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

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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). Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63–165) in the placebo group (p=0·0042). Naloxone challenge 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[1] associated with adverse societal effects including increased morbidity and mortality, poor social functioning, economic dependence, and crime.[2–4] 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.[1,5,6] 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.[7] 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.[5,7–10] 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.[5,6] 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, health-care 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[11] or in the context of intensive behavioural treatments,[12] oral naltrexone has generally been ineffective because of poor adherence.[13]

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[14,15] 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.[16] 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[17] and increased the rate of total abstinence over 6 months in those with initial abstinence compared with placebo,[18] with associated improvements in health and social functioning.[19]

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[20] 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, carmellose, 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.[21] 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.

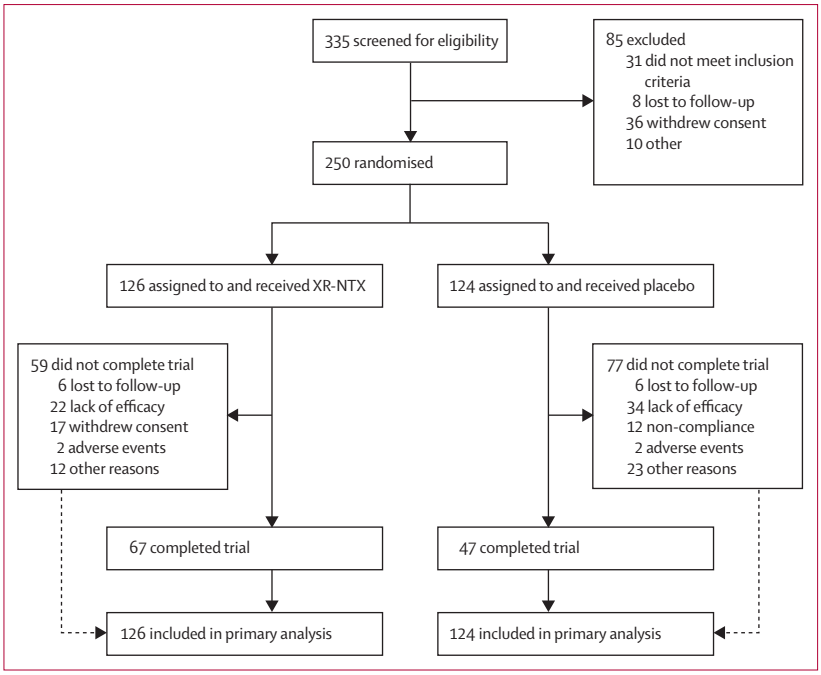

Figure 1: **Trial profile**
XR-NTX=extended-release naltrexone.

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

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

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

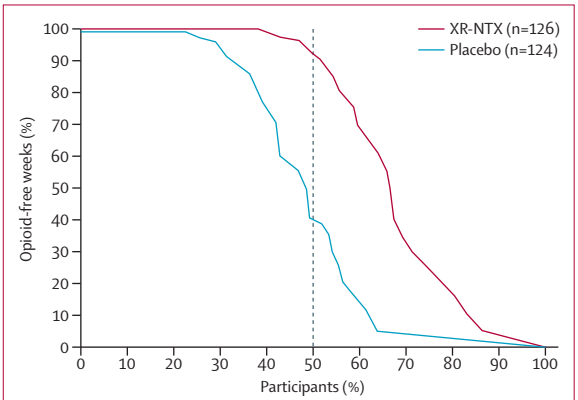

Figure 2: **Percent of confirmed opioid-free weeks (cumulative) among participants treated with XR-NTX compared with placebo**
XR-NTX=extended-release naltrexone.

