



Full length article

The effects of extended-release injectable naltrexone and incentives for opiate abstinence in heroin-dependent adults in a model therapeutic workplace: A randomized trial



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ABSTRACT

Aim: To determine whether extended-release injectable naltrexone (XR-NTX), incentives for opiate abstinence, and their combination reduce opiate use compared to a usual care control and whether the combination reduces opiate use compared to either treatment alone.

Design: Randomized 2 × 2 single-site controlled trial conducted from November 2012 through May 2016. After a detoxification and oral naltrexone induction, participants were assigned to a Usual Care, Abstinence Incentives, XR-NTX, or XR-NTX plus Abstinence Incentives group for a six-month intervention period.

Setting: A model therapeutic workplace where participants could work on automated computer programs that targeted job-skills training for 4 h every weekday for 24 weeks and earn about \$10 per hour.

Participants: 84 heroin-dependent adults who were unemployed and medically approved for naltrexone. Most participants were male (71.4%), African American (80.1%), and cocaine dependent (71.4%).

Measurements: The primary outcome measure was the percentage of urine samples negative for opiates that were collected at once weekly assessments (24 per participant) that were not part of the intervention and for which participants were paid \$10 for completing.

Intervention: Participants who attended the workplace provided thrice-weekly urine samples. Abstinence Incentives participants had to provide opiate-free urine samples to maintain maximum pay. XR-NTX participants received one injection every 4 weeks and were required to take injections in order to work and to maintain maximum pay. Usual Care participants were not offered XR-NTX and opiate urinalysis results did not affect pay.

Findings: A large percentage (65 of 149; 43.6%) of individuals failed the induction protocol required for randomization and to be eligible to receive XR-NTX. When missing urine samples were considered positive, there was no significant interaction between XR-NTX and Abstinence Incentives. XR-NTX plus Abstinence Incentives participants provided significantly more opiate-negative samples (81.3%, SD 39.0%) than XR-NTX participants (64.5%, SD 47.9%; aOR 10.4, 95% CI 1.3–85.5; $P = .030$). When urine samples were not replaced, there was a significant interaction between XR-NTX and Abstinence Incentives (aOR 77.0, 95% CI 1.3–4432; $P = 0.036$); XR-NTX plus Abstinence Incentives participants provided significantly more opiate-negative samples (99.6%, SD 0.1%) than XR-NTX participants (85.0%, SD 35.7%; aOR 147.6, 95% CI 6.3–3472; $P = 0.002$), Abstinence

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Incentives participants (91.9%, SD 27.3%; aOR 121.7, 95% CI 4.8–3067; $P = 0.004$), and Usual Care participants (78.7%, SD 41.0%; aOR 233.4, 95% CI 9.4–5814; $P < .001$). No other group differences were significant. **Conclusion:** XR-NTX plus incentives for opiate abstinence increased opiate abstinence, but XR-NTX alone did not. XR-NTX can promote opiate abstinence when it is combined with incentives for opiate abstinence in a model therapeutic workplace.

1. Introduction

Rates of opioid-related overdose deaths and the prevalence of opioid use disorder have increased to epidemic levels in the United States (Han et al., 2015; Jones et al., 2015; Rudd et al., 2016). The federal government has responded to this crisis by expanding access to medication-assisted treatments (SAMHSA, 2019; Volkow et al., 2014), which include the full agonist methadone, the partial agonist buprenorphine, and the full antagonist naltrexone. There is considerably more evidence of methadone and buprenorphine's efficacy for reducing overdose and opioid use compared to that for naltrexone (Sordo et al., 2017; Mattick et al., 2009, 2014). Nevertheless, naltrexone may be preferred by some patients because it poses no risk of abuse, carries no special prescribing regulations, and is available as a monthly extended-release injection to improve adherence (marketed as Vivitrol; XR-NTX) (Bigelow et al., 2012).

Although developed to increase adherence, many patients who start taking XR-NTX discontinue treatment prematurely for a variety of reasons (e.g., drop-out, felt cured, lack of efficacy) (Jarvis et al., 2018a). In recent clinical trials of XR-NTX, 39% (Lee et al., 2016), 42% (Krupitsky et al., 2011), and 53% (Lee et al., 2018) of participants stopped taking XR-NTX before the end of the 6-month interventions. Like methadone and buprenorphine, the effects of XR-NTX on opioid relapse and use do not persist once treatment is stopped (Lee et al., 2016), and many patients will require treatment beyond 6 months. To address the chronic relapsing nature of opioid use disorder (US Department of Health and Human Services, 2019), treatments must incorporate strategies to promote reliable adherence to XR-NTX over extended periods of time.

Incentive-based treatments (i.e., contingency management) have been shown to increase adherence to medications to treat substance use disorder, including naltrexone (DeFulio et al., 2012). We previously demonstrated that offering financial incentives for accepting oral naltrexone (Dunn et al., 2013), an early injectable naltrexone formulation (Everly et al., 2011), and XR-NTX (DeFulio et al., 2012) significantly increased adherence rates. In the XR-NTX trial, 74% of participants who were offered incentives for taking XR-NTX accepted all six injections compared to 26% of participants not offered incentives for adherence.

