Published in final edited form as:

Addiction. 2017 May ; 112(5): 830–837. doi:10.1111/add.13724.

Effects of incentives for naltrexone adherence on opiate abstinence in heroin-dependent adults

Brantley P. Jarvis, August F. Holtyn, Anthony DeFulio, Kelly E. Dunn, Jeffrey J. Everly, Jeannie-Marie S. Leoutsakos, Annie Umbricht, Michael Fingerhood, George E. Bigelow, and Kenneth Silverman

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine (B P Jarvis PhD, A F Holtyn PhD, K E Dunn PhD, J J Everly PhD, J-M S Leoutsakos PhD, A Umbricht MD, G E Bigelow PhD, K Silverman PhD). Department of Medicine, Johns Hopkins University School of Medicine (M Fingerhood MD). A. DeFulio is now at the Department of Psychology, Western Michigan University. J. J. Everly is now at the Department of Psychology, University of Pittsburgh at Greensburg

Abstract

Aim—To test whether an incentive-based intervention that increased adherence to naltrexone also increased opiate abstinence.

Design—Post-hoc combined analysis of three earlier randomized controlled trials that individually showed that incentives for adherence to oral and to extended-release injection naltrexone dosing schedules increased naltrexone adherence but not opiate abstinence.

Setting—Outpatient therapeutic workplace in Baltimore, MD, USA.

Participants—140 unemployed heroin-dependent adults participating from 2006–2010.

Interventions—Participants were hired in a model workplace for 26 weeks and randomized to a Contingency (n=72) or Prescription (n=68) group. Both groups were offered naltrexone. Contingency participants were required to take scheduled doses of naltrexone in order to work and earn wages. Prescription participants could earn wages independent of naltrexone adherence.

Measures—Thrice-weekly and monthly urine samples tested for opiates and cocaine and measures of naltrexone adherence (percentage of monthly urine samples positive for naltrexone or percentage of scheduled injections received). All analyses included prerandomization attendance, opiate use, and cocaine use as covariates. Additional analyses controlled for cocaine use and naltrexone adherence during the intervention.

Correspondence to: Kenneth Silverman, Center for Learning and Health, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA. ksilverm@jhmi.edu.

Conflicts of Interests: All other authors report no conflicts of interest.

Author's Contributions

BPJ, AFH, J-MSL, GEB, and KS conceived and designed the analysis. AU, MF, GEB, and KS developed the trial protocols. AD, KED, JJE, AU, MF, GEB, and KS obtained the data. BPJ created the figures and tables, and J-MSL analyzed the data. BPJ and KS wrote the first draft of the manuscript. All authors interpreted the data, contributed to, and approved the final manuscript.

Findings—Contingency participants had more opiate abstinence than Prescription participants (68.1% vs. 52.9% opiate-negative thrice-weekly urine samples, respectively; and 71.9% vs. 61.7% opiate-negative monthly urine samples, respectively) based on initial analyses (thrice-weekly samples, OR = 3.3, 95% CI = 1.7–6.5, $p < .01$; monthly samples, OR = 2.6, 95% CI = 1.0–7.1, $p = .06$) and on analyses that controlled for cocaine use (thrice-weekly samples, OR = 3.9, 95% CI = 3.3–4.5, $p < .01$; monthly samples, OR = 3.4, 95% CI = 1.1–11.1, $p = .04$), which was high and associated with opiate use. The difference in opiate abstinence rates between Contingency participants and Prescription participants was reduced when controlling for naltrexone adherence (monthly samples, OR = 1.1, 95% CI = 0.7–1.7, $p = .84$).

Conclusions—Incentives for naltrexone adherence increase opiate abstinence in heroin-dependent adults, an effect that appears to be due to increased naltrexone adherence produced by the incentives.

