shared with the treating providers.

Control of opioid cravings will be assessed using the previously validated Opioid Craving Scale[49] at the 6 months follow-up visit. For this scale, participants rate each of three items on a scale of 0–9, with higher scores indicating greater cravings, and then an overall score is calculated as the average of the three-item-specific scores. We will also explore potential differences in control of cravings at 1 month and 3 months postrandomisation, as well as control of cravings as a continuous measure at 1 month, 3 months and 6 months postrandomisation.

Exploratory outcome

The exploratory outcome is non-fatal or fatal opioid overdose within 12 months postrandomisation. Non-fatal and fatal opioid overdoses will be assessed using statewide data from the Rhode Island Department of Health, including the Emergency Medical Services (EMS) Information System, Opioid Overdose Reporting System (OORS) and Office of the State Medical Examiners (OSME) databases. The EMS database includes all ambulance runs for suspected non-fatal opioid overdose incidents occurring in Rhode Island, including incidents where transport to the hospital is refused. EMS runs for suspected non-fatal opioid overdose are identified using a validated case definition.[50] The OORS database includes all ED visits for suspected opioid overdose at hospitals in Rhode Island, which are mandated to report suspected opioid overdoses to the health department within 48 hours and to include select patient identifiers.[51] The OSME database includes all accidental fatal opioid overdoses occurring in Rhode Island. Participants will be classified as having a non-fatal or fatal opioid overdose within 12 months postrandomisation if they had any EMS run for suspected non-fatal opioid overdose, ED visit for suspected opioid overdose or accidental fatal opioid overdose during that period. We will also explore potential differences in time to non-fatal or fatal opioid overdose over the 12-month period.

Loss to follow-up

Participants who withdraw from the study, move out of state, become incarcerated or die due to a cause other than opioid overdose will be considered lost to follow-up. We will identify such events using study records from the enrolment site, as well as PDMP data (moves out-of-state via out-of-state fills), data from the Rhode Island Department of Corrections (incarceration intakes) and Vital Records data from the Rhode Island Department of Health (deaths due to causes other than opioid overdose).

Sample size

We estimated that a sample size of 125 participants in each randomisation arm would provide more than 80% power to detect a 15% difference in the percentage of participants who are retained in buprenorphine treatment at 6 months postrandomisation (primary outcome), using a two-sided test and significance-level α=0.05. A 15% difference in retention was considered to be clinically meaningful and deemed an appropriate benchmark by key state and national stakeholders. We assumed that approximately 45% of the participants in the control arm (standard 16 mg maintenance daily dose) would be retained in buprenorphine treatment over 6 months based on preliminary PDMP data from Rhode Island. We also assumed less than 5% loss to follow-up because the

primary outcome is measured objectively using statewide administrative data.

Recruitment

Trial participants will be recruited from four outpatient substance use treatment clinics in Rhode Island. The clinics offer a variety of substance use treatment services, including medications for OUD, psychiatric care, therapy, peer support and harm reduction services, among others. In total, the four clinics serve an average of about 450 patients per month who meet our trial eligibility criteria.

Two full-time research assistants will assess patients for eligibility 1–3 days per week at each clinic. Recruitment processes will vary in accordance with the policies and scheduling of medication appointments at each clinic. Research assistants will spend half days recruiting at clinics where appointments for buprenorphine initiation occur in the morning and full days recruiting at clinics where appointments occur all day. At two of the clinics, the research assistants will screen medical charts to identify and recruit potentially eligible participants. At the other two clinics, the provider or other clinical staff member will identify participants who are interested and likely to be eligible for the trial. Interested patients will sign a release to share their information with research assistants for further screening.

We expect to enrol approximately 18 participants per month based on patient volume and prior experience with recruitment. At this rate, we will enrol our total sample of 250 participants over approximately 14 months. This trial anticipates starting recruitment in September 2024 and aims to complete follow-up by mid-2026.

Participants will be compensated for their time completing survey assessments. Participants will receive US$40 for the baseline, US$20 for the 1 month, US$30 for the 3 months and US$40 for the 6 months assessment, for a total of US$130 per person. This level of compensation is on par with that of the investigators' previous studies.

