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A clinical protocol of a comparative effectiveness trial of extended-release naltrexone versus extended-release buprenorphine with individuals leaving jail☆

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ABSTRACT

This study is a randomized, open label, controlled trial of extended-release buprenorphine (XR-B; BRIXADI™ formulation) versus extended-release naltrexone (XR-NTX) in Maryland jails. A 7-site, open-label, equivalence design will randomly assign 240 adults with a history of opioid use disorder (OUD), stratified by gender and jail, who are nearing release to one of two treatment arms: 1) XR-B in jail or 2) XR-NTX in jail, both followed by 6 monthly injections postrelease at a community treatment program. The primary aim is to determine the rate of pharmacotherapy adherence (number of monthly injections received) of XR-B compared to XR-NTX. The proposed study is innovative because it will be the first randomized clinical trial in the U.S. assessing the effectiveness of receiving XR-B vs. XR-NTX in county jails. The public health impact of the study will be highly significant and far-reaching because most individuals with OUD do not receive treatment while incarcerated, thereby substantially raising their likelihood of relapse to drug use, overdose death, and re-incarceration. Understanding how to expand acceptance of medications for OUD in jails, particularly extended-release medications, and supporting treatment engagement and medication adherence in transition to the community, has far-reaching implications for improving treatment access and success in this population.

1. Introduction

Opioid use disorder (OUD) represents a significant public health problem in the U.S., with heroin use and prescription opioid misuse rising significantly over the past 16 years (Lipari & Hughes, 2015; O'Donnell et al., 2017; Volkow & McLellan, 2016) and opioid overdose deaths reaching epidemic proportions (Hedegaard et al., 2018). Incarcerated individuals in the U.S. have disproportionately higher rates of OUDs than the general population (Dolan et al., 2007; Fazel et al., 2006; Kanato, 2008; Kastelic et al., 2009; Kinlock et al., 2011), but very few receive adequate treatment (Brinkley-Rubinstein et al., 2018; Chandler et al., 2009; Farahmand et al., 2017; Krawczyk et al., 2017), and most inmates with OUDs remain untreated (Kinlock et al., 2015; Wakeman & Rich, 2015). There is a growing body of evidence supporting the effectiveness of medications for opioid use disorders (MOUDs) in jail and prison settings in the U.S. (Garcia et al., 2007; Gordon et al., 2008;

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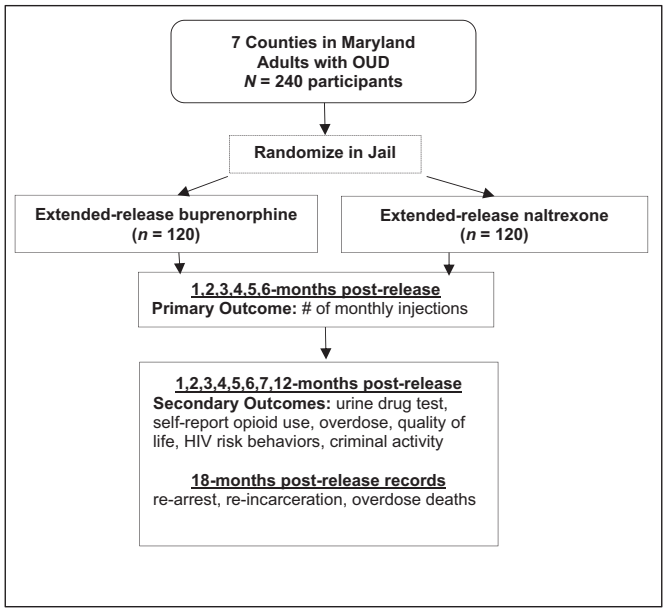

Fig. 1. Study schematic.

Gordon et al., 2014; Gordon et al., 2017; Kinlock et al., 2009; Magura et al., 2009; McKenzie et al., 2012; Rich et al., 2015; Springer et al., 2018; Tomasino et al., 2001; Zaller et al., 2013). However, many correctional administrators remain reluctant to offer opioid agonist pharmacotherapy in their facilities, largely because of their preference for "drug-free" interventions (Friedmann et al., 2012; Nunn et al., 2009; Rich et al., 2005; Zaller et al., 2013), numerous state and federal regulations (Moore et al., 2018), and concerns about diversion of medication, especially with sublingual buprenorphine (Magura et al., 2009). Despite the evidence of effectiveness, only 0.4% and 0.9% of eligible state prisoners and sentenced jail inmates, respectively, reported receiving an MOUD (Bronson et al., 2017; Fox, 2015).

