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# Opioid use and dropout from extended-release naltrexone in a controlled trial: Implications for mechanism

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## Abstract

**Background and aims—**Extended-release formulations of naltrexone have emerged as effective treatment options for opioid use disorder. This post-hoc analysis examined the temporal relationship between episodes of opioid use and subsequent dropout in a placebo-controlled trial of extended-release injection naltrexone (XR-NTX) to draw inferences about the mechanism by which extended blockade of opioid receptors translates into clinical effectiveness.

**Design—**24-week multiple-site, double-blind, randomized trial of monthly XR-NTX versus placebo injections. We analyzed time to dropout from treatment using survival analysis with an extended Cox model as a function of treatment (XR-NTX vs placebo) and with weekly urine drug test (UDT) results for opioids at each week as a time-dependent covariate.

**Setting—**Thirteen addiction treatment programs in Russia; 2008–2009.

**Participants—**250 adults with opioid use disorder who had completed inpatient detoxification.

**Intervention—**XR-NTX injection or placebo injection every 4 weeks with weekly clinic visits and biweekly counseling.

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Conflict of interest information as required by *Addiction*

• COI details for past 3 years

○ Authors are also required to declare any financial conflict of interest arising from involvement with organizations that seek to provide help with or promote recovery from addiction. Any contractual constraints on publishing imposed by the funder must also be disclosed

DATA SHARING STATEMENT

The data collected in this study are proprietary to Alkermes, Inc. Alkermes, Inc. is committed to public sharing of data in accordance with applicable regulations and laws.

**Measurements—**Urine toxicology for opioids measured weekly and week of dropout from treatment.

**Findings—**The Cox model yielded a significant interaction of time-dependent urine toxicology by treatment ($P = 0.024$). Among patients receiving placebo, a positive UDT in a given week increased the risk for dropout from treatment in the subsequent week (hazard ratio [HR], 6.25; 95% confidence interval [CI], 3.6–10.0), whereas among patients receiving XR-NTX, a positive UDT result showed no significant effect on risk for dropout (HR, 1.67; 95% CI, 0.6–4.5). The proportion of patients who completed all 24 weeks without any positive UDT result was 31% on XR-NTX compared with 20% on placebo ($P = 0.051$).

**Conclusions—**Extended-release injection naltrexone (XR-NTX) was effective at reducing the risk of dropout from opioid use disorder treatment after an episode of opioid use. Just under a third of patients (31%) on XR-NTX had no opioid-positive urine tests across the trial, but the hypothesis that this would differ from placebo (20%) was not confirmed.

### Keywords

Extended-release naltrexone; opioid dependence; opioid use disorder; relapse; dropout; medication-assisted treatment

## INTRODUCTION

Long-acting parenteral formulations of the opioid receptor antagonist naltrexone have emerged as a viable option for the treatment of opioid use disorder. Clinical trials with long-acting injectable [1–3] and implanted [4, 5] naltrexone have shown post-induction treatment retention rates in the 40% to 50% range over 6 months, comparable to retention rates from clinical trials of buprenorphine [6–8] and as shown in recent trials directly comparing these two approaches [9, 10], although retention data have been mixed in observational and retrospective studies [11, 12]. This raises interest in the mechanism of the effectiveness of long-acting naltrexone as a treatment strategy—i.e., how does sustained blockade of opioid receptors by naltrexone translate into good clinical response?

Naltrexone binds to opioid receptors with high affinity, blocking the subjective and physiological effects of opioid agonists [13]. Extended-release naltrexone (XR-NTX) is a monthly injection of naltrexone approved for the prevention of relapse to opioid dependence following detoxification from opioids. Naltrexone was originally developed and fast-tracked into clinical use in an oral formulation based on the seminal preclinical work of Wikler, who proposed that an opioid antagonist would be an effective treatment for opioid use disorder based on operant conditioning theory [14–16]. Operant theory would suggest that extinction takes place during treatment with XR-NTX, as patients stop seeking opioids because episodes of opioid use are no longer reinforcing. Patients must be abstinent when they initiate XR-NTX, but subsequent opioid use in the absence of pharmacological blockade would be reinforcing and would engender resumption of regular opioid use. XR-NTX would prevent opioid reward and thus lead to extinction of opioid-taking behavior.