Although the incentive intervention increased XR-NTX adherence nearly threefold, it did not decrease opiate use. One reason is because opiate use continued despite blockade by naltrexone – roughly 60% of participants used opiates at least once while blocked by XR-NTX, and 18% of collected samples among those who were taking XR-NTX tested positive for opiates. Why opiate use may continue despite XR-NTX blockade is not well understood (Jarvis et al., 2018b), but to maximize its clinical potential, XR-NTX may need not only a targeted intervention to improve adherence but also additional components to address opiate use. Incentive-based interventions that target opiate abstinence directly are an ideal choice because they are highly effective in reducing opiate use (Prendergast et al., 2006), including when added to agonist-based treatment (Robles et al., 2002; Holtyn et al., 2014), and they can be seamlessly integrated into incentive-based interventions targeting XR-NTX adherence.

The present study evaluated the combined effects of XR-NTX and incentives for opiate abstinence on opiate use. The aims were to determine whether XR-NTX, incentives for opiate abstinence, and their combination reduce opiate use compared to a usual care control and whether the combination reduces opiate use compared to either treatment alone. We hypothesized that XR-NTX, incentives for opiate abstinence, and their combination would increase opiate abstinence

versus a usual care control. We also hypothesized that combining XR-NTX and incentives for opiate abstinence would increase opiate abstinence relative to each of the interventions presented alone.

2. Methods

2.1. Design

This study was a randomized, 2×2 , single-site, controlled clinical trial conducted from November 2012 through May 2016. The intervention period lasted 24 weeks.

2.2. Participants

Participants ($N = 84$) were recruited from detoxification programs and street outreach in Baltimore, MD from November 2012 through May 2016. Individuals were eligible if they were between 18 and 65 years old, lived in or near Baltimore, MD, were unemployed, met DSM-IV criteria for opioid dependence, reported using heroin at least 21 of the last 30 days while living in the community, reported and showed visible signs (track marks) of injection drug use, and were medically approved for naltrexone. The injection drug criterion was removed in January 2015 in an effort to increase study recruitment. Recruitment for the trial stopped when the funding period ended. Individuals were not eligible if they expressed interest in agonist treatment, earned over \$200 in taxable income in the previous 30 days while living in the community, had current DSM-IV major Axis I disorders (i.e., schizophrenia, psychosis), had current suicidal or homicidal ideation, had physical limitations that prevented them from using a keyboard, required medical use of opioids, were pregnant or breastfeeding, had serum aminotransferase levels over three times normal, or were allergic to naltrexone or other components of XR-NTX. The study was approved by the Johns Hopkins Medicine Institutional Review Board, and all participants provided written informed consent. The trial protocol is available in Supplement 1.⁴

2.3. Treatment setting

The study was conducted in a therapeutic workplace, a model workplace in which employment-based incentives are arranged to address both opiate abstinence and employment. All participants were invited to attend the workplace for 4 h every weekday to work on automated computer programs that targeted job-skills training. Participants could earn \$8 per hour in base pay for attending the workplace and up to \$2 in productivity pay based on their performance on training programs. Counseling was offered to all participants but none consistently used this resource during the study. Detailed descriptions of the therapeutic workplace procedures can be found elsewhere (Silverman et al., 2005).

2.4. Assessments

Assessments were conducted at study intake and weekly after random assignment for 24 weeks. Primary intake assessments included the Addiction Severity Index – Lite (McLellan et al., 1985) to evaluate

⁴ Supplementary material can be found by accessing the online version of this paper at <https://doi.org/10.1016/j.drugalcdep.2018.12.026>.

medical, substance use, legal, educational, employment, and family histories and the Composite International Diagnostic Interview to evaluate psychiatric disorders (Compton et al., 1996). Participants also completed the Balloon Analogue Risk Task (Lejuez et al., 2002) and the Wisconsin Card Sorting Task (Heaton et al., 1993), which measure risk-taking propensity and executive functioning impairment, respectively. At weekly assessments, participants completed questionnaires about past-week risky drug use and sexual behaviors and provided details about past-week cocaine and heroin use. These and other assessments of exploratory measures are not reported here. Participants earned \$10 for completing each weekly assessment.

Urine samples were collected under same-sex staff observations and tested for evidence of opiates (morphine > 300 ng/ml) and cocaine (benzoylecgonine > 300 ng/ml) every Monday, Wednesday, and Friday and at each weekly assessment (if assessment occurred on a Tuesday or Thursday). Blood samples were collected to monitor liver function testing at intake and prior to participants' second and fifth XR-NTX injections. Females received urine pregnancy tests at intake and before each XR-NTX injection. If a participant had aminotransferase levels over three times normal or became pregnant, XR-NTX was discontinued immediately.

