Alkermes, Inc.
852 Winter Street, Waltham, MA 02451-1420 USA
T +1 781 609 6000 F +1 781 890 0524
www.alkermes.com

December 3, 2018

Executive Office of Health & Human Services
Section 35 Commission
One Ashburton Place
Boston, MA 02108

Dear Members of the Section 35 Commission,

I appreciated the opportunity to participate in the panel discussion held at the Section 35 Commission meeting on November 5th to consider opioid detoxification and induction to medications for the treatment of opioid use disorder. Having served as an independent NIDA-funded investigator for many years prior to joining Alkermes, the topic of induction strategies for antagonist therapies for opioid dependence has been a central focus of my research. My Alkermes colleagues and I commend the Commission for taking on the charge to better understand the role of medications for addiction.

During the November 5, 2018 meeting, commission members expressed interest in data on effectiveness of XR-NTX. To respond to this request, I am submitting three publications for the Commission's review. For the commission members' convenience, I am enclosing a one-page summary of each study along with the full publications.

- **Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention X:BOT: A multicentre, open-label, randomised controlled trial. Lee et al., *The Lancet,* November 14, 2017**

- **Effectiveness of injectable extended-release naltrexone vs. daily buprenorphine-naloxone for opioid dependence: A randomized clinical noninferiority trial. Tanum et al., *Journal of the American Medical Association (JAMA) Psychiatry*, October 18, 2017**

- **Injectable extended release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness Krupitsky et al., *Addiction,* September 2013**

These three studies contribute to the growing body of literature on extended-release naltrexone (XR-NTX) for the prevention of relapse to opioid dependence. Currently, there are over 200 peer-reviewed publications that examine various efficacy, safety and cost-effectiveness outcomes of XR-NTX, across various different patient populations, both for opioid and alcohol dependence. The first two studies mentioned above, published in *JAMA Psychiatry,* October 2017 and *The Lancet*, November 2017, are important because these independently conducted trials were the first two large studies to compare extended-release naltrexone and buprenorphine for relapse prevention in the community setting. Both studies found the treatment with extended-release naltrexone to be as effective as the treatment with buprenorphine. These study results reinforce the importance of these two effective but distinctly different

Alkermes

medication treatment options. We know that no one treatment path works for all, and the challenge, ultimately, is to ensure physicians, counselors and other health care professionals are knowledgeable and capable of offering all FDA-approved medication options to their patients, along with wrap-around supports. By offering treatment options, the individual, together with the healthcare provider, can determine which form of treatment is best suited for him or her at that time.

The third study, published in *Addiction,* September 2013, provides long-term safety and effectiveness results in patients with opioid dependence. This is a one-year open-label extension study phase that followed a 6-month randomized, double-blind, placebo-controlled trial comparing injections of extended-release naltrexone (XR-NTX) given every 28 days, along with counseling, vs. placebo and counseling. Patients who received XR-NTX in the six-month study were allowed to continue receiving XR-NTX, and patients receiving the placebo had the opportunity to be switched to XR-NTX in the open-label extension phase. The purpose of this long-term study was to see if the initial treatment gains observed in the 6-month double-blind phase would be maintained during a one-year open-label extension, and whether any new safety concerns emerged. The results showed that XR-NTX patients maintained treatment improvements and patients who were switched to XR-NTX during the extension phase made treatment gains in regard to abstinence from opioids, treatment retention and craving for opioids (which was a secondary endpoint in the 6-month study). Furthermore, no new safety concerns emerged.

I hope this additional information helps provide a broader perspective on the effectiveness and safety of extended-release naltrexone and its role for the prevention of relapse to opioid dependence, following detoxification.

Thank you again for your interest in and attention to this very important topic, and for all your collective efforts to recognize the enormity of the opioid crisis and to seek to address it from multiple perspectives. We at Alkermes would welcome the opportunity to provide additional information as needed to the Commission.

Sincerely,

Maria A. Sullivan

Maria Sullivan, M.D., Ph.D.
Senior Medical Director, Clinical Research and Development, Alkermes

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

Authors: Evgeny Krupitsky, Edward V Nunes, Walter Ling, David R. Gastfriend, Asli Memisoglu, and Bernard L. Silverman.

Addiction, September2013

Study Overview and Objectives

This is a one-year open label study that followed a 6-month randomized, double-blind, placebo-controlled trial of 250 patients, comparing injections given every 28 days of extended-release naltrexone (XR-NTX) and counseling, vs. placebo and counseling for patients with opioid dependence. Patients receiving XR-NTX in the first 6-month phase were allowed to continue receiving the medication in the subsequent open-label phase. Patients receiving the placebo were allowed to switch to XR-NTX treatment during this open-label extension latter. All patients were provided counseling throughout both phases of the study. Patients had been using heroin for an average of 10 years at baseline (before the initial 6-month phase); approximately 88% were hepatitis C positive and nearly half were HIV positive. The purpose of this one-year, long term extension study was to assess the durability of improvements seen in the 6-month double-blind study, patient retention and safety over one year.

Results

- Nearly two thirds (62.3%) of patients continued treatment during the open-label extension phase and completed the full 12 months of treatment with XR-NTX.
- Half of the patients (50.9%) were abstinent (as determined by urine testing) from opioids at all assessments during the one-year extension phase.
- Across the one-year open-label phase, the percentage of opioid-free days was, on average, 83.4%.
- As reported as a secondary end-point in the double-blind phase, patients treated with XR-NTX reported significant reductions in craving for opioids which remained low during the one-year extension phase. Patients who were switched to XR-NTX in the extension phase also reported reductions in craving over time in the extension phase.
- No new safety concerns were observed during the 12-month extension phase.

This study was funded by Alkermes, Inc.

Addiction
RESEARCH REPORT
doi:10.1111/add.12208

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

Evgeny Krupitsky[1], Edward V. Nunes[2], Walter Ling[3], David R. Gastfriend[4], Asli Memisoglu[4] & Bernard L. Silverman[4]

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.

Correspondence to: Evgeny Krupitsky, Department of Addictions, St.-Petersburg Bekhterev Psychoneurological Research Institute, Bekhtereva Street, 3, St. Petersburg 192019, Russia. E-mail: kruenator@gmail.com
Submitted 26 September 2012; initial review completed 20 November 2012; final version accepted 27 March 2013

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 abstinent weeks for XR-NTX versus 35% for PBO over the course of 6 months of treatment ($P = 0.0002$) with 57.9% (73/126) of XR-NTX patients versus 41.9% (52/124) of PBO patients receiving all six double-blind doses. XR-NTX also has demonstrated efficacy in the treatment of alcohol dependence [17], and is now approved in the USA and Russia for both dependencies.

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

METHODS

Overview

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

Participants

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

Study intervention

For the initial 6-month double-blind phase patients were randomized to either XR-NTX 380 mg or PBO in a 1:1 ratio, stratifying by site and gender. The study investigator or a designated staff member injected XR-NTX within a week of detoxification (≥7 days following last opioid dose) and then every four weeks, for a total of six injections. Patients who completed the initial 6-month study were offered the open-label, 1-year extension study, which provided open-label XR-NTX 380 mg injections every four weeks for up to 13 additional doses (total of 19 injections over 18 months) at no expense to patients.

Throughout the 1.5-year study, participants were offered sessions of manualized Individual Drug Counseling (IDC), adapted for opioid dependence [19]. IDC-trained psychologists or psychiatrists reviewed patients' substance use, recovery efforts, functioning and adverse events, providing support and advice. Sessions were biweekly during the initial 6-month double-blind phase

and monthly during the 12-month open-label phase. Counseling sessions occurred when injections occurred, although not necessarily with the same clinician.

