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Cocaine Use Reduction with Buprenorphine (CURB): Rationale, design, and methodology★

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Abstract

Background—Effective medications to treat cocaine dependence have not been identified. Recent pharmacotherapy trials demonstrate the potential efficacy of buprenorphine (BUP) (alone or with naltrexone) for reducing cocaine use. The National Institute on Drug Abuse Clinical Trials Network (CTN) launched the Cocaine Use Reduction with Buprenorphine (CURB) investigation to examine the safety and efficacy of sublingual BUP (as Suboxone®) in the presence of extended-release injectable naltrexone (XR-NTX, as Vivitrol®) for the treatment of cocaine dependence. This paper describes the design and rationale for this study.

Methods—This multi-site, double-blind, placebo-controlled study will randomize 300 participants across 11 sites. Participants must meet the DSM-IV criteria for cocaine dependence and past or current opioid dependence or abuse. Participants are inducted onto XR-NTX after self-reporting at least 7 days of abstinence from opioids and tolerating a naloxone challenge followed by oral naltrexone and are then randomly assigned to one of three medication conditions (4 mg

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Disclosure statement

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BUP, 16 mg BUP, or placebo) for 8 weeks. Participants receive a second injection of XR-NTX 4 weeks after the initial injection, and follow-up visits are scheduled at 1 and 3 months post-treatment. Participants receive weekly cognitive behavioral therapy (CBT). Recruitment commenced in September, 2011. Enrollment, active medication, and follow-up phases are ongoing, and recruitment is exceeding targeted enrollment rates.

Conclusions—This research using 2 medications will demonstrate whether BUP, administered in the presence of XR-NTX, reduces cocaine use in adults with cocaine dependence and opioid use disorders and will demonstrate if XR-NTX prevents development of physiologic dependence on BUP.

Keywords

Cocaine dependence; Buprenorphine; Naltrexone; Clinical Trials Network; Methods; Kappa antagonist

1. Introduction

Cocaine dependence remains a significant public health problem in the United States and throughout the world. In 2009, there were 1.6 million past-month users of cocaine in the U.S., and 1.1 million individuals age 12 or older met criteria for a cocaine use disorder. SAMHSA's 2009 National Survey of Drug Use and Health (NSDUH) estimated that 36.6 million Americans age 12 and over have used cocaine at least once in their lifetime, and 8.4 million have used crack. Approximately one in four drug-related emergency department visits involved cocaine use [1]. Only 25% of individuals in outpatient treatment programs for cocaine-related problems complete treatment [2], suggesting considerable potential for improving treatment methods for cocaine dependence. Despite considerable research efforts, effective medications to treat cocaine dependence have not been established.

One medication that shows promise in treating cocaine use disorders is buprenorphine, a partial agonist at the mu opioid receptor with kappa antagonist and ORL-1 agonist properties [3]. Though FDA approved for the treatment of opioid dependence, buprenorphine has also shown potential efficacy in reducing cocaine use among adults with opioid dependence [4–7]. In addition, evidence from prior literature suggests that buprenorphine administered in combination with naltrexone is well tolerated and may reduce cocaine use. In studies of opioid-dependent individuals receiving oral naltrexone and either 4 mg daily sublingual buprenorphine or placebo, beneficial effects of buprenorphine in reducing cocaine use were demonstrated [8,9] and appeared to be independent of effects on opioid use.

In response to the need to expand treatment options for cocaine dependence, the Cocaine Use Reduction with Buprenorphine (CURB) study was developed within the National Institute on Drug Abuse Clinical Trials Network (CTN) to examine the safety and efficacy of buprenorphine/naloxone (BUP, as Suboxone®) in the presence of extended-release naltrexone (XR-NTX, as Vivitrol®) for the treatment of cocaine dependence. This randomized, double-blind, double-dummy, placebo-controlled investigation aims to enroll 300 adults with cocaine dependence and a history of opioid abuse or dependence across 11 sites nationwide. This paper describes the rationale, design, and implementation of the CURB study, which commenced subject enrollment in 2011.

