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Opioid treatment at release from jail using extended-release naltrexone: a pilot proof-of-concept randomized effectiveness trial

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ABSTRACT

Background and Aims Relapse to addiction following incarceration is common. We estimated the feasibility and effectiveness of extended-release naltrexone (XR-NTX) as relapse prevention among opioid-dependent male adults leaving a large urban jail. **Design** Eight-week, proof-of-concept, open-label, non-blinded randomized effectiveness trial. **Setting** New York City jails and Bellevue Hospital Center Adult Primary Care clinics, USA. **Participants** From January 2010 to July 2013, 34 opioid-dependent adult males with no stated interest in agonist treatments (methadone, buprenorphine) received a counseling and referral intervention and were randomized to XR-NTX ($n = 17$) versus no medication ($n = 17$) within one week prior to jail release. **Intervention** XR-NTX (Vivitrol®; Alkermes Inc.), a long-acting injectable mu opioid receptor antagonist. **Measures** The primary intent-to-treat outcome was post-release opioid relapse at week 4, defined as ≥10 days of opioid misuse by self-report and urine toxicologies. Secondary outcomes were proportion of urine samples negative for opioids and rates of opioid abstinence, intravenous drug use (IVDU), cocaine use, community treatment participation, re-incarceration and overdose. **Findings** Acceptance of XR-NTX was high; 15 of 17 initiated treatment. Rates of the primary outcome of week 4 opioid relapse were lower among XR-NTX participants: 38 versus 88% [$P<0.004$; odds ratio (OR) = 0.08, 95% confidence interval (CI) = 0.01–0.48]; more XR-NTX urine samples were negative for opioids, 59 versus 29% ($P<0.009$; OR = 3.5, 95% CI = 1.4–8.5). There were no significant differences in the remaining secondary outcomes, including rates of IVDU, cocaine use, re-incarceration and overdose. **Conclusion** Extended-release naltrexone is associated with significantly lower rates of opioid relapse among men in the United States following release from jail when compared with a no medication treatment-as-usual condition.

Keywords Extended-release naltrexone, jail, opioid dependence, prisoners, randomized controlled trial, relapse prevention, Vivitrol.

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INTRODUCTION

Heroin or other illicit opioid misuse following release from jail or prison is common, and an important risk factor for accidental overdose death [1,2]. A general lack of availability of evidence-based opioid treatment in criminal justice systems (CJS), specifically opioid agonist medications, buprenorphine and methadone, contributes to cycles of re-incarceration and relapse [3]. When methadone and buprenorphine are accessible during and after incarceration, treatment retention improves, opioid misuse declines and community treatment outcomes are comparable to that of non-CJS-involved patient samples [4–8]. New York City jails provide methadone detoxification at arrest and offer methadone maintenance as standard of care; however, most out-of-treatment opioid-dependent prisoners, who typically comprise 10% of a fluctuating daily jail census of approximately 10 000 people, do not access methadone maintenance pre-release and leave jail detoxed and 'drug free' [9].

Extended-release naltrexone (XR-NTX, Vivitrol®; Alkermes Inc., Waltham, MA, USA) or sustained-release injectable naltrexone, a monthly mu opioid receptor antagonist, is efficacious and Food and Drug Administration (FDA)-approved for opioid relapse prevention following a pivotal double-blind placebo-controlled trial conducted in Russia [10]. The XR preparation produces a 4-week mu opioid receptor blockade, preventing opioid agonist reinforcing effects, including euphoria, pain relief, sedation and physical tolerance/dependence. To date, XR-NTX has not been studied rigorously in US or international CJS populations, and several federally funded studies are ongoing (NCT00781898, NCT01246401, NCT01077310, NCT01999946, NCT02110264). Published findings to date indicate that long-acting naltrexone preparations are acceptable, feasible and safe relapse prevention interventions among prisoners and CJS-involved, community-dwelling participants [11–15].