After the introduction of naltrexone, and partly as a result of clinical experience, it was recognized that the mechanism of naltrexone as treatment for opioid dependence is more

complex than that proposed by operant theory. Classical conditioning, wherein drug and non-drug cues (e.g. environmental stimuli previously associated with opioid use) serve as triggers to resumed opioid use, may be attenuated by naltrexone [17]. Cognition is also likely involved—if patients take opioids and experience that the effects are blocked by a medication, they may not try opioids again unless they have stopped the medication and know it has worn off [14]. This is consistent with clinical experience, wherein, rather than gradual reduction of opioid use as in extinction, patients receiving XR-NTX often report trying just a single dose or a few doses ("hits") of opioids, experiencing the blockade ("I felt nothing, and knew I was wasting my money") then ceasing further use. A related cognitive mechanism would be expectancy—patients refrain from using opioids because they believe the effects will be blocked, even if they have not tested the blockade. An analogous expectancy mechanism has been suggested to explain the effectiveness of disulfiram for alcohol use disorder: patients believe they will get sick so they do not drink [18]. The superiority of XR-NTX in double-blind, placebo-controlled trials [1, 2] argues against expectancy as the sole explanation. Additionally, naltrexone, by supporting initial abstinence, may provide a respite from the drug-using lifestyle, support participation in psychosocial treatment, and thus promote development of personal and lifestyle changes consistent with recovery from addiction.

We previously reported a secondary analysis on a small, 2-month, placebo-controlled trial of two doses of XR-NTX extended-release naltrexone formulation (192 and 394 mg, the latter dose similar to the current approved formulation for XR-NTX) that suggested that mechanisms beyond extinction are at work [19]. Most XR-NTX patients who used opioids, or "tested the blockade" during the study continued with treatment, whereas most placebo patients who used opioids during the study dropped out of treatment. Among the patients receiving XR-NTX who had a positive urine drug test (UDT) result, most had only one or two additional positive UDT results; the rest of the test results were negative. These observations are consistent with an extinction mechanism, blockade of drug cue–induced relapse, or knowledge of blockade discouraging more use. Of further interest, a third (13/40) of patients receiving XR-NTX (at either half or full dose) completed the 8-week trial with no positive UDT results, compared with none (0/17) on placebo. This suggests that XR-NTX may exert an effect on the tendency to use opioids that does not depend on episodes of use or testing the blockade [19].

Here we report a similar retrospective analysis of the effect of opioid use during treatment in a large, 6-month, double-blind, placebo-controlled trial of XR-NTX [2]. We hypothesized that: 1) XR-NTX would reduce the risk for dropout after a positive UDT result compared with placebo; and 2) more patients receiving XR-NTX than receiving placebo would have no opioid-positive UDT results throughout the entire 6-month trial.

## METHODS

### Study design

The design, methods and primary outcome analysis for this trial have been reported [2]. Briefly, this was a randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov, ) to test the efficacy of XR-NTX for the treatment of patients with opioid use disorder. Adults

who met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for opioid dependence were recruited from 13 inpatient treatment programs in Russia between July 3, 2008, and October 5, 2009. After providing informed consent, patients were eligible to be randomly assigned if they had completed detoxification within 30 days and had been abstinent from opioids for at least 7 days. Eligible patients were randomly assigned to active XR-NTX ($n = 126$) or matching placebo ($n = 124$) injections, administered before discharge from the inpatient unit and then every 4 weeks over 24 weeks of outpatient follow-up treatment. Patients were offered biweekly individual counseling for opioid dependence. The primary outcome analysis was a response profile analysis that showed XR-NTX, compared with placebo, was associated with more UDT-confirmed abstinent weeks [2]. A binary outcome reflecting good clinical response, defined as present and abstinent for at least 90% of weekly sessions, was also greater on XR-NTX (52%) than on placebo (31%; P=0.002) [20].