2. Study rationale and design

Preliminary findings from prior studies have demonstrated an effect of BUP in combination with naltrexone in reducing cocaine use in opioid dependent populations. The CURB protocol was developed as a randomized, double-blind, double-dummy placebo-controlled

trial to replicate and extend these findings within a primarily cocaine dependent population. Given concern about eliciting opioid dependence through BUP's partial mu-agonist action, the study was designed to include only cocaine users with concomitant opioid use disorders in order to avoid exposure of opioid-naïve individuals to BUP. To be eligible for enrollment, participants must meet DSM-IV diagnostic criteria for cocaine dependence and either: 1) past-year opioid dependence, 2) past-year opioid abuse, or 3) lifetime opioid dependence with opioid use in the past year. Though providing XR-NTX in combination with BUP is hypothesized to mitigate the risks of developing opioid dependence in this population, opioid use is assessed throughout the trial via self-report and urine drug screens, and evidence of physiologic opioid withdrawal is assessed at follow-up visits after taper off of BUP.

Since evidence of mu blockade has been shown in prior Phase I investigations of naltrexone in combination with BUP up to doses of 16 mg (Reese Jones, unpublished data, 2009), and clinical effect on cocaine use has been demonstrated in prior studies using a BUP dose of 4 mg daily (Gerra, et al., 2006), the study was designed to compare doses of 4 mg and 16 mg with placebo to investigate potential differential BUP dose effects. Naltrexone (XR-NTX) is provided to all participants in the extended-release monthly injectable formulation (Vivitrol®) to eliminate the need for daily medication dosing and improve compliance with this medication. Once inducted onto XR-NTX, participants are randomly assigned to one of three medication conditions: 4 mg BUP (BUP4+XR-NTX), 16 mg BUP (BUP16+XR-NTX), or placebo (PLB+XR-NTX) for 8 weeks of treatment. To reflect clinical practice norms, the Suboxone formulation is provided. Thrice-weekly clinic visits are scheduled with observed in-clinic BUP dosing to enhance medication adherence.

In order to safely induct participants with recent or past-year opioid use onto XR-NTX, several inclusion criteria were designed to ensure abstinence from opioids and avoid the risk of prolonged precipitated opioid withdrawal from XR-NTX including: a) self-reported absence of opioid use for at least 7 days; b) provision of opioid negative urine test; c) successful administration of naloxone challenge test; and d) tolerance of 50 mg oral naltrexone prior to XR-NTX administration. In addition, participants are excluded from the study if they: a) participated in methadone maintenance treatment within 15 days of consent, b) participated in buprenorphine maintenance treatment within 30 days of consent, c) have surgery planned during the study period, or d) require therapy with opioid analgesics during the study period.

3. Study objectives

The primary objective of the CURB study is to determine whether BUP, administered in the presence of XR-NTX, can reduce the number of cocaine use days during the evaluation period, defined as the final 30 days of active medication prior to initiation of the taper (days 25–54). Cocaine use is measured by self-report and corroborated by thrice-weekly urine drug screens. This primary objective was chosen to allow an initial stabilization period of several weeks before evaluation of medication response. Secondary objectives are to assess: 1) safety of the study conditions; 2) use of cocaine and other drugs over the duration of the study; 3) cocaine and opioid craving; 4) change in depressive symptoms; 5) changes in problems related to drug use and quality of life; 6) cocaine abstinence throughout the final two weeks of the evaluation period; and 7) retention in treatment during the active treatment phase.

4. Study organization and sites

The CURB study is being conducted within the National Drug Abuse Treatment Clinical Trials Network (CTN) which operates under the auspices of the National Institute on Drug

Abuse (NIDA). The CTN framework consists of thirteen nodes, each of which consists of a Regional Research and Training Center (RRTC) affiliated with at least one academic institution and several community-based treatment Programs (CTPs). Multi-site clinical trials are conducted at local CTPs and receive support from a Clinical Coordinating Center (CCC) and Data and Statistics Center, both of which are located at the EMMES corporation (Rockville, MD). This framework links a variety of treatment programs and patient populations throughout the country. The CTN provides a broad infrastructure for multi-site testing of promising science-based therapies in real-world community-based treatment settings.

The Pacific Region Node, with its research center located at UCLA (Los Angeles, CA), is the Lead Node responsible for scientific and operational oversight for the entire trial. The CURB Study has 11 CTPs participating in recruitment and data collection nationwide. Potential sites were asked to complete an in-depth survey to evaluate staffing resources, relevant patient population, and prior research experience. Sites were chosen by a selection committee based on their ability to recruit cocaine-dependent adults with opioid use disorders, site personnel's experience with the trial medications, their prior research experience, and lack of other competing research commitments. The CTPs selected for the CURB study are Albert Einstein College of Medicine (Bronx, NY), Atlanta VA Medical Center (Atlanta, GA), Addiction Research and Treatment Services (Denver, CO), Bay Area Addiction Research and Treatment (San Francisco, CA), Bellevue Hospital Center (New York, NY), CODA, Inc. (Portland, OR), Howard University (Washington, DC), Maryhaven (Columbus, OH), Recovery Centers of King County (Seattle, WA), South Texas Veterans Health Care System (San Antonio, TX), and the UCLA Integrated Substance Abuse Programs (Los Angeles, CA).