No trials have been completed in a municipal jail setting, which typically detain and incarcerate opioid users for brief periods of time, during which the individual detoxes but does not typically access evidence-based maintenance or relapse prevention treatment. XR-NTX is a potentially effective but untested medication-assisted alternative for people released from jail and not able to access or not interested in buprenorphine or methadone treatments. This pilot proof-of-concept randomized trial was initiated to gather further feasibility and effectiveness data for XR-NTX as opioid relapse prevention among primarily heroin-dependent adults released from jail incarceration. The primary aims were to establish feasibility and to estimate the effect of XR-NTX on immediate post-release opioid relapse and rates of opioid misuse, compared to a counseling and referral enhanced usual-care condition.

METHODS

Study overview

This was an investigator-initiated clinical trial of XR-NTX treatment initiated prior to release from jail in New York City. The trial was supported initially by a NYU School of Medicine seed grant (2009) and an in-kind study drug agreement with Alkermes, Inc. Subsequent awards (NYU, 2011; Alkermes, 2011) supported more robust recruitment and completion of the trial. The New York University School of Medicine and NYC Department of Health and Mental Hygiene Institutional Review Boards approved the study.

Study design

The design was a pilot, proof-of-concept, open-label, non-blinded randomized 8-week effectiveness trial of XR-NTX versus no medication treatment-as-usual (TAU) among opioid-dependent adults released from NYC jails. The primary aim was to estimate the effectiveness of XR-NTX versus TAU in preventing immediate post-release opioid relapse at week 4. Secondary aims were to compare rates of related outcomes between arms, including overall rates of opioid use and abstinence, cocaine use, HIV risk behaviors, re-arrest and re-incarceration and overdose events.

At the time of study conception and initiation, prior and ongoing trials offered evidence of the efficacy of XR-NTX versus placebo [10,16]. Our center was focused on conducting open-label, non-placebo effectiveness evaluations of XR-NTX and buprenorphine in community and CJS patient populations (NCT00781898, NCT00620750, NCT02032433). This pilot study was similarly designed to estimate feasibility and effectiveness under usual-care conditions and clinical outcomes (i.e. follow-up rates, urine samples, self-reported use).

Initial recruitment efforts in 2010 consisted of individual outreach by the study team to opioid treatment jail staff and potentially interested patients. In 2011, a search algorithm using electronic medical and jail release records was developed to identify potentially eligible opioid-dependent individuals not enrolled into the jail methadone program and with a pending release date, who were then contacted regarding study participation and invited to attend a screening visit.

All study pre-screen interviews and two research visits (screening, randomization/initial treatment) occurred in New York City Department of Corrections jail medical clinics. Potentially eligible or interested patients were invited to the jail medical clinic for a pre-screening interview and, if potentially eligible, completion of informed consent and the initial screening visit. A randomization visit (week 0) and XR-NTX treatment occurred within a week of release. Post-release follow-up visits (weeks 2, 3, 4 and 8) occurred in the adult primary care addiction medicine clinic at Bellevue Hospital Center (BHC) in Manhattan or, in the event of re-incarceration, the jail medical clinics.

Study sample and sites

We recruited opioid-dependent adults incarcerated in New York City Department of Corrections jail facilities. Eligible participants were age >18 years, meeting DSM-IV criteria for opioid dependence prior to arrest, currently incarcerated in NYC jail with a known release date, not currently on or intending to access methadone or buprenorphine treatment, opioid-free by self-report and negative opioid urine toxicology at randomization, without serious, uncontrolled medical or psychiatric illnesses, and able to understand and provide written informed consent in English. Exclusions were pregnancy, liver function tests >3× normal and chronic pain conditions requiring opioid pain therapies.

Randomization and masking

A 1 : 1 permuted blocks random assignment sequence was generated with block size 6 and stratified by gender using Stata. Sealed envelopes were prepared and sequenced initially by the principle investigator (PI). To ensure masking of the PI to the allocation order, envelopes were then shuffled thoroughly by block, which scrambled the original sequence randomly, preserved the block size of 6 and rendered a final masked sequence; participants, investigators and study staff remained masked to allocation prior to the randomization visit. Research staff opened the envelopes at the jail site with the participant during the randomization visit, once final eligibility had been confirmed. Treatment allocation was then non-blinded (open-label).