Introduction

Naltrexone could be an ideal medication for the treatment of opioid use disorder because it blocks the subjective, reinforcing, and physiological effects of opioids;¹ has no abuse liability; and is less regulated.² However, a major limitation is that fewer than one-third of participants who begin taking naltrexone adhere to the medication in the long-term (e.g., six months).³ An extended-release injectable suspension of naltrexone (XR-NTX) was developed and is approved for the treatment of opioid use disorder in the USA. XR-NTX appears to improve adherence compared to oral naltrexone,⁴ but adherence rates are still poor.^{5–9}

In addition to poor adherence, clinical trials evaluating oral naltrexone and XR-NTX have suffered from low and differential retention and differential rates of urine sample collection between treatment groups,^{3,5,10} which has prevented appropriate evaluations of the effects of naltrexone on opioid use.¹¹ An exception to these limitations is a recent open-label trial among criminal justice offenders in the USA,¹² which found XR-NTX increased time to relapse and opioid abstinence compared to treatment as usual. Although these findings are encouraging, only 61% of participants accepted all six injections.

To address poor adherence, we have been systematically evaluating a contingency management intervention¹³ that uses employment-based incentives to promote long-term adherence to naltrexone treatment. Under this intervention, incentives are delivered as wages to participants who we hire and pay to work in a model workplace where they complete job skills training. To promote naltrexone adherence, some participants are randomly assigned to a Contingency group in which they are required to take scheduled doses of naltrexone in order to work and earn maximum pay. Others are assigned to a Prescription group that is offered naltrexone but can work and earn wages independent of taking naltrexone. Because all participants can work and earn wages, this research model produces high rates of retention and data collection in both groups. This has permitted a rigorous analysis of the effects of naltrexone adherence on opiate abstinence.

In three controlled clinical trials using this model,^{14–16} we showed that unemployed, heroin-dependent adults who were randomly assigned to the Contingency group took significantly

more doses of oral and XR-NTX^{14,16} naltrexone than those assigned to the Prescription group. These trials demonstrated that an incentive-based intervention can increase naltrexone adherence. However, none of the trials showed significant between-group differences on opiate abstinence despite consistently higher rates of opiate abstinence among those assigned to the Contingency versus Prescription group.

The purpose of the present study was to combine data from our three earlier trials, thereby achieving a larger overall sample size. We chose these trials because they are the only ones to our knowledge that evaluate the use of incentives for naltrexone adherence and are not confounded by differential rates of data collection. The primary aim was (1) to test whether an incentive-based intervention targeting adherence to oral naltrexone and extended-release injectable suspensions increased opiate abstinence. Because cocaine use and naltrexone nonadherence were both associated with opiate use in the original trials, secondary aims were (2) to test whether cocaine use during the intervention altered the effect of naltrexone adherence on opiate abstinence, and (3) to determine if naltrexone adherence was responsible for the intervention effects on opiate abstinence by testing the effects of the intervention while controlling for naltrexone adherence.

Methods

Design

This was an individual patient post-hoc analysis in which we combined and analyzed data from three previously published clinical trials conducted from 2006–2010.^{14–16} Each trial evaluated the same employment-based incentive intervention for naltrexone adherence implemented in the same setting. One trial used oral naltrexone¹⁵ and two trials used XR-NTX of different formulations (Depotrex®¹⁶ and Vivitrol®¹⁴). Full details on each trial have been reported elsewhere.^{14–16} The methods and outcome measures for each trial were identical unless otherwise noted.

Participants

Participants (N = 140) of the original trials were recruited from opioid detoxification programs and street outreach; were not interested in methadone or buprenorphine maintenance treatment; were at least 18 years old; lived in or near Baltimore City in Maryland, USA; were unemployed; met DSM-IV criteria for opioid dependence;¹⁷ self-reported using heroin on at least 21 of the last 30 days while living in the community; and were medically approved for naltrexone. The oral naltrexone trial¹⁵ also required that participants report injection drug use in the last 30 days, have visible track marks, and provide a urine sample that tested positive for both opiates and cocaine upon entry into opioid detoxification. Individuals were excluded if they had current hallucinations, delusions, or thought disorders; had current homicidal or suicidal ideation; were currently incarcerated, in a halfway house, or under constant monitoring; earned more than \$200 in taxable income in the past 30 days; were pregnant or breastfeeding; were required to use opioids for medical purposes; had physical limitations that prevented use of a keyboard; or had serum aminotransferase levels more than three times above normal.

