Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness

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ABSTRACT

Aims To describe drug use and safety with intramuscular injectable extended-release naltrexone (XR-NTX) in opioid dependence during a 1-year open-label extension phase. Design Following 6 months of randomized, double-blind, placebo (PBO)-controlled injections given every 28 days, patients receiving XR-NTX 380 mg continued and PBO patients were switched to open-label XR-NTX, with monthly individual drug counseling, for a further year. Setting Thirteen clinical sites in Russia. Participants Adult opioid-dependent outpatients. Measurements Monthly urine samples; reports of craving and functioning; adverse events. Findings For the open-label extension (n = 114), 67 continued on XR-NTX and 47 switched from PBO during the double-blind phase to XR-NTX during the open-label phase. Overall, 62.3% (95% CI: 52.7%, 71.2%) completed the extension. Discontinuation occurred most commonly because of withdrawal of consent (18.4%) and loss to follow-up (11.4%); two patients discontinued as a result of lack of efficacy and one because of adverse events. Urine testing revealed that 50.9% (41.5%, 60.4%) were abstinent from opioids at all assessments during the 1-year open-label phase. Adverse events reported by 21.1% of patients were judged to be study drug-related. Injection site reactions were infrequent (6.1%) and the majority were mild. Elevations in liver function tests occurred for 16.7% of patients, but none of these elevations was judged to be clinically significant. No patients died, overdosed or discontinued as a result of severe adverse events. Conclusions During a 1-year open-label extension phase of injectable XR-NTX for the prevention of relapse in opioid dependence, 62.3% of patients completed the phase and 50.9% were abstinent from opioids. No new safety concerns were evident.

Keywords Craving, depot naltrexone, extended-release naltrexone, heroin dependence, injectable naltrexone, opioid dependence, long-term safety, naltrexone, sustained release formulations.

INTRODUCTION

The 2009 National Survey on Drug Use and Health estimated that approximately 1.5 million Americans aged 18 years or older were dependent on opioids in the prior year, including 345 000 dependent on heroin and 1 255 000 on prescription opioid medications used non-medically [1]. Rates of opioid dependence throughout the rest of the world have been on the increase [2]. Opioid dependence is a major public health concern because of increased morbidity and mortality, poor social functioning, unemployment, and crime associated with this disorder [3–5].

Opioid dependence is a chronic disorder requiring long-term treatment [6,7]. Effective options for managing the disorder include several pharmacotherapy agents (methadone, buprenorphine, naltrexone) and psychosocial interventions [8–13]. However, relapse following cessation of treatment is high, with only an estimated 25% of heroin-dependent individuals remaining abstinent after receiving methadone treatment [14]. Relapse following non-compliance with oral naltrexone is a particular concern [9]. Episodes of opioid use during non-compliance have been associated with relapse to full opioid dependence [15].
Concerns about compliance with oral naltrexone led to the development of a once-monthly extended-release formulation of injectable naltrexone (XR-NTX; Vivitrol®, Alkermes, Inc., Waltham, MA, USA). In this formulation, naltrexone is gradually released from microspheres composed of poly- (d,l-lactide-co-glycolide), a polymer used in dissolvable surgical sutures. The efficacy of XR-NTX for the prevention of relapse to opioid dependence following detoxification was recently demonstrated in a multi-center, placebo (PBO)-controlled, randomized clinical trial [16]. This study reported a median of 90% confirmed abstinence weeks for XR-NTX versus 35% for PBO over the course of 6 months of treatment (P = 0.0002) with 57.9% (73/126) of XR-NTX patients versus 41.9% (52/124) of PBO patients receiving all six double-blind doses. XR-NTX also has demonstrated efficacy in the treatment of alcohol dependence [17], and is now approved in the USA and Russia for both dependencies.

Although XR-NTX has shown efficacy for opioid dependence in the context of a 6-month study, the chronic, relapsing nature of this disorder has led to questions regarding long-term treatment. Specifically: Are initial treatment gains from baseline to end of the double-blind phase maintained over time during a 1-year open-label extension?; What proportion of patients continue?; Do any new safety concerns become evident? This study reports descriptively on the results of a 1-year open-label treatment phase that followed the initial 6-month double-blind phase in terms of durability of improvements seen in the initial 6-month period, patient retention and safety of XR-NTX for the treatment of opioid dependence.