2.5. Design and groups

2.5.1. Prerandomization procedures

A total of 149 individuals enrolled in the prerandomization portion of the trial and were required to have completed an opioid detoxification (beforehand or as part of the prerandomization procedure) and an induction onto oral naltrexone to be eligible for randomization, which was overseen by study physicians and guided solely by clinical judgment. Oral naltrexone dosing increased gradually until a maintenance dose of 100 mg on Monday and Wednesday and 150 mg on Friday was reached. Oral naltrexone induction was completed within 2 weeks. The opioid detoxification was completed by most participants prior to their intake ($n = 70$; 83%), and details on the detoxification were not collected. Fifty-six percent (84 of 149) of individuals completed the prerandomization procedures and were randomized in the full trial. Further information on the opioid detoxifications, induction procedures, and outcomes has been previously reported elsewhere (Jarvis et al., 2017a).

2.5.2. Stratification and random assignment

Research staff who were involved in the study used a computerized urn randomization procedure (Lachin et al., 1988) to randomize and balance groups on three characteristics that could influence opiate abstinence: cocaine use, risk-taking propensity, and executive functioning. Cocaine use was based on any cocaine-positive urine sample the week before randomization. Risk-taking propensity and executive functioning were collected at intake and were stratified based on rolling medians. Participants were invited to attend the therapeutic workplace for the 24-week intervention and randomized to one of four intervention groups: Usual Care, XR-NTX, Abstinence Incentives, or XR-NTX plus Abstinence Incentives. All participants were offered substance use counseling and referrals to specialized services (e.g., for housing, legal, mental health problems).

2.5.3. Usual care

Usual Care participants were not offered XR-NTX (or oral NTX) and could work and earn incentives in the therapeutic workplace regardless of whether their urine samples tested positive for opiates.

2.5.4. Abstinence incentives

Abstinence Incentives participants were not offered XR-NTX (or oral NTX). These participants were required to submit opiate-negative samples every Monday, Wednesday, and Friday to maintain the maximum base pay. If a participant submitted an opiate-positive sample or did not provide a urine sample, their base pay was reset to \$1 per hour. Thereafter, base pay increased by \$1 per hour for each day the participant provided an opiate-negative sample and attended the workplace to the maximum of \$8 per hour.

2.5.5. XR-NTX

XR-NTX participants were offered six XR-NTX injections, one every 4 weeks. To promote XR-NTX adherence, these participants were required to accept XR-NTX to work and maintain the maximum base pay. If a participant refused or missed an injection (> 3 days from the scheduled date), they were not allowed to work until the injection was accepted and their base pay was reset to \$1 per hour. After accepting the injection, their base pay increased by \$1 per hour for each day the participant attended the workplace to the maximum of \$8 per hour. There was no impact on workplace access or incentives if participants provided a urine sample that tested positive for opiates.

2.5.6. XR-NTX plus abstinence incentives

XR-NTX and Abstinence Incentives participants were required to accept XR-NTX and submit opiate-negative urine samples every Monday, Wednesday, and Friday, with both impacts on workplace access and incentives as outlined above.

2.6. Outcome measures

The primary outcome measure was the percentage of weekly urine samples negative for opiates (binary yes/no for each of 24 weekly assessments). Weekly assessments were scheduled and incentivized (\$10 per week) independent of work attendance, performance, and group assignment to ensure high and non-differential rates of data collection across groups. The assessment included a urinalysis in addition to other secondary self-report measures (not reported here). The urine results from these once weekly urine assessments were determined *a priori* to be the primary outcome. Secondary outcomes were the percentage of weekly urine samples negative for cocaine, the percentage of XR-NTX injections accepted, the percentage of participants accepting all six XR-NTX injections, the percentage of workdays attending the therapeutic workplace, and retention in the therapeutic workplace. Heroin injection was originally a primary outcome measure also, but it was omitted because injection drug use was eliminated from the inclusion criterion to increase recruitment (see Participants section above).

2.7. Statistical analysis

Sample size calculations were based on the rates of opiate abstinence observed in previous studies evaluating incentives for XRNTX adherence (DeFulio and Silverman, 2012) and incentives for opiate abstinence in participants enrolled in opiate pharmacotherapy (Robles et al., 2002; Holtyn et al., 2014; Silverman et al., 2001). The expected opiate-negative rates for the primary outcome for each group were: Usual Care (55%), XR-NTX (72%), Abstinence Incentives (75%), and XR-NTX plus Abstinence Incentives (92%). Assuming an alpha of .05, we estimated that a sample size of 96 would have 80% power to detect these differences for the four planned group comparisons: Usual Care versus XR-NTX, Usual Care versus Abstinence Incentives, XR-NTX versus XR-NTX plus Abstinence Incentives; Abstinence Incentives versus XR-NTX plus Abstinence Incentives. We chose a target enrollment of 124 participants, but the final sample size was reduced ($N = 84$) because of recruitment difficulties and because of substantial budgetary reductions that were outside of the control of the investigator.