## Statistical analysis

For this secondary analysis, time (weeks) to dropout from treatment over the 24-week study was analyzed using survival analysis with an extended Cox model; the UDT result for opioids (positive or negative) at each week was a time-dependent covariate. The last visit day for patients who dropped out in the randomized treatment phase, consisting of 168 days (24 weeks), was defined as the day of dropout. Patients who continued in the study beyond 24 weeks were censored. Dropout from treatment was chosen as the outcome measure for this analysis because it is the most common failure mode for XR-NTX treatment of opioid use disorder. Patients typically use few opioids while receiving XR-NTX but then drop out of treatment, after which relapse is likely [19, 21]. The risk for dropout at a given week of the study was modeled as a function of the history of positive UDT results for opioids during the treatment period, treatment assignment (XR-NTX vs placebo) and their interaction.

$$\textbf{Model}: log\, h(t) = \alpha(t) + \beta_1 trt + \beta_2 udt(t) + \beta_3 trt * udt(t)$$

In the model, $h(t)$ represents the hazard of dropout from treatment at week $t$; $udt(t)$ represents the part of the weekly UDT results history that influences the hazard of dropout at week $t$. The interaction between treatment and time-dependent UDT was included in the model to test the association between positive UDT results by a given week (week $t$) and the risk for dropout in the next week (week $t + 1$) in relation to treatment (XR-NTX or placebo). In effect, this model takes into account the time-dependent weekly UDT results that change values over the course of the observation period before the patient drops out of the study, and thus provides a more accurate analysis of the data as compared to estimating the risk of dropout at week $t + 1$. No imputations were made for non-monotone missing UDT results. Any non-monotone missing UDT results before dropout were considered missing at random and were included in the UDT result history as missing. To explore the impact of different assumptions about missingness, models were fit imputing non-monotone missing data in four alternative ways: by using last observation carried forward (LOCF), as negative, as positive, or treated as a separate class.

We also examined the temporal pattern of clinic attendance and opioid UDT results descriptively by creating a graph displaying each patient's course over the 24-week trial, with each week marked (color coded) to indicate whether the patient attended treatment with an opioid-negative UDT result, the patient attended treatment with an opioid-positive UDT result, or the patient did not attend treatment. The number and proportion of patients with a positive UDT result in a given week, followed by dropout from treatment the next week, and the number and proportion of patients with all 24 weeks of UDT results present and negative (vs. 1 or more weeks positive or missing) were compared between treatment groups with a chi-square test. All tests were two-sided with an alpha level of 0.05.

## RESULTS

Baseline patient characteristics are shown in Table 1. This sample of patients with opioid dependence admitted to inpatient programs consisted predominantly of male, white heroin users whose average duration of cumulative opioid dependence was just under a decade.

The extended Cox model with treatment as a predictor and weeks of opioid use (UDT result positive) during the 24-week trial as a time-dependent covariate yielded a significant (hazard coefficient, −1.31; $P = 0.024$) interaction between treatment and episodes of opioid use (estimated effects were consistent when missing UDT results were replaced by self-reported opioid use: hazard coefficient, −1.34; $P = 0.022$). Among patients receiving placebo, positive UDT results in any preceding weeks increased the risk for dropout in a subsequent week by a factor of 6 (hazard ratio [HR], 6.25; 95% confidence interval [CI], 3.6–10.0), whereas among patients receiving XR-NTX, positive UDT results in any preceding weeks showed little effect on risk for dropout in a subsequent week (HR, 1.67; 95% CI, 0.6–4.5). Models run using a range of assumptions about the non-monotone missing data yielded similar treatment by episodes of use interactions: LOCF: coefficient = −1.33, $P = 0.022$; missing as negative: coefficient = −1.32, $P = 0.024$; missing as positive: coefficient = −1.39, $P = 0.017$; missing as a separate class: coefficient = −1.31, $P = 0.024$).

Figure 1 and Table 2 summarize the clinical course of each patient over the 24-week trial. In Figure 1, each row of dots represents a patient, and each column represents a week of the trial. The patient-rows are arranged in the following order: at the bottom, patients who attended all 24 weeks and had consistently negative UDT results; in the middle, patients who attended all 24 weeks and had one or more positive or missing UDT results; and at the top, patients who dropped out before completing the trial, arranged in order of the number of weeks completed.

Several patterns emerge on inspection of Figure 1. First, among the patients shown in the upper portion and who eventually dropped out, more patients receiving placebo showed a pattern by which a week with a positive UDT result (green triangle) was followed by dropout the next week: 20/124 patients (16%) receiving placebo compared with 4/126 patients (3%) receiving XR-NTX ($P < 0.001$), consistent with the finding of the Cox model. Meanwhile, an equal number of patients receiving placebo (52/124; 42%) and patients receiving XR-NTX (52/126; 41%) had a negative UDT result in the week before dropout. Second, in the group receiving XR-NTX, weeks of opioid use (green triangles) tended to

occur in isolation—a positive week was followed immediately by a negative week. In one or more instances in 16/124 patients (13%) receiving placebo, a week with a positive UDT result was followed immediately by another week with a positive UDT result, whereas only 6/126 patients (5%) receiving XR-NTX showed this pattern of consecutive weeks of positive UDT results ($P = 0.04$). Finally, on inspection of the lower portion of Figure 1, more patients receiving XR-NTX (31%; 39/126) were present and had negative UDT results across all 24 weeks compared with those receiving placebo (20%; 25/124) ($P = 0.051$).