**Methods**

**Overview**

The current study reports the results from a 52-week extension study that followed the initial 24-week randomized, double-blind, PBO-controlled, multi-site investigation of XR-NTX as a treatment for opioid dependence [16]. In the extension phase, patients who had received XR-NTX during the initial 24-week period continued on open-label XR-NTX for an additional 52 weeks. Patients receiving PBO during the initial 24-week treatment period were switched to open-label XR-NTX for the next 52 weeks. The study was conducted between July 2008 and November 2010 at 13 clinical sites in Russia. At each of the participating sites, an independent ethics committee/institutional review board approved the protocol and participants gave written, informed consent in accordance with the Helsinki Accords. The open-label extension study was conducted from June 2008 to November 2012.

**Participants**

In the initial 6-month double-blind phase the study recruited males and females (≥18 years) meeting Diagnostic and Statistical Manual of Mental Disorders (fourth edition) [18] criteria for opioid (primarily heroin) dependence disorder who were voluntarily seeking treatment and had completed inpatient opioid detoxification (≤30 days). Patients were excluded if they had taken any opioids for ≥7 days prior to screening or if they were under justice system coercion (i.e. parole or probation, or pending legal proceedings with potential for incarceration). To participate, it was required that patients involve a significant other (e.g. spouse, relative) who would supervise the patient’s compliance with the visit schedule and study procedures. Women of childbearing potential agreed to use contraception while participating in the study. Patients did not receive reimbursements for participating in the study, but did receive reimbursements for transportation. Patients were excluded if they were pregnant or breastfeeding, or had any of the following: significant medical conditions; positive naltrexone challenge (appearance of vital sign elevations or opioid withdrawal symptoms); hepatic failure, past/present history of an AIDS-indicator disease, or active hepatitis and/or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3×the upper limit of normal; known intolerance and/or hypersensitivity to naltrexone, carboxymethylcellulose or polylactide-co-glycolide; psychosis, bipolar disorder, major depressive disorder with suicidal ideation, current substance dependence other than opioids or heroin, including alcohol; positive urine test for cocaine/amphetamines; or naltrexone use within the last 6 months.

**Study intervention**

For the initial 6-month double-blind phase patients were randomized to either XR-NTX 380 mg or PBO in a 1:1 ratio, stratifying by site and gender. The study investigator or a designated staff member injected XR-NTX within a week of detoxification (≥7 days following last opioid dose) and then every four weeks, for a total of six injections. Patients who completed the initial 6-month study were offered the open-label, 1-year extension study, which provided open-label XR-NTX 380 mg injections every four weeks for up to 13 additional doses (total of 19 injections over 18 months) at no expense to patients. Throughout the 1.5-year study, participants were offered sessions of manualized Individual Drug Counseling (IDC), adapted for opioid dependence [19]. IDC-trained psychologists or psychiatrists reviewed patients’ substance use, recovery efforts, functioning and adverse events, providing support and advice. Sessions were biweekly during the initial 6-month double-blind phase.
and monthly during the 12-month open-label phase. Counseling sessions occurred when injections occurred, although not necessarily with the same clinician.

Patients were advised to not use the following medications at any time during the 18-month protocol: oral naltrexone, buprenorphine, levomethadyl acetate/LAAM, methadone, other prescription opioids, antipsychotics, anticonvulsants, antidepressants and anxiolytics. Permitted medications included anticonvulsants if dosing was stable and short-acting PRN (as needed) insomnia medications, for example zopiclone.

Efficacy and safety assessments

Urine drug testing for opioids (immunochromatography-based one-step in vitro tests) was performed at scheduled visits, weekly for 6 months during the double-blind phase and monthly during the 1-year extension phase, detecting urine morphine and methadone concentrations at 300 ng/mL. Urine results for weeks 1–4 were prospectively omitted because participants might challenge the blockade during this period. Self-report of drug use, using the Timeline Follow-back (TLFB) method [20], was used to confirm negative urine results. The TLFB method uses calendars and daily recall of substance use on specific days to record opioid quantity/frequency. If use of opioids for a given week was evident from the TLFB, the week was coded as ‘not abstinent’. In addition, the Addiction Severity Index (ASI) [21] was administered at baseline and the monthly visits during the open-label phase. From the ASI, days in the past 30 using individual types of drugs and alcohol were examined.

