Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders

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ABSTRACT

Extended-release naltrexone, a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, is effective for the prevention of relapse to opioid dependence. Data supporting its effectiveness in U.S. criminal justice populations are limited.

METHODS

In this five-site, open-label, randomized trial, we compared a 24-week course of extended-release naltrexone (Vivitrol) with usual treatment, consisting of brief counseling and referrals for community treatment programs, for the prevention of opioid relapse among adult criminal justice offenders (i.e., persons involved in the U.S. criminal justice system) who had a history of opioid dependence and a preference for opioid-free rather than opioid maintenance treatments and who were abstinent from opioids at the time of randomization. The primary outcome was the time to an opioid-relapse event, which was defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 10 days of opioid use. Post-treatment follow-up occurred at weeks 27, 52, and 78.

RESULTS

A total of 153 participants were assigned to extended-release naltrexone and 155 to usual treatment. During the 24-week treatment phase, participants assigned to extended-release naltrexone had a longer median time to relapse than did those assigned to usual treatment (10.5 vs. 5.0 weeks, P<0.001; hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.68), a lower rate of relapse (43% vs. 64% of participants, P<0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65), and a higher rate of opioid-negative urine samples (74% vs. 56%, P<0.001; odds ratio, 2.30; 95% CI, 1.48 to 3.54). At week 78 (approximately 1 year after the end of the treatment phase), rates of opioid-negative urine samples were equal (46% in each group, P=0.91). The rates of other prespecified secondary outcome measures — self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and reincarceration — were not significantly lower with extended-release naltrexone than with usual treatment. Over the total 78 weeks observed, there were no overdose events in the extended-release naltrexone group and seven in the usual-treatment group (P=0.02).

CONCLUSIONS

In this trial involving criminal justice offenders, extended-release naltrexone was associated with a rate of opioid relapse that was lower than that with usual treatment. Opioid-use prevention effects waned after treatment discontinuation. (Funded by the National Institute on Drug Abuse; ClinicalTrials.gov number, NCT00781898.)
OPID-USE DISORDER IS A CHRONIC RELAPSING condition that has serious public health consequences. Opioid dependence disproportionately affects U.S. criminal justice system populations, and relapse and overdose deaths occur at high rates after release from incarceration. Evidence-based opioid-agonist maintenance therapies for opioid dependence (methadone and buprenorphine) are effective in prison, jail, and community reentry (i.e., parole) settings but have historically been unavailable or discouraged among criminal justice clients.

Extended-release naltrexone (Vivitrol, Alkermes), a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, was approved by the Food and Drug Administration in 2010 for the prevention of relapse to opioid dependence. Extended-release naltrexone may be particularly appealing and beneficial to patients and providers who are unlikely to access opioid-agonist maintenance treatment or who prefer a relapse-prevention medication. As a noncontrolled substance with no known abuse or diversion potential, extended-release naltrexone has gained increasing acceptance in the criminal justice system despite limited data on effectiveness.

Extended-release naltrexone gradually releases sufficient naltrexone to block the euphoric effects of opioids for approximately 1 month after injection and is efficacious as compared with placebo. A pilot study that was performed at the same five sites that participated in this trial used a single-group observational cohort design and showed the feasibility of using Depotrex, an alternative formulation of extended-release naltrexone, as a treatment option for outpatient parolees and probationers. We conducted a large, multisite, randomized trial to examine the effectiveness of extended-release naltrexone among community-dwelling criminal justice offenders who were at high risk for opioid relapse and related adverse outcomes.

METHODS

TRIAL DESIGN, SITES, AND OVERSIGHT

This open-label, randomized, controlled effectiveness trial compared six monthly injections of extended-release naltrexone (Vivitrol, Alkermes) with usual treatment (brief counseling and referrals for community treatment programs) for the prevention of opioid relapse among criminal justice offenders. We hypothesized that the likelihood of an opioid-relapse event would be lower, the time to relapse longer, and overall rates of opioid use lower with extended-release naltrexone than with usual treatment.

Five independently funded sites implemented a common collaborative protocol: University of Pennsylvania (Philadelphia), New York University School of Medicine and Bellevue Hospital Center (New York), Rhode Island Hospital and Brown University (Providence, Rhode Island), Columbia University Medical Center (New York), and Friends Research Institute (Baltimore). The University of Pennsylvania, which was the lead site, hosted the regulatory and data management cores and the data and safety monitoring board.

The rationale, protocol development, design, and methods of this trial are described in full elsewhere. All sites obtained approval from the local institutional review board and the U.S. Office for Human Research Protections for the common trial protocol. The authors alone designed and implemented the trial; collected, accessed, and analyzed the data; and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. The first author wrote the initial draft of the manuscript, and all the authors participated in revisions and approved the final draft. The sponsor (National Institute on Drug Abuse) and the manufacturer of extended-release naltrexone (Alkermes) did not have editorial control or access to trial data. The manufacturer contributed Vivitrol in kind through an investigator-initiated trial contract, which allowed for review of and comment on the manuscript before submission for publication.

PARTICIPANTS

We recruited community-dwelling adult volunteers who were criminal justice offenders and who had a history of opioid dependence. Eligibility criteria were current (within the previous 12 months) or lifetime (any previous) opioid dependence (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV]); a stated goal of opiate-free treatment rather than opioid-agonist or partial-agonist maintenance therapy; an opioid-free status as confirmed by negative urine toxicologic screening for all opioids before randomization; residence in the community and receipt of an adjudicated sentence that included...
supervision (e.g., parole, probation, outpatient drug-court programs, or other court-mandated treatment) or, in the previous 12 months, release from jail or prison, a plea-bargain arrangement, or any community supervision as above; general good health as determined by history and physical examination; an age of 18 to 60 years; and the ability to provide written informed consent.

Exclusion criteria were other drug or alcohol dependence requiring a level of care that would interfere with trial participation; pregnancy or a plan to conceive within the 24-week treatment phase, lactation, or an inability to use adequate contraceptive methods; an untreated psychiatric disorder or medical condition that might make participation hazardous, including liver-enzyme levels more than three times the upper limit of the normal range and a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of more than 40; allergy to naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the diluent; a current diagnosis of chronic pain for which opioids were prescribed; or a drug overdose in the previous 3 years requiring inpatient hospitalization.

We recruited participants by standard outreach to community-dwelling at-risk populations through print, radio, and online publicity and provider detailing (e.g., letters to clinic directors); in an effort to minimize potential coercion, we did not recruit through direct referrals from criminal justice authorities, including departments of corrections, probation, or parole and drug courts or other diversion programs. Prescreening questionnaires were used to briefly evaluate potential participants and to schedule an in-person screening visit at which written informed consent was obtained; participants were required to establish their comprehension of consent information by passing an informed-consent quiz.

**Randomization and Trial Treatments**

Participants were randomly assigned, in a 1:1 ratio, to extended-release naltrexone or usual treatment for opioid-relapse prevention. An urn randomization procedure ensured balance with respect to trial site, sex, and status regarding the need for opioid detoxification. An independent, centralized, automated telephone system made the treatment assignments after eligibility of the participants was confirmed.

**Clinical Assessments**

Follow-up and assessment procedures were the same in the two groups. Visits occurred at screening, randomization, and then every 2 weeks for 24 weeks during the treatment phase. Post-treatment follow-up assessments occurred at weeks 27, 52, and 78 (three visits only). The visits occurring every 2 weeks and at weeks 27, 52, and 78 included urine toxicologic screening and self-report of opioid, cocaine, alcohol, and intrave-
nous drug use with the use of the Timeline Followback calendar method for count data.29 Urine samples were tested for opiates (a level >300 ng per milliliter was considered to indicate a positive test), oxycodone, methadone, buprenorphine, and cocaine metabolites. Data on unsafe sex were captured every 6 months with the use of the Sex Risk subscale of the Risk Assessment Battery (on which scores range from 0 to 18, with higher scores indicating a greater risk of contracting and spreading human immunodeficiency virus [HIV] infection through sexual behaviors).20 Self-reported information about criminal activity, rearrests, and days of reincarceration was collected every 2 weeks with the use of the Timeline Followback method for days in controlled environments, monthly with the use of the Crime and Legal Activities Report,21 and every 6 months with the use of the legal-status items in the Addiction Severity Index Lite.22

OUTCOMES
The primary outcome was the time (in weeks) to an opioid-relapse event during the 24-week treatment phase. A relapse event was defined as 10 or more days of opioid use in a 28-day (4-week) period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use. Relapse was considered to be a one-time event and corresponded to the loss of persistent opioid abstinence after randomization, when all participants had been opioid-free and had endorsed a goal of opioid abstinence. Related opioid-use outcomes were rates of opioid-negative (vs. opioid-positive or missing) urine samples, the percentage of 2-week intervals with no opioid use as assessed by self-report or by testing of urine samples (confirmed abstinence), the percentage of days with self-reported opioid use, and post-treatment rates of opioid use as assessed by self-report (percentage of 2-week intervals with any opioid use vs. no opioid use) and by testing of single urine samples at weeks 52 and 78. The primary relapse outcome used during the treatment phase, defined by assessments performed every 2 weeks, self-report, and testing of urine samples, was not available during long-term follow-up because visits were scheduled only at weeks 52 and 78. Secondary outcomes of interest were rates of alcohol and nonopioid drug use, HIV risk behaviors, rearrests and reincarcerations, and adverse events including opioid overdose.

STATISTICAL ANALYSIS
We calculated that a sample size of 164 participants per group, with an assumed loss toattrition of approximately 5% per month, would provide the trial with 80% power to detect a hazard ratio for relapse with usual treatment of 1.53 or higher, equivalent to an estimated difference in relapse rates of 15 percentage points (45% vs. 30%).9,13 The primary outcome analysis tested whether extended-release naltrexone resulted in a longer time to relapse than that with usual treatment, with the use of Cox proportional-hazards regression models. We compared overall relapse rates using intention-to-treat mixed-effects logistic-regression models and compared rates of positive urine tests and days with self-reported opioid use using a linear mixed-effects model for count data. Missed visits and missing data on urine samples were counted as positive for opioid use; thus, dropouts contributed to a relapse event. Missing data for secondary outcomes (cocaine, alcohol, and intravenous drug use; score on the Sex Risk subscale of the Risk Assessment Battery; and reincarceration) were estimated from available data only.