METHODS: ASSIGNMENT OF INTERVENTION

Allocation

Participants will be randomly assigned 1:1 between the two interventions. Randomisation will occur using Randomize.net, which is an online, FDA 21 CFR Part 11-compliant service with 24/7 access. Each new participant will be sequentially assigned to a particular treatment group through adaptive randomisation with minimisation. Minimisation is a dynamic randomisation algorithm designed to minimise imbalance of prognostic covariates between treatment arms.[52 53] The randomisation algorithm considers the participant's specific covariates and the covariates of previously randomised participants. To do this, an 'imbalance score' is calculated for each treatment arm in real-time, and the treatment arm with the lowest imbalance score is assigned to the new participant.[52 53] Based on prior work of the investigative team and others, buprenorphine treatment status (new vs continuing), age, sex assigned at birth, race/ethnicity, concomitant medications and clinic type (office-based vs OTP) are important covariates and will be included in the minimisation algorithm. Office-based opioid treatment (OBOT) refers to OUD treatment provided by an outpatient provider practising outside of a licensed OTP. This can occur in a number of treatment settings including primary care or specialised addiction medicine practices.[54 55] OTPs are federally regulated and must follow specific guidelines to receive accreditation. Buprenorphine treatment for OUD is available in both OBOT and OTP settings in the USA. Due to the small sample size, standard stratified randomisation was considered less ideal (ie, small strata), and simple randomisation would risk an imbalance of important covariates.

Blinding (masking)

Participants, providers and research assistants cannot be blinded to participants' intervention assignment. However, laboratory staff and staff conducting the administrative data linkages will be blinded to the intervention assignment.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection

Enrolment and follow-up data will be collected at baseline, and at 1, 3 and 6 months after enrolment. Study visits will be scheduled during the participants regularly scheduled appointments to promote participant retention. If patients miss an appointment, we will attempt to reach them to schedule the study follow-up.

Study-specific data will be collected using Qualtrics software, an online platform designed to support data capture for research studies. This software is located on a secure, password-protected server with automated backup. Qualtrics will be used to collect baseline and follow-up quantitative questionnaires administered at study visits, as well as enter select clinical data at the study sites (eg, intervention assignment, treatment details and UDS and fentanyl test strip results). Questionnaires will be completed by participants on a tablet computer with a cellular data plan. Study research assistants may assist participants with completion of the questionnaires, as needed. Additionally, data for the primary outcome and the exploratory outcome will be collected using statewide administrative databases at the Rhode Island Department of Health; the Rhode Island Department of Behavioral Healthcare, Developmental Disabilities and Hospitals and the Rhode Island Department of Corrections.

Data management

Brown University will be the central location for data management. Qualtrics data will be linked to administrative data sources using deterministic linkage procedures based on name and date of birth. This linkage approach has generally performed well in Rhode Island, as data

quality is relatively high and the state has a relatively small population (approximately 1 096 000 residents). If a deterministic record linkage is not sufficiently accurate, we will use standard probabilistic record linkage procedures (eg, fuzzy matching).

Statistical methods

Interim futility analyses

We will conduct two rounds of interim analyses to inform whether the clinical trial may be stopped early for futility due to evidence of no treatment effect, an insufficient number of participants with the study outcome for meaningful analysis, or the inability to enrol a sufficient sample size for meaningful analysis. The use of administrative data for objective measurement of the primary outcome will avoid substantial missing data that can lead to early stopping for futility in some trials.

The interim futility analyses will be completed when the trial is one-third and two-thirds complete (ie, when n=84 and n=167 participants have completed study follow-up, respectively). Each round of interim futility analyses will consider the trial's 'conditional power' for detecting a statistically significant difference in retention in treatment (primary outcome) between the randomisation arms, if one truly exists, across a range of scenarios.[56] The scenarios will incorporate the data collected thus far, along with varied assumptions about the data that will be collected in the future including observation of (1) the original hypothesised effect (45% vs 60%), (2) no difference (45% vs 45%), (3) the trend based on the data collected thus far and (4) an optimistic trend (45% vs 70%). If the trial's conditional power for any scenario drops below 20%, the data and safety monitoring board (DSMB) will consider recommending early stopping for futility. When making their recommendation, the DSMB will consider the conditional power and other relevant factors (eg, findings from other studies, the potential need for more safety data, the extent of data quality control for the interim analyses, underlying study design assumptions and the recruitment rate).