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

Efficacy and safety assessments

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

Also included to assess the durability of effects were measures of retention, opioid craving, functioning and global improvement. Craving was assessed weekly during the first 6 months and monthly during the 1-year extension phase with a self-report Visual Analogue Scale of 'need for opioids' (scale: 0–100, i.e. 'not at all' to 'very much so') [11]. Health functioning was measured with the SF-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 37.9% (47/124; $P = 0.017$) who were randomized to PBO, but were switched to XR-NTX for the open label phase. The primary reasons for attrition during the 1-year open-label phase were withdrawal of consent (18.4%; 21/114) and becoming lost to follow-up (11.4%; 13/114).

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

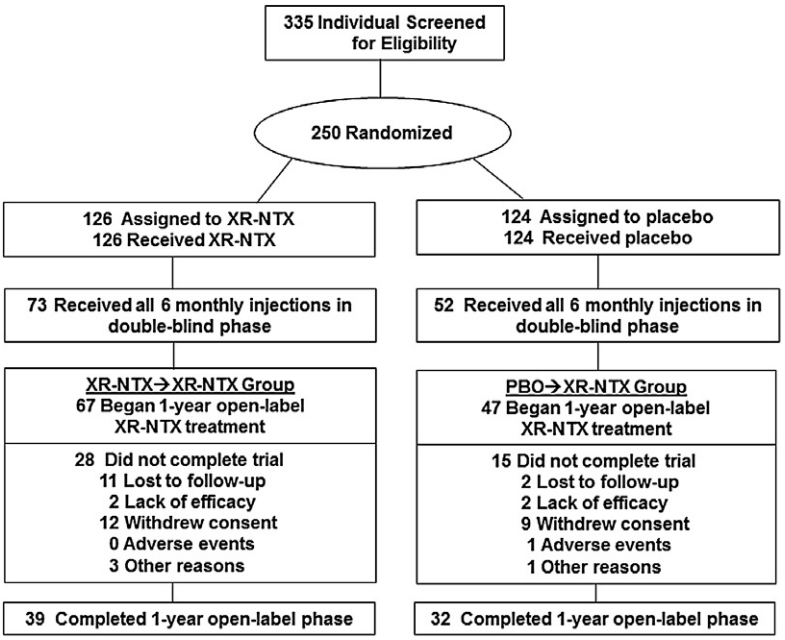


Figure 1 Flow diagram and subject disposition
PBO = placebo; XR-NTX = extended release naltrexone.

Table 1 Patient demographic and baseline clinical characteristics.

	6-month double-blind phase		*1-year open-label phase*	
	XR-NTX 380 mg	*PBO*	*XR-NTX→XR-NTX*	*PBO→XR-NTX*
Characteristic	*n = 126*	*n = 124*	*n = 67*	*n = 47*
Age, mean years (SD)	29.4 (± 4.8)	29.7 (± 3.6)	29.5 (± 5.0)	29.4 (± 3.8)
Sex, *n* (%) male	113 (89.7%)	107 (86.3%)	62 (92.5%)	40 (85.1%)
Race, *n* (%) white	124 (98.4%)	124 (100%)	67 (100%)	47 (100%)
Duration of opioid dependence (years), mean (SD)	9.1 (± 4.5)	10.0 (± 3.9)	9.0 (± 4.2)	9.4 (± 4.0)
Days of pre-study inpatient detoxification, mean (SD)	18 (± 9)	18 (± 7)	15.9 (± 8.2)	15.5 (± 6.8)
Opioid Craving Scale, mean (SD)	18 (± 23)	22 (± 24)	20.7 (± 22.5)	18.6 (± 23.5)
HIV serology, *n* (%) positive	51 (40.5%)	52 (41.9%)	31 (46.3%)	15 (31.9%)
Hepatitis C, *n* (%) positive	111 (88.1%)	117 (94.4%)	58 (86.6%)	42 (89.3%)

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

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

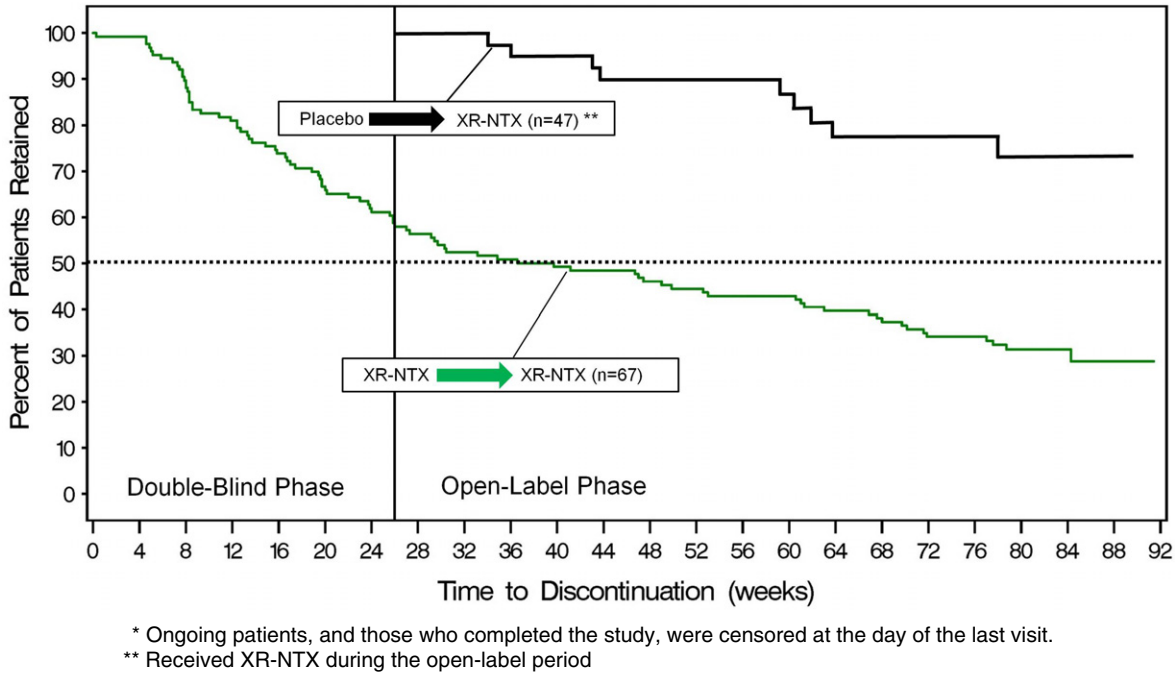


Figure 2 Time to discontinuation from extended release naltrexone (XR-NTX) for two cohorts: patients initially randomized to XR-NTX versus subsequently switched to XR-NTX from placebo*

Table 2 Mean (SD) values for Addiction Severity Index self-reported drug and alcohol days used in past 30 days over the course of the double-blind and open-label phases.