Treatment Context

The original trials were conducted in the Therapeutic Workplace, a model workplace where participants could earn hourly wages for participating in jobs skills training.¹⁸ Participants could work four hours each week day and earn \$8 per hour in hourly pay plus about \$2 per hour for their performance on training programs. All participants were offered individual substance abuse counseling.

Assessments

The main assessments collected at intake included the Addiction Severity Index-Lite¹⁹ to evaluate medical, substance use, legal, educational, employment, and family histories; and the Composite International Diagnostic Interview,²⁰ a diagnostic tool for psychiatric disorders. Liver function tests were performed routinely, and participants who became pregnant or had significantly abnormal liver function were discontinued from naltrexone. Urine samples were collected under direct observation and tested for opiates and cocaine every Monday, Wednesday, and Friday. Additional assessments were conducted each month in conjunction with collection and testing of urine samples for opiates, cocaine, buprenorphine, methadone, benzodiazepines, and amphetamines. Use of drugs other than opiates and cocaine was rare (<7% of samples tested).

Naltrexone Induction

All participants completed extended or brief in-patient detoxification before being invited to attend the Therapeutic Workplace. Participants who completed extended in-patient detoxification were immediately inducted onto oral naltrexone. Those completing brief in-patient detoxification were required to continue outpatient detoxification at the Therapeutic Workplace, and during this time attendance and wages were contingent on providing opioid-negative samples. Induction onto oral naltrexone was guided by clinical judgment, and all participants reached maintenance doses of 100 mg on Monday and Wednesday and 150 mg on Friday. The induction phase lasted approximately two weeks for the XR-NTX trials^{14,16} or four weeks for the oral naltrexone trial.¹⁵

Experimental Groups

Following oral naltrexone induction, participants were invited to the Therapeutic Workplace for 26 weeks, and assigned randomly to a Contingency or Prescription group with stratification by attendance, opiate-negative urine samples, and cocaine-negative urine samples during the study induction period. Contingency participants were required to take scheduled doses of naltrexone to attend the Therapeutic Workplace and earn maximum pay. If participants in the Contingency group did not take a scheduled dose of naltrexone, they were not permitted to enter the workplace until they resumed naltrexone, and their hourly pay was reset from \$8 per hour to \$1 per hour. Pay increased by \$1 per hour, to the maximum of \$8 per hour, for each day of attendance once naltrexone was resumed. Prescription participants could attend the workplace and earn maximum wages independent of naltrexone adherence.

Naltrexone formulation and dosing varied across the three trials. For the oral naltrexone trial,¹⁵ adherence was directly observed every Monday (100 mg), Wednesday (100 mg), and

Friday (150 mg). The XR-NTX Depotrex® trial¹⁶ verified receipt of injections given once every three weeks, and the XR-NTX Vivitrol® trial¹⁴ verified receipt of injections given once every four weeks. Participants assigned to the Prescription groups in the oral naltrexone trial were given a monthly supply of oral naltrexone¹⁵ or offered injections at the appropriate intervals for the XR-NTX trials.^{14,16} All medications were provided at no cost to participants.

Outcome Measures

The primary outcome measures were adherence to naltrexone, opiate abstinence, and cocaine abstinence. Adherence in the oral naltrexone trial¹⁵ was defined as providing a urine sample at monthly assessments that tested positive for naltrexone (i.e., 5 ng/ml). Adherence in the XR-NTX trials^{14,16} was observed directly. At monthly assessments, participants were categorized as under naltrexone blockade based on their urine sample for the oral naltrexone trial¹⁵ or whether they were within the protection window for the XR-NTX trials (3 weeks for Depotrex®¹⁶ and 4 weeks for Vivitrol®¹⁴). Opiate and cocaine abstinence were assessed from urine samples collected thrice weekly and at monthly assessments. If urinary morphine or benzoylecgonine concentrations were at or below 300 ng/ml, the sample was considered negative for opiates or cocaine, respectively.