Final analyses

We will use an intention-to-treat approach for all analyses in order to estimate the average treatment effect and avoid potential problems inherent in following only intervention completers (eg, self-selection effects, decreased generalisability). Baseline characteristics (eg, demographics, recent drug use and recent treatment experience) that are imbalanced across intervention arms will be included as covariates, as appropriate.[57–59] A 'per-protocol' sensitivity analysis will be conducted for each outcome among only those who maintain the randomly assigned buprenorphine dose.

For the primary outcome, we will compare the percentage of participants in each intervention arm who are retained in buprenorphine treatment at 6 months postrandomisation using a χ^2 test. A log-binomial regression model will also be used to estimate the independent effect of the intervention arm on retention in treatment, adjusting for any baseline covariates as described above.

For the secondary outcomes (treatment response based on use of non-prescribed opioids and control of cravings at 6 months postrandomisation), we will repeat the analyses outlined above. We will also explore differences between treatment arms in the count of monthly follow-up visits with use of non-prescribed opioids using Poisson regression. Additionally, we will explore differences between treatment arms in control of cravings as a continuous measure using linear regression. Finally, the same set of analyses will be used to explore potential differences in non-prescribed opioid use and control of cravings by treatment arm at 1 month and 3 months postrandomisation.

Finally, for our exploratory outcome (non-fatal or fatal opioid overdose within the 12 months postrandomisation), we will compare the percentage and rate of participants in each treatment arm with a non-fatal or fatal opioid overdose in the 12 months postrandomisation. We will also estimate the time to non-fatal or fatal opioid overdose by treatment arm using survival analyses. Participants with no opioid overdose will be administratively censored at the end of the 12-month period. We will use the Kaplan-Meier method to visualise the time to first opioid overdose, and Breslow's method to test for differences by arm. Breslow's method was chosen as it gives greater emphasis to earlier overdoses, which have greater clinical significance. Finally, a Cox proportional hazards model will be used to estimate the association of interest, adjusting for baseline characteristics as needed. We will also extend the Cox model approach for recurrent-event analyses, as participants may experience multiple opioid overdoses during follow-up.

METHODS: MONITORING

Data and safety monitoring

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including emergency medicine physicians. Members of the DSMB will be independent of the research team and free of conflicts of interest. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organisational meeting of the DSMB. The DSMB will meet with the co-PIs and study coordinator quarterly to review protocol adherence and assess safety and effectiveness data for each treatment arm of the trial. The study investigators will monitor the trial for adverse events that change the study risk level. If an adverse event occurs which changes the study risk level, the investigators will immediately report this event to the institutional review board. Additionally, the DSMB will be notified within 24 hours of any serious adverse events that could possibly have a relationship with the study. The DSMB will convene at the earliest possible time, and no more than 30 days from the time of notification, to discuss the adverse event. Since the study drug, buprenorphine,

is FDA approved for treatment of OUD, and the study drug daily dosage range proposed for use in the trial is regularly used in clinical practice, the investigators do not anticipate any unusual risks to participants in this trial. All research staff will be trained in appropriate procedures to recognise signs of distress for those participating in the study. Though this trial does not assess suicidality, the research staff will use a depression/suicide algorithm in the event a participant is distressed.

Dose and medication changes

Transitions to other buprenorphine doses, naltrexone, methadone and inpatient or residential treatment during study follow-up will be documented as dose or treatment changes. We will identify such transitions using study records from the enrolment site, as well as PDMP data (other buprenorphine doses and naltrexone treatment) and data from the Rhode Island Department of Behavioral Healthcare, Developmental Disabilities and Hospitals (methadone and inpatient or residential treatment). Dose changes will be permitted if clinically required for patient safety.