1.1. Extended-release injectable buprenorphine and naltrexone

BRIXADI™ is a depot subcutaneous injection that the Food and Drug Administration (FDA) recently awarded tentative approval for OUD treatment, with expected commercial release in early 2021. It provides sustained buprenorphine release in both weekly and monthly formulations with several available dosages. Administration ensures delivery and medication adherence, while potentially minimizing risks of diversion, misuse, and accidental exposure. BRIXADI™ has been evaluated in 7 phase 1–3 clinical trials (Albayaty et al., 2017; Haasen et al., 2017; Lofwall et al., 2018; Walsh et al., 2017) and its safety has been found to be consistent with sublingual buprenorphine, with the exception of mild/moderate injection-site adverse events (Lofwall et al., 2018). With tentative approval, the FDA has concluded that BRIXADI™ has met all required quality, safety, and efficacy standards necessary for approval but is not eligible for marketing in the U.S. until December 2020 because of exclusivity considerations.

VIVITROL®, an extended-release injectable naltrexone, is a promising form of treatment for individuals in jail (Lee et al., 2015). It blocks the intoxicating and reinforcing effects of opioids, but has no opioid-like effects. It is administered by intramuscular (IM) gluteal injection every 4 weeks. In 2010, the FDA approved it for the prevention of relapse to opioid dependence, following opioid detoxification.

2. Materials and methods

2.1. Study design

This study is a multi-site randomized controlled trial of extended-release buprenorphine (XR-B; BRIXADI™) versus extended-release naltrexone (XR-NTX; VIVITROL®) in Maryland jails. A 7-site, open-label, equivalence design will randomly assign 240 adults with a history of OUD stratified by gender and jail site, who are nearing release, to one of two treatment arms: XR-B in jail, followed by 6 monthly injections postrelease at a community treatment program; or XR-NTX in jail followed by 6 monthly injections postrelease at a community treatment program. The study will evaluate all participants in jail and at 1-, 2-, 3-, 4-, 5-, 6-, 7- (safety visit) and 12-months after release from jail (see Fig. 1 [Study Schematic]). We will also gather official records from jails, state prisons, and state vital statistics for re-arrest, re-incarceration, and overdose deaths at 18-months postrelease. The study will be conducted under an IND from the FDA due to the complex regulatory status of BRIXADI™.

2.2. Research questions, outcomes, and hypotheses

The primary research question is to determine the effectiveness of XR-B compared to XR-NTX in terms of: (a) pharmacotherapy adherence (i.e., number of monthly injections received). Secondary outcomes of interest include: (b) illicit opioid urine screening test results; (c) self-reported illicit opioid use; (d) overdose events (nonfatal and fatal); (e) quality of life (i. physical health; ii. mental health); (f) HIV risk behaviors (i. sexual behavior; ii. needle use or sharing); and (g) criminal activity (i. crime days; ii. re-arrest; iii. re-incarceration). The study will also calculate the cost to the correctional health system of implementing and continually managing an XR-B or XR-NTX program, and estimate the cost-effectiveness of each strategy from a state policy-maker and societal perspective. We hypothesize that the XR-B treatment arm will display similar levels of pharmacotherapy adherence compared to the XR-NTX treatment arm, and therefore anticipate similar levels of downstream health care and criminal justice resource utilization, school and workplace productivity, time abstinent from opioids, and quality-adjusted life-years (QALYs), in which case the relative economic value of each strategy would largely depend on the cost associated with the corresponding induction process, and the cost of each medication.

2.3. Study sites

2.3.1. County jails, community treatment clinics, and health departments

Seven geographically diverse counties in Maryland are participating in this trial: three counties are located in the Baltimore region, two counties on the eastern shore, one county in the southern region, and one county is in the DC region. Two of the counties have multiple jails. The jail censuses range from <80 to >600 individuals. Jail censuses have been reduced due to COVID-19 and sentencing reform. There was a range of existing MOUD programs across the 7 participating counties (jails) consisting of the following: 1) offered all three FDA approved medications, 2) offered VIVITROL only, 3) offered methadone and VIVITROL, and 4) no medication. The study chose community treatment programs and/or health department treatment sites from each county based on their availability and established relationships for accepting treatment referrals for individuals released from jail.

2.4. Eligibility criteria

Individuals in jail who are scheduled to be released within 120 days, meet DSM-5 criteria of opioid use disorder, and are willing to take either XR-B and/or XR-NTX are eligible for participation. All individuals will undergo a history and physical to determine general health and we will exclude individuals with active medical illnesses that may preclude

involvement such as LFTs > 4 times normal or untreated psychiatric disorders. Individuals currently enrolled in a jail-based MOUD program will not be eligible (see below for a more detailed list).