Data Analysis

Participant characteristics at intake were compared across treatment groups using chi-square tests for categorical variables and *t*-tests for continuous variables. The main analyses were based on data from when the naltrexone incentive intervention was in effect, which varied across trials. For urine samples collected thrice weekly, the number of samples included was 54 for the XR-NTX Depotrex® trial,¹⁶ 72 for the XR-NTX Vivitrol® trial,¹⁴ and 78 for the oral naltrexone trial.¹⁵ For urine samples collected at monthly assessments, the number of samples included was 4 for the XR-NTX Depotrex® trial,¹⁶ 5 for the XR-NTX Vivitrol® trial,¹⁴ and 6 for the oral naltrexone trial.¹⁵ Missing urine samples were analyzed both as missing-positive (missing samples counted as positive) and missing-missing (missing samples omitted from calculations) for opiates and cocaine and are reported as missing-positive unless noted otherwise. Tests of urine samples for adherence from the oral naltrexone trial¹⁵ were analyzed as missing-negative (missing samples counted as negative). Longitudinal mixed effects regression models²¹ with random effects for both study and participant were used to account for heterogeneity across trials. These models give equal weight to early and later outcomes during the intervention. These analyses were used to evaluate the effects of the incentive-based intervention (Contingency vs. Prescription groups) on naltrexone adherence, drug abstinence, and their relationships. All analyses were intent-to-treat and were adjusted for attendance, opiate-negative urine samples, and cocaine-negative urine samples during the induction period. Statistical analyses were conducted using Stata v.13,²² and alpha was set at .05.

Results

Participant Characteristics

Table 1 displays participant characteristics at intake by group collapsed across trials. Participants were mostly male, Black, middle-aged, and dependent on cocaine. More than one-third had not completed high school or earned a GED, and approximately half were on parole or probation. The only significant difference between groups was on past 30 day income obtained from employment, but for both groups this income was very small.

Effect of Incentives for Naltrexone Adherence

Contingency participants had significantly higher rates of naltrexone adherence than Prescription participants (Table 2). Significantly more participants in the Contingency group also had perfect adherence to naltrexone throughout the study than participants in the Prescription group (Table 2).

Associations of Naltrexone Adherence, Cocaine Abstinence, and Opiate Abstinence

Naltrexone adherence was associated with significantly more opiate-negative urine samples at monthly assessments (Figure 1B). Rates of opiate-negative samples were 85.0% when participants were under naltrexone blockade compared to 62.7% when participants were not under blockade (missing-missing, *OR* [95% CI] = 3.6 [2.5–5.4], *p* < .01).

Urine samples that tested negative for cocaine were significantly more likely also to test negative for opiates, both at monthly (missing-missing, *OR* [95% CI] = 17.5 [10.6–29.1], *p* < .01) and thrice-weekly assessments (missing-missing, *OR* [95% CI] = 11.5 [9.8–13.5], *p* < .01). Rates of opiate-negative urine samples were 92.5% when samples were cocaine-negative compared to 49.6% when samples were cocaine-positive at monthly assessments (Figure 1). For urine samples collected thrice weekly, rates of opiate-negative urine samples were 93.8% when urine samples were cocaine-negative compared to 58.3% when cocaine-positive.

The adverse relation of cocaine use to opiate abstinence occurred for both Contingency and Prescription participants (Figure 1A) and when participants were and were not under naltrexone blockade (Figure 1B). The association of naltrexone blockade with opiate abstinence was still significant after controlling for cocaine-positive samples (Figure 1B). There were no significant interactions between cocaine use and group or between cocaine use and naltrexone blockade.

Effect of Incentives for Naltrexone Adherence on Opiate and Cocaine Abstinence

During the one-week period prior to randomization, Contingency and Prescription participants did not differ significantly on rates of opiate-negative urine samples (92.6% vs. 92.7%, respectively, *p* = .99) or cocaine-negative urine samples (81.0% vs. 77.5%, respectively, *p* = .58).