Harms

This trial will use the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, whether or not the occurrence is considered intervention related.[60]

ETHICS AND DISSEMINATION

Research ethics approval

This protocol was approved by the Brown Institutional Review Board (application STUDY00000075).

Protocol amendments

Modifications to the protocol that may impact the conduct of the trial, potential benefits to participants, participant safety, or the study objectives, design, population, sample size, or procedures will require an amendment.

Consent

Trained research assistants will discuss the trial with potential participants and provide the consent form for their review. Potential participants will have opportunities throughout the process to ask questions and request clarifications. Research assistants will ensure that potential participants understand the requirements of the study and that their participation is voluntary. Following this process, research assistants will obtain written informed consent from interested potential participants. The consent form is available in online supplemental appendix.

Confidentiality

Trial participants' privacy is protected under a certificate of confidentiality issued by the National Institutes of Health. The study data entry and study management systems used by Brown University research staff will be secured and password protected. Participants' contact information will be securely stored at each clinical site for internal use during the study. Individual participants and their research data will be identified by a unique study identification number. Paper forms will be stored in locked cabinets, and informed consent forms with identifying information will be stored separately. At the end of the study, all study databases will be deidentified and securely stored for at least 5 years.

Access to data

The study sponsor (the National Institutes of Health) and select staff at Brown University will have access to study data for routine audits and to ensure compliance with relevant policies and regulations.

Dissemination policy

This trial is registered at ClinicalTrials.gov (NCT06316830), and a summary of the trial results will be shared on their platform when available. Results from the trial will also be shared at scientific meetings and submitted for publication in peer-reviewed journals.

Reproducible research

Deidentified data will be made available on request in accordance with the policies and procedures of the Brown University and Rhode Island Department of Health Institutional Review Boards and collaborating state and local institutions.

DISCUSSION

Clinicians are prescribing higher doses of buprenorphine for patients with a history of fentanyl use in response to clinical experience and reports that current dosing strategies are insufficient to control cravings and prevent withdrawal. However, there is still insufficient evidence to guide clinical practice and inform updated dosing recommendations in response to high rates of fentanyl use among patients with OUD. Patients and healthcare providers often face insurance or health system barriers when attempting to prescribe higher doses of buprenorphine for OUD including set dosing limits or the requirement of prior authorisation. This trial will provide novel and rigorous evidence regarding the effectiveness of a high buprenorphine maintenance dose for patients with fentanyl use to inform best practices and treatment guidelines.

The trial will benefit from a comprehensive data sharing framework between key state agencies and academic researchers in Rhode Island, which was developed and is maintained as a part of the statewide strategic plan to respond to the overdose crisis.[61] This data sharing framework was essential for the investigators' completion of the retrospective study to inform this trial[27] and will facilitate objective ascertainment of the primary trial outcome (treatment retention) and a critical exploratory

trial outcome (non-fatal or fatal opioid overdose), even among participants who are no longer in care at the enrolment site.

The trial findings will need to be interpreted in the context of some limitations. First, while variation across providers in the initial dosing process and potential adjustments to the maintenance dose are important for patient safety and understanding real-world effectiveness, it may lead to heterogeneity in patient outcomes. It is possible that the findings would differ with tight control of prescribing practices. Second, the trial will provide evidence for a high maintenance daily dose of 24 mg, though some providers prescribe doses of up to 32 mg.[26] We will not randomise participants to doses of more than 24 mg due to insufficient preliminary evidence regarding effectiveness. In our recent retrospective study, only 13 patients (0.2%) were prescribed a dose of more than 24 mg, compared with 668 patients (10%) who received a maintenance dose of 24 mg.[27] Those data combined with guidance from the trial's expert panel, which recommends focusing on 16 mg and 24 mg doses as these are the most common doses prescribed in clinical practice, and the existence of other ongoing studies of higher doses (32 mg)[46] were weighed when determining the high-dose treatment arm. However, consideration of doses of more than 24 mg is an important area for future work. Third, this trial focuses on English-speaking patients, and socio-cultural factors may impact the generalisability of the findings to other populations.