At the week 52 and week 78 visits, participants provided 6 months of self-reports on opioid use and a single urine sample. We analyzed the percentage of opioid-negative (vs. opioid-positive or missing) urine samples at both visits using mixed-effects logistic models. We used a logistic mixed-effects model for repeated measures to analyze self-reported opioid use from week 1 to week 78 and to test for differences in the treatment groups over time with the use of an interaction term between group and time.

RESULTS
SCREENING AND RANDOMIZATION
Recruitment began in February 2009 and continued through November 2013. The five sites obtained consent from and screened 437 persons, of whom 308 underwent randomization; 153 were assigned to extended-release naltrexone and 155 to usual treatment (Fig. 1). Common reasons for exclusion were an incomplete screening visit, incomplete detoxification or a lack of opioid abstinence before randomization, and
serious medical or psychiatric coexisting conditions. Two potential participants were excluded because of a BMI of more than 40 and therefore a potentially elevated risk of a severe injection-site reaction.

**Participants**

The characteristics of the trial groups were similar at baseline. The mean age was 44 years; 85% of the participants were male, 77% were black or Hispanic, 74% were on parole or probation, and 65% had not used heroin or other opioids in the previous 30 days (Table 1). All reported a history of DSM-IV opioid dependence. A total of 88% of the participants reported heroin use and 41% reported injection-drug use during their lifetimes; 34% reported any opioid (heroin or other) use in the previous 30 days. A total of 9% of the participants required opioid detoxification to enter the trial.

**Attendance at Scheduled Visits and Adherence to Medication**

Most of the visits that were scheduled every 2 weeks (3096 of 4004, 77%) were attended; participants assigned to extended-release naltrexone attended 79% of the scheduled visits, and those assigned to usual treatment attended 75%. A total of 75% of the participants completed an end-of-treatment-phase visit at week 27. Overall, participants assigned to extended-release naltrexone completed 711 of the 918 planned monthly injections (77%). Seven participants (5%) declined any injections after randomization; 146 (95%) completed the first injection, 132 (86%) the second injection, 119 (78%) the third injection, 111 (73%) the fourth injection, 100 (65%) the fifth injection, and 93 (61%) the sixth injection.

**Primary Outcome and Related Opioid-Use Outcomes**

During the 24-week treatment phase, the time to relapse was significantly longer in the extended-release naltrexone group than in the usual-treatment group: 10.5 weeks versus 5.0 weeks (P<0.001; hazard ratio for relapse, 0.49; 95% confidence interval [CI], 0.36 to 0.68) (Fig. 2). A relapse event was detected in 66 participants assigned to extended-release naltrexone (43%) as compared with 99 assigned to usual treatment (64%) (P<0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65); this finding is consistent with the higher rate of opioid-negative urine samples, the lower percentage of days with self-reported opioid use, and the higher percentage of 2-week intervals with confirmed abstinence that we observed with extended-release naltrexone than with usual treatment (Table 2). An alternative analysis of missing urine data, in which only two consecutive confirmed positive urine screening results or self-reports of opioid use contributed to a “confirmed relapse outcome,” also favored extended-release naltrexone (rate of relapse, 15% vs. 37%; P<0.001; hazard ratio, 0.33; 95% CI, 0.21 to 0.54). The treatment effect did not differ significantly according to site.
Several important secondary outcomes did not differ significantly between the groups: rates of cocaine, alcohol, and intravenous drug use; the score on the Sex Risk subscale of the Risk Assessment Battery; and self-reported reincarceration (percentage of participants with any reincarceration and total days of incarceration) (Table 3). Participation in other, nontrial treatment in the community for opioid-use disorders did not differ significantly between the groups.
Shown is the incidence-density ratio calculated with a GEE mixed-effects Poisson regression model, with trial site as the repeated measure and with adjustment for trial site and week.

Shown is the odds ratio calculated with a GEE mixed-effects logistic-regression model for repeated measures, with participant as the repeated measure.

Shown is the odds ratio calculated with a generalized estimating equation (GEE) mixed-effects logistic-regression model, with trial site as the repeated measure.

Shown is the hazard ratio for relapse, calculated with a Cox proportional-hazards model.

Shown is the median time to relapse if a relapse event occurred.

CI denotes confidence interval.

\* Shown is the median time to relapse if a relapse event occurred.

\† Shown is the hazard ratio for relapse, calculated with a Cox proportional-hazards model.

\§ Shown is the odds ratio calculated with a GEE mixed-effects logistic-regression model for repeated measures, with participant as the repeated measure and with adjustment for trial site and week.

\¶ Shown is the incidence-density ratio calculated with a GEE mixed-effects Poisson regression model, with trial site as the repeated measure and with adjustment for log days at risk.

Table 2. Opioid Relapse and Related Outcomes during the 24-Week Treatment Phase.\*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Extended-Release Naltrexone (N=153)</th>
<th>Usual Treatment (N=155)</th>
<th>Hazard Ratio, Odds Ratio, or Incidence-Density Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: median time to relapse — wk†</td>
<td>10.5</td>
<td>5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Opioid-relapse event — no. (%)</td>
<td>66 (43.1)</td>
<td>99 (63.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of 2-wk intervals with confirmed abstinence</td>
<td>71.1</td>
<td>49.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of opioid-negative urine samples</td>
<td>74.1</td>
<td>55.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of days with self-reported opioid use</td>
<td>4.6</td>
<td>12.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Table 2. Opioid Relapse and Related Outcomes during the 24-Week Treatment Phase.\***

* CI denotes confidence interval.
† Shown is the median time to relapse if a relapse event occurred.
‡ Shown is the hazard ratio for relapse, calculated with a Cox proportional-hazards model.
§ Shown is the odds ratio calculated with a generalized estimating equation (GEE) mixed-effects logistic-regression model, with trial site as the repeated measure.
¶ Shown is the incidence-density ratio calculated with a GEE mixed-effects Poisson regression model, with trial site as the repeated measure and with adjustment for log days at risk.

**SAFETY AND LONG-TERM OPIOID-USE OUTCOMES**

Adverse events, including medication-related adverse events, were more common among participants assigned to extended-release naltrexone than among those assigned to usual treatment (Table 4); however, significantly more serious adverse events occurred in the usual-treatment group than in the extended-release naltrexone group. All recorded overdose events, fatal or nonfatal, occurred among participants assigned to usual treatment (0 events in the extended-release naltrexone group vs. 5 in the usual-treatment group from week 0 to 25, P=0.010; 0 vs. 7 events from week 0 to 78, P=0.02); no overdoses occurred in the extended-release naltrexone group after discontinuation of the agent. The percentage of participants with opioid-negative urine samples was similar in the two groups after completion of the treatment phase: 49% in the extended-release naltrexone group and 46% in the usual-treatment group at week 52 (P=0.61), and 46% in both groups at week 78 (P=0.91). Self-reported opioid use showed an interaction between treatment and time: participants assigned to extended-release naltrexone reported less use than those assigned to usual treatment during the active treatment phase, but the increase after the active treatment phase was greater in the extended-release naltrexone group, with the result that opioid use was similar in the two groups.
Extended-Release Naltrexone in Offenders

This U.S. multisite, randomized, controlled trial showed that extended-release naltrexone resulted in a lower rate of opioid relapse than the rate with usual treatment in a predominantly male and minority population of outpatient, voluntary participants with criminal justice involvement and opioid abstinence at baseline. During a 24-week treatment phase, the percentage of participants with a relapse event was lower among participants assigned to extended-release naltrexone than among those assigned to usual treatment (43% vs. 64%), corresponding to an absolute difference in risk of 21 percentage points and a number needed to treat of 5. The prevention of opioid use by extended-release naltrexone did not persist through follow-up at week 52 and week 78, approximately 6 months and 12 months, respectively, after the treatment phase had ended. In addition, we did not detect a benefit of extended-release naltrexone on several important secondary outcomes, including rates of cocaine, heavy alcohol, and injection-drug use. Rates of self-reported reincarceration and days of incarceration through week 27 were also not significantly lower in the extended-release naltrexone group than in the usual-treatment group.

There was not an increased risk of overdose events during treatment with extended-release naltrexone or immediately after its discontinuation; indeed, no overdose events were observed among participants assigned to extended-release naltrexone through 78 weeks, during which time seven overdose events occurred among partici-