	Baseline		*Beginning of open-label phase (6 months)*		*End of open-label phase (18 months)*	
	PBO→ XR-NTX	*XR-NTX→ XR-NTX*	*PBO→ XR-NTX*	*XR-NTX→ XR-NTX*	*PBO→ XR-NTX*	*XR-NTX→ XR-NTX*
Opioids						
Heroin	18.4 (±11.8)	20.9 (±10.1)	0.3 (±1.5)	0.0 (±0.2)	0.1 (±0.5)	0.8 (±3.8)
Methadone	1.2 (± 4.5)	0.2 (± 0.9)	0.0 (±0.2)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)
Other opiates	0.7 (± 3.0)	0.5 (± 1.4)	0.1 (±0.7)	0.0 (±0.3)	0.1 (±0.4)	0.0 (±0.0)
Alcohol	6.4 (± 8.1)	4.3 (± 5.9)	7.1 (±7.1)	5.9 (±6.5)	6.5 (±7.9)	5.5 (±6.6)
Cocaine	0.3 (± 1.9)	0.0 (± 0.0)	0.0 (±0.3)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)
Cannabis	0.7 (± 2.4)	1.5 (± 4.7)	0.6 (±1.4)	0.5 (±1.7)	0.6 (±2.6)	0.3 (±1.0)
Hypnotics/tranquilizers	1.3 (± 3.2)	1.6 (± 4.7)	0.2 (±0.8)	0.1 (±0.5)	0.0 (±0.0)	0.0 (±0.0)

PBO = placebo; PBO→XR-NTX = subgroup of patients who were randomized to PBO during the double-blind (initial 6-month) phase and then switched to XR-NTX for the open-label phase; XR-NTX→XR-NTX = subgroup of patients who were randomized to XR-NTX during the double-blind phase and continued on XR-NTX for the open-label phase; 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

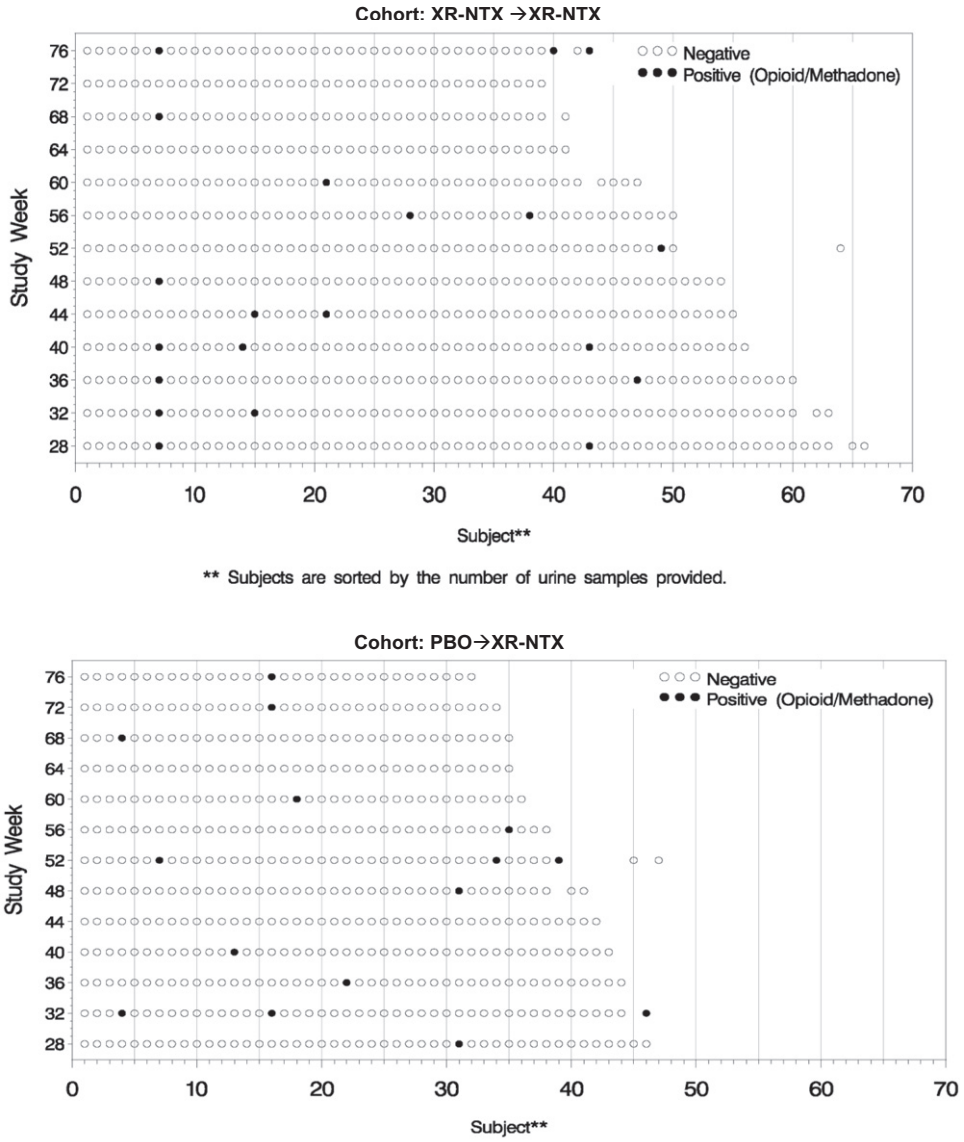


Figure 3 Urine opioid drug testing—complete results for individual patients by month
PBO = placebo; XR-NTX = extended release naltrexone.

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

Safety

During the 1-year extension, overall, 21.1% (24/114) of patients reported an adverse event that was judged to be study drug related (Table 3). No specific type of adverse

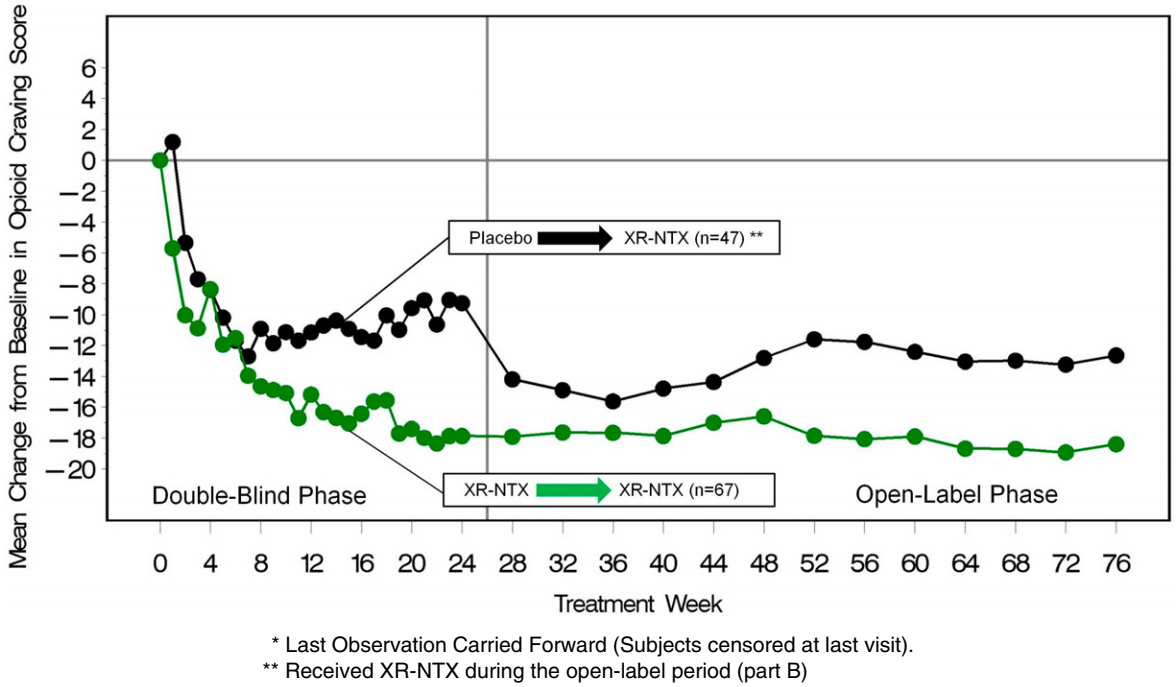


Figure 4 Mean changes in opioid craving over the course of double-blind and open-label phases for cohorts of patients that entered open-label treatment*
XR-NTX = extended release naltrexone.