To our knowledge, this is the first trial designed to evaluate the effectiveness of a high 24 mg maintenance daily dose of buprenorphine compared with the standard 16 mg dose to improve retention in treatment, reduce use of non-prescribed opioids, decrease cravings and prevent opioid overdose. The trial will provide critically needed evidence to inform clinical practice and treatment guidelines for patients who use fentanyl. In the midst of soaring overdose rates and widespread availability of fentanyl, updating buprenorphine dosing strategies may be an effective means to improve retention in treatment, reduce non-prescribed fentanyl use, decrease cravings and prevent opioid overdose.

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REFERENCES

1 Jalal H, Buchanich JM, Roberts MS, *et al*. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science* 2018;361:eaau1184.
2 Ahmad F, Cisewski J, Rossen L, *et al*. Provisional drug overdose death counts. Available: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm [Accessed 1 Sep 2024].
3 Olfson M, Zhang VS, Schoenbaum M, *et al*. Trends in Buprenorphine Treatment in the United States, 2009-2018. *JAMA* 2020;323:276–7.
4 Krawczyk N, Mojtabai R, Stuart EA, *et al*. Opioid agonist treatment and fatal overdose risk in a state-wide US population receiving opioid use disorder services. *Addiction* 2020;115:1683–94.
5 Sordo L, Barrio G, Bravo MJ, *et al*. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017;357:j1550.
6 Wakeman SE, Larochelle MR, Ameli O, *et al*. Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. *JAMA Netw Open* 2020;3:e1920622.
7 Mattick RP, Breen C, Kimber J, *et al*. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014;2014:CD002207.
8 Edelman EJ, Chantarat T, Caffrey S, *et al*. The impact of buprenorphine/naloxone treatment on HIV risk behaviors among HIV-infected, opioid-dependent patients. *Drug Alcohol Depend* 2014;139:79–85.
9 Weiss L, Botsko M, Egan J, *et al*. Integrating buprenorphine treatment into hiv clinical care. Poster Presentation at the XVII International AIDS Conference 2008; Mexico City, Mexico.
10 Jacobs P, Ang A, Hillhouse MP, *et al*. Treatment outcomes in opioid dependent patients with different buprenorphine/naloxone induction dosing patterns and trajectories. *Am J Addict* 2015;24:667–75.
11 Gryczynski J, Nichols H, Schwartz RP, *et al*. Fentanyl exposure and preferences among individuals starting treatment for opioid use disorder. *Drug Alcohol Depend* 2019;204:107515.