Longitudinal mixed effects multivariable logistic regression was used to analyze the effects of the study interventions on weekly opiate and cocaine urinalysis results during the 24-week treatment period. Correlations over time within individuals were accounted for with random intercepts. Analyses were adjusted using the three stratification variables (cocaine use, risk-taking propensity, and executive function) that were selected *a priori*. In order to assess the possible synergistic effects of XR-NTX and abstinence incentives, this model included terms for each intervention, as well as their interaction. Comparisons among the four groups were made via linear combinations of the parameter estimates from this interaction model. In this way, we compared each of the

three intervention groups to the Usual Care group, and also compared the XR-NTX plus Abstinence Incentives group to the XR-NTX group and to the Abstinence Incentives group. Rates of missing urine samples between groups were compared using one-way ANOVA. Urinalysis results were analyzed two ways – with missing data considered missing and omitted from the analysis (missing missing) and with missing data considered as positive for opiates and cocaine (missing positive). The missing positive analysis was considered primary.

Retention in the workplace was analyzed using a Cox proportional hazards model. Group summary measures of XR-NTX adherence and attendance were analyzed using independent *t*-tests. The group comparison of perfect XR-NTX adherence was analyzed using a chi-square test. Alpha was set at .05 for all tests and models were conducted using Stata version 13.

3. Results

3.1. Participant characteristics and flow through study

Participants' characteristics at study intake and flow through the study are shown in Table 1 and Fig. 1, respectively. Of the 84 participants, 71.4% were men and 80.1% were black or African American; mean age (SD) was 42.7 (10.5) years. Participants reported using heroin for a mean (SD) of 16.4 (10.2) years. Most participants reported intravenous heroin use as their primary route of administration (81.0%) and were also dependent on cocaine (71.4%).

3.2. Opiate use

Many participants (36%) continued to use opiates while under XR-NTX blockade (see XR-NTX participants, Fig. 2), but combining incentives for opiate abstinence with XR-NTX significantly decreased opiate use: Only 2 of the 451 (< 1%) collected samples for participants in the XR-NTX plus Abstinence Incentives group tested positive for opiates (Fig. 2), and no participants in the XR-NTX plus Abstinence Incentives group tested positive for opiates while under XR-NTX blockade. Table 2 contains observed rates and adjusted odds ratios for comparisons among the groups derived via linear combinations of parameter estimates from the longitudinal logistic mixed effects model (reported in Supplement 3).⁴ XR-NTX plus Abstinence Incentives participants submitted significantly higher rates of opiate-negative samples

than the XR-NTX participants based on both the missing-missing and missing-positive analyses (Fig. 2, Table 2), with adjusted odds ratios of 147.63 (95% CI: 6.3–3472) and 10.4 (95% CI: 1.3–85.5), respectively. XR-NTX plus Abstinence Incentives participants submitted significantly higher rates of opiate-negative samples compared to the Abstinence Incentives (aOR: 121.7; 95% CI: (4.8–3067) and Usual Care participants (aOR: 233.4; 95% CI: 9.4–5814) in the missing-missing analysis, but these effects were not statistically significant in the missing-positive analysis. Neither the Abstinence Incentives participants nor the XR-NTX participants differed from the Usual Care participants on either type of analysis (missing-missing or missing-positive).

Of the 2016 scheduled weekly urinalyses for opiates and cocaine, 1606 (79.7%) were completed. There were no differences in rates of urine sample collection between the intervention groups ($F_{3,80} = 0.42$, $P = .74$; M [SD] Usual Care: 84.7% [22.9], Abstinence Incentives: 77.3% [28.5], XR-NTX: 75.8% [30.4], and XR-NTX plus Abstinence Incentives: 81.7% [29.3]). Opiate abstinence rates were high in general across the groups, including Usual Care (all groups > 64% missing positive; > 78% missing missing).

3.3. Cocaine use

Cocaine abstinence rates did not differ between any of the intervention groups and Usual Care or between the combined XR-NTX plus Abstinence Incentives intervention and individual intervention groups (Table 2).

3.4. Workplace attendance

Participants spent a mean (SD) of 58.7% (30.4) of days attending the workplace during the intervention and were retained in the workplace intervention for 20.3 (7.0) of the 24 weeks (Table 3). Attendance ($F_{3,80} = 0.58$, $P = .63$) and workplace retention ($\chi^2 = 3.1$, $P = .68$) did not differ between the intervention groups.

3.5. XR-NTX

Of the 288 scheduled XR-NTX injections offered to participants, 233 (80.9%) were received. Continuous adherence to XR-NTX for all six injections occurred for 30 of 48 (62.5%) participants. There were no differences in adherence ($t = 0.85$, $P = .40$) or continuous adherence (χ^2

Table 1
Participant Characteristics at Study Intake.