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

Events	*Overall* *n = 114*	*XR-NTX*[a]*→XR-NTX* *n = 67*	*PBO*[b]*→XR-NTX* *n = 47*
Any adverse event	48 (42.1%)	29 (43.3%)	19 (40.4%)
Discontinued owing to non-serious adverse event	1	0	1 (2.1%)
Toothache	7 (6.1%)	3 (4.5%)	4 (8.5%)
Influenza	6 (5.3%)	4 (6.0%)	2 (4.3%)
Bacteriuria	3 (2.6%)	2 (3.0%)	1 (2.1%)
Injection site pain	3 (2.6%)	1 (1.5%)	2 (4.3%)
Deaths	0	0	0
Serious adverse events	3 (2.6%)	3 (4.5%)	0
Study drug-related adverse events[c]	24 (21.1%)	14 (20.9%)	10 (21.3%)

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

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

occurred during either the 6-month double-blind phase or the 1-year extension phase.

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

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

DISCUSSION

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

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

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

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

further reduce attrition (e.g. with behavioral interventions and comorbidity measures), safety and what proportion may, in fact, sustain abstinence even after XR-NTX is discontinued.

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

Trial registration

Clinicaltrials.gov Identifier: NCT00678418.

Declaration of interests

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 N43AA001002).

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

We would like to acknowledge the staff at Alkermes, PSI and Cytel for their work in the implementation and biostatistical analysis of this study, especially Elliot Ehrich, Doreen Campbell, Handong Zhang, Anna O'Rourke and Stanislav Nikitin. We thank Dr Edward Schweizer of Paladin Consulting Group, Inc. (Princeton, NJ, USA), who provided medical writing assistance with the manuscript, and was compensated by Alkermes, Inc., for his assistance.

References

1. Substance Abuse and Mental Health Services Administration. *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings* (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586 Findings). Rockville, MD: Substance Abuse & Mental Health Services Administration–the US Department of Health and Human Services; 2010.
2. UNODC. *World Drug Report 2010 (United Nations Publication, Sales No. E.10.XI.13)*. 2010. Available at: http://www.unodc.org/documents/wdr/WDR_2010/World_Drug_Report_2010_lo-res.pdf (accessed 22 August 2012). (Archived by WebCite® at http://www.webcitation.org/60NzBlRJC).
3. Hser Y., Anglin M. D., Powers K. A 24-year follow-up of California narcotics addicts. *Arch Gen Psychiatry* 1993; **50**: 577–84.
4. Wilcox H. C., Conner K. R., Caine E. D. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. *Drug Alcohol Depend* 2004; **76S**: S11–S19.
5. National Institute of Drug Abuse. *NIDA Research Report-Heroin Abuse and Addiction*. NIH Publication No. 05–4165, 2005.
6. Leshner A. I. Drug addiction research: moving toward the 21st century. *Drug Alcohol Depend* 1998; **51**: 5–7.
7. McLellan A. T., McKay J. R. Components of successful addiction treatment. In: Graham A. W., Schultz T. K., Mayo-Smith M. F., Ries R. K., Wilford B. B., editors. *Principles of Addiction Medicine*, 3rd edn. Chevy Chase: American Society of Addiction Medicine; 2003, p. 429–42.
8. Mattick R. P., Kimber J., Breen C., Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2008; 2: CD002207.
9. Minozzi S., Amato L., Vecchi S., Davoli M., Kirchmayer U., Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 2011; 4: CD001333.
10. Mattick R. P., Breen C., Kimber J., Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009; 3: CD002209.
11. Krupitsky E. M., Zvartau E. E., Masalov D. V., Tsoi M. V., Burakov A. M., Egorova V. Y. *et al*. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. *J Subst Abuse Treat* 2004; **26**: 285–94.
12. Fudala P. J., Bridge T. P., Herbert S., Williford W. O., Chiang C. N., Jones K. *et al*. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003; **349**: 949–58.
13. Newman R., Whitehill W. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. *Lancet* 1979; **8**: 485–8.
14. Dekimpe M. G., Van De Gucht L. M. V., Hanssens D. M., Powers K. I. Long run abstinence after narcotics abuse: what are the odds? *Manage Sci* 1998; **44**: 1478–92.
15. Sullivan M., Garawi F., Bisaga A., Comer S. D., Carpenter K., Raby W. N. *et al*. Management of relapse in naltrexone maintenance for heroin dependence. *Drug Alcohol Depend* 2007; **91**: 289–92.
16. Krupitsky E., Nunes E. V., Ling W., Illeperuma A., Gastfriend D. R., Silverman B. L. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011; **377**: 1506–13.
17. Garbutt J. C., Kranzler H. R., O'Malley S. S., Gastfriend D. R., Pettinati H. M., Silverman B. L. *et al*. Efficacy and tolerability

of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; **293**: 1617–25.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. *text revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.
19. Mercer D., Woody G. E. *Individual Drug Counseling*. NIH Publication Number 99-4380; Rockville, MD: National Institute on Drug Abuse; 1999.
20. Sobell L. C., Sobell M. B. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten R. Z., Allen J. P., editors. *Measuring Alcohol Consumption: Psychosocial and Biological Methods*, Totowa, NJ: The Humana Press; 1992, p. 41–72.
21. McLellan A. T., Kushner H., Metzger D., Peters R., Smith I. *et al*. The fifth edition of the addiction severity index. *J Subst Abuse Treat* 1992; **9**: 199–213.
22. Ware J. E., Kosinski M., Dewey J. E. *How to Score Version Two of the SF-36 Health Survey*. Lincoln RI: QualityMetric Incorporated; 2000.
23. Euroqol Group. Euroqol—A new facility for the measurement of health-related quality of life. *Health Policy (New York)* 1990; **16**: 199–208.
24. Guy W. *ECDEU Assessment for Psychopharmacology, Revised Edition*. Rockville, MD: NIMH Publication; 1976, p. 76–338.
25. Lucey M. R., Silverman B. L., Illeperuma A., O'Brien C. P. Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. *Alcohol Clin Exp Res* 2008; **32**: 498–504.
26. Baser O., Chalk M., Fiellin D. A., Gastfriend D. R. Cost and utilization outcomes of opioid-dependence treatments. *Am J Manag Care* 2011; **17**: S235–48.