Table 2 shows observed rates and regression results for opiate abstinence, cocaine abstinence, and collection rates during the intervention period. Collection rates did not differ

significantly between the Contingency and Prescription groups. Contingency participants submitted higher rates of opiate-negative urine samples than Prescription participants (Table 2; Figure 2). This effect was significant for thrice-weekly urinalyses for both methods of handling missing data (missing-positive and missing-missing) but not for monthly urinalyses ($p = .06$). There were no significant differences on any measures of cocaine abstinence between the Contingency and Prescription participants.

When we controlled for cocaine-positive samples, Contingency participants had significantly higher rates of opiate-negative urine samples than Prescription participants for monthly and thrice-weekly samples (Table 2). A separate regression analysis that adjusted for naltrexone adherence revealed that the effect of incentives on monthly opiate abstinence decreased for missing-missing and missing-positive samples (Table 2), suggesting that greater opiate abstinence in the Contingency participants was due to increased adherence to naltrexone.

Discussion

The present analysis showed that incentives for naltrexone adherence produced statistically significant increases in opiate abstinence. Compared to participants who could earn incentives independent of taking naltrexone, those required to take scheduled doses of naltrexone to earn incentives had a 43% increase in adherence to naltrexone and roughly a 10% to 17% increase in rates of opiate-negative urine samples, depending on the measure used (see Table 2). The magnitude of the opiate abstinence effect was small relative to the magnitude of the naltrexone adherence effect. Cocaine use was high in the study populations, and cocaine use was associated with decreases in opiate abstinence. When we controlled for cocaine use, participants exposed to incentives for naltrexone adherence (i.e., Contingency participants) had significantly higher rates of opiate abstinence than participants not exposed to those incentives (i.e., Prescription participants). Importantly, when the analysis that assessed the effect of incentives on opiate abstinence was adjusted for naltrexone adherence, the effect of incentives for naltrexone adherence on opiate abstinence was reduced. This suggests that higher rates of opiate abstinence for participants who received incentives for naltrexone adherence (Contingency group) were due to increased naltrexone adherence.

In the absence of psychosocial interventions that target medication adherence, naltrexone's effectiveness is limited, even with the newer FDA-approved XR-NTX formulation specifically designed to limit dosing frequency and improve adherence. In the three trials reported here, nearly two-thirds of scheduled doses were not taken when incentives for adherence were not provided. Offering incentives for taking scheduled doses of naltrexone more than doubled rates of adherence and promoted increases in opiate abstinence.

Although incentives increased naltrexone adherence and, in turn, opiate abstinence, some participants continued to use opiates while under naltrexone blockade.^{23,24} In the present analysis, we found that challenging the naltrexone blockade was strongly associated with cocaine use. Of the 58 monthly samples that tested positive for opiates while under blockade, 49 (84.5%) also tested positive for cocaine. Why cocaine use is associated with opiate use for participants under naltrexone blockade is unclear. Participants may have used

both drugs concurrently and through the same route (i.e., “speedballing”) or opiate use may have simply been more likely when participants were in cocaine-using environments. For participants not under blockade, this adverse association of cocaine use with opiate use was still present. Cocaine use did not eliminate the beneficial increase in opiate abstinence observed in those who received the incentive-based intervention.

Cocaine use throughout the trials was negatively associated with opiate abstinence. The use of incentives to promote cocaine abstinence is effective among individuals receiving agonist treatment for opioid use disorder²⁵ and may be necessary to maximize the effectiveness of antagonist treatment among individuals who take naltrexone but continue to use cocaine. The use of incentives to promote opiate abstinence is also effective among individuals receiving agonist treatment for opioid use disorder^{26,27} and could also be used to enhance further the effectiveness of antagonist treatment among individuals who take naltrexone but continue to use opiates under naltrexone blockade.

Although we used the same outcomes and data analytic approach that was reported in each of the three earlier individual trials, a notable limitation of the present study was that it was conducted as a post-hoc analysis. This was done because of the importance of determining whether beneficial effects on naltrexone adherence translated to beneficial effects on opiate use, and because the individual trials were underpowered to detect a significant difference on opiate abstinence.