Study medication and interventions

XR-NTX participants underwent a 0·8 mg naloxone challenge to confirm opioid abstinence prior to the initial XR-NTX 380 mg intramuscular injection. If an induced XR-NTX participant's release date was postponed unexpectedly, XR-NTX induction was repeated prior to the new release date. A second XR-NTX dose was offered post-release at week 4. A physician-delivered Medical Management approach supported XR-NTX treatment and emphasized medication adherence, opioid abstinence and other community and 12-Step recovery support [17].

All participants received brief motivational enhancement counseling and referrals to community treatment, which ensured that the TAU condition exceeded actual usual care and was consistent with federal guidelines for research among prisoners. Counseling was specific to opioid relapse prevention, treatment readiness and aftercare options. Referrals before and after release to appropriate general medical, psychiatry and addiction services at BHC were offered to all participants. This included referrals to post-release buprenorphine and methadone treatment if participants in either arm had reconsidered these options.

Study assessments and outcomes

Baseline assessments consisted of demographics and substance use history adapted previously from the Addiction Severity Index [18], self-reported pre-arrest opioid and other substance use (time-line follow-back, TLFB) [19], electronic medical record audit for substance use, medical and psychiatric diagnoses and liver function tests, the Risk Assessment Battery (RAB) for pre-arrest intravenous drug use history and HIV risk scores [20] and urine toxicologies for opioids (opiates 300 ng/ml, methadone, oxycodone, buprenorphine) and cocaine. TLFB, urine toxicologies, an adverse event log and the Non-study Medical Service [21] assessment for community treatment uptake were completed at each follow-up visit (weeks 2, 3, 4 and 8). The RAB was repeated at weeks 4 and 8. Audits of the NYC jail admission database and the National Death Index established rates of re-incarceration and mortality following missed visits and among those lost to follow-up.

Feasibility outcomes included the proportion of eligible participants initiating XR-NTX prior to release and accepting a second injection at week 4, post-release follow-up rates and safety events. The primary effectiveness outcome was post-release opioid relapse at week 4, measured by self-report and urine toxicologies, and defined as ≥10 of 28 days of self-reported opioid misuse following jail release or two or three positive of the three urine samples during weeks 2, 3 and 4. A single positive or missing urine result counted as 7 opioid misuse days. This definition of relapse aligned with that of four ongoing large XR-NTX randomized effectiveness trials (NCT00781898, NCT02032433, NCT01999946, NCT02110264). This immediate week 4 primary outcome assessed the effects of the initial and only pre-release dose of XR-NTX and is a period during which TAU post-release relapse rates are high.

Secondary outcomes of interest were proportion of urine toxicologies positive versus negative for opioids, rates of confirmed abstinence (negative urine sample and self-report), opioid use outcomes at week 8, injection drug use and HIV sexual risk behavior, cocaine use, community addiction treatment uptake and adverse events including overdose.

Statistical analysis

Baseline differences were summarized and compared using *t*-tests and Fisher's exact tests. Intention-to-treat analysis tested for two-sided differences in the dichotomous week 4 relapse primary outcome using Fisher's exact test and logistic regression. The primary outcome of post-release relapse at week 4 was measured by self-report and urine toxicologies; missing urine samples counted as positive. This was an imputation strategy for missing data similar to a return to baseline approach, as all participants reported using opioids daily, primarily heroin, pre-arrest. An alternative imputation approach of last observed status to account for missing data was also examined for the primary outcome. The same comparisons were made between arms for secondary outcomes of interest: total opioid negative urine sample rates, confirmed opioid abstinence, other non-study treatment participation, cocaine use, re-incarceration and adverse events, including overdose and death.

An original target sample size estimate of $n = 40$ was powered to detect a 50% two-tailed difference in relapse rates, assuming an estimated 75% relapse rate among controls. The assumptions in the power analysis were based on

the treatment effect in the XR-NTX pivotal trial and the very high post-release relapse rates observed historically among opioid users [1,2,9,10].