## DISCUSSION

In accordance with our hypothesis, XR-NTX in this post hoc analysis was associated with a reduced risk for dropout from treatment immediately after episodes of opioid use, whereas for those receiving placebo, the risk for dropout after episodes of opioid use was high. This observation replicates the finding of our previous study [19] and suggests XR-NTX prevents episodes of opioid use (testing the blockade) from turning into dropout from treatment and presumably into relapse. This finding is consistent with the therapeutic mechanism suggesting that blockade by XR-NTX of reinforcing effects of opioids during episodes of use (testing the blockade) leads to the cessation of opioid-taking behavior. Inspection of Figure 1 also suggests that among patients receiving XR-NTX who showed evidence of opioid use, use was sporadic; most weeks being opioid-negative, with the occasional positive week occurring in isolation and not followed by one or more consecutive positive weeks. These findings also suggest the importance of XR-NTX blocking the reinforcing or priming effects of opioids when patients test the blockade.

In addition, we sought to test the hypothesis that XR-NTX would reduce the proportion of patients who test the blockade at all. This hypothesis was prompted by our previous study [19], which showed that a third of patients treated with long-acting naltrexone showed no evidence of opioid use across that 8-week trial. This complete lack of opioid use suggests an effect of XR-NTX on the tendency to use opioids that does not depend on testing the blockade. In the present trial, the proportion of patients who attended all 24 weeks and showed no evidence of opioid use (i.e. did not test the blockade) was numerically greater in patients receiving XR-NTX (31%) than in those receiving placebo (20%), but the difference was not significant ($P = 0.051$).

Clinical experience and data from other trials suggest that patients with opioid use disorder maintained on XR-NTX (once they complete detoxification and transition to XR-NTX) generally feel well and experience improved mood and reduced craving [22, 23]. This inference is supported by the finding in the primary outcome report from this trial that subjective craving for opioids was reduced with XR-NTX compared with placebo [2]. These findings run contrary to the traditional theory that persons with opioid use disorder have an inherent deficit in endogenous opioid activity and that blockade of opioid receptors would make them feel worse and would provoke craving. Blockade of opioid receptors by naltrexone might block conditioned drug-like effects [24], thereby blocking cue-induced craving and associated dysphoria. Several studies have suggested that long-acting naltrexone attenuates subjective craving in response to heroin cues and modulates the brain response to cues [25–27], although, for ethical reasons in a treatment-seeking population, these studies

did not include placebo controls; thus non-specific effects cannot be ruled out. Naltrexone might reduce dysphoria and increase well-being by blocking kappa receptors, though most animal models of antidepressant effects have studied more specific kappa antagonists [28, 29], or by blocking autoreceptors leading to increased release of endogenous opioids [30]. Such mechanisms might underlie beneficial effects of naltrexone in the absence of testing of the blockade.

The rate of placebo response in this trial is notable; 31% of patients receiving placebo achieved at least 90% abstinence [20], and 20% on placebo were present and abstinent across all 24 weekly visits. This placebo response could be related to the psychosocial platform of the clinical trial. Patients received counseling as part of the trial, and to be eligible for the trial, patients had to have a supportive family member available to supervise adherence to clinic visits. It is possible that an expectancy effect—the belief that effects of opioid use will be blocked with the long-lasting injection, reducing craving and motivation to seek opioids—was operating for at least some patients. And finally, patients' fear of repercussions for relapse may also have been operating, given that the study was conducted in Russia, where opioid addiction is particularly stigmatized.

Studies of oral naltrexone for treatment of opioid use disorder have yielded considerably higher dropout rates, with typically 70% or more dropping out by 6 months [5, 8, 31–33], and results inferior to injection or implant naltrexone in head-to-head trials [5, 8]. The blockade wears off a few days after discontinuing oral naltrexone, whereas taking an injection of XR-NTX is a commitment to at least 4 weeks of blockade, and patients are aware of this. The low frequency of testing the blockade illustrated in the present data suggests a role for cognition (a patient takes opioids, experiences the blockade and knows it will endure at least 4 weeks after the last injection) or expectation of the clinical effectiveness of injection naltrexone.