Due to concerns regarding poor adherence, naltrexone use as a primary treatment for opioid use disorder has been discouraged except for individuals who are highly motivated to stop using opioids, such as healthcare professionals²⁸ and criminal justice offenders¹² who may face job loss and/or incarceration for continuing opioid use. However, the analysis reported here shows that, by harnessing the power of incentives, challenging populations who are not interested in agonist therapy can be motivated to adhere to naltrexone and that this treatment can increase opiate abstinence. Future work should evaluate models of extending and maintaining incentive-based interventions to promote long-term naltrexone adherence and drug abstinence.²⁹

Acknowledgments

AU is a consultant for Braeburn Pharmaceuticals and has stock ownership in the following pharmaceutical and biotech companies: Novartis, Roche Holding, Actelion, Galenica, Gilead Sciences, Incyte Corp., Sonova Holding, Straumann Holding, and Titan Pharmaceuticals. GEB has received research support from Orexo Pharmaceuticals and consulted for Transcept Pharmaceuticals and Braeburn Pharmaceuticals.

Role of Funding Source

This work was supported by the National Institute on Drug Abuse of the National Institutes of Health (R01DA019386, R01DA019497, and T32DA07209). Alkermes, Inc. supplied the medication (Vivitrol®) at no cost for one of the trials.¹⁷ Neither Alkermes, Inc. or the National Institutes of Health had any further role in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication. The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

References

1. Bigelow GE, Preston KL, Schmittner J, Dong Q, Gastfriend DR. Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: dose-effects and time-course. *Drug Alcohol Depend.* 2012; 123:57–65. [PubMed: 22079773]
2. Substance Abuse and Mental Health Services Administration. Federal Guidelines for Opioid Treatment Programs. HHS Publication. 2015 PEP15-FEDGUIDETOTP.
3. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev.* 2011; 4 CD001333.
4. Brooks AC, Comer SD, Sullivan MA, et al. Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: a quasi-experiment. *J Clin Psychiatry.* 2010; 71:478–1378.
5. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *The Lancet.* 2011; 377:1506–1513.
6. Bisaga A, Sullivan MA, Glass A, et al. A placebo-controlled trial of memantine as an adjunct to injectable extended-release naltrexone for opioid dependence. *J Subst Abuse Treat.* 2014; 46:546–552. [PubMed: 24560438]
7. Cousins SJ, Denering L, Crèvecœur-MacPhail D, et al. A demonstration project implementing extended-release naltrexone in Los Angeles County. *Subst Abuse.* in press.
8. Stein MD, Risi MM, Bailey GL, Anderson BJ. Linkage to primary care for persons first receiving injectable naltrexone during inpatient opioid detoxification. *J Subst Abuse Treat.* in press.
9. Wang A, Elman I, Lowen S, et al. Neural correlates of adherence to extended-release naltrexone pharmacotherapy in heroin dependence. *Translational Psychiatry.* 2015; 5:e531. [PubMed: 25781230]
10. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry.* 2006; 63:210–218. [PubMed: 16461865]
11. Silverman K, DeFulio A, Leoutsakos J. The potential value of a negative finding: an illustrative example. *JAMA Psychiatry.* 2013; 70:571–572. [PubMed: 23575653]
12. Lee JD, Friedmann PD, Kinlock TW, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med.* 2016; 374:1232–1242. [PubMed: 27028913]
13. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry.* 2008; 165:179–187. [PubMed: 18198270]
14. DeFulio A, Everly JJ, Leoutsakos JS, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. *Drug Alcohol Depend.* 2012; 120:48–54. [PubMed: 21782353]
15. Dunn KE, Defulio A, Everly JJ, et al. Employment-based reinforcement of adherence to oral naltrexone treatment in unemployed injection drug users. *Exp Clin Psychopharmacol.* 2013; 21:74–83. [PubMed: 23205722]
16. Everly JJ, DeFulio A, Koffarnus MN, et al. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: a randomized controlled trial. *Addiction.* 2011; 106:1309–1318. [PubMed: 21320227]
17. American Psychiatric Association. Diagnostic and statistical manual-text revision. Washington DC, USA: 2000.
18. Silverman K, Wong CJ, Grabinski MJ, et al. A web-based therapeutic workplace for the treatment of drug addiction and chronic unemployment. *Behav Modif.* 2005; 29:417–463. [PubMed: 15657415]
19. McLellan AT, Luborsky L, Cacciola J, et al. New data from the Addiction Severity Index: reliability and validity in three centers. *J Nerv Ment Dis.* 1985; 173:412–423. [PubMed: 4009158]
20. Compton WM, Cottler LB, Dorsey KB, Spitznagel EL, Magera DE. Comparing assessments of DSM-IV substance dependence disorders using CIDI-SAM and SCAN. *Drug Alcohol Depend.* 1996; 41:179–187. [PubMed: 8842630]

21. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982; 38:963–974. [PubMed: 7168798]
22. StataCorp LP. Stata Statistical Software: Release 13. 2013
23. Sullivan MA, Garawi F, Bisaga A, et al. Management of relapse in naltrexone maintenance for heroin dependence. *Drug Alcohol Depend*. 2007; 91:289–292. [PubMed: 17681716]
24. Sullivan MA, Bisaga A, Mariani JJ, et al. Naltrexone treatment for opioid dependence: Does its effectiveness depend on testing the blockade? *Drug Alcohol Depend*. 2013; 133:80–85. [PubMed: 23827259]
25. Peirce JM, Petry NM, Stitzer ML, et al. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: a National Drug Abuse Treatment Clinical Trials Network study. *Arch Gen Psychiatry*. 2006; 63:201–208. [PubMed: 16461864]
26. Silverman K, Wong CJ, Higgins ST, et al. Increasing opiate abstinence through voucher-based reinforcement therapy. *Drug Alcohol Depend*. 1996; 41:157–165. [PubMed: 8809505]
27. Robles E, Stitzer ML, Strain EC, Bigelow GE, Silverman K. Voucher-based reinforcement of opiate abstinence during methadone detoxification. *Drug Alcohol Depend*. 2002; 65:179–189. [PubMed: 11772479]
28. Ling W, Wesson DR. Naltrexone treatment for addicted health-care professionals: a collaborative private practice experience. *J Clin Psychiatry*. 1984; 45:46–48.
29. Silverman K, Holtyn AF, Morrison R. The therapeutic utility of employment in treating drug addiction: science to application. *Translational Issues in Psychological Science*. 2016; 2:203–212. [PubMed: 27777966]

Figure 1.

Percentage of urine samples negative for opiates during the intervention period by whether the sample was cocaine-positive, arranged by (A) whether the sample was submitted by a Contingency or Prescription group participant and (B) whether the sample was submitted while under naltrexone blockade. Numbers above each bar indicate the number of opiate-negative samples and total number within the category. Each odds ratio is shown with its 95% confidence interval. * = comparison statistically significant ($p < .05$) † = comparison controlled for cocaine urinalysis. Data are from monthly urine assessments for all three trials. Missing data were considered missing.

Figure 2.

(A) Percentage of urine samples negative for opiates during the intervention period by group. Bars show group means, and filled circles show percentages for individual participants. (B) Cumulative frequency distribution of opiate abstinence during the intervention period by group. Lines show the percentage of participants who submitted the corresponding percentage of opiate-negative samples on the x-axis or greater. For example, 76% of participants in the Contingency group submitted 50% or greater of samples negative for opiates compared to 63% of participants in the Prescription group. Data are from monthly urinalyses for all three trials. Missing data were considered positive.

Table 1

Participant Characteristics by Group (Collapsed across Trials)