RESULTS

Recruitment took place from January 2010 to April 2013. Randomization (17 to each condition) resulted from 48 consented and screened out of 142 potentially eligible individuals (Fig. 1). Reasons for lack of screening completion included logistics (23% of 142 pre-screened individuals did not attend a screening visit) and no interest in the study (20%). Of the 14 of 48 consented but ineligible participants, 10 of 14 were persistently urine-positive for illicit (non-prescribed) opioid use, after self-reporting no current opioid use. Notably, of the 17 women pre-screened, none were study eligible and no women were enrolled, primarily because most pre-release opioid-dependent female inmates had enrolled in pre-release methadone maintenance.

One participant received XR-NTX, but remained incarcerated indefinitely and was withdrawn from the study, yielding a final analyzed sample of $n = 33$. Baseline characteristics were similar, with the exception of significantly younger mean age (40 versus 47) among XR-NTX participants (Table 1). Two randomized participants declined XR-NTX. One XR-NTX-induced participant had an initial release date delayed and received a second XR-NTX injection prior to his eventual release. Twelve (75%) XR-NTX participants accepted the second injection at the week 4 visit following release. Time from XR-NTX injection to release was a mean 6 days (median, 5 days). There were no differences in rates of complete study visits versus dropout between arms; overall, 70% completed the week 4 visit and 50% the week 8 visit (Fig. 1).

Table 1 Baseline characteristics at arrest, extended-release naltrexone (XR-NTX) versus no-medication controls ($n = 33$).

	XR-NTX ($n = 16$)	*No medication* ($n = 17$)
Male	16 (100%)	17 (100%)
Age, years (mean, range)	40 (26–52)	47 (39–58)[a]
Homeless	4 (25%)	7 (41%)
Employed	5 (31%)	2 (12%)
Health insurance (Medicaid)[b]	12 (75%)	14 (82%)
Heroin misuse, 7 days pre-arrest	15 (94%)	17 (100%)
Heroin bags/day (group mean, range)	7 (0–25)	7 (1–23)
Prescription opioid misuse, 7 days pre-arrest	2 (13%)	3 (18%)
Injection drug use, 7 days pre-arrest	3 (19%)	2 (12%)
Injection drug use, life-time	7 (44%)	4 (24%)
Cocaine use, 7 days pre-arrest	11 (69%)	10 (59%)
Alcohol, drinks/day (group mean, range)	3 (0–24)	2 (0–14)

[a]$P<0.01$ for difference in mean age between arms (t-test). [b]All participants with health insurance-reported active NY State Medicaid coverage.