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[28]—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

	XR-NTX (n=126)	Placebo (n=124)	Treatment effect*	p value
Primary endpoint				
Proportion of weeks of confirmed abstinence	90·0% (69·9 to 92·4)	35·0% (11·4 to 63·8)	55·0 (15·9 to 76·1)	0·0002
Patients with total confirmed abstinence	45 (35·7%, 27·4 to 44·1)	28 (22·6%, 15·2 to 29·9)	1·58 (1·06 to 2·36)	0·0224
Secondary endpoint				
Proportion of self-reported opioid-free days over 24 weeks	99·2% (89·1 to 99·4)	60·4% (46·2 to 94·0)	38·7 (3·3 to 52·5)	0·0004
Craving: mean change in VAS score from baseline	−10·1 (−12·3 to −7·8)	0·7 (−3·1 to 4·4)	−10·7 (−15·0 to 6·4)	<0·0001†
Number of days of retention	>168‡	96 (63 to 165)	0·61 (0·44 to 0·86)	0·0042†
Participants with positive naloxone challenge test	1 (0·8%, 0·0 to 2·3)	17 (13·7%, 7·7 to 19·8)	17·3 (2·3 to 127·8)	<0·0001
Other outcomes				
Patients who completed double-blind treatment period	67 (53·2%, 44·5 to 61·9)	47 (37·9%, 29·4 to 46·4)	1·40 (1·06 to 1·85)	0·0171
Risk for HIV: mean change in behaviour scores from baseline	−0·187 (−0·224 to −0·150)	−0·130 (−0·173 to −0·087)	−0·057 (−0·113 to −0·001)	0·0212
Mean change from baseline in VAS self-ratings on EQ-5D	14·1 (9·6 to 18·7)	2·7 (−1·9 to 7·8)	11·4 (5·0 to 17·8)	0·0005
Proportion rated as much or very much improved on CGI	85·9% (77·8 to 94·0)	57·5% (45·7 to 69·5)	1·49 (1·19 to 1·87)	0·0002

Data are median (95% CI) or number (%, 95% CI), unless otherwise stated. XR-NTX=extended release naltrexone. VAS=visual analogue scale. EQ-5D=EuroQol-5 dimensions questionnaire. CGI=clinical global impression. *Difference between XR-NTX and placebo for location parameters and relative risk for proportions. Hazard ratio of early termination (Cox model) is shown for retention. †Adjusted for multiplicity by the Bonferroni-Holm method[29] to preserve family-wise type 1 error at 0·05. ‡95% CI cannot be calculated because median exceeds the study duration.

Table 2: **Clinical outcomes**

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 χ^2 tests or Fisher's exact test for categorical endpoints. Adverse events were compared by Fisher's exact test.

Missing urine drug test results were imputed as positive for opioids; retention was censored upon discontinuation, craving was imputed using last observation carried forward, and missing TLFB data were imputed using patients' rates of opioid-free days during the 30 pre-detoxification days. For all other endpoints, all available data were included in analyses.

The primary endpoint was tested with a two-sided $\alpha=0\cdot05$. For craving and retention outcomes p values were adjusted for multiplicity using the Bonferroni-Holm method[29] to preserve family-wise type 1 error at 0·05.

A full statistical analysis was also done by an independent academic statistician who came to the same conclusions.

Role of the funding source

The sponsor designed the protocol in collaboration with participating investigators. The sponsor had the overall responsibility for the conduct of the study. Data were collected and monitored by Alkermes and PSI (Zug, Switzerland), a contract research organisation. Data were managed and analysed by Alkermes clinical and regulatory personnel, and staff at Cytel (Cambridge, MA, USA), and were interpreted by the authors with input from Alkermes clinical and statistical staff. The first author had full access to all study data and had final responsibility for the decision to submit for publication.