5. Data and patient safety monitoring

The CTN has a Data Safety and Monitoring Board (DSMB) to oversee ongoing trial progress. One of the major purposes of this board is to determine whether risks emerge during the conduct of the trial that make continuation unethical (e.g., safety concerns, clear and significant superiority of one condition over another). This process provides the IRBs, the sponsor (NIDA), and investigators with assurance that participants receive an accurate and ongoing risk evaluation within CTN research trials. Safety monitoring begins with the initial review of the protocol during the study development process. If serious or unexpected AEs occur during the trial, the site medical clinician reports these occurrences within the specified time frames to the DSMB, IRBs, NIDA, state agencies, and the FDA as required. The DSMB meets twice a year to review safety data, and an interim analysis of data is planned at the enrollment midpoint.

A NIDA-assigned Medical Safety Monitor is responsible for overseeing safety and for evaluating all AEs. Serious Adverse Events (SAEs) are also reviewed by the PI and lead node team, and are discussed on the weekly operations call. Quality Assurance monitors visit all sites to: 1) confirm accuracy of entered data by comparing it with source documents, 2) review the storage and accounting procedures for all study medications, 3) audit the informed consent and randomization process, and 4) evaluate the performance of Good Clinical Practice guidelines [10] by study staff.

6. Study procedures

The study schema is presented in Fig. 1. Individuals responding to study recruitment materials initially undergo a pre-screening assessment to determine potential eligibility. Participants who appear eligible are invited to participate in informed consent procedures, and those who voluntarily consent to participate then enter a screening phase. Assessments

conducted during screening determine whether participants meet the eligibility criteria and do not meet any of the safety exclusion criteria (see Table 1), and baseline measures of drug use and other life domains (e.g., HIV risk, family/social problems, legal problems, etc.) are collected. Participants who meet the eligibility criteria, self-report no opioid use for at least 7 days and provide a urine drug screen negative for opioids are given a naloxone challenge to confirm the absence of physiological dependence on opioids. While the method of naloxone challenge administration (i.e., intravenous, subcutaneous or intramuscular) is up to the discretion of the site medical clinician, a minimum 0.8 mg bolus must be given to determine that a challenge is negative. If no opioid withdrawal symptoms are witnessed or reported after an observation period, participants receive an initial dose of oral naltrexone, the amount of which is at the site medical clinician's discretion. All participants must receive a total of 50 mg oral naltrexone as an in-clinic dose and show no signs of discomfort or opioid withdrawal on the day of the first XR-NTX administration. XR-NTX is provided to participants as a gluteal intramuscular injection (380 mg) immediately prior to randomization.

Following successful induction onto XR-NTX and a final assessment of eligibility, participants are randomly assigned in a 1:1:1 ratio to one of the three conditions: (BUP4+XR-NTX), (BUP16+XR-NTX) or (PLB+XR-NTX) for 8 weeks of treatment. Randomization is stratified according to site and opioid use levels according to the following strata:

- *High*, defined as 1) ever injected an opioid; 2) greater than or equal to 2 years of regular opioid use (per Addiction Severity Index); or 3) self-reported opioid use on 20 or more days in the month preceding screening (per Timeline Follow-back)
- *Low*, defined as not meeting the criteria for high opioid use

The randomization procedure is a centralized process administered through the Data and Statistics Center. The randomization schedule uses balanced blocks of varying sizes (range: 3–6) within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. The study is being conducted under double-blind, placebo-controlled conditions, so participants and study staff are unaware of medication assignment.

Administration of full daily doses of BUP or PLB is observed in-clinic three times a week, with sufficient take-home medication provided at each clinic visit for self-administration until the next scheduled clinic visit. The sublingual formulation of buprenorphine with naloxone (BUP) at 4:1 ratio contains 2 mg/0.5 mg of buprenorphine/ naloxone, or 8 mg/2 mg buprenorphine/naloxone. BUP tablets and matched placebo tablets are manufactured by Reckitt-Benckiser Pharmaceuticals, Inc. (Hull, UK) and are shipped to a NIDA contractor for distribution to the sites. Although Suboxone® contains the opioid antagonist naloxone, the sublingual administration confers negligible bioavailability of naloxone.