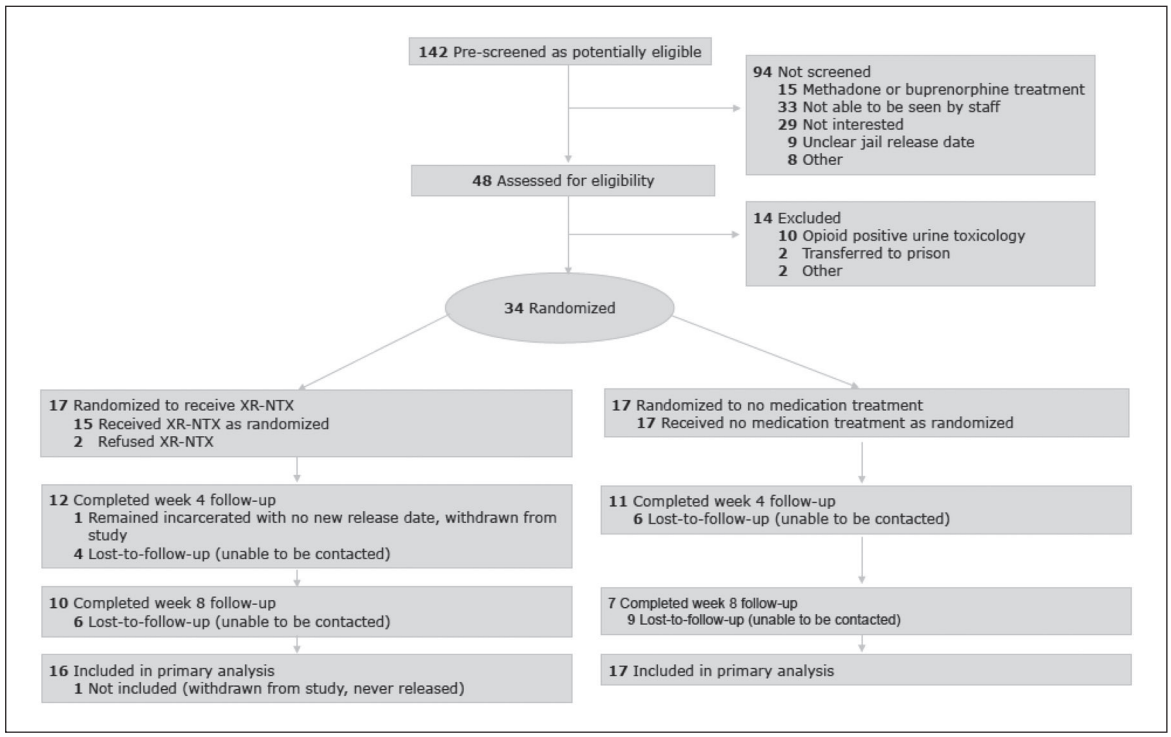

Figure 1 Participant flow (CONSORT diagram)

The primary outcome of opioid relapse at week 4 was observed in six (38%) XR-NTX and 15 (88%) controls, a significant difference, and odds ratio (OR) of 0.08 [95% confidence interval (CI) = 0.01–0.48] (Table 2). An adjusted OR for age was similar (0.05, CI = 0.01–0.42). Rates of negative opioid urine toxicologies (neither positive or missing) and confirmed abstinence, defined as all visits completed with negative opioid urines and negative self-report, were significantly higher for XR-NTX participants at weeks 4 and 8.

Results for other secondary outcomes showed no differences between arms: post-release injection drug use (25% XR-NTX versus 6% controls), cocaine misuse (56 versus 47%), participation in other community drug treatment (19 versus 12%) and re-incarceration rates (31 versus 41%). Re-incarceration rates were lower among eight participants completing both XR-NTX injections versus the remaining 25 participants from both arms receiving only the one pre-release injection or none [one (13%) versus 11 (44%) re-incarcerated, $P<0.03$]. There were no study-related serious adverse events, including no observed or self-reported accidental opioid overdoses or deaths.

DISCUSSION

In this proof-of-concept randomized controlled pilot effectiveness trial, XR-NTX was effective as opioid relapse prevention among primarily heroin-dependent adult males leaving a large urban jail. XR-NTX's long-acting injectable formulation was acceptable to a large proportion of participants, half (eight of 16) of whom left jail and remained opioid-abstinent after 4 weeks versus two of 17 among controls. To our knowledge, this is the first published effectiveness evaluation of pre-release XR-NTX opioid treatment among a soon-to-be-released prisoner population.

While this was a small pilot study, the results are in line with previous estimations of XR-NTX's opioid relapse prevention treatment effects. In the Krupitsky *et al.* pivotal trial, rates of confirmed abstinence (versus any opioid use or dropout) at week 4 were roughly 80% among XR-NTX and 60% among placebo, versus 50 and 13% among XR-NTX and TAU, respectively, in this trial. These lower rates of clinical success in both arms of this study may reflect higher expected relapse rates and myriad other re-entry challenges facing released prisoners versus community-recruited clinical trial volunteers in the Russian pivotal trial. Our results are also comparable with previous randomized and cohort evaluations of methadone and buprenorphine therapies for soon-to-be-released opioid-dependent jail and prison inmates, all of which demonstrate feasibility and a clear effectiveness advantage versus referral- or post-release-only treatment initiation [4–8,22]. Opioid disorders now have several FDA-approved and effective maintenance (buprenorphine, methadone) and relapse prevention (naltrexone) medications. Prisons and jails are ideal environments for the promotion of these treatments [23].