Characteristic	No. (%)			
	Usual Care (n = 18)	Abstinence Incentives (n = 18)	XR-NTX (n = 25)	XR-NTX + Abstinence Incentives (n = 23)
Demographic characteristic				
Age, mean (SD), y	42.2 (11.4)	41.1 (11.1)	43.9 (10.3)	43.1 (10.0)
Male	15 (83)	14 (78)	15 (60)	16 (70)
Black/African American	15 (83)	13 (72)	19 (76)	21 (91)
Not married	16 (88)	17 (94)	22 (88)	22 (96)
High school diploma or GED	11 (61)	13 (72)	18 (72)	12 (52)
Currently on parole/probation	3 (17)	5 (28)	6 (24)	5 (22)
Usually unemployed past 3 years	10 (56)	6 (33)	16 (64)	12 (52)
Drug use characteristics				
Heroin^a				
Past 30-d use, mean (SD), d	29.8 (0.5)	29.3 (1.8)	29.2 (1.8)	28.7 (2.6)
Lifetime use, mean (SD), y	15.9 (9.5)	16.8 (11.3)	18.6 (10.8)	14.3 (9.3)
Primary route of administration IV	14 (78)	17 (94)	22 (88)	15 (65)
Cocaine				
Cocaine-dependent	12 (67)	12 (67)	20 (80)	16 (70)
Past 30-d use, mean (SD), d	13.9 (14.0)	13.9 (13.9)	12.3 (13.5)	15.6 (13.5)
Primary route of administration IV	8 (44)	5 (28)	8 (32)	11 (48)
Lifetime drug treatments received, mean (SD)	6.3 (5.0)	5.8 (5.7)	6.5 (6.4)	3.8 (3.4)

Abbreviations: XR-NTX, extended-release injectable naltrexone; GED, General Educational Development test; IV, intravenous.

^a Opioid dependence (heroin) was an inclusion criterion.

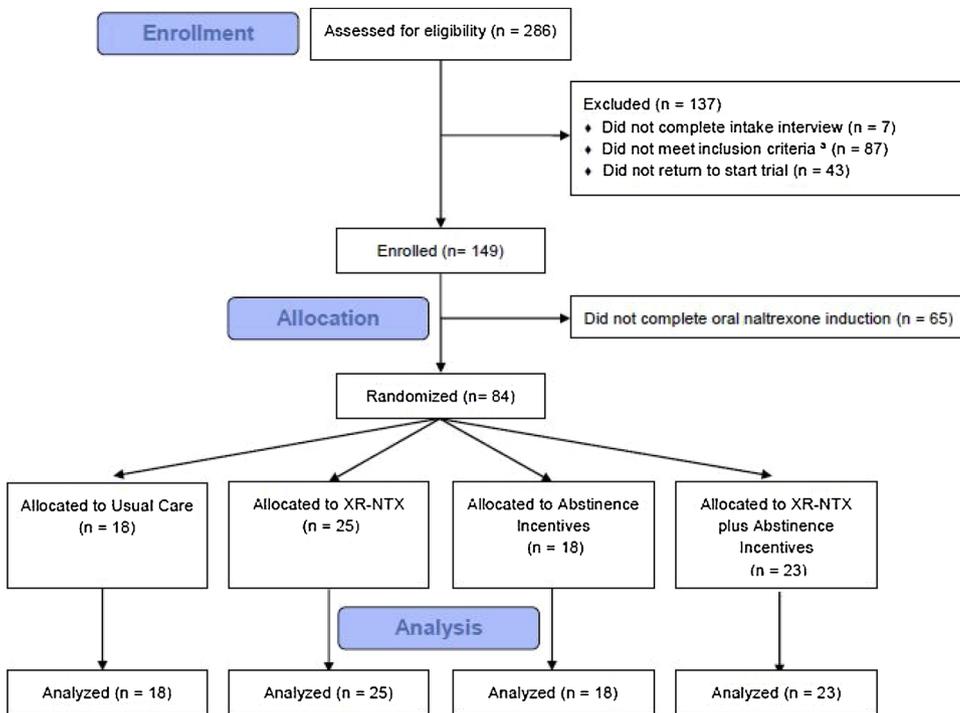


Fig. 1. Consort Diagram. Abbreviations: XR-NTX, extended-release injectable naltrexone ^a Top three reasons included not reporting using heroin at least 21 of the last 30 days (n = 28), earning over \$200 in taxable income in the previous 30 days (n = 19), and not having visible track marks (n = 12; note this criterion was removed midway through trial to increase recruitment).

= 0.1, $P = .71$) between the two intervention groups offered XR-NTX. The most common reason for not receiving an XR-NTX injection was missing a scheduled appointment (50/55; 90.1%). Five injections were medically withheld. Injections were withheld from two participants in the XR-NTX group due to elevated aminotransferase levels (Participants 11 and 13, Injections 5 and 6; Fig. 2). The first injection for a female participant in the XR-NTX plus Abstinence Incentives group (Participant 1; Fig. 2) was withheld due to a positive pregnancy test. This participant did not return for subsequent XR-NTX injections.