Table 3. Secondary Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Extended-Release Naltrexone (N = 153)</th>
<th>Usual Treatment (N = 155)</th>
<th>P Value</th>
<th>Odds Ratio or Incidence-Density Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of days with cocaine use†</td>
<td>3.9</td>
<td>4.3</td>
<td>0.71</td>
<td>0.91 (0.56–1.48)‡</td>
</tr>
<tr>
<td>Heavy drinking in past 30 days at wk 27 — no. (%)‡</td>
<td>16 (13.9)</td>
<td>17 (14.9)</td>
<td>0.77</td>
<td>0.89 (0.43–1.87)¶</td>
</tr>
<tr>
<td>Any intravenous drug use — %¶</td>
<td>7 (5.9)</td>
<td>10 (8.6)</td>
<td>0.43</td>
<td>0.67 (0.25–1.82)¶</td>
</tr>
<tr>
<td>Mean score on Sexual Risk subscale of RAB at wk 27**</td>
<td>2.75</td>
<td>2.86</td>
<td>0.68†‡</td>
<td></td>
</tr>
<tr>
<td>Any reincarceration — no. (%)∥</td>
<td>35 (22.9)</td>
<td>45 (29.0)</td>
<td>0.38</td>
<td>0.71 (0.33–1.52)‡‡</td>
</tr>
<tr>
<td>Total days of reincarceration</td>
<td>1651</td>
<td>2628</td>
<td>0.22</td>
<td>0.63 (0.32–1.23)‡</td>
</tr>
<tr>
<td>Days incarcerated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among participants with any reincarceration</td>
<td>47.2±41.8</td>
<td>58.4±51.4</td>
<td>0.30††</td>
<td></td>
</tr>
<tr>
<td>Among all participants</td>
<td>11.1±28.4</td>
<td>17.6±38.9</td>
<td>0.10††</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
† Data are based on self-report for weeks 1 to 25 with the use of the Timeline Followback calendar method. No Timeline Followback data were available for 4 participants in the extended-release naltrexone group and 6 participants in the usual-treatment group.
‡ Shown is the incidence-density ratio calculated with a GEE mixed-effects Poisson regression model, with trial site as the repeated measure and adjustment for log days at risk.
§ Data on self-reported heavy drinking for weeks 1 to 25 were missing for 38 participants in the extended-release naltrexone group and 41 participants in the usual-treatment group.
¶ Shown is the odds ratio calculated with a chi-square test.
∥ Data on self-reported intravenous drug use for weeks 1 to 25 were missing for 35 participants in the extended-release naltrexone group and 39 participants in the usual-treatment group.
** Scores on the Sex Risk subscale of the Risk Assessment Battery (RAB) range from 0 to 18, with higher scores indicating a greater risk of contracting and spreading HIV infection through sexual behaviors.
†† The P value was calculated with a t-test.
‡‡ Shown is the odds ratio calculated with a GEE mixed-effects logistic-regression model, with trial site as the repeated measure and adjustment for log days at risk.
## Table 4. Adverse Events and Serious Adverse Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Extended-Release Naltrexone (N = 153)</th>
<th>Usual Treatment (N = 155)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of participants (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 Adverse event</td>
<td>119 (77.8)</td>
<td>90 (58.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adverse event related to trial drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>59 (38.6)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Leading to discontinuation of trial drug</td>
<td>5 (3.3)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>42 (27.5)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (2.6)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>29 (19.0)</td>
<td>13 (8.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>28 (18.3)</td>
<td>3 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15 (9.8)</td>
<td>17 (11.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11 (7.2)</td>
<td>8 (5.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Flulike symptoms</td>
<td>6 (3.9)</td>
<td>2 (1.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (1.3)</td>
<td>11 (7.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Serious adverse events†</td>
<td>16 (10.5)‡</td>
<td>45 (29.0)§</td>
<td>0.006</td>
</tr>
<tr>
<td>Depression or suicidality</td>
<td>3 (2.0)</td>
<td>6 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.3)</td>
<td>5 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (1.3)</td>
<td>4 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal symptom</td>
<td>2 (1.3)</td>
<td>4 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>5 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>0</td>
<td>4 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal overdose</td>
<td>0</td>
<td>4 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Exacerbation of preexisting condition</td>
<td>0</td>
<td>3 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Surgery for colon cancer</td>
<td>0</td>
<td>2 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Any overdose</td>
<td>0</td>
<td>7 (4.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Weeks 1–27</td>
<td>0</td>
<td>5 (3.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Weeks 28–78</td>
<td>0</td>
<td>2 (1.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Fatal overdose</td>
<td>0</td>
<td>3 (1.9)</td>
<td>0.25</td>
</tr>
<tr>
<td>Weeks 1–27</td>
<td>0</td>
<td>2 (1.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Weeks 28–78</td>
<td>0</td>
<td>1 (0.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (1.3)</td>
<td>5 (3.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Weeks 1–27</td>
<td>0</td>
<td>2 (1.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Weeks 28–78</td>
<td>2 (1.3)</td>
<td>3 (1.9)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* COPD denotes chronic obstructive pulmonary disease, and NA not applicable.
† A serious adverse event was defined as an adverse event that was life-threatening or that resulted in death, hospitalization or prolongation of hospitalization, persistent or clinically significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event. Included in the table are serious adverse events that affected two or more participants in a trial group.
‡ Serious adverse events in the extended-release naltrexone group also included one event each of abdominal pain, dehydration, acute renal failure, opioid withdrawal related to the trial drug, and hospitalization of unknown cause. Of the two deaths, one each was caused by homicide and seizure.
§ Serious adverse events in the usual-treatment group also included one event each of abdominal pain, asthma, cancer, influenza, hypertension, hypoglycemia, pancreatitis, and pneumonia. Of the five deaths, three were caused by overdose and one each was caused by homicide and cardiopulmonary arrest. Of the three events related to a preexisting condition (i.e., resulting from exacerbation or treatment of a preexisting condition), one each was related to deep-vein thrombosis, diabetes, and musculoskeletal injury.
pants assigned to usual treatment. Product labeling and expert reviews describe an increased risk of opioid overdose among patients receiving extended-release naltrexone, both during treatment, when a patient may “super-dose” opioids to overcome the naltrexone blockade, or after therapy, when tolerance is low and resumption of opioid use is even more dangerous.23,24

The trial groups did not differ significantly at baseline in terms of demographic characteristics and criminal justice status, and results were not modified by site, missed visits, or missing data. Main relapse-prevention effects were similar to those in the placebo-controlled pivotal efficacy trial, in which the median percentage of weeks of confirmed abstinence was 90% in the extended-release naltrexone group, as compared with 35% in the placebo group.12 On the basis of self-reports and a single urine sample at week 52 and week 78, months after extended-release naltrexone therapy had ended, the relapse-prevention effects had waned. As is the case with any chronic illness, symptoms of opioid-use disorder are more likely to recur with the discontinuation of effective pharmacotherapy.25 Future research would be needed to determine whether long-term or continuous treatment with extended-release naltrexone — similar to buprenorphine or methadone maintenance therapy — could help maintain the short-term benefits observed in this trial and improve longer-term outcomes.

This trial had important limitations. First, the trial was not blinded. Although an open-label effectiveness design may increase generalizability, it may also increase attention, recall, and assessment biases. The agreement between the results of this trial and those of other recent trials is reassuring with respect to validity.12,26 Second, sites were in the U.S. Northeast corridor, and participants were former or current heroin users; implications for other U.S. regions and prescription-opioid disorders are unclear. Third, eligibility criteria did not distinguish among levels of previous opioid use or grades of severity of opioid-use disorder; randomization was stratified according to whether or not detoxification was required before randomization. The majority of participants enrolled in this trial had not used opioids in the previous 30 days and did not require detoxification. Fourth, intensity and methods of community supervision varied according to state and site (e.g., parolees in home confinement vs. mandated residential treatment), though the main effects did not vary according to site. Finally, this trial did not directly compare extended-release naltrexone with the standard of opioid-agonist maintenance treatment, a comparison that is being assessed in an ongoing trial (ClinicalTrials.gov number, NCT02032433).

In summary, this U.S. multisite, open-label, randomized effectiveness trial showed that among adult offenders who had a history of opioid dependence, the rate of relapse was lower among participants assigned to extended-release naltrexone than among those assigned to usual treatment.

Supported by the National Institute on Drug Abuse (NIDA) through a collaborative clinical trial mechanism, PAR-07-232 (R01DA024549, to Dr. Friedmann; R01DA024550, to Dr. Kinlock; R01DA024553, to Dr. O’Brien; R01DA024554, to Dr. Nunes; and R01DA024555, to Dr. Lee), and additional support (K24DA022412, to Dr. Nunes). Trial medication was provided in kind from an investigator-initiated grant from Alkermes. Funding from the Dana Foundation to Dr. O’Brien supported the conduct of a five-site pilot study.

Dr. Lee reports receiving grant support and study medication from Alkermes and study medication from Indivior (formerly Reckitt Benckiser). Dr. Friedmann reports receiving fees for serving on an advisory board and travel support from Indivior and an honorarium for leading a roundtable discussion from Orexo. Dr. Kinlock reports receiving grant support and study medication from Alkermes. Dr. Nunes reports serving on an advisory board for Alkermes, receiving study medication from Reckitt Benckiser and Duramed Pharmaceuticals, being lead investigator for a NIDA-funded study of a computer-delivered behavioral intervention supplied by HealthSim, and being site principal investigator for a study funded by, and receiving travel support from, Brainway. Dr. Rotrosen reports receiving study medication from Alkermes and Indivior. Dr. Gordon reports receiving grant support and study medication from Alkermes. Dr. Fishman reports receiving travel support from Alkermes. Dr. O’Brien reports receiving consulting fees from Alkermes. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the trial participants and combined research staff across all sites.

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SHARING DATA IN A PUBLIC HEALTH EMERGENCY

The case for sharing data, and the consequences of not doing so, have been brought into stark relief by the Ebola and Zika outbreaks. In response, the New England Journal of Medicine has become a journal signatory to the following statement. “In the context of a public health emergency of international concern, it is imperative that all parties make available any information that might have value in combating the crisis. As research funders and journals, we are committed to working in partnership to ensure that the global response to public health emergencies is informed by the best available research evidence and data. Journal signatories will make all content concerning the Zika virus free access. Any data or preprint deposited for unrestricted dissemination ahead of submission of any paper will not be preempt later publication in these journals. Funder signatories will require researchers undertaking work relevant to public health emergencies to establish mechanisms to share quality-assured interim and final data as rapidly and widely as possible, including with public health and research communities and the World Health Organization.

We urge other journals and research funders to make the same commitments.”
Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness

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Bekhterev Research Psychoneurological Institute and St. Petersburg State Pavlov Medical University, St. Petersburg, Russian Federation,¹ New York State Psychiatric Institute and Department of Psychiatry, Columbia University, New York City, NY, USA,² Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA ³ and Alkermes, Inc., Waltham, MA, USA ⁴

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 multicenter, 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 ($\geq 18$ 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 ($\leq 30$ days). Patients were excluded if they had taken any opioids for $\geq 7$ 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 x 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 ($\geq 7$ 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.
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 abstenent’. 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-36v2™ Health Survey [22] and the 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% (52/124) 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 41.9% (52/124) PBO patients (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/analgesics.

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

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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</td>
<td>PBO</td>
</tr>
<tr>
<td>Age, mean years (SD)</td>
<td>n = 126</td>
<td>n = 124</td>
</tr>
<tr>
<td></td>
<td>29.4 (± 4.8)</td>
<td>29.7 (± 3.6)</td>
</tr>
<tr>
<td>Sex, n (%) male</td>
<td>113 (89.7%)</td>
<td>107 (86.3%)</td>
</tr>
<tr>
<td>Race, n (%) white</td>
<td>124 (98.4%)</td>
<td>124 (100%)</td>
</tr>
<tr>
<td>Duration of opioid dependence (years), mean (SD)</td>
<td>9.1 (± 4.5)</td>
<td>10.0 (± 3.9)</td>
</tr>
<tr>
<td>Days of pre-study inpatient detoxification, mean (SD)</td>
<td>18 (± 9)</td>
<td>18 (± 7)</td>
</tr>
<tr>
<td>Opioid Craving Scale, mean (SD)</td>
<td>18 (± 23)</td>
<td>22 (± 24)</td>
</tr>
<tr>
<td>HIV serology, n (%) positive</td>
<td>51 (40.5%)</td>
<td>52 (41.9%)</td>
</tr>
<tr>
<td>Hepatitis C, n (%) positive</td>
<td>111 (88.1%)</td>
<td>117 (94.4%)</td>
</tr>
</tbody>
</table>

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

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**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—a→XR-NTX</th>
<th>PBO—→XR-NTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 114</td>
<td></td>
<td>n = 67</td>
<td>n = 47</td>
</tr>
<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.
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 subgroup 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**
This study was funded by Alkermes, Inc. The Medisorb preparation used in XR-NTX was developed with support from the National Institute on Drug Abuse (grant R43DA013531) and the National Institute on Alcohol Abuse and Alcoholism (grant NA03AA001002).