Two independent clinical trials compared the effectiveness of extended-release naltrexone (XR-NTX/VIVITROL®) versus buprenorphine-naloxone (BUP-NX)*

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention X:BOT: A multicentre, open-label, randomised controlled trial

Joshua D Lee, MD; Edward V Nunes, Jr MD; Patricia Novo, MPH; Ken Bachrach, PhD; Genie L Bailey, MD; Snehal Bhatt, MD; Sarah Farkas, MA; Marc Fishman, MD; Phoebe Gauthier, MPH; Candace C Hodgkins, PhD; Jacquie King, MS; Robert Lindblad, MD; David Liu, MD; Abigail G Matthews, PhD; Jeanine May, PhD; K Michelle Peavy, PhD; Stephen Ross, MD; Dagmar Salazar, MS; Paul Schkolnik, PhD; Dikla Shmueli-Blumberg, PhD; Don Stablein, PhD; Geetha Subramaniam, MD; John Rotrosen, MD

The Lancet, November 14, 2017

Study Overview and Objectives

This study compared the effectiveness of treatment for six months (24 weeks) with extended-release naltrexone (VIVITROL) to buprenorphine-naloxone for opioid dependent patients initiating treatment in short-term residential units (detoxification) and continuing care as outpatients. This was an open-label study conducted in eight community-based treatment programs across the U.S. affiliated with the NIDA Clinical Trials Network.

The study included 570 randomized participants of which 474 patients were successfully started on medication. Patients were randomized to receive VIVITROL once-monthly injectable or buprenorphine-naloxone via take-home, daily sublingual dosing. The study was funded by the National Institute on Drug Abuse (NIDA) Clinical Trials Network.

Results

- XR-NTX was as effective as BUP-NX treatment in maintaining patients relapse-free once patients began study medication.
- In those patients who began study medication, several secondary measures were similar for XR-NTX and BUP-NX groups, including number of abstinent days, number of negative urine tests, and reduction in cravings. Self-reported opioid craving was initially less with extended-release naltrexone than with buprenorphine-naloxone, and then converged by week 24.
- Other than mild-to-moderate injection site reactions when utilizing extended-release naltrexone, adverse events including overdose were similar in the two treatment groups.
- This study reinforces the importance of the availability of two effective, yet very distinct, medication options.

Expert Commentary

"The US X:BOT trial, funded by the National Institute on Drug Abuse and reported by Joshua D Lee and colleagues in The Lancet, and a trial done in Norway, suggest that BUP-NX and XR-NTX are similarly effective at increasing treatment retention and preventing relapse. Results of the US trial do not support the widespread belief that patients with more severe opioid use disorder require agonist therapy."

Nora D. Volkow, MD
Director, National Institute on Drug Abuse, National Institutes of Health
The Lancet, "Medications for opioid use disorder: bridging the gap in care" (Comment)
November 14, 2017

"Both medications worked quite similarly and, therefore, both should be discussed as treatment options. The problem is not enough people are getting into treatment anyway, and when they do go into treatment, they don't get any of these treatment options. Enough of the circular firing squad among the addiction treatment providers, and the war amongst all these different medications."

Joshua Lee, MD
Associate Professor, NYU School of Medicine
STAT, "Long-awaited study finds month shot Vivitrol as effective as daily pill for opioid addiction,"
November 14, 2017

Effectiveness of Injectable Extended-Release Naltrexone vs. Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial

Lars Tanum, MD, DMSci; Kristin Klemmetsby Solli, MSc; Zill-e-Huma Latif, MD; Jūratė Šaltytė Benth, PhD; Arild Opheim, MSc; Kamni Sharma-Haase, MD; Peter Krajci, MD, PhD; Nikolaj Kunoe, MSc, PhD

Journal of the American Medical Association (JAMA) Psychiatry. October 18, 2017

Study Overview and Objectives

This study sought to determine whether treatment with extended-release naltrexone is as effective as daily buprenorphine hydrochloride with naloxone hydrochloride in maintaining abstinence from heroin and other illicit substances in newly detoxified individuals. It was an open-label study conducted over twelve weeks, assessed 159 patients with opioid dependence who received outpatient care at five urban addiction clinics in Norway. Patients were randomized to receive extended-release naltrexone (VIVITROL) once-monthly or daily oral flexible dose buprenorphine-naloxone following detoxification.

Results

- Extended-release naltrexone was as effective as buprenorphine-naloxone as measured by all primary endpoints including retention in treatment and maintaining short-term abstinence from heroin and other illicit opioids in opioid-dependent individuals following detoxification.
- XR-NTX patients reported significantly less heroin craving, which was a secondary endpoint, than BUP-NX patients.
- Overall more patients reported adverse events in the extended-release naltrexone group versus those in the buprenorphine-naloxone group. Ten patients discontinued treatment in the study: six in the buprenorphine-naloxone group and four in the extended-release naltrexone group. There were no deaths, including overdose deaths, reported for the 143 participants who took at least one-dose of either study medication.

Expert Commentary

"This study is the first-ever direct comparison of extended-release naltrexone and buprenorphine-naloxone in a randomized-controlled clinical setting. These data showed that treatment with extended-release naltrexone was as effective as buprenorphine-naloxone, the current standard of treatment, in maintaining short-term abstinence from heroin and other illicit opioids."

Lars Tanum, MD, DMSci
Associate Professor, Norwegian Centre for Addiction Research, University of Oslo, Norway
Head of Research Unit, Dept. of R&D in Mental Health Services, Akershus University Hospital, Norway
Alkermes Press Release, "New Study Comparing Effectiveness of Extended-Release Naltrexone to Buprenorphine-Naloxone for Opioid Dependence Published in JAMA Psychiatry," October 18, 2017

"Given its effectiveness and appeal to patients, extended-release naltrexone clearly deserves a place alongside methadone and buprenorphine in opioid addiction treatment. As recommended both by the U.S. Surgeon General and the White House Commission on the Opioid Crisis, expanding access to all three of these medications should be central to the health-care system's response to the opioid epidemic."

Keith Humphreys, PhD
Professor, Psychiatry and Behavioral Sciences, Stanford University
Washington Post, "In clinical trials, medications show promise for treating heroin addiction," November 8, 2017

**Alkermes provided no financial support to either study. Study drug was provided for the Norway study. No support of any kind provided to the NIDA X:BOT Trial.*

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Joshua D Lee, Edward V Nunes Jr, Patricia Novo, Ken Bachrach, Genie L Bailey, Snehal Bhatt, Sarah Farkas, Marc Fishman, Phoebe Gauthier, Candace C Hodgkins, Jacquie King, Robert Lindblad, David Liu, Abigail G Matthews, Jeanine May, K Michelle Peavy, Stephen Ross, Dagmar Salazar, Paul Schkolnik, Dikla Shmueli-Blumberg, Don Stablein, Geetha Subramaniam, John Rotrosen

Summary

Background Extended-release naltrexone (XR-NTX), an opioid antagonist, and sublingual buprenorphine-naloxone (BUP-NX), a partial opioid agonist, are pharmacologically and conceptually distinct interventions to prevent opioid relapse. We aimed to estimate the difference in opioid relapse-free survival between XR-NTX and BUP-NX.

Methods We initiated this 24 week, open-label, randomised controlled, comparative effectiveness trial at eight US community-based inpatient services and followed up participants as outpatients. Participants were 18 years or older, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and had used non-prescribed opioids in the past 30 days. We stratified participants by treatment site and opioid use severity and used a web-based permuted block design with random equally weighted block sizes of four and six for randomisation (1:1) to receive XR-NTX or BUP-NX. XR-NTX was monthly intramuscular injections (Vivitrol; Alkermes) and BUP-NX was daily self-administered buprenorphine-naloxone sublingual film (Suboxone; Indivior). The primary outcome was opioid relapse-free survival during 24 weeks of outpatient treatment. Relapse was 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use. This trial is registered with ClinicalTrials.gov, NCT02032433.