3.6. Adverse events

Study-related adverse events were rare and did not differ across groups (see Supplement 2).⁴ One death was recorded in the Abstinence Incentives group approximately six months after the intervention ended when staff attempted to contact the participant for a study assessment. The cause of death is not known.

4. Discussion

As in previous research with XR-NTX (DeFulio et al., 2012) and studies with different formulations of naltrexone (Dunn et al., 2013;

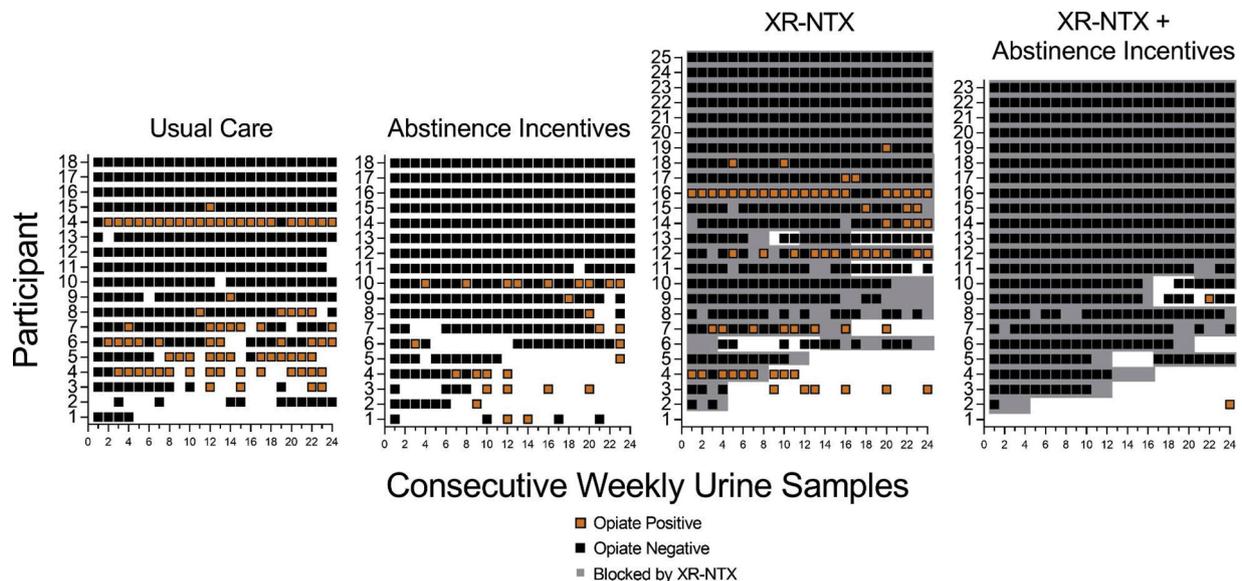


Fig. 2. Participant-level Opiate Use and XR-NTX Adherence During Treatment. Within each panel, rows of data represent an individual participant. Urinalysis results were determined *a priori* to be from the 24 once weekly assessments completed during the intervention period. Urine samples were considered blocked by XR-NTX if they were collected within 31 d of receiving XR-NTX. Empty squares represent missed assessments. Data are arranged within each panel from top to bottom (highest to lowest) first by collection rates and then by rates of opiate abstinence. Abbreviations: XR-NTX, extended-release injectable naltrexone.

Table 2
Observed Rates and Group Comparisons of Weekly Opiate and Cocaine Urinalysis Results.

	Observed Rates (% Negative)				Comparison to Usual Care						Comparison of XR-NTX + Abstinence Incentives to group			
	Usual Care	Abstinence Incentives	XR-NTX	XR-NTX + Abstinence Incentives	Abstinence Incentives		XR-NTX		XR-NTX + Abstinence Incentives		Abstinence Incentives		XR-NTX	
	Mean % (SD)	Mean % (SD)	Mean % (SD)	Mean % (SD)	Odds Ratio ^a (95% CI)	P	Odds Ratio ^a (95% CI)	P	Odds Ratio ^a (95% CI)	P	Odds Ratio ^a (95% CI)	P	Odds Ratio ^a (95% CI)	P
Opiate Negative														
Missing-missing ^b	78.7 (41.00)	91.9 (27.30)	85 (35.70)	99.6 (0.07)	1.92 (0.1–24.4)	0.62	1.58 (0.1–18.4)	0.72	233.39 (9.4–5814)	< .001	121.74 (4.8–3067)	0.004	147.63 (6.3–3472)	0.002
Missing-positive ^c	66.7 (47.20)	71.1 (45.40)	64.5 (47.90)	81.3 (39.00)	2.26 (0.2–21.6)	0.48	0.58 (0.1–4.6)	0.61	6.00 (0.7–54.9)	0.11	2.66 (0.3–24.9)	0.39	10.4 (1.3–85.5)	0.03
Cocaine Negative														
Missing-missing ^b	80.6 (39.60)	72.3 (44.60)	80.2 (39.90)	83.4 (37.30)	0.12 (0.004–3.0)	0.20 ^a	0.66 (0.03–15.2)	0.80 ^d	0.95 (0.04–23.7)	0.97 ^d	7.84 (0.4–168.0)	0.19 ^d	1.43 (0.1–27.9)	0.82 ^d
Missing-positive ^c	68.3 (46.60)	56.3 (49.70)	60.8 (48.90)	68.1 (46.60)	0.36 (0.1–2.4)	0.30	0.2 (0.03–1.2)	0.08	0.9 (0.1–5.8)	0.91	2.47 (0.4–15.8)	0.34	4.46 (0.8–26.1)	0.09