Characteristic ^a	Contingency (n = 72)	Prescription (n = 68)	<i>p</i>
Age (years), mean (<i>SD</i>)	43.4 (8.2)	44.3 (8.2)	.51
Male (%)	59.7	55.9	.65
Black (%)	86.1	89.7	.52
Married (%)	12.7	16.2	.56
High school diploma or GED (%)	58.3	66.2	.34
Past 3 years usually unemployed (%)	65.3	64.7	.94
Income (\$), mean (<i>SD</i>), past 30 days by source			
Employment	0.0 (0.0)	7.5 (28.2)	.03
Welfare	108.0 (162.0)	150.8 (176.6)	.14
Pension, benefits, Social Security	120.6 (413.2)	133.3 (474.4)	.87
Mate, family, friends	288.1 (1229.4)	126.0 (288.0)	.29
Illegal	1143.1 (2413.8)	1189.7 (2750.0)	.92
Total income	1659.7 (2604.6)	1607.2 (2713.5)	.91
Lifetime 1 felony conviction (%)	86.1	94.1	.11
Currently on parole/probation (%)	45.8	50.0	.62
Past 30 days amount spent on drugs (\$), mean (<i>SD</i>)	1943.2 (2502.8)	1563.2 (2529.4)	.37
Past 30 days injection primary route of administration for 1 drug (%)	55.6	58.8	.70
BDI score (<i>SD</i>)	14.0 (10.8)	10.8 (9.0)	.06
Past 30 days cocaine use, mean (<i>SD</i>)	16.2 (12.4)	18.9 (11.6)	.20
Cocaine dependent (%) ^b	76.4	80.9	.52
Past 30 days experienced any drug problem, mean (<i>SD</i>)	24.7(10.6)	26.4 (8.2)	.29

Note.^aUnless otherwise noted, characteristics are taken from the Addiction Severity Index-Lite.^bTaken from the Composite International Diagnostic Interview. Bolded values indicate significant differences between groups.*SD* = standard deviation, GED = General Educational Development test, BDI = Beck Depression Inventory

Observed Rates and Mixed Effects Regression Results of Collection Rates, Naltrexone Adherence, and Drug Abstinence by Group (Collapsed across Trials)

Table 2

Outcome	Percentage ^a		Contingency vs. Prescription		Adjusted for Cocaine Use		Adjusted for Naltrexone Adherence	
	Contingency (n = 72)	Prescription (n = 68)	OR (95% CI) ^b	p	OR (95% CI) ^b	p	OR (95% CI) ^b	p
Rates of naltrexone adherence	78.0	35.0	8.9 (6.2–12.7)	<.01	c	c	d	d
Perfect naltrexone adherence	56.9	17.6	8.3 (3.5–19.8)	<.01	c	c	d	d
Monthly urinalysis ^e								
Opiate-negative								
Missing-positive	71.9	61.7	2.6 (1.0–7.1)	.06	3.4 (1.1–11.1)	.04	1.1 (0.7–1.7)	.84
Missing-missing	82.1	70.6	2.9 (1.0–8.6)	.06	3.8 (1.2–11.9)	.02	0.7 (0.5–1.1)	.08
Cocaine-negative								
Missing-positive	56.2	53.5	1.3 (0.4–3.8)	.64	d	d	c	c
Missing-missing	64.2	61.3	1.1 (0.3–3.7)	.88	d	d	c	c
Collected	87.5	87.9	1.1 (0.3–4.6)	.91	c	c	c	c
Thrice-weekly urinalysis ^e								
Opiate-negative								
Missing-positive	68.1	52.9	3.3 (1.7–6.5)	<.01	f	f	g	g
Missing-missing	90.3	73.0	3.2 (2.8–3.7)	<.01	3.9 (3.3–4.5)	<.01	g	g
Cocaine-negative								
Missing-positive	52.6	46.6	1.6 (0.7–3.4)	.27	d	d	c	c
Missing-missing	69.6	64.3	1.2 (0.3–4.3)	.82	d	d	c	c
Collected	75.3	72.4	1.8 (0.9–3.5)	.08	c	c	c	c

Note:

^aPercentages are observed and unadjusted values.

^bOdds ratios are from a mixed effects longitudinal regression model with random effects for both trial and subject.

^cOutcome variable was not expected to change based on covariate and so analysis was not performed.

^dOutcome variable was included as a covariate in the adjusted model and so is not reported.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Missing-positive", indicates that missing samples were treated as positives in calculations; "Missing-missing", indicates that missing samples were omitted from calculations.

Model did not converge.

The relationship between naltrexone adherence and opiate use was not possible to determine for thrice-weekly urinalyses; thrice-weekly adherence data were not collected from both groups in all trials.