Once randomized, participants are inducted onto BUP (or PLB) by provision of half of their randomly assigned dose (i.e. placebo, 4 mg, or 16 mg) for the first two days of the treatment period (Days 1 and 2). Two tablets are provided to each participant: one 2 mg tablet and one 8 mg tablet (in active or placebo combinations, depending on condition; see Fig. 2 for illustration of dosing). On Day 3 daily dosage is increased to the full assigned dose at which time four tablets are provided to each participant: two 2 mg tablets and two 8 mg tablets. This dose continues until the taper period during the last two days of the active treatment phase (Days 55 and 56) at which time the daily dose is halved such that each participant takes one 2 mg and one 8 mg tablet daily. If at any point after receiving the full dose the participant reports intolerable side effects, and it is deemed appropriate by the site medical clinician, a one-time dose reduction may occur to half of the participant's randomly assigned dose. If dose reduced, the participant continues on this reduced dose for the remainder of the

treatment phase. Participants who are removed from study medication due to an adverse event or participant choice are encouraged to continue attending scheduled study visits and providing study data through the end of the study. If a participant does stop medication early, an end-of-medication visit is performed at that time.

XR-NTX is administered by injection to all participants immediately prior to randomization and again at the first visit of Week 5 via gluteal intramuscular injection (380 mg). If clinically indicated, the baseline induction procedure (i.e. naloxone challenge and provision of oral naltrexone) may be repeated before the second XR-NTX injection. All participants are also scheduled to receive once-weekly individual CBT conducted by a trained therapist over the 8-week treatment phase. Therapy sessions are completed in approximately 45 min and are guided by a treatment manual for stimulant dependence adapted specifically for this study [11]. Follow-up assessments are scheduled at 1 month and 3 months post-treatment to assess substance use, medication safety, and other secondary outcomes.

7. Study assessments

The schedule of assessments is presented in Table 2. To assess the primary outcome of cocaine use days over the 30-day evaluation period, the Timeline Follow-back (TLFB) procedure [12,13] is used to collect self-report data, corroborated by thrice-weekly urine drug screens. The TLFB is administered at each study visit during screening, throughout the active treatment phase and through the end of the follow-up period to document the participant's self-reported use of substances for each day since the previous TLFB assessment, and for the 30 days prior to screening. Urine specimens are collected using FDA-approved QuickTox temperature-controlled urine drug test cups and screened for the presence of cocaine, opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamine, marijuana, methadone and ecstasy (MDMA). Samples are automatically tested using enzyme immunoassay techniques and read by staff via bands that appear in the control and test regions. An adulterant check for creatinine, nitrite, glutaraldehyde, pH, specific gravity, bleach and pyridinium chlorochromate is performed on each sample. Prior to the naloxone challenge, an Opi300 urine dipstick is administered to test for opioids at the more sensitive 300 ng/mL cut-off in addition to the one-step 10-panel urine drug screen.

Secondary outcome measures include: 1) safety of the study conditions as measured by adverse events (AEs); 2) cocaine use during the active treatment phase using the Treatment Effectiveness Score [14]; 3) severity of opioid and cocaine craving, assessed weekly using a visual analog scale (VAS) ranging from 0 (no craving) to 100 (most intense craving) [15]; 4) other substance use (including opiates, methadone, and oxycodone, barbiturates, benzodiazepines, amphetamine, meth-amphetamine, marijuana, and ecstasy (MDMA)), assessed via thrice-weekly urine drug screens and TLFB; 5) reduction in drug-related problems as indicated on the ASI; 6) severity of depression symptoms, assessed weekly using the Beck Depression Inventory [16]; 7) quality of life, assessed at baseline, treatment-end and follow-up using the World Health Organization Quality of Life (WHOQOL)-BREF [17]; 8) cocaine abstinence during the final two weeks of the evaluation period; 9) retention in treatment across the duration of the active treatment phase; 10) changes in life domains (i.e. substance use, personal responsibilities, health, and citizenship) assessed monthly using the Treatment Effectiveness Assessment, a 4-item self-administered Likert scale assessment [18]; and 11) cocaine use during the follow-up period.