Abbreviations: XR-NTX, extended-release injectable naltrexone.

^a Odds ratios are calculated as linear combinations of parameter estimates from a model adjusting for *a priori* specified stratification variables (cocaine use, risk-taking propensity, and executive functioning). Only one XR-NTX and Abstinence Incentive interaction was significant (aOR 77.0, 95% CI 1.3–4432; *P* = .036; opiates, missing-missing; see Supplement 3 for model parameter⁴).

^b A total of 1606 samples estimates).

^c A total of 2016 samples.

^d Adjusted model did not converge. Values are from unadjusted model.

Everly et al., 2011), many participants who received naltrexone continued to use opiates while under naltrexone blockade. Relative to the usual care control group, combining incentives for opiate abstinence with XR-NTX significantly decreased opiate use based on the missing-missing analysis but not the missing-positive analysis. The combination of XR-NTX and opiate abstinence incentives had significant and robust effects on opiate abstinence compared to XR-NTX alone, independent of how missing urine samples were handled. However, neither XR-NTX alone nor opiate abstinence incentives alone affected opiate abstinence. All groups provided high and comparable rates of urine samples, confirming the rigorous nature of the analysis and the obtained results. Taken together, this study suggests that XR-NTX may be useful in promoting opiate abstinence when it is combined with incentives for opiate abstinence, but not when it is used alone.

Incentives may be an ideal adjuvant to treatment with XR-NTX since incentives can be used simultaneously to promote adherence to XR-NTX and to promote opiate abstinence. In this study, participants offered XR-NTX were required to take scheduled injections of XR-NTX to continue attending the therapeutic workplace and earning incentives, and participants took a remarkably high percentage of XR-NTX injections. Specifically, participants took about 81% of the available injections; and 62% of participants took all scheduled XR-NTX injections. Our previous research showed that incentives were effective in substantially increasing

adherence to different formulations of naltrexone (Dunn et al., 2013; Everly et al., 2011), including XR-NTX (DeFulio et al., 2012). The additional requirement that participants also provide opiate-negative urine samples to maintain maximum pay transformed XR-NTX from an ineffective (i.e., when used alone) to a highly effective intervention.

In contrast to two previous studies of XR-NTX (Lee et al., 2016; Krupitsky et al., 2011), this study failed to show an effect on opiate use of XR-NTX compared to a usual care control group. Although we cannot know for certain why the results of this study differ from those previous trials, a few differences in the studies should be noted. The initial study that evaluated XR-NTX (Krupitsky et al., 2011) showed an effect of XR-NTX on opiate use, but that effect was confounded with differences in treatment retention. In that study, XR-NTX significantly increased retention in treatment, yet the study considered missing urine samples positive for opiates. As a result, it is not clear that XR-NTX actually affected opiate use or whether it just improved treatment retention. In contrast, in this study, all four groups were retained at comparable rates and provided high and statistically similar rates of urine samples. The excellent retention and high rates of urine sample collection across groups in this study might be due to the fact that this study was conducted in the therapeutic workplace. All participants could earn about \$10 per hour, 4 h per day, 5 days per week and attended the workplace at very high rates independent of urinalysis results. We have seen a

Table 3
Workplace Attendance and XR-NTX Adherence.

Outcome	Observed Rates			
	Mean (SD)			
	Usual Care	Abstinence Incentives	XR-NTX	XR-NTX + Abstinence Incentives
Workplace attendance, % ^a	59.2 (28.4)	61.0 (32.2)	52.4 (32.9)	63.5 (28.2)
Workplace retention, week ^a	22.7 (4.5)	19.5 (7.3)	19.4 (7.9)	20.0 (7.2)
XR-NTX injections accepted, % ^a			77.3 (32.2)	84.8 (27.9)
Received all 6 XR-NTX injections, % ^a			60.0	65.2

^a No significant between-group difference.

similar benefit of conducting studies of naltrexone in the therapeutic workplace previously (DeFulio et al., 2012; Dunn et al., 2013; Everly et al., 2011). Because of its effect in retaining patients in treatment, the therapeutic workplace may be an ideal context to study medications like XR-NTX.