Evgeny Krupitsky, MD, PhD, is a consultant for Alkermes and received research funding for this study from Alkermes.

Edward V. Nunes, MD, was a member of the Advisory Board to Alkermes that designed this trial and served as an unpaid consultant to an expert panel convened by Alkermes.

Walter Ling, MD, has been an Advisory Board member for Alkermes and US World Med; has received research funding from Titan Pharmaceuticals and investigator-initiated research funding from Hythiam; and research support, an unrestricted educational grant and speaker support from Reckitt Benckiser.

David R. Gastfriend, MD, Asli Memisoglu, ScD, and Bernard L. Silverman, MD, are employees of Alkermes, Inc.

**Acknowledgement**
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**References**
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Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial

Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman

Summary

Background Opioid dependence is associated with low rates of treatment-seeking, poor adherence to treatment, frequent relapse, and major societal consequences. We aimed to assess the efficacy, safety, and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone (XR-NTX) for treatment of patients with opioid dependence after detoxification.

Methods We did a double-blind, placebo-controlled, randomised, 24-week trial of patients with opioid dependence disorder. Patients aged 18 years or over who had 30 days or less of inpatient detoxification and 7 days or more off all opioids were enrolled at 13 clinical sites in Russia. We randomly assigned patients (1:1) to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and gender in a centralised, permuted-block method. Participants also received 12 biweekly counselling sessions. Participants, investigators, staff, and the sponsor were masked to treatment allocation. The primary endpoint was the response profile for confirmed abstinence during weeks 5–24, assessed by urine drug tests and self-report of non-use. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence. Analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00678418.

Findings Between July 3, 2008, and Oct 5, 2009, 250 patients were randomly assigned to XR-NTX (n=126) or placebo (n=124). The median proportion of weeks of confirmed abstinence was 90·0% (95% CI 69·9–92·4) in the XR-NTX group compared with 35·0% (11·4–63·8) in the placebo group (p=0·0002). Patients in the XR-NTX group self-reported a median of 99·2% (range 89·1–99·4) opioid-free days compared with 60·4% (46·2–94·0) for the placebo group (p=0·0004). The mean change in craving was −10·1 (95% CI −12·3 to −7·8) in the XR-NTX group compared with 0·7 (−3·1 to 4·4) in the placebo group (p<0·0001). Mardia test confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p<0·0001). XR-NTX was well tolerated. Two patients in each group discontinued owing to adverse events. No XR-NTX-treated patients died, overdosed, or discontinued owing to severe adverse events.

Interpretation XR-NTX represents a new treatment option that is distinct from opioid agonist maintenance treatment. XR-NTX in conjunction with psychosocial treatment might improve acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.

Funding Alkermes.

Introduction

Opioid dependence is a potentially life-threatening illness associated with adverse societal effects including increased morbidity and mortality, poor social functioning, economic dependence, and crime. The worldwide incidence of opioid dependence has increased during the past decade, and many patients are not receiving treatment for the disorder, although rates of treatment are increasing in many countries. The main treatments consist of either maintenance pharmacotherapy with counselling or drug-free psychosocial treatment. Although abstinence is the primary goal, drug-free treatment is associated with high rates of relapse. Agonist maintenance, such as with the μ-opioid receptor agonist methadone or the partial agonist buprenorphine, has an established role in the management of opioid dependence, with studies, reviews, and meta-analyses reporting a variety of public-health and safety benefits. These benefits include decreases in illicit drug use; reduced rates of HIV seroconversion, and improved morbidity, mortality, HIV risk behaviours, and patient functioning. However, in 122 of 192 UN member states, agonist therapy is restricted or unavailable because of philosophical preferences for opioid-free treatment or policy concerns about physiological dependence or abuse and illegal drug diversion. Furthermore, agonist therapy might be less suitable for certain subgroups of patients, particularly young people, patients with a brief history of addiction or who are new to treatment, and patients whose employment might prohibit opioid use (eg, healthcare providers, pilots, and police, fire, emergency and military personnel).
An alternative pharmacotherapy that supports abstinence is naltrexone, a µ-opioid receptor antagonist that does not have opioid agonist effects, produces no euphoria or sedation, and is not addictive. Antagonist pharmacotherapy is particularly appropriate for patients who have achieved abstinence during inpatient treatment or incarceration and are at risk of relapse after discharge. Naltrexone cessation causes no symptoms of withdrawal because patients are not physically opioid dependent. However, apart from when dosing is supervised, such as for recovering physicians or in the context of intensive behavioural treatments, oral naltrexone has generally been ineffective because of poor adherence.

In 1976, the US National Institute on Drug Abuse requested development of a long-acting opioid antagonist. Responses to this request consisted of subcutaneous naltrexone implants, which have shown efficacy but are associated with adverse events related to surgical insertion; and a long-acting injectable naltrexone formulation, which was effective in a small, 2-month long controlled trial. A once-monthly extended-release formulation of injectable naltrexone (XR-NTX, Vivitrol, Alkermes, Waltham MA, USA) has been approved in the USA and Russia for treatment of alcohol dependence. This formulation, administered via intramuscular injection by a health-care provider, gradually releases naltrexone from microspheres composed of medical-grade poly-(d,l-lactide-co-glycolide)—a polymer used in dissolvable surgical sutures. In patients with alcohol dependence, XR-NTX reduced the incidence of heavy drinking and increased the rate of total abstinence over 6 months in those with initial abstinence compared with placebo, with associated improvements in health and social functioning.

We did a multicentre, randomised, placebo-controlled 24-week trial to assess the efficacy, safety, and patient-reported outcomes of once-monthly XR-NTX for the treatment of opioid dependence.

Methods

Patients

Men and women aged 18 years or over who met the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria for opioid dependence disorder, who were completing inpatient opioid detoxification (<30 days), and who were off opioids for at least 7 days were enrolled at 13 clinical sites in Russia. Patients were voluntarily seeking treatment and were excluded if they were under justice system coercion—ie, parole or probation, or pending legal proceedings with potential for incarceration. Every patient also had a significant other (eg, spouse or relative) who supervised their compliance with the visit schedule and study procedures. Women of childbearing potential agreed to use contraception during the study.

Exclusion criteria were pregnancy or breastfeeding; significant medical conditions (eg, acute renal failure, endocarditis, and tuberculosis); positive naloxone challenge (increases in vital signs or opioid withdrawal symptoms); hepatic failure; past or present history of an AIDS-indicator disease; active hepatitis or aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal; known intolerance or hypersensitivity to naltrexone, carmelllose, or polylactide-co-glycolide; psychosis, bipolar disorder, major depressive disorder with suicidal ideation, or present dependence on substances other than opioids or heroin, including alcohol; positive urine test for cocaine or amphetamines; and naltrexone use within the past 6 months.

Each site’s independent ethics committee or institutional review board approved the protocol and participants gave written, informed consent in accordance with the Declaration of Helsinki.

Randomisation and masking

We randomly assigned patients (1:1) to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and sex with a centralised, permuted-block method with a block size of four. This system was also used to manage the supply of masked study drugs. Participants, investigators, staff, and the sponsor were masked to treatment allocation. To ensure masking, amber vials and syringes were used, and different personnel did counselling and data collection.

Procedures

Patients received an injection of XR-NTX or placebo within 1 week after detoxification and then every 4 weeks thereafter, for a total of six injections over 24 weeks. Participants were also offered 12 biweekly sessions of individual drug counselling, adapted for opioid dependence. Psychologists or psychiatrists who were trained in individual drug counselling reviewed patients’ substance use, recovery efforts, functioning, and adverse events, and provided support and advice to patients. Upon completion of the 24-week treatment period, all patients were offered open-label XR-NTX treatment for an additional year. All treatment was offered at no expense to patients. Urine drug testing for opioids (immunochromatography-based one-step in-vitro tests) was done weekly for 24 weeks and detected urine morphine and methadone at concentrations greater than 300 ng/mL.

The following drugs were prohibited during the study: naltrexone, buprenorphine, levacetylmethadol, methadone, other prescription opioids, antipsychotics, anticonvulsants, antidepressants, and anxiolytics. Permitted drugs were anticonvulsants if dosing was stable and short-acting insomnia drugs, such as zopiclone, as required.

The primary endpoint was the response profile for confirmed abstinence during weeks 5–24. We prospectively omitted weeks 1–4 from this endpoint because participants might challenge the blockade during this period, after which abstinence should stabilise.
Confirmed abstinence was defined as a negative urine drug test and no self-reported opioid use on the timeline follow-back (TLFB) survey.22 The TLFB survey uses calendars and daily recall of substance use on specific days to record quantity or frequency of opioid use. Omission of any of these criteria resulted in failure to confirm abstinence for the week.

Secondary a-priori endpoints were self-reported opioid-free days according to the TLFB, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence. Because use of opioids might produce relapse to physiological opioid dependence, measurement of both opioid use and physiological dependence was important. Craving was assessed with a weekly self-report visual analogue scale (VAS) of need for opioids (scale 0–100, 0=not at all; 100=very much so).23 Physiological dependence was assessed via naloxone challenge at baseline, upon any positive urine drug screen, at treatment discontinuation, and at week 24. Patients were removed from the study if the naloxone challenge test was positive, to protect the patient from the possibility of a prolonged precipitated withdrawal with XR-NTX. Other health outcomes that were also assessed included the HIV risk assessment battery,24 the 36-item short form health survey (version 2),25 patients’ VAS assessments of their general health on the EuroQol-5 dimensions questionnaire,26 and investigators’ revised clinical global impression ratings.27 Safety was assessed by weekly monitoring of treatment-emergent adverse events, vital signs, biochemistry and haematology on urine and blood samples, including liver function tests, monthly physical examination of injection sites, and baseline and endpoint electrocardiographs.