12 Walker EA, Young AM. Differential tolerance to antinociceptive effects of mu opioids during repeated treatment with etonitazene, morphine, or buprenorphine in rats. *Psychopharmacology (Berl)* 2001;154:131–42.
13 Winger G, Woods JH. The effects of chronic morphine on behavior reinforced by several opioids or by cocaine in rhesus monkeys. *Drug Alcohol Depend* 2001;62:181–9.
14 Hjelmström P, Banke Nordbeck E, Tiberg F. Optimal dose of buprenorphine in opioid use disorder treatment: a review of pharmacodynamic and efficacy data. *Drug Dev Ind Pharm* 2020;46:1–7.
15 Comer SD, Cahill CM. Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. *Neurosci Biobehav Rev* 2019;106:49–57.
16 Greenwald M, Johanson C-E, Bueller J, *et al*. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. *Biol Psychiatry* 2007;61:101–10.
17 Greenwald MK, Johanson C-E, Moody DE, *et al*. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 2003;28:2000–9.
18 Greenwald MK, Schuh KJ, Hopper JA, *et al*. Effects of buprenorphine sublingual tablet maintenance on opioid drug-seeking behavior by humans. *Psychopharmacology (Berl)* 2002;160:344–52.
19 Rosen MI, Wallace EA, McMahon TJ, *et al*. Buprenorphine: duration of blockade of effects of intramuscular hydromorphone. *Drug Alcohol Depend* 1994;35:141–9.
20 Baca-Atlas MH, Williams JB. Treatment of Opioid Use Disorder Attributed to Fentanyl With High-Dose Buprenorphine: A Case Report. *J Clin Psychopharmacol* 2021;41:83–5.
21 Antoine D, Huhn AS, Strain EC, *et al*. Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone. *Am J Addict* 2021;30:83–7.
22 Greenwald MK, Herring AA, Perrone J, *et al*. A Neuropharmacological Model to Explain Buprenorphine Induction Challenges. *Ann Emerg Med* 2022;80:509–24.
23 Bisaga A. What should clinicians do as fentanyl replaces heroin? *Addiction* 2019;114:782–3.
24 Silverstein SM, Daniulaityte R, Martins SS, *et al*. "Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl. *Int J Drug Policy* 2019;74:76–83.
25 Danilewitz M, McLean M. High-dose buprenorphine for treatment of high potency opioid use disorder. *Drug Alcohol Rev* 2020;39:135–7.
26 Grande LA, Cundiff D, Greenwald MK, *et al*. Evidence on Buprenorphine Dose Limits: A Review. *J Addict Med* 2023;17:509–16.
27 Chambers LC, Hallowell BD, Zullo AR, *et al*. Buprenorphine Dose and Time to Discontinuation Among Patients With Opioid Use Disorder in the Era of Fentanyl. *JAMA Netw Open* 2023;6:e2334540.
28 Substance Abuse and Mental Health Services Administration. Table 90a - substance use, perceptions of great risk, and mental health measures: among people aged 12 or older in rhode island; by age group, percentages. 2021. Available: https://www.samhsa.gov/data/sites/default/files/reports/rpt39467/2021NSDUHsaeSpecificStatesTabs122022_0/NSDUHsaeRhodeIsland2021.pdf [Accessed 1 Sep 2024].
29 Substance Abuse and Mental Health Services Administration. Table 90b - substance use disorder and treatment in the past year: among people aged 12 or older in rhode island; by age group, percentages. 2021. Available: https://www.samhsa.gov/data/sites/default/files/reports/rpt39467/2021NSDUHsaeSpecificStatesTabs122022_0/NSDUHsaeRhodeIsland2021.pdf [Accessed 1 Sep 2024].
30 US Centers for Disease Control and Prevention. Drug overdose mortality by state. Available: https://www.cdc.gov/nchs/pressroom/sosmap/drug_poisoning_mortality/drug_poisoning.htm [Accessed 1 Sep 2024].
31 Prevent Overdose RI. Overdose death data. Available: https://preventoverdoseri.org/overdose-deaths/ [Accessed 1 Sep 2024].
32 Wightman RS, Perrone J, Scagos R, *et al*. Opioid Overdose Deaths with Buprenorphine Detected in Postmortem Toxicology: a Retrospective Analysis. *J Med Toxicol* 2021;17:10–5.
33 Weidele HR, Hallowell BD. Accidental drug overdose deaths in Rhode Island: January 1, 2019-December 31, 2023. *R I Med J* 2024;107:61–3.
34 Neighborhood Health Plan of Rhode Island. Neighborhood integrity (medicare-medicaid plan) 2024 formulary: list of covered drugs. Available: https://www.nhpri.org/wp-content/uploads/2024/01/2024-MMP-English-Formulary.pdf [Accessed 1 Sep 2024].
35 Hirchak KA, Amiri S, Kordas G, *et al*. Variations in national availability of waivered buprenorphine prescribers by racial and ethnic composition of zip codes. *Subst Abuse Treat Prev Policy* 2022;17:41.
36 Dunphy CC, Zhang K, Xu L, *et al*. Racial–Ethnic Disparities of Buprenorphine and Vivitrol Receipt in Medicaid. *Am J Prev Med* 2022;63:717–25.