Inclusion criteria are: (1) Adult inmates at participating jails who are eligible for release within 120 days; (2) history of OUD (i.e., meeting DSM-5 criteria of moderate or severe OUD at the time of incarceration; individuals not meeting the OUD criterion will be eligible if they were treated in an opioid agonist treatment program during the year before incarceration); (3) suitability for XR-B and/or XR-NTX treatment as determined by medical evaluation; (4) willingness to enroll in XR-B or XR-NTX treatment in jail; and (5) Planning to live in one of the seven participating or surrounding counties.

Exclusion criteria are: (1) Liver function test levels greater than 4 times normal; (2) active medical illness that may make participation hazardous; (3) conditions or medications that may predispose to QTc prolongation (e.g. hypokalemia [low potassium levels in blood] and macrolide antibiotics [azithromycin, clarithromycin, and erythromycin]); (4) untreated psychiatric disorder that may make participation hazardous; (5) history of allergic reaction to naltrexone or buprenorphine; (6) current chronic pain diagnosis for which opioids are prescribed; (7) pregnancy; (8) breast-feeding; (9) suicidal ideation (within the past 6 months); (10) Body Mass Index (BMI) > 40; (11) inability to pass a study enrollment quiz; (12) currently enrolled in jail-based MOUD pharmacotherapy; and (13) enrolled in a methadone treatment program in the past 30 days.

2.5. Recruitment, informed consent, screening, and randomization

Research assistants (RAs) will work with jail staff at the county jails to identify individuals interested in participating. We will not engage with individuals in jail who are actively going through withdrawal or the detoxification process. After signing the informed consent form, participants must pass an informed consent quiz, to ensure comprehension, and the study medical provider will perform a medical evaluation. Once we confirm eligibility, they will be randomized to one of the two study arms (XR-B or XR-NTX), using a stratified block randomization procedure with random block sizes (Domanski & McKinlay, 2009), such that half will be assigned to the XR-B condition ($n = 120$), and half to the XR-NTX condition ($n = 120$). This randomization process ensures that both male and female participants will have an equal chance of being assigned to either condition. Participants randomized to XR-B will begin dose induction immediately. Participants randomized to XR-NTX must be opiate free for 10 days before initiation of study drug, which self-report and urine drug screen will determine.

2.6. Data management

RAs will complete baseline study assessments (in jail) and follow-up assessments using paper forms due to differing local jail policies on electronics and inconsistent Internet access. An RA will enter completed forms into REDCap, a web-based application for managing electronic databases, within 48 h.

3. Regulatory affairs and data and safety monitoring

3.1. Approvals and certification

The Western Institutional Review Board (WIRB) and Weill Cornell Medicine Institutional Review Boards approved the study. The U.S. Office of Human Research Protections (OHRP) also approved the study protocol. We registered the study at ClinicalTrials.gov (NCT04408313).

3.2. Data and safety monitoring

A NIDA Data and Safety Monitoring Board (DSMB) is monitoring the study. The WIRB, DSMB, and NIDA (the study sponsor) will monitor recruitment, retention, and study safety. We will report all serious adverse events related to study procedures to the WIRB, DSMB, and NIDA.

4. Interventions

4.1. Study arm. Pre-release and postrelease extended-release buprenorphine

The research medical team will conduct all in-jail screening, history and physical, blood draw, and medication administration. XR-B comes in varying dosage strengths, which include weekly doses of 8 mg, 16 mg, 24 mg, and 32 mg; and monthly doses of 64 mg, 96 mg, and 128 mg. We will induct participants randomized to XR-B using sublingual (SL) buprenorphine/naloxone doses of 2 mg for 3–5 days, then 4 mg for 3–5 days. Participants must be on 4 mg SL dose prior to the first XR-B injection. The research medical team will base induction speed on the participant's response to SL buprenorphine/naloxone. The research medical team will give an 8 mg dose of XR-B between days 7 and 11 of dosing, depending on the duration of the SL buprenorphine/naloxone induction period. During week 3 of dosing, the prescriber will give either an 8 mg or a 16 mg weekly dose of XR-B, based on the participant's response to the previous dose. Alternatively, a corresponding monthly dose of 64 mg may be administered during week 3 or thereafter, depending on the clinical judgment of the prescriber and expected timing of the participant's release.