**Statistical analysis**

Before the trial, we calculated that a sample size of 125 patients per treatment group would provide 85% and 96% power to detect an effect size of Cohen’s d 0·4 and 0·5, respectively, by a Wilcoxon rank-sum test at a two-sided significance level of 0·05. Intent-to-treat analyses of efficacy endpoints were done with all randomised patients. We created response profiles by calculating the number of confirmed abstinence weeks for weeks 5–24 for each patient and then dividing by the number of scheduled tests (20). The response profile for each treatment group is the cumulative distribution function of percent of opioid-free weeks. For between-group comparisons we used a two-sided Van der Waerden test—a non-parametric test of whether k population distributions are equal. To assess the effect of baseline characteristics, the rate of opioid-negative urine drug tests were analysed with ANCOVA, containing factors for treatment group, sex, and sex-by-treatment interaction, and with age, duration of opioid dependence, and duration of last pre-study inpatient detoxification as covariates. Consistency of the effects of treatment on opioid-free weeks across subgroups

**Figure 1: Trial profile**

XR-NTX=extended-release naltrexone.

**Table 1: Demographics and baseline clinical characteristics**

<table>
<thead>
<tr>
<th></th>
<th>XR-NTX (n=126)</th>
<th>Placebo (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29·4 (4·8)</td>
<td>29·7 (3·6)</td>
</tr>
<tr>
<td>Men</td>
<td>113 (90%)</td>
<td>107 (86%)</td>
</tr>
<tr>
<td>White</td>
<td>124 (98%)</td>
<td>124 (100%)</td>
</tr>
<tr>
<td>Duration of opioid dependence (years)</td>
<td>9·1 (4·5)</td>
<td>10·0 (3·9)</td>
</tr>
<tr>
<td>Days of pre-study inpatient detoxification</td>
<td>18 (9)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Opioid craving scale</td>
<td>18 (23)</td>
<td>22 (24)</td>
</tr>
<tr>
<td>HIV serology positive</td>
<td>51 (40%)</td>
<td>52 (42%)</td>
</tr>
<tr>
<td>Hepatitis C positive</td>
<td>111 (88%)</td>
<td>117 (94%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%). XR-NTX=extended-release naltrexone.

**Figure 2: Percent of confirmed opioid-free weeks (cumulative) among participants treated with XR-NTX compared with placebo**

XR-NTX=extended-release naltrexone.
defined by baseline characteristics (sex, age, duration of opioid dependence, and duration of pre-study detoxification) and site was measured with ANCOVA models. Retention was assessed with Kaplan-Meier curves and a log-rank test. Changes from baseline in weekly craving scores were analysed with a generalised estimation equation model, assuming normal distribution and autoregressive correlation structure, with baseline craving as a covariate. For secondary endpoints, group differences were tested with the Van de Waerden test for continuous endpoints and \( \chi^2 \) tests or Fisher’s exact test for categorical endpoints. Adverse events were tested with the Bonferroni-Holm method to preserve family-wise type 1 error at 0.05. Adjusted for multiplicity by the Bonferroni-Holm method to preserve family-wise type 1 error at 0.05. ‡95% CI cannot be calculated because median exceeds the study duration.

### Table: Clinical outcomes

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>XR-NTX (n=126)</th>
<th>Placebo (n=124)</th>
<th>Treatment effect*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of weeks of confirmed abstinence</td>
<td>90.0% (69.9 to 92.4)</td>
<td>35.0% (11.4 to 63.8)</td>
<td>55.0 (15.9 to 76.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Patients with total confirmed abstinence</td>
<td>45 (35.7%, 27.4 to 44.1)</td>
<td>28 (22.6%, 15.2 to 29.9)</td>
<td>1.58 (1.06 to 2.36)</td>
<td>0.0224</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoint</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of self-reported opioid-free days over 24 weeks</td>
<td>99.2% (89.1 to 99.4)</td>
<td>60.4% (46.2 to 94.0)</td>
<td>38.7 (3.3 to 52.5)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Craving: mean change in VAS score from baseline</td>
<td>-10.1 (-12.3 to -7.8)</td>
<td>0.7 (-3.1 to 4.4)</td>
<td>-10.7 (-15.0 to 6.4)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Number of days of retention</td>
<td>&gt;168†</td>
<td>96 (63 to 165)</td>
<td>0.61 (0.44 to 0.86)</td>
<td>0.0042†</td>
</tr>
<tr>
<td>Participants with positive naloxone challenge test</td>
<td>1 (0.8%, 0.0 to 2.3)</td>
<td>17 (13.7%, 7.7 to 19.8)</td>
<td>17.3 (2.3 to 127.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Results

Between July 3, 2008, and Oct 5, 2009, 335 candidates were screened, 250 of whom were randomly assigned to XR-NTX or placebo (figure 1). Participants were predominantly young, white men (table 1) who had been addicted to heroin for about 10 years. High rates of HIV and hepatitis C infection were reported in the study population (table 1). In the 30 days before the first injection, heroin was used by 221 (88%) of 250 participants, methadone by 29 (12%), and other opioids or analgesics by 33 (13%). Demographic and baseline clinical characteristics showed no substantial inter-group differences (table 1).

Of 4285 urine drug tests and TLFB responses obtained, 4178 (97.5%) were in agreement. On 53 (1.2%) of 4285 occasions, participants self-reported using opioids despite opioid-negative urine tests. During weeks 5–24, there were 2098 of 5000 (42.0%) missing urine samples, 1255 (50.6%) of 2480 with placebo and 833 (33.1%) of 2520 with XR-NTX; 2096 of 2098 missing samples were because of early termination. Patients in the XR-NTX group received 1191 (99.7%) of 1194 scheduled counselling sessions (median 12; range 1–13) versus 922 (99.6%) of 926 for the placebo group (median 8; range 1–13).

The percentage of opioid-free weeks was significantly higher in the XR-NTX group than the placebo group (p=0.0002), with substantial separation between groups across all measured values of opioid-free weeks (figure 2). The median proportion of patients who had confirmed abstinence was higher in the XR-NTX group than the placebo group (p=0.0002; table 2).
abstinence was reported in 36% of patients in the XR-NTX group compared with 23% in the placebo group (p=0·0224; table 2). When efficacy was analysed on the basis of the full 24-week period, including weeks 1–4, results were still significant (p=0·0001). 119 (94%) of 126 patients in the XR-NTX group were opioid free compared with 96 (77%) of 124 in the placebo group by week 2, and this separation persisted through to the end of the trial (figure 3). No significant relation was noted between age, sex, or duration of opioid dependence and the rate of opioid-free urine tests (data not shown). The treatment effect was consistent across baseline variables and study sites (data not shown).

All four secondary endpoints also showed significant differences between the treatment groups (table 2). Median self-report of opioid-free days over 24 weeks was 99% for the XR-NTX compared with 60% for the placebo group (p=0·0004; table 2; figure 3). There was a statistically and clinically significantly greater reduction in opioid craving in the XR-NTX group than the placebo group by week 8 (p=0·0048), which persisted every week through to week 24 (baseline to week 24: XR-NTX 18·2–8·8 vs placebo 21·8–22·5; p<0·0001, adjusted for multiplicity; table 2; figure 3). Median number of days of retention was 168 days (ie, still retained at the end of the study) in the XR-NTX group compared with 96 days for the placebo group (p=0·0042, adjusted for multiplicity; table 2; figure 3). All six injections were received by 73 (57·9%) of patients in the XR-NTX group compared with 52 (41·9%) of the placebo group (XR-NTX:placebo ratio 1·37, 95% CI 1·06–1·78; p=0·0171). Relapse to physiological opioid dependence was identified in one patient (who had missed two previous injections) in the XR-NTX group compared with 17 on placebo (p<0·0001; table 2).

Health outcome measures were similar between groups at baseline; however, the XR-NTX group had significantly greater improvement from baseline than placebo in reduction of HIV risk, increased general health, and investigators’ clinical global impression improvement ratings. Baseline and post-treatment 36-item short form physical component summary scores were normal for both groups. The mental component score was well below US population norms (ie, score of 50) for both groups at baseline, but at study end the XR-NTX group (but not the placebo group) had normalised and was significantly better than placebo by 0·5 SD (mean 50·37 [SD 9·18] vs 45·28 [10·47]; difference 5·09, 95% CI 2·09–8·09; p=0·0043). Similar results were found on all four subscales, including vitality (58·13 [8·43]) and were similar to Russian normative population scores.

XR-NTX was generally well tolerated; two patients in each group discontinued owing to adverse events (table 3). 103 (41%) of 250 patients experienced at least one adverse event; a higher proportion of patients in the XR-NTX group than the placebo group had at least one adverse event; a higher proportion of patients in the XR-NTX group than the placebo group had at least one adverse event; a higher proportion of patients in the XR-NTX group than the placebo group had at least one
adverse event (p=0.005). All non-serious adverse events were deemed mild or moderate by investigators and most were judged to be unrelated to the study drug. Serious adverse events were uncommon and no episodes of intractable pain management were reported. No overdose events, suicide attempts, or deaths, or other severe adverse events were reported.

The mean increase from baseline of alanine aminotransferase was 6–9 IU/L in the XR-NTX group and 5–6 IU/L in the placebo group, and for aspartate aminotransferase the mean increase from baseline was 3–8 IU/L in the XR-NTX group and 6–7 IU/L for placebo. Hepatic enzyme abnormalities were more common with XR-NTX (data not shown).

<table>
<thead>
<tr>
<th>Table 3: Clinical adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XR-NTX</strong> (n=126)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Inomnia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Influenza</td>
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<tr>
<td>Injection site pain</td>
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<tr>
<td>Toothache</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>≥1 adverse event</td>
</tr>
<tr>
<td>≥1 drug-related adverse event</td>
</tr>
<tr>
<td>≥1 serious adverse event*</td>
</tr>
<tr>
<td>Discontinued owing to adverse events</td>
</tr>
</tbody>
</table>

Data are number (%). XR-NTX=extended-release naltrexone. *Three patients in the XR-NTX group reported four serious adverse events (infectious processes, eg, AIDS or HIV) and four patients in the placebo group reported five serious adverse events (two infectious, one drug dependence, one psychiatric disorder, and one peptic ulcer).

Discussion

Detoxified, opioid-dependent adults voluntarily seeking treatment who received XR-NTX had more opioid-free weeks than those who received placebo. Efficacy did not vary by age, sex, or duration of opioid dependence. There was a persistent anti-craving effect over weeks 8–24, 94% fewer naloxone-confirmed relapses to dependence, and nearly double the median length of retention in treatment in patients who received XR-NTX than those on placebo. Onset was rapid, with an anti-craving effect at week 1, an increase in abstinent days within 2 weeks, and improved retention at 1 month.