Information about demographic characteristics of the participant, including sex, date of birth, ethnicity/race, education, employment pattern, and marital status is collected at screening. An abbreviated Opioid Use Questionnaire is administered at screening to

distinguish the main type of opioid used by the participant, the onset of the use, the participant's perception of the substance that is most problematic, and their present treatment goal. The DSM-IV-TR Checklist provides current diagnoses for substance use disorders based on DSM-IV diagnostic criteria at screening to determine eligibility. The Risk Assessment Battery (RAB) [19] is self-administered at screening and treatment-end to assess engagement in activities that increase the likelihood of contracting HIV. The Self-Help Assessment measures previous self-help group participation (e.g. Alcoholics Anonymous, Narcotics Anonymous) at screening and end of treatment. The Addiction Severity Index (ASI)-Lite [20] is used to assess severity of substance use and areas of functioning impacted by addiction (e.g., employment, legal status, medical and psychiatric issues) at screening, treatment-end, and follow-up. The Fagerström Test for Nicotine Dependence (FTND) is used to assess nicotine dependence [21] at screening and end of treatment. (See Table 1 for a schedule of assessments.)

Safety assessments include a medical and psychiatric history and physical examination at baseline to determine eligibility and ensure that there are no medical issues that might preclude safe participation in the study. An ECG and laboratory studies, including chemistry panel, liver function tests (i.e., AST, ALT, GGT, ALP, and bilirubin), hematology panel, and a standard urinalysis are performed at baseline to help determine eligibility and are repeated at week 4 and at treatment-end. Baseline, HIV and hepatitis B and C serology tests are conducted for participants who are randomized. Pregnancy and use of birth control are assessed at screening and throughout the study. The injection site is examined at screening and at the visits following the first and second XR-NTX administrations. Body habitus must be appropriate for deep intramuscular gluteal injection in order for participants to be randomized into the trial. Participants are asked to report immediately any injection site reactions to study staff for evaluation, monitoring, and possible referral for treatment, if needed. Vital signs are recorded at screening, once weekly throughout the active treatment phase, and at the end-of-medication visit (last visit of Week 8 or sooner if medication is stopped early). Vital signs are also recorded before and after administration of naloxone, first dose of oral naltrexone, XR-NTX, and first dose of BUP (or PLB). In addition, orthostatic vital signs are recorded at screening, at Week 5, and at the end-of-medication visit.

Information about use of prescription and over-the-counter medications is collected at screening and throughout the study. AEs are recorded at each visit after consent. The medical clinician evaluates all AEs for relatedness to study medication. SAEs are reviewed, reported, and tracked in accordance with applicable regulatory requirements. The PRISM Suicide and Homicide Screening form [22] is used as a periodic assessment of suicide and homicide risk throughout the study. Participants who represent a significant suicidal/homicidal risk, or who score greater than or equal to 15 on the BDI must be assessed by a qualified site clinician before leaving the clinic. To assess compliance, dose logs are used to document medication administered in-clinic, dispensed for take-home dosing, and reported as taken by the participant. A CBT attendance log is completed to document attendance or non-attendance at each weekly CBT session during the active treatment phase.

8. Data analysis of the primary endpoint

The primary endpoint is the number of cocaine use days as measured by self-report during the 30 day evaluation period (Days 25–54), corroborated by thrice-weekly urine drug screens (UDS), and will be compared among the three treatment arms using the rank sum statistic. The opioid history stratum (high vs low) will be analyzed to determine if it is a significant predictor of number of cocaine use days. If a mean difference of more than 3.0 days is found between the high and low opioid use groups, this factor will be used in the

analysis of the primary endpoint and a stratified Wilcoxon test will be performed. The experiment-wise Type 1 error will be controlled at 5% by using 2 pairwise 2.5% level one-sided tests comparing each of the two buprenorphine arms (BUP4+XR-NTX and BUP16+XR-NTX) versus the no-buprenorphine arm (PLB+XR-NTX).

The algorithm for combining the self-report use data with the results of the thrice-weekly urine drug screens will be based on a previously-developed algorithm [23]. Briefly, to determine whether there is a contradiction between UDS and self-report, the algorithm designates the day of urine collection of a positive UDS as day 0. If a window running from day-3 to day-1 is found in which the UDS is positive and all self-reports are negative, the self-report for the last day in the window is modified from negative to positive in an attempt to eliminate perceived contradiction between self-report and UDS. If any self-reports in a window are positive, or if the corresponding UDS is negative, the self-reports are left unchanged.

The primary analysis will be performed in the group of individuals who initiate the evaluation period as minimal loss is anticipated between randomization and this time point given the short time period. For those participants who initiate the evaluation period but then withdraw prematurely from the study, their use rate will be imputed to be equal to that observed through the period prior to withdrawal.