During week 4 of dosing, the team will give either a 16 mg or 24 mg dose of XR-B if a monthly dose of 64 mg of XR-B has not already been administered. During week 5 of dosing, the medical team will give a 16 mg, 24 mg, or 32 mg dose if they have not already administered a monthly dose of XR-B. In all cases, the team will base the dose selected on the participant's response to the previous weeks' dose. The medical team will individualize participants' titrations of XR-B, with a goal of switching to monthly dosing of 96 mg or 128 mg in the week prior to their release. Participants who do not receive a 24 mg or 32 mg dose will receive a 64 mg monthly dose prior to release; however, we will endeavor to get participants on the 96 mg or 128 mg dose, as there is a lack of opioid blockade data for the 64 mg dose. We will offer participants a total of 7 monthly (1 in jail and 6 in the community) injections of the 64 mg, 96 mg, or the 128 mg dose, based on clinical judgment. The first injection of 96 mg or 128 mg may not provide opioid blockade through the initial 28 day dosing interval, but should provide blockade for the 28 day period with subsequent doses. Participants receiving monthly doses of XR-B may have their doses adjusted at the request of the participant or the judgment of the study physician/nurse practitioner.

4.2. Study arms: pre-release and postrelease extended-release naltrexone

Participants will receive one to two XR-NTX injections prior to release. The research medical team will administer extended-release, injectable naltrexone by intramuscular injection to the buttocks (alternating sides monthly), at a volume of 4 cc (380 mg of naltrexone). Participants who deny opioid use in the past 10 days and who provide a urine specimen that tests negative for opioids will receive naloxone followed by a low dose of oral naltrexone (25 mg) to further determine whether they will be able to tolerate extended-release naltrexone.

4.3. Treatment coordination for both arms

The research team will help to facilitate warm hand-offs to community treatment programs, and use assertive outreach techniques to promote ongoing treatment engagement. The research team will collaborate with the community treatment programs to coordinate and provide ongoing monthly injections. The study will provide medication and medical monitoring as a supplement to other standard treatment-as-

	In Jail		In Community								
	Pre-screening	Visit 1 and titration	Visit 2: 1mo	Visit 3: 2mo	Visit 4: 3mo	Visit 5: 4mo	Visit 6: 5mo	Visit 7: 6mo	Visit 8: 7mo safety	Visit 9: 12mo	Records Review:18-months
Screening (DSM-5)	✓										
Informed consent	✓										
Informed consent quiz	✓										
COVID-19 screener		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Jail electronic medical record		✓									
Medical history		✓									
General physical exam		✓									
Pregnancy		✓	✓	✓	✓	✓	✓	✓	✓		
Liver enzymes		✓			✓				✓		
Hepatitis		✓			✓				✓		
SMA-6		✓			✓				✓		
HIV (optional)		✓							✓		
Vital signs		✓	✓	✓	✓	✓	✓	✓	✓		
Concomitant medications		✓	✓	✓	✓	✓	✓	✓	✓		
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓		
Urine toxicology		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Randomization		✓									
Sublingual buprenorphine		✓									
Extended-release buprenorphine		✓	✓	✓	✓	✓	✓	✓			
Naloxone challenge		✓									
Oral naltrexone		✓									
Extended-release naltrexone		✓	✓	✓	✓	✓	✓	✓			
Medical management		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Demographics		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Controlled environment		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Crime and legal		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medications for OUD		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Non-study medical & other services		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Treatment preference		✓									
Substance use history		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Opioid time line follow back		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Risk Assessment Battery		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Overdose		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Visual Analog Scale - Cravings		✓	✓	✓	✓	✓	✓	✓	✓	✓	
PROMIS		✓	✓	✓	✓	✓	✓	✓	✓	✓	
Treatment program records		✓	✓	✓	✓	✓	✓	✓	✓	✓	

Fig. 2. Schedule of activities.

usual resources. We will encourage participants to participate in psychosocial interventions at the community treatment programs, but it will not be a requirement for ongoing participation and receipt of medication. Participants who drop out and/or relapse will continue to be followed in the study, and we will encourage them to re-engage in treatment.

5. Assessments

Assessment of participants' characteristics and/or performance will involve a multidimensional set of instruments that trained research interviewers administer. Sources of information will include: (1) self-report; (2) official records; (3) urine drug screening results; and (4) treatment program records (see Fig. 2). We will pay participants in both conditions $75 for each follow-up visit ($600 total). The study will not pay participants for baseline assessments in jail due to the fact that such payments may be coercive.