Although this study did not include a comparison with oral naltrexone, a meta-analysis of ten studies of oral naltrexone compared with placebo in multiple countries with 696 participants in total and a mean duration of 6 months did not find benefits for retention or prevention of relapse (panel). Similarly, a study of oral naltrexone compared with treatment without naltrexone did not report an anti-craving effect, whereas in the present study treatment with XR-NTX resulted in a rapid progressive decline in craving to 50% of baseline compared with no change with placebo. These differences might have been because oral naltrexone was self-administered daily and because XR-NTX has different release kinetics, which, compared with daily oral naltrexone, yields about four times the area-under-the-curve plasma concentration of naltrexone and reduced exposure to β-naltrexol. Comparison of the present results with a small study of an injectable formulation of naltrexone are difficult because the previous study was only 8 weeks long, used a different psychosocial intervention, and was done in the USA. However, both studies reported that extended-release, injectable naltrexone was superior to placebo for the outcome of opioid-negative urine.

XR-NTX was generally well tolerated and no new safety findings were reported. Adverse events of any kind were reported by half of patients in the XR-NTX group compared with a third of those in the placebo group; however, rates of discontinuations owing to adverse events and serious adverse events were similar in both groups. High baseline incidence of opioid dependence-related medical comorbidity, including hepatitis C and HIV infection, might have affected liver enzyme measurements. Abnormal liver function tests occurred only in patients with existing hepatitis C infection (data not shown). An FDA warning previously advised US providers of the occurrence of injection site reactions and the importance of proper injection technique; injection site pain was more prevalent in the XR-NTX group compared with the placebo group, although no severe adverse reactions were reported. No instances of intractable pain were reported, although patients with acute or chronic pain or anticipated pain episodes (eg, elective surgery) were excluded and study investigators were instructed in pain management alternatives to opioid analgesics. Previous studies have shown that the selective blockade of naltrexone can be overcome: rats given XR-NTX, and then either hydrocodone or fentanyl at 10–20 times the usual doses achieved an analgesia response and did not have significant respiratory depression or sedation.

A strength of this study was its geographic setting in Russia—one of the many countries where opioid agonist therapy is unavailable, but where there is an alarming growth in availability of heroin and the fastest-growing HIV infection rate in the world. The report of efficacy in these seriously ill patients is important both in Russia and as a model for the rest of the world. Patients included in this study share similarities with the opioid-dependent population in other countries, including relatively young age, predominantly male sex, and high rates of infection with HIV and hepatitis C. Nevertheless, given the population and treatment system differences, generalizability of these results beyond Russia is a topic for further research. However, in countries with a viable system of opioid agonist maintenance treatment, patient resistance
Articles

Panel: Research in context

Systematic review
In systematic reviews, opioid substitution treatment (buprenorphine and methadone) was effective in the treatment of opioid dependence, but such agonist treatments are restricted or unavailable in many countries and might not be suitable for all patients. Systematic reviews of antagonist maintenance with oral naltrexone have generally reported the treatment to be ineffective because of poor adherence.

Interpretation
In this study, once-monthly extended release naltrexone (XR-NTX) was superior to placebo with respect to the endpoints of confirmed abstinence, craving for opioids, retention, and prevention of relapse to opioid dependence. XR-NTX offers a new treatment option without risk of physical dependence or illegal diversion. This approach might aid community and cultural acceptance of opioid dependence pharmacotherapy.

to placebo treatment or ethical considerations might make it difficult to do a placebo-controlled trial. The extent of patient interest in XR-NTX when opioid substitution treatments are available remains a topic for future health services research; however, there might be interest among those whose employment prohibits opioid use, those with a relatively recent addiction to opioids, and those who wish to secure their recovery after a successful course of agonist therapy. In countries where both XR-NTX and opioid substitution treatments are available, the relative costs of such treatments might be an important factor in their clinical use and accessibility. Another strength of this study was the rigorous definition used for opioid abstinence, which included both self-report and urine testing. Furthermore, the imputation that patients who were lost to treatment represented treatment failures was a conservative interpretation that is consistent with the importance of treatment retention and abstinence.

There are several limitations of this study. There was a substantial clinical response to placebo; however, the treatment group still showed greater benefits than those in the placebo group. Retention in the placebo group might have been reduced by recognition upon opioid use that one was on placebo or—among patients in the placebo group who had relapsed to regular opioid use—by reluctance to return to the clinic and face a withdrawal reaction from a naloxone challenge test. Despite these possibilities, the placebo group showed a substantial retention and response profile, and a markedly higher rate of positive naloxone challenge tests. Drug use might have been under-reported on self-report; however, there was a high degree of agreement between results from urine tests and self-report and the urine data was a required confirmatory element of the primary efficacy measure. The high retention rate might have been influenced by the inclusion criterion that patients have someone available to supervise attendance, the provision of individual counselling, the absence of alternative treatments (eg, methadone or buprenorphine) in Russia, and the promise of active XR-NTX treatment for all patients after 6 months in the subsequent open-label extension safety study.

Additional research on the practical aspects of opioid antagonist treatment might support further improvement of patient outcomes. Patients must be fully detoxified before receiving opioid antagonists to avoid precipitation of opioid withdrawal; thus, methods for antagonist induction and treatment transition need to be optimised. Studies are needed on the differential roles of agonist and antagonist maintenance therapies—eg, in early versus late stage illness, in the context of chaotic versus structured social supports, in patients with versus those without chronic pain, or in judicial or employment settings. The worldwide societal effects of this disease lend an urgency to the replication of these results and call for research into this treatment approach in different countries and settings, such as primary-care offices; in different populations, including those that might be less compliant than the patients included in this study; and on the appropriate duration of treatment, long-term benefits and safety, and the health economic and policy aspects.

The results of this study suggest that XR-NTX offers a new approach—distinct from opioid-agonist mainten ance—that assists patients in abstaining from opioids and prevents relapse to opioid dependence. Given the heterogeneity of patient needs, to provide optimum care for patients who are opioid dependent, a comprehensive set of treatment options is needed, including existing agonist maintenance treatments, which are well validated both in efficacy and effectiveness research and psycho-social management. The findings of the present study suggest that antagonist therapy could also play a part. A once-monthly supervised pharmacological treatment with proven efficacy that is free of physical dependence and is not subject to illegal diversion might aid community and cultural acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.

Contributors
EK had full access to the original data, reviewed the data analyses, contributed to data interpretation, wrote the first draft of the manuscript, made final decisions on all parts of the report, and approved the final version of the submitted report. All other authors had access to the data used in the paper and additional data when requested were made and wrote the final draft. EK, EVN, AI, DRG, and BLS designed the study. EK enrolled patients. AI did the statistical analyses and generated tables and figures. EK, DRG, and BLS provided study supervision and administrative support.

Conflicts of interest
The Medisorb preparation used in XR-NTX was developed with support from the National Institute on Drug Abuse (grant R43DA013531) and National Institute on Alcohol Abuse and Alcoholism (grant N43AA001002). EK is a consultant for Alkermes and received research funding for this study from Alkermes. EVN was a member of the
Alkermes advisory board that designed this trial and was an unpaid consultant to an expert panel convened by Alkermes, with approval from the Columbia University Department of Psychiatry. WL has been an advisory board member for Alkermes and US W
the Columbia University Department of Psychiatry. WL has been an
consultant to an expert panel convened by Alkermes, with approval from
Alkermes advisory board that designed this trial and was an unpaid
consultant to an expert panel convened by Alkermes, with approval from

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References


Injectable extended-release naltrexone for the prevention of relapse to opioid dependence following opioid detoxification
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Opioid dependence continues to be a worldwide problem [101,102]. Prevalence rates for heroin and other opiates range between 0.3 and 0.5% of the world's population aged between 15 and 64 years [101]. A dramatic rise in the non-medical use of opioid pain medications has also been occurring, particularly in the USA, with an estimated 1.9 million Americans abusing or dependent on prescription pain medications in 2010 [1]. Dependence on opioids is associated with increased morbidity and mortality, poor social functioning, economic dependence and crime [2-4]. The economic burden to society of opioid-use disorders is large, with total US societal costs of prescription opioid abuse estimated at US$55.7 billion in 2007 [5] and total US costs of heroin addiction estimated at US$21.9 billion in 1996 [6].

Available treatment modalities vary across different countries, with the most common approaches consisting of either agonist maintenance pharmacotherapy or drug-free psychosocial treatment. Maintenance pharmacotherapy options include methadone (a µ-opioid receptor agonist) or buprenorphine (a partial agonist). The efficacy and safety of buprenorphine and methadone are documented by numerous studies [7,8]. In the majority of UN member countries (122 of 192), however, agonist therapy is unavailable or restricted owing to concerns about physiological dependence or abuse and illegal diversion [2]. In addition, agonist therapy is sometimes not the preferred treatment for specific types of patients. This includes young people, those with a brief history of addiction or who are new to treatment, and those whose employment may prohibit opioid use (e.g., healthcare providers, pilots and police, fire, emergency and military personnel). Drug-free psychosocial treatment is an option for these and other patients, but is associated with high rates of relapse [9].

Opioid dependence can also be treated with naltrexone, a µ-opioid receptor antagonist. However, in general, problems with adherence to oral naltrexone have undermined its efficacy in the treatment of opioid dependence [10]. This problem with adherence was anticipated by the US National Institute on Drug Abuse as early as 1976 and led to requests for the development of a long-acting opioid antagonist. Following this request, Alkermes, Inc. (MA, USA) developed a once-monthly extended-release formulation of injectable naltrexone (XR-NTX, Vivitrol®) [11]. XR-NTX gradually releases naltrexone from microspheres composed of medical-grade polylactide-co-glycolide, a polymer used in dissolvable surgical sutures. This article will review the clinical trial data on which approval of XR-NTX for opioid dependence was based, and present information
on its administration, clinical pharmacology, mechanism of action, pharmacodynamics, pharmacokinetics and its associated adverse events and labeled warnings.

**Indications & usage**

In its oral form, naltrexone was approved by the US FDA for treatment of opioid dependence in 1984. The extended-release formulation was approved more recently (October 2010) in the USA for prevention of relapse to opioid dependence among detoxified individuals as part of a comprehensive management program that includes psychosocial support. Prior to its approval for opioid dependence, XR-NTX was approved for use in the treatment of alcohol dependence in both the USA and Russia.

XR-NTX is contraindicated in patients with acute hepatitis or liver failure, patients receiving opioid analgesics, patients with current physiologic opioid dependence, patients in acute opioid withdrawal, any individual who has failed a naloxone challenge test or has a positive urine screen for opioids, and patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide, carboxymethyl cellulose or any other components of the diluent.