Rates of important secondary outcomes were similar between arms. Re-incarceration for new criminal charges occurred in more than half of participants, and no deaths or non-fatal overdoses were observed in either arm. While the study was powered a priori to detect significant differences in the primary opioid relapse outcome at week 4, it was not powered to detect much less frequent events, including overdose or death, or other common outcomes with multiple contributing factors, such as re-incarceration. Following participation in this pilot study, several participants from both arms enrolled into a related community-based, CJS-focused XR-NTX randomized trial (NCT00781898) and were subsequently followed for a further 18 months. This will allow for a future exploratory analysis of longer-term post-release outcomes in a small subset of participants. Few participants in either arm pursued other addiction treatments post-release, probably reflecting the overall challenge of engaging drug-involved populations in evidence-based treatment at re-entry without mandates or other incentives [24].

There are clear limitations to this pilot, proof-of-concept study. In keeping with a randomized effectiveness design intended to duplicate real-world treatment conditions, this

Table 2 Post-release opioid relapse and related outcomes, extended-release naltrexone (XR-NTX) versus no medication controls ($n = 33$).

	XR-NTX (*n = 16*)	*No medication* (*n = 17*)	*Fisher's* (*P-value*)	*Crude odds ratio* (*95% CI*)
Primary outcome: opioid relapse weeks 1–4	6 (38%)	15 (88%)	<0.004	0.08 (0.01–0.48)*
Confirmed opioid abstinence,† weeks 1–4	8 (50%)	2 (13%)	<0.03	7.5 (1.3–44)
% Opioid negative urine toxicologies, weeks 1–4	59% (24 of 41)	29% (13 of 45)	<0.009	3.5 (1.4–8.5)
Opioid relapse, weeks 1–8	8 (50%)	16 (93%)	<0.03	0.13 (0.02–0.78)
Confirmed opioid abstinence,† weeks 1–8	8 (50%)	1 (7%)	<0.007	16 (1.7–151)
% Opioid negative urine toxicologies, weeks 1–8	59% (34 of 57)	24% (15 of 62)	<0.0001	4.6 (2.1–10)

*Adjusted odds ratio 0.05 (0.01–0.42) for opioid relapse at week 4 by treatment assignment, adjusted for age.
†Confirmed opioid abstinence was defined as attending all follow-up visits and providing only negative opioid self-reports and urine toxicologies. CI = confidence interval.

trial did not include a placebo control, blinded treatment assignment or blinded outcome assessments, factors which introduced treatment and/or retention biases compared to the more strictly controlled conditions of a placebo efficacy design. We justified a pilot study of 'intervention versus no intervention' based on previously established efficacy data for XR-NTX, our experience with a similar open-label non-placebo, jail-based opioid treatment study [4], and while concurrently conducting and planning much larger trials evaluating XR-NTX's effectiveness, all of which employ non-placebo, non-blinded RCT designs (NCT00 781898, NCT01999946, NCT02032433). Similar rates of follow-up visit attendance between arms and the use of an objective biological assessment (urine samples) in determining the primary outcome strengthened external validity.

Other limitations included the failure to enroll any female participants. Our finding that most pre-screened female inmates were already on pre-release methadone maintenance and were therefore naltrexone ineligible demonstrated a long-standing acceptance and adoption of methadone in NYC jails, as well as the practical challenges to alternative trial designs, such as an agonist versus antagonist comparison. Further, this limited study sample did not represent widespread adoption of a new treatment paradigm by a large urban jail with thousands of opioid-dependent individuals incarcerated annually; rather, a small study team worked for 3 years to recruit and implement the trial. Follow-up randomized trials at two US sites intend to recruit a much larger sample while oversampling women (NCT01246401, NCT02110264). Clearly, further research is needed to confirm our initial finding of XR-NTX's post-release relapse prevention effectiveness, assess outcomes over a longer post-release period and study XR-NTX's dissemination and potential cost-effectiveness on a wider scale.

In conclusion, in this pilot proof-of-concept randomized effectiveness trial XR-NTX was associated with lower opioid relapse rates among opioid-dependent adult males released from a large urban jail. XR-NTX appears to be an important treatment option for CJS-involved individuals not otherwise accessing or interested in methadone or buprenorphine maintenance.

Clinical trial registration

ClinicalTrials.gov Identifier: NCT01180647

Declaration of interests

None.

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