Limitations of this analysis include its post hoc nature and the use of dropout from treatment as a proxy for relapse, used because patients were not followed up after dropout from treatment in this trial. Dropout is certainly a key clinical phenomenon in medication treatment of opioid use disorder, and longitudinal studies show discontinuation of medication is associated with relapse to opioid use [34, 35]. Follow-up of patients with opioid use disorder after dropout from treatment is challenging but should be attempted in future trials of this type. There are limitations to the effort to infer the clinical mechanism of XR-NTX from the types of outcome data presented here. The data available from such a trial are focused on basic clinical outcomes, appropriate for a pivotal clinical trial such as this but rudimentary to address mechanism. Potential mechanisms that would involve blockade by naltrexone of the effects of opioids (i.e. episodes of testing the blockade) include operant extinction, blockade of the cue or priming effect of doses of opioids, or rule-governed behavior based on knowledge that opioid effects are blocked. Potential mechanisms not involving testing of the blockade could include attenuation by naltrexone of the conditioned effects of non-drug cues, or reductions in craving or anhedonia. To tease apart these alternatives, specifically designed studies would be needed. For example, several studies have examined and support an effect of naltrexone on cue-induced craving among patients with alcohol use disorder [36–38]. A small study showed persons with opioid use disorder

experienced craving in response to both drug cues and stress, though the study was not placebo controlled [39]. As noted, studies with a before-and-after within-subjects design suggest XR-NTX attenuates cue response [25–27]. More work of this type is needed in opioid-dependent patients treated with XR-NTX.

In summary, this post-hoc analysis supports the premise that XR-NTX reduces the risk for dropout from treatment after an episode of opioid use (testing the blockade). The low frequency of weeks positive for opioids on XR-NTX is also notable. These data support the model that XR-NTX, by blocking the reinforcing effects of opioids, leads to extinction of opioid-taking behaviour, or blocks cue or priming effects of doses of opioids. From a clinical perspective, the data highlight the importance of regular adherence to XR-NTX. As long as a patient continues to receive the monthly injection of XR-NTX, the patient is likely to remain mostly, if not entirely, abstinent. Even if the patient has occasional episodes of use, he or she will be relatively protected from relapse and treatment dropout, although negative consequences of an opioid use episode (e.g. HIV or other infections due to unsafe injection practices) remain. The hypothesis that more patients receiving XR-NTX than receiving placebo would show no evidence of opioid use at all throughout the trial was not supported, as the difference was not statistically significant. The observed difference was in the predicted direction, and just under a third of patients (31%) on XR-NTX showed no opioid-positive urine tests across the 24 week trial. This seems of heuristic interest, meriting further attention to the idea that naltrexone might exert an effect on drug taking that does not depend on testing of the blockade - perhaps blockade of craving triggered by non-drug cues, or blockade at autoreceptors or kappa receptors. Delineating the precise mechanisms through which naltrexone exerts its beneficial effects on opioid use disorder may be helpful to future treatment development efforts, from designing behavioral regimens, to improving adherence to XR-NTX, to steering the development of new pharmacotherapies.

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Conflict of Interest Information [for the past 3 years]