Two additional secondary intent-to-treat analyses of the primary endpoint will be performed using all randomized participants, one in which the maximally pessimistic situation (i.e., participants in the two buprenorphine arms are assumed to use cocaine daily and participants in the no buprenorphine arm are assumed to never use) will be used to impute the endpoint score for participants who withdraw early and the second in which the cocaine use level observed in the 30 days prior to screening will be used for imputation purposes. In addition, the treatment effect in the two levels (high vs low) of the opioid history stratum will be evaluated.

9. Interim analysis

Given the relatively small sample size, short duration of the study and need for precise estimation of multiple outcome measures, early termination for efficacy is not planned. Any claim of treatment difference between the active and control arms will be made at the end of the trial in which all Type I error is spent. Regarding the possibility of early termination for lack of efficacy, an interim analysis of data for futility was initially planned after endpoint information for half of the planned study sample was available. However, a DSMB review of the data at the enrollment midpoint indicated a lack of safety concerns. The study's safety profile coupled with the fact that the study is accruing more rapidly than expected led the DSMB to determine that an interim analysis would not be necessary.

10. Sample size calculation

The study has been designed to include 300 individuals randomly assigned in a 1:1:1 ratio to the 3 treatment arms. The sample size was developed from a simulation study of the anticipated trial characteristics considering the number of use days, probability of study withdrawal, probability of underreporting of drug use, and effect size. In a prior study of a similar population (NIDA CTN-0007 Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics), participants had about 9 cocaine use days in a 30 day period, with a standard deviation nearly the size of the mean (mean=9.5, sd=8.5). Under the null hypothesis of no treatment effect, it is assumed that each participant's daily use follows a Bernoulli distribution, but that participants' use risk varies, with sufficient population variability to match the anticipated extra-binomial variability noted from the prior study.

Specifically, a beta-binomial distribution is assumed for daily use with the following parameters: $b_1=.45$ and $b_2=1$. Since the mean of the beta binomial is b_1/b_1+b_2 , then the expected number of use days in a 30 day period is 9.31 and the standard deviation is 9.08.

While verification of some daily self-reports will be substantiated with urine testing, underreporting of use may occur. It is anticipated that this underreporting may vary among participants. In the simulation, underreporting of use is modeled under assumptions of complete accuracy (0% underreporting), 20% underreporting and 40% underreporting of use days. Conditional on use, the probability of underreporting is modeled with a beta-binomial distribution with parameters of (.2, .8) for the 20% level and (.4, .6) for the 40% level.

Losses to follow-up are assumed to occur in 5% of the participants prior to initiation of the evaluation period. In addition, a daily loss probability is presumed that is scaled by the participants' mean use probability from the initial beta-binomial distribution. Thus, participants with higher use rates are more likely to discontinue. In the simulation, the unscaled daily probability is set at .008 resulting in an 18% dropout rate during the evaluation period.

Under the above assumptions, a simulation with a sample size of 300 (100 per arm) and 1000 replications of each condition showed that a reduction of 3.16 use days in the 30-day evaluation period can be reliably detected with greater than 85% power if the underreporting percentage is bounded by 20%. When the reduction in use days is 3.94, over 90% power is available even if the underreporting percentage is as high as 40%. As a reduction in 3–4 use days was thought to be a clinically meaningful difference, a sample size of 300 was chosen for this study.

11. Current status of the study

The CURB study commenced recruitment in September 2011, and all 11 sites nationwide were endorsed and recruiting participants by February 2012. At the time of writing of this manuscript, enrollment, active medication and follow-up phases are ongoing. Recruitment is exceeding targeted enrollment rates. Results related to primary and secondary outcomes will be reported in future publications.

12. Discussion

The lack of pharmacotherapy for cocaine dependence underscores the need for further medication development research. The design of this study and its implementation within CTPs will yield valuable findings on a number of levels. First, this study will examine if BUP in the presence of XR-NTX is effective in a real-world treatment setting. This combination of buprenorphine and naltrexone was examined through earlier work by Gerra et al. [9] in an open-label study with 60 primary heroin users. Significant improvements in opioid use, cocaine use, and retention were demonstrated in participants who received buprenorphine and naltrexone relative to those who received naltrexone alone. These findings suggest that buprenorphine may have benefit in reducing cocaine use and underscore the importance of conducting this larger, randomized and blinded trial that specifically recruits individuals with primary cocaine dependence.