**Dosage & administration**

The standard dosage of XR-NTX is 380 mg delivered as an intramuscular gluteal injection. Injections are delivered every 4 weeks (or once a month) by a healthcare professional. It is recommended that injections be administered in alternating buttocks over the course of treatment. If a dose is missed, the next dose should be administered as soon as possible. To assure proper release kinetics and avoid microsphere particle entry into the circulatory system, XR-NTX should never be administered intravenously.

It is not required that patients be pretreated with oral naltrexone before beginning XR-NTX injections, however, patients should be opioid free for 7-10 days prior to treatment with XR-NTX.

**Clinical pharmacology**

* **Mechanism of action**

Naltrexone, and its active metabolite 6-[beta]-naltrexol, are antagonists with a high affinity for the µ-opioid receptor. The clinical efficacy of naltrexone results from blocking the effects of opioids through competitive binding at these receptors. The ability of XR-NTX to sustain a blockade of opioid receptors in opioid abusers over the month following an injection was recently demonstrated in an opioid challenge experiment $^{[12]}$. In this study, low subjective ratings of 'any drug effect', indicating blockade, were maintained for a full 28-day period for each of three dosage levels that were tested in the experiment (75, 150 and 300 mg) of XR-NTX, and the FDA-approved formulation is marketed at a higher naltrexone dose (380 mg).
With XR-NTX, extended release is achieved through the embedding of naltrexone within a matrix of microspheres (<100 µm diameter) made of polylactide-co-glycolide. Polylactide-co-glycolide is a common biodegradable copolymer that has been used safely in various human applications, including sutures, orthopedics, bone plates and other extended-release medications.

* Pharmacodynamics

Beyond its opioid-blocking properties, naltrexone has few effects on the human body. Some pupillary constriction is evident with naltrexone, but the mechanism of this effect is unknown. XR-NTX is not associated with the development of tolerance or dependence on naltrexone. However, in individuals who are physiologically dependent on opioids, naltrexone and XR-NTX will precipitate acute withdrawal. This is why individuals must be detoxified from opioids before initiating XR-NTX.

Clinical concerns about the effects of sustained blockade of the µ-opioid receptor on experienced pleasure have led to research investigating whether or not XR-NTX reduces pleasure from activities such as sex, exercise, food and other daily activities. In one report, alcohol-dependent patients (n = 74), at the end of receiving XR-NTX injections nearly continuously for 3-5 years were asked to rate how pleasurable a number of daily activities were on a 1 ('not at all') to 5 ('very much') scale in the prior 90 days [13]. A minority of patients rated drinking alcohol as 'moderately', 'quite a bit' or 'very much' pleasurable, whereas 60-92% rated exercise, sex, eating good food and six other common activities in these categories [13]. Although the study did not assess baseline pleasure ratings or outcomes with opioid-dependent patients, it suggests that the effect of long-term XR-NTX on hedonic response may operate on a gradient, with greater attenuation for alcohol reward than for other rewarding and more healthy stimuli.

Enhanced reactivity to conditioned cues is believed to play an important role in relapse with substance-use disorders. The impact of XR-NTX on such conditioned cues as measured by a blood-oxygen-level-dependent/functional MRI cue-reactivity procedure has been investigated with alcohol-dependent subjects [14]. In this study, the blood-oxygen-level-dependent functional MRI cue-reactivity procedure was conducted immediately before, and 2 weeks after, an XR-NTX or placebo injection. Results indicated that XR-NTX attenuates the salience of cues that have been associated with alcohol. This effect of XR-NTX on brain function may interrupt the process through which conditioned cues can trigger 'slips' and relapse. However, the extent to which these results generalized to opioid-dependent individuals is not known.

* Pharmacokinetics

Following an injection with XR-NTX, there is an initial peak in naltrexone plasma concentrations after approximately 2 h [15]. A second peak occurs approximately 2-3 days later. Concentrations slowly decline 14 days postinjection, but measurable levels persist for more than 1 month. The overall median peak concentration obtained in the pharmacokinetic study was 12.9 ng/ml [15]. Other investigations have indicated that
plasma concentrations of naltrexone of less than 1 ng/ml are sufficient to antagonize heroin-induced effects [16,17].

Maximum plasma concentration and the area under the curve for naltrexone and 6-[beta]-naltrexol (the major metabolite of naltrexone) after administration of XR-NTX are proportional to dose [15]. Total naltrexone dose is lower with a single dose of 380 mg XR-NTX compared with oral dosing with 50 mg naltrexone over 28 days (i.e., 1400 mg), but the area under the curve is three- to fourfold higher [15]. Following the first injection, a steady state is reached at the end of the 1-month dosing interval. Repeat injections of XR-NTX show minimal accumulation (<15%) of naltrexone or 6-[beta]-naltrexol.

Naltrexone is extensively metabolized in humans. Production of the metabolite 6-[beta]-naltrexol is mediated by dihydrodiol dehydrogenase. The cytochrome P450 system is not involved in naltrexone metabolism. Two other minor metabolites are 2-hydroxy-3-methoxy-6-[beta]-naltrexol and 2-hydroxy-3-methoxy-naltrexone.

Significantly less 6-[beta]-naltrexol is generated with injection of XR-NTX compared with oral administration of naltrexone owing to a reduction in first-pass hepatic metabolism with XR-NTX [15]. Elimination of naltrexone and its metabolites occurs primarily via urine; there is minimal excretion of unchanged naltrexone. The elimination half-life of naltrexone and 6-[beta]-naltrexol following administration of XR-NTX is 5-10 days [15].

Clinical evidence

* Overview of randomized, placebo-controlled clinical trials

The first evidence of efficacy for a long-acting injectable naltrexone formulation came from a small, short-term (2 month) controlled trial using a product that was not submitted for approval in the USA [18]. This study compared placebo with 192 and 384 mg of long-acting injectable naltrexone to placebo. Retention in treatment was dose related, with 39, 60 and 68% of patients, respectively, remaining in treatment at the end of 2 months. The percentage of urine samples negative for opioids, methadone, cocaine, benzodiazepines and amphetamines was significantly higher for the 384-mg group versus placebo (p < 0.001) and for 192 mg versus placebo (p = 0.046) when missing urines were considered positive. However, when missing urines were not considered positive, these group comparisons were no longer significant.

The primary efficacy study for the marketed version of XR-NTX was a 6-month placebo-controlled study conducted at 13 clinical sites in Russia [19]. This study is the only published controlled trial of XR-NTX for opioid dependence. The current review therefore focuses on the results of this trial.

Opioid-dependent (primarily heroin) individuals who had completed inpatient opioid detoxification participated. Following detoxification, XR-NTX was injected every 4 weeks, for a total of six injections over 24 weeks. Patients were randomized to XR-NTX (n = 126) or placebo (n = 124), with all participants also receiving up to 12 biweekly
sessions of individual drug counseling in conjunction with injection visits. The primary efficacy measure was a response profile, defined as the proportion of patients at each possible response level of confirmed opioid-free weeks who achieved that amount (or greater) of opioid-free weeks (using only data from weeks 5 to 24). Weekly confirmed abstinence was defined as the following: the patient provided urine for drug testing, the testing was negative and the patient reported no opioid use. Thus, missing urines were coded as positive for opioids. Patients who used illicit opioids during the trial continued on treatment.

The results of the trial indicated that XR-NTX was statistically and clinically superior to placebo on all a priori primary (p = 0.0002) (Figure 1) and secondary efficacy measures (Table 1). The median XR-NTX patient had confirmed abstinence for [greater than or equal]90% of weeks versus 35% for placebo and the mean total of confirmed abstinence was 35.7% weeks with XR-NTX versus 22.6% with placebo. There was a greater reduction in opioid craving in the XR-NTX group compared with placebo by week 8 and that difference persisted every week through week 24 (p 168 days for the XR-NTX group versus 96 days for the placebo group, with 67 in the XR-NTX group and 47 in the placebo group completing all six injections (p = 0.017). XR-NTX patients attended a median of 12 counseling sessions versus eight for placebo patients. The XR-NTX group also improved more than the placebo group with regard to relapse to physiological opioid dependence (p < 0.0001), HIV-risk behaviors (p = 0.025), self-reported health status (p = 0.0005), clinician ratings of global improvement (p = 0.0002), and health-related quality of life (mental component; p = 0.0043). It should be noted that the absolute levels of improvement in both the XR-NTX and placebo groups occurred in conjunction with the provision of individual drug counseling. Further research is needed to determine the contribution of counseling to the overall degree of improvement evident with XR-NTX.

*Health economic outcomes*

The healthcare costs associated with treatment of opioid dependence with psychosocial treatment alone, methadone, buprenorphine, oral naltrexone or XR-NTX have been examined using claims data from a large US health plan [20]. In this study, analyses focused on 6-month medication persistence, healthcare utilization, direct paid claims for opioid-dependence medications, detoxification and rehabilitation, opioid-related and nonrelated inpatient admissions, outpatient services and total costs. Although the pharmacy costs for XR-NTX are more than other treatments, total healthcare costs (combining inpatient, outpatient and pharmacy) were found to be greatest with psychosocial treatment alone, and XR-NTX total costs were not significantly different from oral naltrexone or buprenorphine and were 49% lower than with methadone. Although study limitations include retrospective design using case-mix adjustment, lack of indirect costs (e.g., job absenteeism or criminal justice costs) and a focus only on individuals with commercial insurance, XR-NTX-treated patients had fewer opioid-related and nonopioid-related hospitalizations than patients receiving any of the approved oral medications for opioid dependence.
* Adverse reactions

XR-NTX is generally well tolerated. In the published Phase III clinical trial, two patients in both groups discontinued treatment due to adverse events (drug-dependence relapse, psychotic disorder, hepatitis C and nausea) [19]. Moreover, no overdose events, suicide attempts, deaths or other severe adverse events were reported in the trial. Overall, more patients in the XR-NTX group reported an adverse event than in the placebo group (50 vs 32.3%), but no adverse events were judged to be severe.

Rates of specific adverse events with the use of XR-NTX in an opioid-dependent population were low (Table 2) [21]. Only one adverse event (insomnia) showed a significantly greater incidence for the XR-NTX group compared with placebo (6 vs 1%). Injection-site pain was more prevalent in XR-NTX versus placebo patients (5 vs 1%), and a FDA warning has advised US providers of the occurrence of injection-site reactions and the importance of proper injection technique.