Findings Between Jan 30, 2014, and May 25, 2016, we randomly assigned 570 participants to receive XR-NTX (n=283) or BUP-NX (n=287). The last follow-up visit was Jan 31, 2017. As expected, XR-NTX had a substantial induction hurdle: fewer participants successfully initiated XR-NTX (204 [72%] of 283) than BUP-NX (270 [94%] of 287; p<0·0001). Among all participants who were randomly assigned (intention-to-treat population, n=570) 24 week relapse events were greater for XR-NTX (185 [65%] of 283) than for BUP-NX (163 [57%] of 287; hazard ratio [HR] 1·36, 95% CI 1·10–1·68), most or all of this difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures. Among participants successfully inducted (per-protocol population, n=474), 24 week relapse events were similar across study groups (p=0·44). Opioid-negative urine samples (p<0·0001) and opioid-abstinent days (p<0·0001) favoured BUP-NX compared with XR-NTX among the intention-to-treat population, but were similar across study groups among the per-protocol population. Self-reported opioid craving was initially less with XR-NTX than with BUP-NX (p=0·0012), then converged by week 24 (p=0·20). With the exception of mild-to-moderate XR-NTX injection site reactions, treatment-emergent adverse events including overdose did not differ between treatment groups. Five fatal overdoses occurred (two in the XR-NTX group and three in the BUP-NX group).

Interpretation In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective. Future work should focus on facilitating induction to XR-NTX and on improving treatment retention for both medications.

Funding NIDA Clinical Trials Network.

Introduction

Opioid μ-receptor full agonist (methadone), partial agonist (buprenorphine), and antagonist (extended-release naltrexone; XR-NTX) pharmacotherapies are superior to placebo treatment and counselling-only treatment for opioid use disorders.[1–4] Buprenorphine (provided a buprenorphine prescribing waiver is obtained) and XR-NTX can be prescribed in any US medical setting, and are key components of a public health response to the current epidemic of opioid use disorders and overdose deaths. Comparative effectiveness data are needed to inform treatment decisions among patients and providers of these two distinct treatment approaches.

Buprenorphine products (sublingual tablets, films, buccal patches, and implants) are now the most commonly prescribed, most accessible form of evidence-based opioid treatment in the USA.[5–7] Extended-release

Published **Online** November 14, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32812-X

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(17)32872-6 and http://dx.doi.org/10.1016/S0140-6736(17)32893-3

Department of Population Health (J D Lee MD) **and Department of Psychiatry** (P Novo MPH, S Farkas MA, P Gauthier MPH, S Ross MD, J Rotrosen MD), **New York University School of Medicine, New York, NY, USA; Department of Psychiatry; New York State Psychiatric Institute, Columbia University Medical Center, New York, NY, USA** (E V Nunes Jr MD); **Tarzana Treatment Centers, Tarzana, CA, USA** (K Bachrach PhD); **Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence RI, USA** (G L Bailey MD); **Stanley Street Treatment and Resources, Fall River, MA, USA** (G L Bailey); **Department of Psychiatry and Behavioral Sciences, University of New Mexico School of Medicine, Albuquerque, NM, USA** (S Bhatt MD); **Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (M Fishman MD); **Maryland Treatment Centers, Baltimore, MD, USA** (M Fishman); **Gateway Community Services Inc, Jacksonville, FL, USA** (C C Hodgkins PhD); **The Emmes Corporation, Rockville, MD, USA** (J King MS, R Lindblad MD, A G Matthews PhD, J May PhD, D Salazar MS, D Shmueli-Blumberg PhD, D Stablein PhD); **National Institute on Drug Abuse, Rockville, MD, USA** (D Liu MD,

G Subramaniam MD); **Evergreen Treatment Services, Seattle, WA, USA** (K M Peavy PhD); **and Maryhaven Inc, Columbus, OH, USA** (P Schkolnik PhD)

Correspondence to: Dr Joshua D Lee, NYU School of Medicine, Department of Population Health, New York, NY 10016, USA
joshua.lee@nyumc.org

Research in context

Evidence before this study

We searched PubMed, MEDLINE, and Cochrane Reviews for clinical trials and systematic reviews evaluating extended-release naltrexone (XR-NTX) for opioid use disorders, with no restrictions by date or language. Naltrexone oral daily tablets have not been shown to be effective treatment for opioid use disorders in adults, as summarised in a 2011 Cochrane Systematic Review. A 2008 Cochrane Systematic Review on sustained-release formulations of naltrexone for opioid dependence concluded that evidence to evaluate effectiveness was insufficient on the basis of too few studies. Since 2008, XR-NTX, or naltrexone for extended-release injectable suspension, has been approved in the USA for prevention of opioid relapse following detoxification on the basis of a placebo-controlled, industry phase 3 trial done in Russia. A 2016 US evaluation of XR-NTX versus treatment as usual among adults with opioid use disorders and criminal justice involvement, which was ongoing during the start of our current study, found XR-NTX to be effective at preventing opioid relapse; relapse was reduced by about 30% (odds ratio 0·43, 95% CI 0·28–0·65). To our knowledge, no previous studies have compared XR-NTX with a standard of care for opioid-agonist maintenance with either methadone or buprenorphine. This study was done in parallel with a Norwegian randomised trial also evaluating XR-NTX versus buprenorphine.

Added values of this study

To our knowledge, this study is the first US trial and the larger and longer of the two US and Norwegian trials to evaluate XR-NTX versus buprenorphine-naloxone (BUP-NX) among adults with opioid use disorders admitted to community detoxification and treatment programmes. In our trial, most participants were actively using heroin at baseline and are likely to represent the current US opioid epidemic. Study sites varied in timing of treatment assignment and specific detoxification protocols, allowing real-world estimates of XR-NTX induction success. We aimed to replicate usual community outpatient conditions across the 24 week outpatient treatment phase in this open-label, comparative effectiveness trial.

Implications of all the available evidence

Both the US and Norwegian studies found that for those participants able to begin treatment, XR-NTX and BUP-NX were equally safe and effective in preventing relapse. Induction to XR-NTX remains a challenge, which was quantified in the US study and which limited effectiveness in the overall population because those participants not initiating treatment relapsed quickly. Induction success varied with different detoxification approaches. The Norwegian study bypassed the induction hurdle by assigning the treatment after detoxification was largely completed. Conversely, BUP-NX has no induction hurdle. Patients, families, and providers now have data to help them make complex treatment decisions involving personal preferences, detoxification options and risks, and long-term outcomes.

injectable naltrexone was developed to provide sustained opioid receptor blockade, improve long-term adherence compared with daily oral naltrexone tablets, and improve overall effectiveness, and was approved by the US Food and Drug Administration, in 2010, for the prevention of opioid relapse following detoxification. Results of clinical trials[3,4,8,9] have shown XR-NTX to be superior to placebo treatment[3,8] and drug-free treatment-as-usual among participants not interested in opioid-agonist maintenance.[4,9] XR-NTX differs from buprenorphine both in terms of induction and ongoing care. XR-NTX cannot be initiated until patients are fully detoxified without risking precipitated withdrawal. Once initiated, XR-NTX produces no opioid-like effects and no physiological dependence, while physiological and subjective effects of exogenous opioids are blocked.[10] By contrast, buprenorphine can be initiated as soon as patients are in mild-to-moderate withdrawal. It maintains physiological opioid dependence, and withdrawal is likely to occur on discontinuation; usual effects of other opioids are also blocked.[11]

Previous opioid antagonist or agonist comparisons have evaluated oral naltrexone and long-term naltrexone implants, but not monthly XR-NTX treatment.[12–15] Important clinical issues remain unanswered, beyond the established efficacy of either XR-NTX or BUP-NX. How feasible is XR-NTX induction compared with buprenorphine-naloxone (BUP-NX) among active opioid users admitted voluntarily to real-world, community detoxification centres? Do comparable proportions of individuals remain on medication after induction, and how do they compare in terms of avoiding illicit opioid use? Is the typical community use of XR-NTX as safe as BUP-NX, particularly with regard to overdose events?