Also included to assess the durability of effects were measures of retention, opioid craving, functioning and global improvement. Craving was assessed weekly during the first 6 months and monthly during the 1-year extension phase with a self-report Visual Analogue Scale of ‘need for opioids’ (scale: 0–100, i.e. ‘not at all’ to ‘very much so’) [11]. Health functioning was measured with the SF-36 and EQ-5D [23]. The SF-36 and EQ-5D were obtained at baseline, end of the double-blind phase (month 6), and months 9, 12, 16 and last visit (month 19, which occurred 1 month after the last injection at month 18). Global improvement was measured with the Clinical Global Impression Improvement (CGI-I) scale [24]. ‘Responders’ were defined a priori as having a CGI-I score of 1 (very much) or 2 (much) improved. The CGI-I was obtained at baseline and months 6, 12 and 19.

Safety was assessed during the 1-year extension phase through monthly monitoring of treatment-emergent adverse events, vital signs, biochemistry and hematology urine/blood tests (including liver function tests), and physical examination of injection sites. Laboratory tests were evaluated relative to established norms and changes from baseline. Determinations of severity and clinical significance were made by investigators at each site. Electrocardiograms (ECGs) were obtained at baseline, month 6, month 12 and month 19.

Statistical analysis

Missing urine drug test results were imputed as positive for opioids; retention was censored upon discontinuation: craving, SF-36, EQ-5D, ASI and CGI-I scores were imputed using last post-dose observation carried forward.

Retention was examined through a Kaplan–Meier time-to-discontinuation survival analysis, using the sample of patients who entered the open-label phase. Safety results are presented descriptively in terms of the number and percent of patients displaying any adverse events or other safety concerns.

To allow descriptive comparisons with the results from the double-blind phase, we present here data for those patients (n = 114) who completed the double-blind phase and then entered the open-label phase. Statistical analyses were performed using SAS (v. 9.1).

RESULTS

Patient characteristics and disposition

There were 335 individuals screened for the initial double-blind phase, and 250 of these (74.6%) were randomized to XR-NTX or PBO (Fig. 1). Of these, 57.9% (73 of 126) XR-NTX patients versus 41.9% (52 of 124) PBO patients received all six double-blind doses. Of the initial 250 randomized patients, 53.2% (67/126) continued with XR-NTX into the 1-year open label phase versus 37.9% (47/124; \( P = 0.017 \)) who were randomized to PBO, but were switched to XR-NTX for the open label phase. The primary reasons for attrition during the 1-year open-label phase were withdrawal of consent (18.4%; 21/114) and becoming lost to follow-up (11.4%; 13/114).

In general, patients who continued into the 1-year open-label phase were similar to the subset that did not complete the preceding double-blind phase and did not enter the open-label extension phase (Table 1). The sample was predominantly young, male, white, addicted to heroin for about 10 years, and had high rates of HIV and hepatitis C infection. In the sample entering the 1-year continuation phase, 89.5% (102/114) were using heroin at baseline (prior to entering the double-blind study), 8.8% (10/113) were using methadone and 9.8% (11/112) were using other opioids/analgescics.

Retention and durability of effects

Of the group that began the extension phase, 62.3% (71/114; 95% CI: 52.7%, 71.2%) completed the full 1-year of
treatment. This included 58.2% (39/67; 45.4%, 70.2%) of those continuing on XR-NTX and 68.1% (32/47; 52.9%, 80.9%) of those who switched from PBO to XR-NTX. During the double-blind phase, significantly more XR-NTX patients were retained. However, once the PBO patients switched to XR-NTX during the open-label phase, their rate of attrition over time leveled off (Fig. 2).

Of the original sample randomized to XR-NTX at the outset of the double-blind study, 31% (39/126; 23.0%, 39.8%) persisted with 18 months of treatment (24 weeks of double-blind plus 52-week extension).