Hepatic enzyme abnormalities were more common with XR-NTX compared with placebo and XR-NTX has a boxed warning regarding naltrexone hepatotoxicity [16]. The Phase III trial sample had a high baseline incidence of hepatitis C (89%) and HIV infection (41%); however, abnormal liver function tests over the course of treatment occurred only in patients with existing hepatitis C infections, were transient and not clinically meaningful.

A clinical concern with the use of naltrexone is whether the blockade of µ-opioid receptors is potentially surmountable. There has been one published case report of an individual who overcame the blockade from a surgically implanted version of long-acting naltrexone (approved for use in Russia) by using very large amounts of heroin [22]. In an animal study, rats administered XR-NTX showed no significant respiratory depression or sedation when given hydrocodone or fentanyl at ten- to 20-times the usual doses to achieve an analgesic response [23]. There have been published reports of death from opioid overdose with the implanted version of long-acting naltrexone both during treatment and following removal of the implant [24,25].

* Use in special populations

The use of XR-NTX in patients with hepatic impairment deserves comment. A boxed warning in the package insert for oral naltrexone, and subsequently XR-NTX, in relation to hepatotoxicity was prompted by early studies reporting hepatotoxicity at very high dosages of oral naltrexone (350 mg/day) in obese patients and those with senile dementia [26]. To address this concern, a study examined the pharmacokinetics of XR-NTX at the 190-mg dose (although not at the full 380-mg marketed dose) among a small sample of individuals with mild-to-moderate hepatic impairment [27]. Results of the study indicated no difference in pharmacokinetic parameters between those with mild-to-moderate hepatic impairment compared with controls following administration of XR-NTX. Similarly, transient and clinically insignificant enzyme elevations were found but
no evidence for hepatotoxicity in a detailed analysis of hepatic safety in the use of XR-NTX for alcohol dependence \[28\].

The safety, efficacy and pharmacokinetics of XR-NTX in a pediatric population has not been examined to date. The use of XR-NTX during pregnancy, labor and delivery and with nursing mothers, has also not been investigated.

XR-NTX is contraindicated in patients known or expected to have a need for opioid analgesia. Administration of XR-NTX in conjunction with other medications has not been explored in clinical drug interaction studies to date. Prescribers should therefore weigh the risks and benefits of concomitant drug use when considering XR-NTX. However, in the Phase III study of XR-NTX for treatment of alcohol dependence, almost 30% of patients were taking concomitant antidepressants without any evident safety concerns \[29\].

* Clinical & practice issues

Although XR-NTX has demonstrated efficacy in a 6-month trial, clinicians will need guidance on how long to continue the injections. This issue remains to be addressed in future studies.

Another key issue for clinical practice is how best to rapidly and safely transition a patient from agonist use to XR-NTX antagonist therapy. Recommendations have been provided for such a transition that tailor the detoxification strategy to the severity of physiological opioid dependence \[30\]. The suggested approach typically begins with a 4-8 mg dose of buprenorphine, particularly for moderate-to-severely dependent individuals; no buprenorphine may be needed for mildly dependent individuals. This is combined with clonidine and other ancillary medications, followed by 1-2 days of progressive oral naltrexone doses before initiating XR-NTX. Moderately dependent individuals may require partial hospitalization for this regimen and severely dependent individuals may require an inpatient setting. One limitation of this buprenorphine-clonidine-naltrexone procedure is that precipitated withdrawal must be anticipated and actively managed. Furthermore, the efficacy and safety of this approach needs to be investigated in controlled trials. As mentioned, the product labeling for XR-NTX requires that a patient be opioid free for a minimum of 7-10 days.

An alternative method of detoxification involves a gradual taper, first substituting 2-4 mg buprenorphine when withdrawal symptoms emerge, usually 12-18 h after the last dose of heroin or other short-acting opioid, and then titration up to 4-16 mg of buprenorphine per day until withdrawal symptoms are suppressed, then tapering to 0 mg over the next 7-14 days. This would then be followed by the appropriate opioid-free period before initiating XR-NTX \[30\].

A further consideration in the use of XR-NTX is pain management. Two options are regional analgesia and use of nonopioid analgesics. If possible, a patient can schedule surgery after discontinuing XR-NTX. Because the blockade of µ-opioid receptors by
naltrexone is competitive, it is surmountable. Thus, opioid pain therapy can be implemented as part of anesthesia or analgesia. However, if opioids are used, the patient needs to be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The healthcare professional providing the opioid therapy should be trained in the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation and the setting equipped and staffed for cardiopulmonary resuscitation.

Although the challenges of successful transition from agonist use and pain management are important clinical issues, the approaches to these challenges described above have been met with success in routine practice [30,31]. In addition, these challenges are not dissimilar to those evident with the use of short-acting opioid antagonists. These challenges also have to be weighed in the context of a once-monthly treatment for prevention of relapse in opioid-dependent individuals that is free of physical dependence, addresses the compliance of oral medications and is not subject to illegal diversion. XR-NTX represents a distinct alternative to previously existing treatment options for eligible patients.

Table 1. Efficacy results from a Phase III clinical trial of extended-release naltrexone versus placebo.

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th>XR-NTX (n = 126)</th>
<th>Placebo (n = 124)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response profile, median proportion (95% CI) of weeks of confirmed abstinence for weeks 5-24</td>
<td>90.0% (69.9-92.4)</td>
<td>35.0% (11.4-63.8)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Median (95% CI) self-report of opioid-free days over 24 weeks</td>
<td>99.2% (89.1-99.4)</td>
<td>60.4% (46.2-94.0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Total confirmed abstinence over weeks 5-24 (percent; 95% CI)</td>
<td>45 (27.4-44.1)</td>
<td>28 (15.2-29.9)</td>
<td>0.0224</td>
</tr>
<tr>
<td>Craving, VAS score, mean change from baseline (95% CI; scale: 0-100; baseline: XR-NTX 18.2; PBO 21.8)</td>
<td>-10.1 (-12.3 to -7.8)</td>
<td>+0.7 (-3.1 to 4.4)</td>
<td>168[^double_dagger] 96 (63-165) 0.0042[^dagger]</td>
</tr>
<tr>
<td>Treatment completion, number (percent; 95% CI) of patients who completed double-blind treatment period</td>
<td>67 (53.2%; 44.5-61.9)</td>
<td>47 (37.9%; 29.4-46.4)</td>
<td>0.0171</td>
</tr>
<tr>
<td>Relapse to physical opioid dependence; number (percent; 95% CI) of participants with positive naloxone challenge test</td>
<td>1 (0.8%; 0.0-2.3)</td>
<td>17 (13.7%; 7.7-19.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk for AIDS behavior scores; change from baseline, mean (95% CI; scale: 0-1; baseline: XR-NTX 0.300; PBO 0.279)</td>
<td>-0.187 (-0.224 to -0.150)</td>
<td>-0.130 (-0.173 to -0.087)</td>
<td>0.0212</td>
</tr>
<tr>
<td>EQ-5D[^trademark] General Health State VAS self-ratings; change from baseline,</td>
<td>+14.1 (9.6-18.7)</td>
<td>+2.7 (-1.9 to 7.8)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>
Efficacy measure
mean (95% CI; scale: 0-100; baseline: XR-NTX 68.7; PBO 69.9)
CGI improvement ratings; percentage of patients rated by investigators as much or very much improved (95% CI)

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th>XR-NTX (n = 126)</th>
<th>Placebo (n = 124)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>68.7</td>
<td>69.9</td>
<td></td>
</tr>
<tr>
<td>CGI</td>
<td>85.9%</td>
<td>57.5%</td>
<td>0.0002</td>
</tr>
<tr>
<td>(77.8-94.0)</td>
<td>(45.7-69.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[dagger] p-value adjusted for multiplicity.

[double dagger] Confidence interval could not be calculated because median exceeds study duration.

CGI: Clinical Global Impression; PBO: Placebo; VAS: Visual analog scale; XR-NTX: Extended-release naltrexone.

Data taken from [14].

Table 2. Adverse events in the extended-release naltrexone Phase III trial.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>XR-NTX 380 mg; n = 126; n (%)</th>
<th>Placebo; n = 124; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>9 (7)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (6)[dagger]</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (5)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 (5)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>6 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (3)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

[dagger] p < 0.05 different from placebo.

Data taken from [16].

Practice points

* Injectable extended-release naltrexone (XR-NTX), approved in the USA for the prevention of relapse among detoxified opioid-dependent individuals, was formulated to address the adherence problem that limited the clinical usefulness of oral naltrexone.

* XR-NTX is administered monthly by intramuscular injection by a healthcare professional and should be accompanied by psychosocial counseling.

* A Phase III multicenter, placebo-controlled, randomized clinical trial found XR-NTX to be superior to placebo on all primary and secondary end points.
* Naturalistic analysis of a large healthcare claims database found that total healthcare costs following treatment with XR-NTX were not significantly different from oral naltrexone or buprenorphine, and were 49% lower than with methadone.

* In the Phase III trial, adverse events were mild-to-moderate in severity, with nasopharyngitis, insomnia and injection-site pain occurring more frequently with XR-NTX than placebo. Discontinuations due to adverse events were similar in both groups.

* Unanswered questions include the efficacy of XR-NTX therapy in different settings, such as primary care offices, and the appropriate duration and long-term safety of XR-NTX treatment.

**CAPTION(S):**

Figure 1. Percentage of confirmed opioid-free weeks (cumulative) among participants treated with extended-release naltrexone versus placebo in the Phase III trial.

On this graph, the y-axis represents each decile of possible opioid-free weeks (for the 20-week period of weeks 5-24; the first 4 weeks were excluded to take into account patient testing/opioid use extinction). The x-axis is the percentage of participants who achieved each amount (or greater) of aggregated opioid-free weeks. For example, the percentage of patients who achieved 100% confirmed opioid-free weeks was 23% for placebo versus 36% for XR-NTX; the median placebo patient (vertical dashed line) achieved 35% of opioid-free weeks versus 90% in the XR-NTX group.

XR-NTX: Extended-release naltrexone.

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**References**

Papers of special note have been highlighted as: * of interest ** of considerable interest


* Comprehensive review of all studies that have focused on the use of extended-release naltrexone (XR-NTX) in a variety of populations.


** Phase III randomized trial conducted in Russia that was the primary study confirming the safety and efficacy of 6-months of XR-NTX for opioid dependence.


* Analysis of a large claims database that found that healthcare costs following treatment with XR-NTX were not significantly different from oral naltrexone or buprenorphine, and were 49% lower than with methadone.


* Phase III randomized, placebo-controlled, multicenter trial demonstrating the efficacy of XR-NTX with alcohol-dependent patients.


* Websites


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