Individuals with cocaine dependence exhibit reduced dopa-minergic function, which may contribute to dysphoria and relapse [24]. Increased activity of endogenous kappa agonist systems after chronic drug use may contribute to this dysfunction [25] and enhance stress-induced relapse [26]. Elevated levels of dynorphin, the primary endogenous kappa receptor ligand involved in a feedback loop that suppresses dopaminergic activity, have been observed in chronic cocaine users [27]. Animal models show that antagonism at kappa

receptors blocks stress-induced re-instatement of cocaine self-administration and ameliorates dysphoria. As such, kappa antagonists are under development as potential pharmacotherapies for cocaine dependence [28,26].

Findings from this study will be important to determine how effectively XR-NTX blocks the mu effects of BUP when used in real-world treatment settings. Prior clinical [9] and laboratory (Reese Jones, unpublished data, 2009) results have suggested an absence of clinically meaningful mu effects when BUP is administered with naltrexone in doses up to 16 mg. Furthermore, newly published results of the effects of buprenorphine and naltrexone on cocaine use in rodents demonstrate reduction in cocaine use without producing opioid-seeking behavior [29], providing additional evidence that concurrent administration of these medications may not produce opioid dependence. The combination of buprenorphine and naltrexone creates a functional kappa antagonist with other potential mechanisms of action (such as ORL-1 agonism). If increases in opioid use, mu receptor effects, or opioid craving are not observed over the course of this trial, safety data could provide justification to consider future studies of the combination in individuals without a history of opioid use disorders. Replicating findings from prior work could expand the potential to utilize this medication combination in cocaine users who have no prior or current opioid use.

The population recruited will enhance generalizability of results, with 11 study sites across geographically varied regions of the US facilitating the recruitment of a diverse population of cocaine-dependent individuals. Additionally, participants are not excluded if they are Hepatitis C or HIV positive, nor are they automatically excluded if dependent on other substances unless their pattern of use would preclude safe participation in the study. Nevertheless, there are limitations to what can be learned from this first multi-site clinical trial examining the combination of BUP plus XR-NTX. A notable limitation is the generalizability of the results to opioid-naïve cocaine users given the specific population being recruited, in which a past or current opioid use disorder diagnosis is required for enrollment. In addition, this study does not control for the potential independent effect of naltrexone on treatment outcomes given that all three study groups receive XR-NTX. This study was designed to replicate and extend results of prior clinical trials evaluating the combination of BUP and naltrexone; future studies could evaluate the differential effects on cocaine use of XR-NTX administered alone or in combination with BUP.

Additionally, if this study determines the combination is effective, further pre-clinical studies may be required to elucidate the mechanism of action. With the combination of naltrexone, a mu opioid antagonist, and buprenorphine, a mu opioid partial agonist that has high affinity for, but low intrinsic activity at mu receptors, it could be proposed that any effect seen could be attributed to a non-mu receptor effect. Given that buprenorphine also has partial or full agonist activity at the ORL1 and δ -opioid receptor, and competitive antagonist activity at the κ -opioid receptor, the exact mechanism of action will warrant additional exploration if the combination is found to be effective.

Despite these limitations, the CURB study has a number of strengths and will be informative in a variety of important areas. This study will address safety concerns, particularly regarding risks of opioid use escalation after exposure to BUP in combination with XR-NTX. The clinical experience gained with this combination of medications will also be important to evaluate procedures for induction onto XR-NTX formulations for participants with a history of opioid use disorders. Clinical implications of induction procedures will be examined, informing the potential development of clinical guidelines based on the experience of using XR-NTX in different patient groups.

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Extended-release injectable naltrexone (Vivitrol) = XR-NTX

Buprenorphine+naloxone (Suboxone) = BUP

Fig. 1.
Study schema.

Day	Dose of Bup (expressed as amount of buprenorphine)					
	4mg Group	Dispense	16mg Group	Dispense	Placebo Group	Dispense
1	2mg		8mg		0mg	
2	2mg		8mg		0mg	
3-54	4mg		16mg		0mg	
55	2mg		8mg		0mg	
56	2mg		8mg		0mg	

Key: Active Placebo

Fig. 2.

Buprenorphine/placebo induction, maintenance and taper dose by study day.