This study (X:BOT [CTN-0051]), sponsored by the National Institute on Drug Abuse (NIDA), was a randomised, comparative effectiveness trial of 24 weeks of treatment with XR-NTX versus BUP-NX following an acute inpatient detoxification admission, done at typical community-based treatment programmes across the USA. The primary aim was to estimate the difference, if any, between XR-NTX and BUP-NX treatment for relapse to regular opioid use (time to relapse). Secondary outcomes included failure to initiate medication, opioid use during treatment, and adverse events including overdoses. We hypothesised that XR-NTX would be, relative to BUP-NX, no different in enabling relapse-free-survival, more difficult to initiate, associated with increased opioid abstinence, and no different in adverse events, including overdoses.

Methods

Study design and participants

We did this 24 week, open-label, randomised trial to compare the effectiveness and safety of XR-NTX versus BUP-NX. Eight study sites were National Drug Abuse Treatment Clinical Trials Network (CTN)-affiliated community treatment programmes with high volumes of opioid detoxification admissions and outpatient medical management capabilities. We recruited participants, who gave consent and were screened, at any point during voluntary, usual care, inpatient detoxification admissions. Although community advertising and outreach efforts varied by study site, we primarily recruited participants in person after admission, and they were typically not aware of the study before admission. Methods and design rationale have been published before (appendix).[16,17]

Participants were 18 years or older, spoke English, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and had used non-prescribed opioids in the past 30 days. We excluded participants if they had other serious medical, psychiatric, or substance use disorders; transaminase concentrations were more than 5 times the upper limit of normal; were suicidal or homicidal; had allergy or sensitivity to XR-NTX or BUP-NX; had methadone maintenance treatment (≥30 mg/day); had chronic pain requiring opioids; had a legal status precluding study completion; and were not able to have safe intramuscular XR-NTX treatment. We excluded women if they were pregnant, breastfeeding, planning conception, or unwilling to use birth control.

All sites obtained local Institutional Review Board approval and all participants provided written informed consent. The CTN Greater New York Node had primary responsibility for leading the study; the Emmes Corporation (CTN's Data and Statistics Center and Clinical Coordinating Center) provided data management and analysis, and monitored safety and quality. The NIDA Center for CTN (CCTN) coordinated the Data Safety Monitoring Board.

Randomisation and masking

Randomisation to XR-NTX or BUP-NX (1:1) followed eligibility determination and was stratified by treatment site and opioid use severity (high severity was ≥6 bags or equivalent intravenous heroin per day in the 7 days before admission). We chose these stratification variables because we expected site differences in the magnitude of the detoxification hurdle, and we expected that high-severity participants would have worse outcomes than low-severity participants. We used a web-based permuted block design with random equally weighted block sizes of four and six for randomisation. This open-label trial involved no masking of treatment or outcomes.

Procedures

Detoxification protocols and length of stay were not protocol-derived and varied by site. Detoxification approaches included no opioids (clonidine or so-called comfort medications only at two sites), 3–5 day methadone tapers (four sites), and 3–14 day buprenorphine tapers (two sites). Timing of randomisation was flexible. Participants were randomised early, during methadone or buprenorphine tapers, or later, after completion of detoxification. We expected participants in the early randomisation group to have more difficulty completing detoxification and initiating XR-NTX than those participants in the late randomisation group. We designated participants a priori to the early randomisation group (randomised within 72 h of last opioid use—including opioids used for detoxification) or the late randomisation group (>72 h following last opioid use). A prespecified interim analysis plan required a minimum of 350 participants to be randomised later. Following randomisation, participants were inducted as quickly as possible.

See Online for appendix

XR-NTX (4 mL, about 380 mg naltrexone base) was Vivitrol (Alkermes, Dublin, Ireland). Before XR-NTX induction, participants had to complete detoxification (≥3 days from last opioid use), have opioid-negative urine,

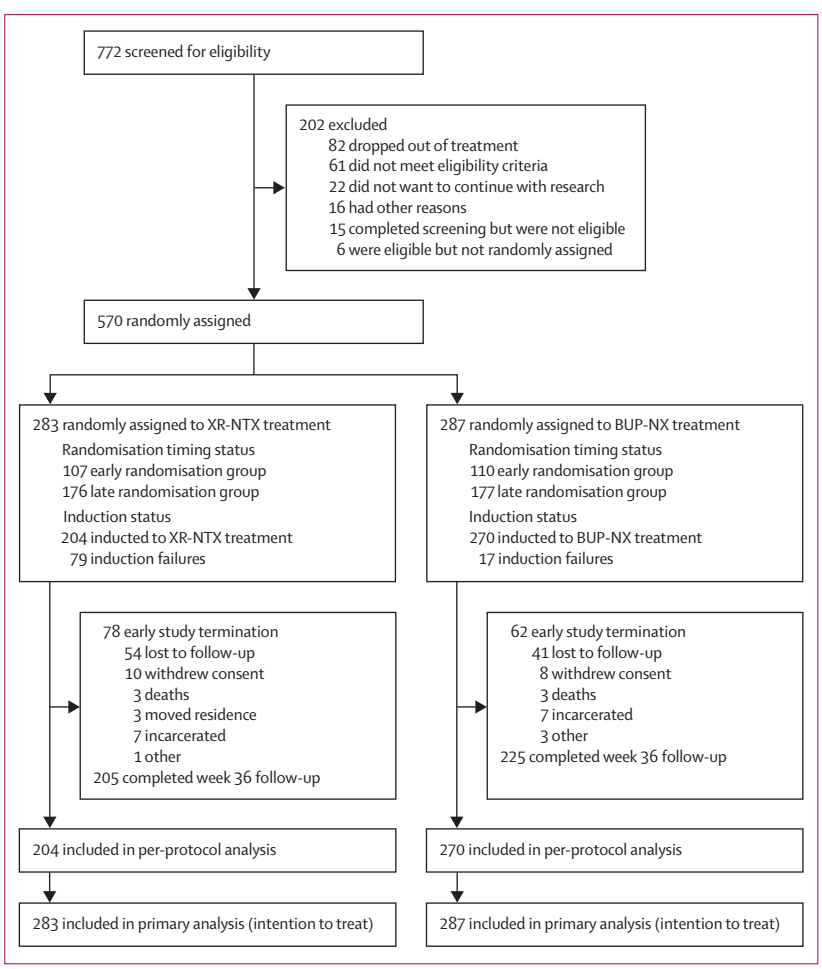


Figure 1: **Trial profile**
XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone.