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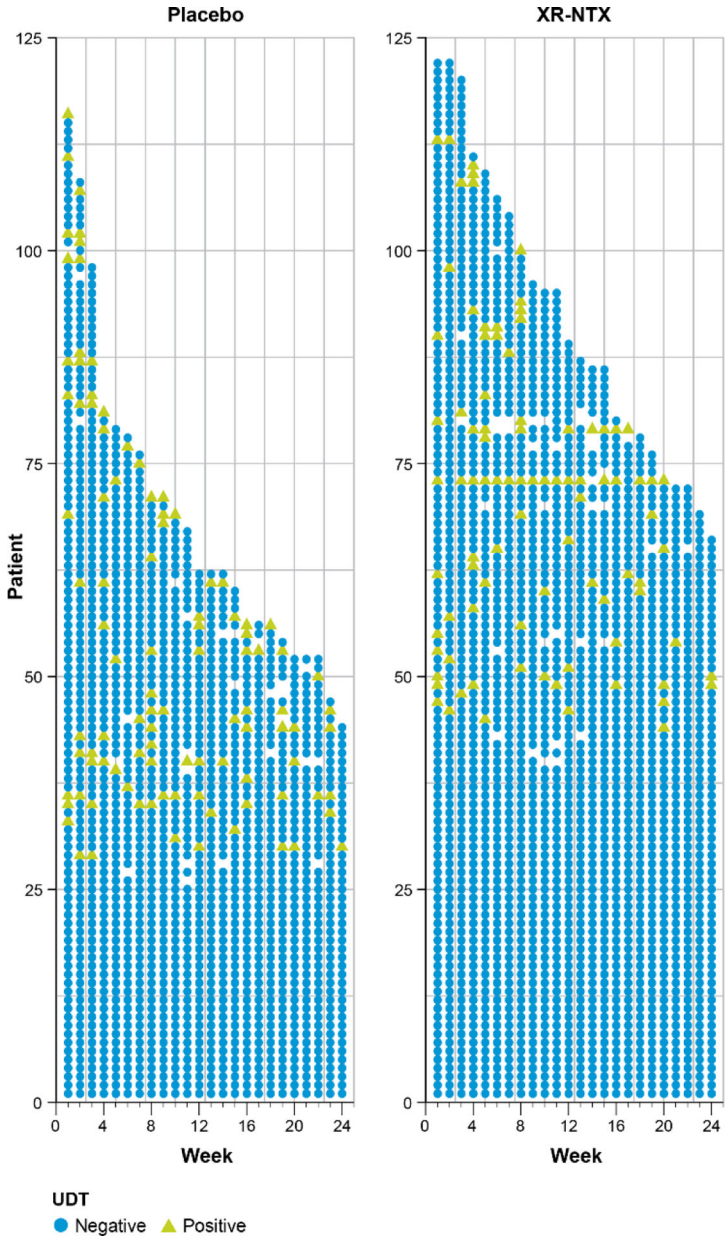


**Figure 1.**

Weekly treatment attendance and opioid UDT results across a 24-week placebo-controlled trial of XR-NTX for opioid dependence. Each row represents an individual patient's 24-week course. Blue dots indicate weeks when the patient attended treatment and the UDT result was negative for opioids. Green triangles indicate weeks when the patient attended treatment and the UDT result was positive for opioids. Blanks indicate weeks with a missing UDT. UDT = urine drug test; XR-NTX = extended-release injection naltrexone.

## Table 1

Patient baseline characteristics.

| Characteristic | XR-NTX n = 126 | Placebo n = 124 | Total N = 250 |
|---|---|---|---|
| Mean age, years (SD) | 29.4 (4.8) | 29.7 (3.6) | 29.0 (4.8) |
| Male, *n* (%) | 113 (89.7) | 107 (86.3) | 220 (88.0) |
| White | 124 (98.4) | 124 (100.0) | 248 (99.2) |
| Opioids used within 30 days of baseline, *n* (%) | | | |
| Heroin | 111 (88.1) | 110 (88.7) | 221 (88.4) |
| Methadone[a] | 11 (8.7) | 18 (14.6) | 29 (11.6) |
| Prescription Opioids[b] | 21 (16.8) | 12 (9.8) | 33 (13.3) |
| Mean duration of opioid dependence, years (SD) | 9.1 (4.5) | 10.0 (3.9) | 9.6 (4.2) |

SD = standard deviation; XR-NTX = extended-release naltrexone.

[a]XR-NTX, *n* = 126; placebo, *n* = 123.

[b]XR-NTX, *n* = 125; placebo, *n* = 123.

## Table 2

Outcomes on XR-NTX vs placebo with respect to opioid use.

| | XR-NTX n = 126 | Placebo n = 124 | Rate Ratio (95% CI) |
|---|---|---|---|
| Patients with ≥2 consecutive positive UDT results | 4.8% (6) | 12.9% (16) | 0.37 (0.15–0.91) |
| Dropout immediately preceded by a positive UDT result | 3.2% (4) | 16.1% (20) | 0.20 (0.07–0.56) |
| Completed the study with no positive or missing UDT results | 31.0% (39) | 20.2% (25) | 1.53 (0.99–2.38) |

UDT = urine drug test; XR-NTX = extended-release naltrexone.