Overall, 50.9% (58/114; 95% CI: 41.5%, 60.4%) of patients were abstinent from opioids at all scheduled monthly assessments during the open-label phase with similar results in both groups: 49.3% of those continuing with XR-NTX and 53.2% of those who switched from PBO. Of the 13 scheduled monthly urine drug tests, an average of 76.7% (SD = 31.5) of tests were negative for opioids (Fig. 3). Among open-label patients who received XR-NTX or PBO during the double-blind phase, an average of 73.7% (SD = 33.2) and 81.0% (SD = 28.6), respectively, of the tests were negative for opioids. Across the 1-year open-label phase, the percent of opioid-free days was, on average, 83.4% (SD = 27.5). For those who received XR-NTX or PBO during the double-blind phase, there were an average of 80.6% (SD = 29.7) and 87.4% (SD = 23.8) opioid-free days. Three patients (of 47) who received PBO during the double-blind phase had a positive urine test for opioids at the start of the open-label phase.

Self-reported use of opioids, other drugs and alcohol is shown in Table 2. For all drugs, mean use in the past 30 days at the end of the open-label phase remained at a similar low level, as was evident at the end of the

### Table 1: Patient demographic and baseline clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>6-month double-blind phase</th>
<th>1-year open-label phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XR-NTX 380 mg n = 126</td>
<td>XR-NTX→XR-NTX n = 67</td>
</tr>
<tr>
<td></td>
<td>PBO n = 124</td>
<td>PBO→XR-NTX n = 47</td>
</tr>
<tr>
<td>Age, mean years (SD)</td>
<td>29.4 (± 4.8)</td>
<td>29.5 (± 5.0)</td>
</tr>
<tr>
<td>Sex, n (%) male</td>
<td>113 (89.7%)</td>
<td>62 (92.5%)</td>
</tr>
<tr>
<td>Race, n (%) white</td>
<td>124 (98.4%)</td>
<td>67 (100%)</td>
</tr>
<tr>
<td>Duration of opioid dependence (years), mean (SD)</td>
<td>9.1 (± 4.5)</td>
<td>9.0 (± 4.2)</td>
</tr>
<tr>
<td>Days of pre-study inpatient detoxification, mean (SD)</td>
<td>18 (± 9)</td>
<td>15.9 (± 8.2)</td>
</tr>
<tr>
<td>Opioid Craving Scale, mean (SD)</td>
<td>18 (± 23)</td>
<td>20.7 (± 22.5)</td>
</tr>
<tr>
<td>HIV serology, n (%) positive</td>
<td>51 (40.5%)</td>
<td>31 (46.3%)</td>
</tr>
<tr>
<td>Hepatitis C, n (%) positive</td>
<td>111 (88.1%)</td>
<td>58 (86.6%)</td>
</tr>
</tbody>
</table>

PBO = placebo; XR-NTX = extended release naltrexone.

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double-blind phase. Alcohol use was not highly elevated at baseline (mean of approximately 5 days per month), and showed little change over the double-blind and open-label phases. For patients using any opioids at the end of the open-label phase, the median was 7.5 days of opioid use in the past 30 days. As previously reported, in the double-blind phase XR-NTX patients had significant reductions in craving for opioids compared with PBO [16]. When PBO patients were switched to XR-NTX, craving for opioids was also reduced over time within this group (Fig. 4). For those continuing on XR-NTX, mean craving for opioids remained low into and throughout the 1-year extension phase.