6. Statistical analysis

The study will use a generalized linear model (Aitkin et al., 2005) to examine all outcomes measured once (e.g., number of injections, time to re-arrest, and time to incarceration), while the study will use a generalized linear mixed model (Littell et al., 2006; Stroup, 1999) to conduct analyses of all outcomes measured repeatedly. In addition, we will use the two one-sided test procedure (Schuirmann, 1987) to test for

equivalence between the treatment arms on three major outcomes: (1) number of injections received in the community; (2) number of positive opioid urine drug screen results; and (3) time to first re-arrest. For the economic analysis, we will combine adjusted resource costs with the adjusted effectiveness measures of time abstinent and QALYs, to create incremental cost-effectiveness ratios (ICERs) for each stakeholder perspective. We will then estimate acceptability curves to measure the uncertainty surrounding each ICER (Glick et al., 2014).

6.1. Sample size, power, and effect size

We plan to recruit 240 participants and randomize them equally into the two study arms. When calculating power for the proposed sample size (Zhu, 2017), we considered three clinically important outcomes: (1) number of injections received in the community; (2) number of positive opioid urine drug test results; (3) time to first re-arrest. We determined margins of equivalence (the region in which differences or ratios between treatment conditions are considered equivalent for the purposes of significance testing) by a top-down approach where we defined margins by what would be considered clinically significant (i.e., meaningful differences between the treatment conditions as determined by expert opinion and a review of relevant literature). We performed all power analyses assuming the proposed sample size of $N = 240$ and a type I error rate of $\alpha = 0.05$. The study team considered power resulting from these calculations satisfactory if they reached or exceeded $1 - \beta = 0.80$ (Ellis, 2010).

7. Design considerations

We considered using methadone, and a different extended-release formulation of buprenorphine (SUBLOCADE™), as potential additional study arms. However, only a specially licensed opioid treatment provider (OTP) can provide methadone, which requires a number of stringent regulations. SUBLOCADE™ lacks the dosing flexibility of XR-B, which offers weekly formulations for dose induction or augmenting monthly doses. We also considered a patient preference clinical trial, but it would have required an increased sample size and additional time to determine preference prior to the initiation of the trial, both of which we considered infeasible. We also considered the inclusion of a non-medication arm, but, based on our own research in prisons, individuals assigned to a nonmedication comparison group (Gordon et al., 2008) or a medication after release group (Gordon et al., 2014) had the worst outcomes. We elected to conduct an equivalence trial between XR-B and XR-NTX for several reasons. (1) A standard superiority trial is not appropriate for the proposed design as the bar for superiority precludes a finding of noninferiority, which is a clinically significant outcome when comparing new treatments to existing ones. (2) We do not expect there to be significant differences between XR-B and XR-NTX in terms of the primary outcomes. (3) XR-B offers several practical advantages over XR-NTX, therefore demonstrating equivalence is still clinically significant. (4) If XR-B is determined to be nonequivalent, we can conduct tests for superiority without a statistical penalty (Moyé, 2003).

8. Challenges of conducting research in jails

Initiating clinical trials in jails involves several additional steps that can be quite cumbersome. The IRB must contain a prisoner advocate, the OHRP must also approve the protocol, and the cooperation and approval of jail personnel, often including the county Sheriff and Warden, are necessary. Treatment, corrections, and research personnel must work together to ensure agreement on the basic design and implementation of the study, particularly with regard to logistics and daily operations. Without these crucial steps of collaboration, it is infeasible to evaluate the development, implementation, and effectiveness of new interventions. Finally, research has recommended that all parties involved in the research provide feedback on the unique implementation challenges, strategies to overcome barriers, and other lessons learned. These rich data will serve as a guide for subsequent corrections-treatment-research partnerships. Although research, treatment, and corrections agency personnel may have different priorities and agendas, opioid addiction and its consequences are serious public health problems that these stakeholders can reduce with careful planning and collaboration.

9. Conclusions

This study will help to evaluate the relative strengths of two different XR-MOUD treatments; help to strengthen the case for the role of OUD pharmacotherapy initiated during incarceration and continued through facilitated transition to community treatment (including the economic value proposition); contribute to understanding design and implementation best practices around justice-involved MOUD studies; and help to strengthen working partnerships among the local corrections, research, and treatment communities.

Declaration of competing interest

Braeburn Pharmaceuticals is supplying free Brixadi (extended-release buprenorphine). Michael Gordon reports support (study drug) from Alkermes and research grant support from MedicaSafe. Frank Vocci reports consultation with Braeburn Pharmaceuticals, Lyndra Pharmaceuticals, and is Co-PI on a NIH grant with Nirsum Laboratories. Marc Fishman reports consultation and grant support from Alkermes, consultation with Drug Delivery LLX, Verily Life Sciences; and grant support from MedicaSafe. Sean Murphy reports having consulted for Sandoz Inc. The other authors report no conflicts.

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