The results of the second study (Lee et al., 2016) did not appear to be affected by differential urine sample collection, but the participants included in that study were very different from the participants in the current study. In the prior study (Jarvis et al., 2018a) only 9% of participants required an opioid detoxification before receiving the first injection of XR-NTX, only about one third of participants used any opioid in the 30 days before enrolling in that study, and participants used cocaine at relatively low rates. In marked contrast, all participants in the current study completed an opioid detoxification prior to enrolling in the trial, all participants reported using heroin at least 21 of the last 30 days while living in the community, and most participants in this study (71%) met criteria for cocaine dependence. Related to this last point, our prior research showed that opiate use under naltrexone blockade was associated with cocaine use (DeFulio et al., 2012; Dunn et al., 2013; Everly et al., 2011).

There are several limitations of the current study. First, the study employed a fairly small sample size, which may have been partially responsible for the failure of this study to show effects of XR-NTX on opiate use. Our previous research failed to show clear effects of different formulations of naltrexone in three studies with relatively small sample sizes (DeFulio et al., 2012; Dunn et al., 2013; Everly et al., 2011), but we did see a small effect of naltrexone on opiate use when the results of those three trials were combined (Jarvis et al., 2017b). Nevertheless, because of the large effect of the XR-NTX plus Abstinence Incentives intervention, the sample size of this study was sufficient to detect an effect of the incentives for opiate abstinence on opiate use compared to XR-NTX alone.

Second, not all effects of the XR-NTX plus Abstinence Incentives intervention were significant based on the different methods of handling missing data, and the confidence intervals for significant effects were very wide. The effect of the XR-NTX plus Abstinence Incentives intervention produced significant increases in opiate abstinence relative to the XR-NTX alone based both on the missing-missing analysis and missing-positive analysis. Thus, the superiority of XR-NTX plus Abstinence Incentives compared to XR-NTX alone is clear. However, the XR-NTX plus Abstinence Incentives intervention only increased opiate abstinence relative to the Abstinence Incentives only and Usual Care control groups based on the missing-missing analysis. As a result, the effect of XR-NTX plus Abstinence Incentives compared to the Abstinence Incentives only and Usual Care control groups should be considered tentative.

Third, our method for weekly testing of illicit opioid use did not consider prescription opioids or other synthetic formulations (e.g., fentanyl). We chose our weekly outcome measure because participants were dependent heroin users. However, it is possible that participants used other opioids that we did not test for weekly. We tested for other illicit opioid use (i.e., oxycontin) at monthly assessments, and rates of urine samples testing positive for oxycontin were low overall (< 2.5%), suggesting this did not occur often. Monthly urine tests that were positive for buprenorphine or methadone were also low overall (< 10%), and all but one urine sample reflected illicit use rather than enrollment in a treatment program. We did not test urine samples for naltrexone, and information on engagement in non-study oral NTX or XR-NTX for participants assigned to the Usual Care or Abstinence Incentives groups were not tracked. However, we suspect few participants, if any, in the Usual Care or Abstinence Incentives groups continued any NTX after randomization. Fourth, because randomization occurred after successful oral naltrexone induction, our abstinence results do not take induction failures into account, which were high (44%), similar to those observed in previous studies (Lee et al., 2018), and highlight a significant barrier to clinical use of XR-NTX that our trial did not directly

address. Although our final sample may represent a particularly highly motivated group of individuals, this may be the case for all studies of XR-NTX, which requires 7–10 days of abstinence to begin. Fifth, rates of opiate-negative urine samples provided by participants in the Usual Care group were higher than expected and higher than treatment as usual control groups in other studies (Lee et al., 2016; Krupitsky et al., 2011), which limited our ability to detect significant differences. These higher abstinence rates may be explained by unique aspects of our control group (e.g., all were given a part-time job as part of the treatment).

Financial incentives have been used effectively to promote a wide range of health behaviors (Volpp et al., 2009; El-Sadr et al., 2017), including drug abstinence (Halpern et al., 2015; Peirce et al., 2006; Pilling et al., 2007). This study used employment-based incentives, which are particularly useful for the many adults with opioid use disorder who are unemployed. However, these findings were derived from a specialized treatment setting that may not generalize to other populations (e.g., employed adults, prescription opioid users) though should be relevant to other incentive interventions.

5. Conclusion

Many participants who received XR-NTX continued to use opiates while under XR-NTX blockade; however, combining incentives for opiate abstinence with XR-NTX decreased opiate use. The combination of XR-NTX and opiate abstinence incentives had significant and robust effects on opiate abstinence, but neither XR-NTX alone nor opiate abstinence incentives alone affected opiate abstinence. Taken together, this study suggests that in a model therapeutic workplace XR-NTX may be useful in promoting opiate abstinence when it is combined with incentives for opiate abstinence, but not when it is used alone. The combination of XR-NTX and incentives for opiate abstinence could be remarkably effective in treating opioid use disorders and reducing the risk of opioid overdose.

Conflicts of interest

None of the study authors have conflicts of interest or disclosures to declare.

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Contributors

Drs. Silverman and Jarvis had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2018.12.026>.

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