In the double-blind phase, the percentage of patients who achieved responder status on the CGI-I, and mean changes in the SF-36 mental components scores and EQ-5D were significantly greater for XR-NTX versus PBO [16]. In the XR-NTX group, 91.0% of those who completed (n = 67) the double-blind phase and began the open-label phase were rated CGI-I responders; after the
switch, by the end of the 1-year open-label extension phase, PBO→XR-NTX patients had a similar percent of responders, 89.4% (n = 47), while the XR-NTX→XR-NTX responder rate remained high (97.0%, n = 67). Changes in the SF-36 through the 1-year open-label phase indicated that, for patients continuing on XR-NTX, overall patient health functioning gains evident over time from baseline to the end of the double-blind phase were maintained over the course of the open-label phase. Mean ± SD scores on the SF-36 Physical and Mental Component scores, respectively, were 55.3 ± 3.8 and 50.6 ± 9.2 for the XR-NTX group at end of the double-blind phase for those continuing into the open-label phase (n = 67), and 56.3 ± 4.2 and 50.2 ± 8.9 with continuation on XR-NTX at the end of the 1-year open label phase (n = 62). On the SF-36 Mental Component score, scores for PBO patients were stable: 49.4.1 ± 8.7 (end of double-blind) (n = 47) to 50.1 ± 7.3 after switching to XR-NTX (end of open-label) (n = 46). The SF-36 Physical Component score for this group also remained stable (54.4 ± 6.2 to 56.6 ± 4.0 from end of double-blind to end of open-label phases). EQ-5D scores showed continued improvement over the course of the open-label phase in both groups [XR-NTX in both phases: 81.6 ± 12.4 (n = 67) to 83.8 ± 12.7 (n = 67); PBO→XR-NTX: 77.9 ± 18.10 (n = 47) to 82.7 ± 15.1 (n = 47)].

Safety
During the 1-year extension, overall, 21.1% (24/114) of patients reported an adverse event that was judged to be study drug related (Table 3). No specific type of adverse
event predominated. Injection site reactions were infrequent (6.1%; 7/114) and the majority were mild (3 pain; 2 extravasation; 1 induration; 1 swelling). One patient discontinued treatment during the 1-year extension phase owing to a non-serious adverse event. This patient, who had ongoing hepatitis B and C infections, had elevated liver enzymes at baseline (ALT 136 IU/L, AST 87 IU/L, gamma-glutamyl transferase [GGT] 523 IU/L) and while receiving PBO (after three injections: ALT 420 IU/L, AST 448 IU/L, GGT 1510 IU/L) during the 6-month double-blind phase. These elevations continued during the extension phase and the patient was discontinued (6 weeks after last dose of XR-NTX: ALT 553 IU/L, AST 615 IU/L, GGT 754 IU/L). Three patients experienced a total of four serious adverse events (SAEs) during the 1-year extension phase. No individual SAE was reported by more than one patient. The SAEs were acute pancreatitis, cardiomyopathy, hepatitis A and pulmonary tuberculosis (the latter two occurring in the same patient). The pancreatitis was judged as possibly related to XR-NTX and the cardiomyopathy was judged as probably not related to XR-NTX. No deaths or overdoses

**Table 3** Adverse events during 1-year open label treatment with extended release naltrexone (XR-NTX).

<table>
<thead>
<tr>
<th>Events</th>
<th>Overall</th>
<th>XR-NTX→XR-NTX</th>
<th>PBO→XR-NTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>48 (42.1%)</td>
<td>29 (43.3%)</td>
<td>19 (40.4%)</td>
</tr>
<tr>
<td>Discontinued owing to non-serious adverse event</td>
<td>1</td>
<td>0</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>7 (6.1%)</td>
<td>3 (4.5%)</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 (5.3%)</td>
<td>4 (6.0%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Bacteriuria</td>
<td>3 (2.6%)</td>
<td>2 (3.0%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3 (2.6%)</td>
<td>1 (1.5%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>3 (2.6%)</td>
<td>3 (4.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Study drug-related adverse events</td>
<td>24 (21.1%)</td>
<td>14 (20.9%)</td>
<td>10 (21.3%)</td>
</tr>
</tbody>
</table>

PBO = placebo. aPatients who received XR-NTX in the 6-month double-blind phase and remained on XR-NTX for the 1-year open-label phase. bPatients who received placebo in the 6-month double-blind phase and were switched to XR-NTX for the 1-year open-label phase. cOnly adverse events that were coded by investigators as study drug-related are included here.

**Figure 4** Mean changes in opioid craving over the course of double-blind and open-label phases for cohorts of patients that entered open-label treatment.

XR-NTX = extended release naltrexone.
occurred during either the 6-month double-blind phase or the 1-year extension phase.

During the open-label phase, 22 patients [7 (14.9%) who switched and 15 (22.4%) who were continuing on XR-NTX] had laboratory abnormalities. Of these, 17 were considered to be related to XR-NTX. Specific increases in liver enzymes were experienced by 13 (19.4%) of patients who continued on XR-NTX, and 6 (12.8%) of those who switched from PBO to XR-NTX during the open-label phase [overall: 19 (16.7%)]. All laboratory abnormalities were judged mild or moderate in severity. None of the laboratory abnormalities were viewed as clinically meaningful by the investigators’ judgment.