Table 1**Study eligibility criteria.**

<i>Inclusion criteria</i>	
1	Age between 18 and 65 years of age;
2	In good general health;
3	Meet DSM-IV criteria for cocaine dependence;
4	Meet DSM-IV criteria for either: a) opioid dependence in the past year, b) opioid abuse in the past year, or c) opioid dependence during the lifetime with past-year opioid use
5	Interested in receiving treatment for cocaine dependence;
6	Provision of a negative urine drug test for opioids immediately prior to naloxone challenge;
7	Meet objective or subjective definition of being "opioid detoxified" as per study medical clinician's determination;
8	Tolerate induction onto oral naltrexone and XR-NTX;
9	If female of childbearing potential, willing to practice an effective method of birth control for the duration of participation in the study;
10	Able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study.
<i>Exclusion criteria</i>	
1	Evidence of an acute psychiatric disorder as assessed by the study medical clinician that would make participation difficult or unsafe;
2	Presence of suicidal or homicidal ideation that requires immediate attention;
3	Known allergy or sensitivity to buprenorphine, naloxone, naltrex-one, PLG (polyactide-co-glycolide), carboxymethylcellulose or any other component of the XR-NTX diluent;
4	Serious medical illness that, in the opinion of the study medical clinician, would make participation medically hazardous;
5	Evidence of second or third degree heart block, atrial fibrillation, atrial flutter, prolongation of the QTc, or any other finding on the screening ECG that, in the opinion of the medical clinician, would preclude safe participation in the study;
6	LFT values>5 times the upper limit of normal as per laboratory criteria;
7	INR>1.5 or platelet count<100 k;
8	Body habitus that precludes gluteal intramuscular injection of naltrexone with provided needle;
9	Participation in another investigational drug study within 30 days of study consent;
10	Receiving ongoing treatment with tricyclic antidepressants, chlorpromazine, modafinil, disulfiram, or any medication that, in the judgment of the study medical clinician, could interact adversely with study drugs;
11	Participation in methadone maintenance treatment within 15 days of consent;
12	Participation in buprenorphine maintenance treatment within 30 days of consent;
13	Pending legal action or other situation that might prevent remaining in the area for the duration of the study;
14	Planned or scheduled surgery during the study period;
15	Requiring therapy with opioid-containing medicines (e.g., opioid analgesics) during the study period;
16	Current pattern of alcohol, benzodiazepine, or other sedative hypnotic use, as determined by the study medical clinician, which would preclude safe participation in the study;
17	Currently pregnant or breastfeeding.

Table 2

Schedule of assessments.

Assessment	Frequency
Informed consent	Baseline
<i>General measures</i>	
Inclusion/exclusion	Baseline
Locator form	Baseline and then every two weeks
Demographics form	Baseline
Family origin	Baseline
Treatment satisfaction survey	Week 8 ^a
End of medication form	Week 8 ^a
End of study form	3 month follow-up (FU)
<i>Safety and medical measures</i>	
Medical and psychiatric history	Baseline
Physical examination	Baseline and Week 8 ^a
Injection site examination	Baseline and at 1st visit post-injections
Electrocardiogram	Baseline, Week 5, and Week 8 ^a
Clinical laboratory tests	Baseline, Week 4, And Week 8 ^a
Buprenorphine and naltrexone blood levels	Week 5 and Week 8 ^a
Pregnancy and birth control assessment ^b	Baseline, Week 5, And Week 8 ^a
Vital signs ^c	Baseline, then weekly during active medication phase
Prior and concomitant medications	At each study visit
Adverse events and serious adverse events	At each study visit
<i>Drug use and psychological measures</i>	
Timeline follow-back	At each study visit
Urine drug screen	At each study visit
Visual analog craving scale	Baseline, weekly during active medication, and at FU visits
Beck Depression Inventory	Baseline, weekly during active medication, and at FU visits
Treatment Effect Assessment	Week 5, Week 8 ^a , and at FU visits
WHO Quality of Life BREF	Baseline, Week 8 ^a , and 3 month FU
PRISM — Suicide and Homicide Screening	Baseline, Week 5, and Week 8 ^a
Opioid Use Questionnaire	Baseline
DSM IV-TR Checklist	Baseline
Risk Assessment Battery	Baseline and Week 8 ^a
Self-Help Assessment	Baseline, Week 8 ^a , and FU visits
Addiction Severity Index Lite	Baseline, Week 8 ^a , and FU visits
Fagerström Test for Nicotine Dependence	Baseline and Week 8 ^a
<i>Compliance measures</i>	
Dose logs	Each visit during screening and active medication phase
CBT attendance log	Weekly during active medication phase

^aOr collected at Week 5 if study medication ended early.

^bCollected according to table of assessments, including prior to naloxone challenge and XR-NTX administrations.

^cCollected according to table of assessments, including before and after naloxone challenge, first dose of oral naltrexone, XR-NTX, and first dose of BUP/placebo.