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). Total

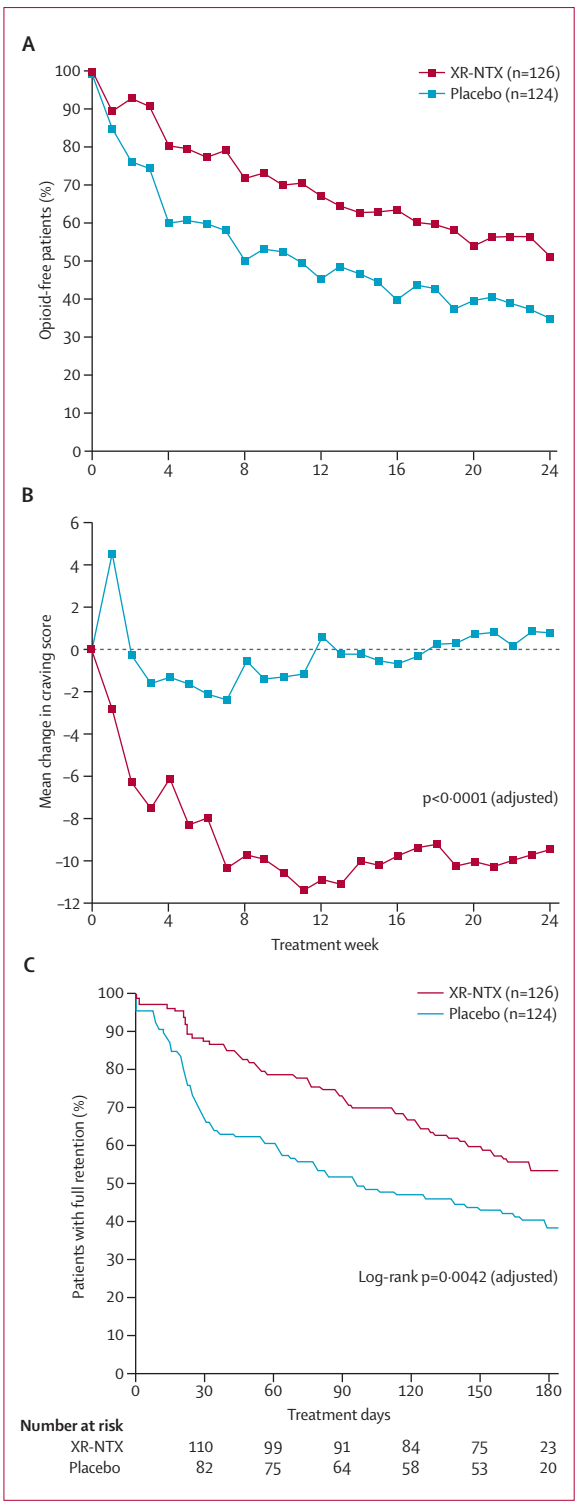

Figure 3: **Key secondary efficacy outcomes**
(A) Proportion of opioid-free patients by timeline follow-back self-report. (B) Mean change from baseline in craving. p value is based on a generalised estimating equation model assuming normal distribution and autoregressive correlation structure. (C) Time-to-discontinuation of study treatment. p values for analyses of craving (B) and retention (C) are adjusted for multiplicity. XR-NTX=extended-release naltrexone.

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.[30]

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

	XR-NTX (n=126)	Placebo (n=124)	p value
Nasopharyngitis	9 (7%)	3 (2%)	0·14
Insomnia	8 (6%)	1 (1%)	0·036
Hypertension	6 (5%)	4 (3%)	0·75
Influenza	6 (5%)	5 (4%)	>0·99
Injection site pain	6 (5%)	1 (1%)	0·12
Toothache	5 (4%)	2 (2%)	0·45
Headache	4 (3%)	3 (2%)	>0·99
≥1 adverse event	63 (50%)	40 (32%)	0·005
≥1 drug-related adverse event	33 (26%)	12 (10%)	0·001
≥1 serious adverse event*	3 (2%)	4 (3%)	0·72
Discontinued owing to adverse events	2 (2%)	2 (2%)	..

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 psychotic disorder, and one peptic ulcer).

Table 3: **Clinical adverse events**

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).

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).[13] Similarly, a study of oral naltrexone compared with treatment without naltrexone did not report an anti-craving effect,[31] 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 6β-naltrexol.[32] 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.[16] 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 competitive 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.[33]

A strength of this study was its geographic setting in Russia—one of the many countries where opioid agonist therapy is unavailable,[6] but where there is an alarming growth in availability of heroin and the fastest-growing HIV infection rate in the world.[34] 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, generalisability 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

Panel: Research in context

Systematic review

In systematic reviews, opioid substitution treatment (buprenorphine and methadone) was effective in the treatment of opioid dependence,[8,9] 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.[13]

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.[35] 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 maintenance—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[7–10] and psychosocial 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 requests 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 World Med, has received research funding from Titan Pharmaceuticals, investigator initiated research funding from Hythiam, and research support, an unrestricted educational grant, and speaker support from Reckitt Benckiser. AI, DRG, and BLS are full-time employees of Alkermes.

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