37 US Food and Drug Administration. SUBOXONE sublingual tablets label. 2018. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020733s022lbl.pdf [Accessed 1 Sep 2024].
38 US Food and Drug Administration. SUBOXONE sublingual film label. 2010. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf [Accessed 1 Sep 2024].
39 US Food and Drug Administration. SUBUTEX sublingual tablets label. 2018. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020732s018lbl.pdf [Accessed 1 Sep 2024].
40 Substance Abuse and Mental Health Services Administration. Buprenorphine quick start guide. Available: https://www.samhsa.gov/sites/default/files/quick-start-guide.pdf [Accessed 1 Sep 2024].
41 Weimer MB, Herring AA, Kawasaki SS, *et al*. ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids. *J Addict Med* 2023;17:632–9.
42 Moss LM, Algera MH, Dobbins R, *et al*. Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: A placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients. *PLoS One* 2022;17:e0256752.
43 McHugh RK, Murray HW, Hearon BA, *et al*. Predictors of Dropout from Psychosocial Treatment in Opioid-Dependent Outpatients. *American J Addict* 2013;22:18–22.
44 Warden D, Subramaniam GA, Carmody T, *et al*. Predictors of attrition with buprenorphine/naloxone treatment in opioid dependent youth. *Addict Behav* 2012;37:1046–53.
45 Fishman M, Vo HT, Burgower R, *et al*. Treatment Trajectories During and After a Medication Trial for Opioid Use Disorder: Moving from Research as Usual to Treatment as Usual. *J Addict Med* 2020;14:331–6.
46 Nunes E, Rotrosen J, Weiss R. ClinicalTrials.gov: optimizing retention, duration and discontinuation strategies for opioid use disorder pharmacotherapy (rdd) (nct04464980). Available: https://clinicaltrials.gov/study/NCT04464980 [Accessed 1 Sep 2024].
47 Fals-Stewart W, O'Farrell TJ, Freitas TT, *et al*. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *J Consult Clin Psychol* 2000;68:134–44.
48 Lofwall MR, Walsh SL, Nunes EV, *et al*. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. *JAMA Intern Med* 2018;178:764–73.
49 McHugh RK, Fitzmaurice GM, Carroll KM, *et al*. Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. *Drug Alcohol Depend* 2014;145:121–6.
50 Hallowell BD, Chambers LC, Rhodes J, *et al*. Using Emergency Medical Services Data to Monitor Nonfatal Opioid Overdoses in Real Time : Development, Validation, and Use of a Case Definition, Rhode Island, 2018. *Public Health Rep* 2021;136:40S–46S.
51 Rhode Island Department of Health. Rules and regulations pertaining to opioid overdose prevention and reporting. 2014. Available: https://risos-apa-production-public.s3.amazonaws.com/DOH/7886.pdf [Accessed 1 Sep 2024].
52 Weng H, Bateman R, Morris JC, *et al*. Validity and power of minimization algorithm in longitudinal analysis of clinical trials. *Biostat Epidemiol* 2017;1:59–77.
53 Xiao L, Lavori PW, Wilson SR, *et al*. Comparison of dynamic block randomization and minimization in randomized trials: a simulation study. *Clin Trials* 2011;8:59–69.
54 Cope K, DeMicco J, Salib J, *et al*. Three-year Retention Rates With Office-based Treatment of Buprenorphine for Opioid Use Disorder in a Private Family Medicine Practice. *J Addict Med* 2022;16:716–21.
55 Gunderson EW, Fiellin DA. Office-based maintenance treatment of opioid dependence: how does it compare with traditional approaches? *CNS Drugs* 2008;22:99–111.
56 Ellenberg SS, Shaw PA. Early Termination of Clinical Trials for Futility - Considerations for a Data and Safety Monitoring Board. *NEJM Evid* 2022;1.
57 Hernández AV, Steyerberg EW, Habbema JDF. Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements. *J Clin Epidemiol* 2004;57:454–60.
58 Austin PC, Manca A, Zwarenstein M, *et al*. A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals. *J Clin Epidemiol* 2010;63:142–53.

59 Saquib N, Saquib J, Ioannidis JPA. Practices and impact of primary outcome adjustment in randomized controlled trials: meta-epidemiologic study. *BMJ* 2013;347:f4313.
60 Code of Federal Regulations. 21 cfr part 312.32: ind safety reporting. Available: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312 [Accessed 1 Sep 2024].
61 Rhode Island Governor's Overdose Prevention and Intervention Task Force. Rhode island's strategic plan on addiction and overdose: four strategies to alter the course of an epidemic. 2015. Available: https://health.ri.gov/news/temp/RhodeIslandsStrategicPlanOnAddictionAndOverdose.pdf [Accessed 1 Sep 2024].