There were no clinically significant abnormalities detected through measurement of vital signs or through physical examinations. An abnormality of mild severity was evident on an ECG recording for one patient (shortened PR).

**DISCUSSION**

In this long-term study of patients who received XR-NTX during an open-label, 1-year extension phase following 6 months of double-blind treatment with XR-NTX or PBO, XR-NTX patients maintained their improvements over time in regard to abstinence from opioids, craving for opioids and overall health functioning. Patients who switched from PBO treatment during the double-blind phase to 1 year of open-label XR-NTX treatment were a select subpopulation of those initially randomized to PBO (with only 3 of 47 of these patients testing positive for opioids at the beginning of the open-label phase). However, even this self-selected subgroup appeared to improve further in craving for opioids over time once these patients began receiving XR-NTX during the open-label extension phase. About half of all patients who began the extension phase were completely abstinent from opioids across the additional year of assessment. Opioid use was rare during the follow up, and episodes of use, which may have represented testing the blockade, did not appear to result in dropout and relapse. Because of the clinical importance of retention and abstinence, opioid-negative urine was analyzed imputing missing urine as positive—a conservative approach to describing the pattern of results. There was no evidence that patients increased their use of other drugs and alcohol after decreasing their use of opioids over the course of the double-blind and open-label phases.

No new safety concerns were observed for XR-NTX during the open-label extension. Long-term treatment with XR-NTX showed a low rate of adverse events, the absence of severe adverse events, and a low overall rate (2.6%) of injection site pain, with no serious injection site reactions. No patients discontinued the open-label extension owing to serious adverse events. In this sample, in which 88% had chronic hepatitis C at baseline, elevations in liver function tests occurred in about 10% of patients, and were not clinically meaningful. These results extend the analyses of liver function tests conducted on the 6-month double-blind phase in the treatment of opioid dependence [16], as well as a 6-month study of hepatic safety for XR-NTX in the treatment of alcohol dependence [25], which concluded there was no evidence for hepatotoxicity with XR-NTX taken in the approved dosage.

Retention rates over 18 months of XR-NTX treatment were encouraging. Of those initially randomized to XR-NTX in the double-blind phase, 31% completed 18 months of treatment, and of those who began the 1-year extension phase, 62.2% completed it. Systematic long-term studies of opioid dependence treatment are rare, and it is difficult to compare the retention rates found here to other studies because retention will vary depending on the design of the initial treatment phase, length of treatment, setting, country where study was conducted, and other study and patient characteristics.

Several limitations of this study should be noted. Long-term efficacy of XR-NTX with individual drug counseling was based on open-label treatment, without randomization. In the course of long-term studies, differential attrition may be expected. Because of the double-blind phase preceding this extension study, opioid-dependent patients who survived in treatment with PBO and counseling for 6 months and then sought to enter the open-label extension study may have represented a subgroup with higher motivation, resulting in more favorable outcomes once switched to active XR-NTX during the open-label phase. A potential limitation is that this study was conducted in Russia. The generalizability of these results to other countries that have different systems for providing services to addicted individuals is not known. Further research is needed to confirm these findings in other settings. However, a large retrospective analysis of US insurance claims across all approved treatments reported favorable total health-care cost findings and rates of re-hospitalization in XR-NTX-treated patients [17]. An important limitation is that patients were not tracked after dropout from treatment in either the acute trial [16] or the long-term extension reported here. Dropout from treatment for opioid dependence and relapse is, unfortunately, a common outcome [9,14,15]. Risks after dropout include relapse and death from opioid overdose, and future research on treatments for opioid dependence should track dropouts to better understand relapse rates, how to
further reduce attrition (e.g., with behavioral interventions and comorbidity measures), safety and what proportion may, in fact, sustain abstinence even after XR-NTX is discontinued.

In summary, improvements over time following a 6-month double-blind phase were maintained during 1 year of long-term treatment with XR-NTX and no new safety concerns were evident.

Trial registration
Clinicaltrials.gov Identifier: NCT00678418.

Declaration of interests
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