	Intention-to-treat population		Per-protocol population	
	XR-NTX group (n=283)	BUP-NX group (n=287)	XR-NTX group (n=204)	BUP-NX group (n=270)
Demographics				
Sex				
Female	88 (31%)	81 (28%)	66 (32%)	77 (29%)
Male	195 (69%)	206 (72%)	138 (68%)	193 (71%)
Age (years)	34·0 (9·5)	33·7 (9·8)	33·7 (9·3)	33·7 (9·8)
Ethnic origin				
Hispanic or Latino	45 (16%)	54 (19%)	27 (13%)	53 (20%)
Black or African American	29 (10%)	28 (10%)	20 (10%)	27 (10%)
White	206 (73%)	215 (75%)	157 (77%)	201 (74%)
Marital status				
Never married	187 (66%)	189 (66%)	134 (66%)	180 (67%)
Have been married	96 (34%)	98 (34%)	70 (34%)	90 (33%)
Employment				
Working now	48 (17%)	57 (20%)	34 (17%)	50 (19%)
Unemployed	179 (63%)	181 (63%)	125 (61%)	172 (64%)
Clinical characteristics				
Intravenous drug use	177 (63%)	183 (64%)	131 (64%)	171 (63%)
Primary opioid used in the 7 days before detox admission				
Buprenorphine	6 (2%)	2 (1%)	4 (2%)	2 (1%)
Opioid analgesics	43 (15%)	47 (16%)	36 (18%)	45 (17%)
Methadone	3 (1%)	4 (1%)	3 (1%)	4 (1%)
Heroin	230 (81%)	233 (81%)	160 (78%)	218 (81%)
Cost per day for primary opioid (US$)	$90·7 (76)	$96·3 (74)	$91·0 (84)	$94·1 (73)
Age at onset of any opioid use	21·2 (6·5)	21·4 (7·6)	20·8 (6·5)	21·4 (7·6)
Duration of opioid use (years)	12·8 (9.0)	12·2 (9·0)	12·9 (9·1)	12·3 (9·1)
Index admission is first opioid treatment episode	100 (35%)	109 (38%)	75 (37%)	105 (39%)
Stimulant use (past 30 days)	133 (47%)	164 (57%)	99 (49%)	155 (57%)
Sedative use (past 30 days)	72 (25%)	93 (32%)	53 (26%)	86 (32%)
Heavy alcohol use (past 30 days)	71 (25%)	77 (27%)	56 (27%)	74 (27%)
Cannabis use (past 30 days)	122 (43%)	133 (46%)	86 (42%)	130 (48%)
Hamilton Depression Scale (0–50)	8·6 (6·5)	9·3 (6·6)	8·5 (6·4)	9·5 (6·7)
History of psychiatric disorders, self-report	190 (67%)	191 (67%)	141 (69%)	183 (68%)
Subjective opioid withdrawal scale (0–64)	15·6 (13·4)	15·6 (13·2)	15·3 (13·5)	15·9 (13·2)

Data are n (%) or mean (SD). XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone.

Table 1: **Baseline characteristics**

and a negative naloxone challenge (no or minimal opioid withdrawal symptoms following intramuscular, subcutaneous, or intravenous administration of ≥0·4 mg dose of naloxone, a short-acting opioid antagonist). Subsequent XR-NTX injections were scheduled every 28 days. If injections were missed and physical re-dependence was likely to have occurred, a repeat naloxone challenge or another detoxification programme was required to reinitiate XR-NTX treatment.

BUP-NX was Suboxone (Indivior, Slough, UK) sublingual film, 4 mg/1 mg and 8 mg/2 mg strengths. Typical induction included observed dosing on the detoxification unit once substantial withdrawal symptoms emerged. Subsequently, the study team dispensed BUP-NX to participants at weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 20 for self-administration at daily doses of 8–24 mg (higher or lower as clinically indicated). Both study medications were provided free of charge.

Study medications were discontinued following the primary outcome (a relapse event), at the end of 24 weeks, or per safety concerns or participant preference. Thereafter, participants were managed by the same treatment programmes or referred elsewhere in the community as clinically indicated. We universally encouraged extended treatment with buprenorphine, methadone, or naltrexone after the study.

Standard physician or nurse-led office-based medical management was done at each outpatient visit and guided medication treatment. Medical management focused on provider–patient rapport, medication adherence and side-effects, non-study opioid abstinence, and promoted other psychosocial treatment. Additional voluntary ancillary psychosocial counselling was recommended and available at all sites.

Research visits occurred weekly and post-treatment at weeks 28 and 36. We assessed demographic, medical, psychiatric, drug use, and treatment history, quality of life and current health status, and blood and urine testing at baseline. Treatment phase assessments included weekly monitoring of self-reported opioid and other substance use, analysis of urine toxicology samples, ratings of opioid cravings, and adverse events.

Outcomes

The primary outcome measure was the time to a relapse event. Relapse was defined as the use of non-study opioids any time after day 20 post-randomisation: at the start of 4 consecutive opioid use weeks or at the start of 7 consecutive days of self-reported opioid use days. A so-called use week was defined as any week during which the participant reported at least 1 day of non-study opioid use with the Timeline Followback method,[18] provided a urine toxicology sample that was positive for non-study opioids (buprenorphine, methadone, morphine [heroin, codeine, morphine], or oxycodone), or did not provide a urine sample (missed visits or refusals). Day 21 was the start of the relapse-event observation period and chosen primarily because participants recently detoxified were likely to have positive urine samples for long-acting opioids prescribed as part of the detoxification regimen (non-study buprenorphine or methadone) for 2–3 weeks after being randomly assigned a treatment (not indicating relapse to illicit or non-study opioid use).

Secondary outcomes were the proportion of participants successfully inducted onto an initial dose of study medication, safety (adverse events), frequency of non-study opioid use per Timeline Followback and assessment of weekly urine toxicology samples, and opioid craving. Adverse events, including overdose events, were queried

with the standard Medical Dictionary for Regulatory Activities terminology and reviewed by the NIDA CTN Medical Monitor. Opioid cravings were self-rated using a 0–100 visual analogue scale.

Statistical analysis

The target sample size was based on the width of the 95% CI for the hazard ratio (HR) of the difference between treatments (XR-NTX *vs* BUP-NX), projecting relapse-free survival of about 50% for each medication after induction[2] (described previously[16]). On the basis of simulation results, the 95% CI width for HR decreases as the sample size increases by 50 per group to 250 per group (from a base of 50 per group) by 31%, 19%, 14%, and 11%, respectively. A preplanned interim analysis increased the overall target sample size from an initial 400 participants to about 600 participants to achieve a minimum sample of 350 participants in the late randomisation group. Sample size calculations indicated that 350 participants would yield a similar (only slightly wider) 95% CI to the original sample size target of 400 participants, and preserved the aim to achieve a precise estimate of the difference in relapses between groups.

We analysed endpoints according to the intention-to-treat principle as part of the primary analysis and additionally among a per-protocol population. The per-protocol population consisted of only those participants who were successfully inducted onto an initial dose of study medication.

The primary outcome analysis was the construction of the asymptotic 95% CI for the HR of the difference between the treatment groups among the intention-to-treat population in the time-to-event (relapse) distribution with the earliest relapse day assessed at day 21. We administratively censored participants at week 24. The binary baseline covariate of early versus late randomisation was examined for an interaction with treatment; this covariate was not significant ($p>0·10$), and thus dropped from the final model. Unadjusted Kaplan-Meier survival curves and the extended Cox model HRs compared relapse by group. We examined the proportional hazard assumption via the interaction of treatment and time.

Logistic regression yielding odds ratios contrasted induction success and overall 24 week opioid relapse by group. We used Pearson's χ^2 or Fisher's exact tests, and logistic regression for analyses of dichotomous secondary outcomes. We used Cox models for time-to-event secondary outcomes and Wilcoxon rank-sum tests and mixed effects models for continuous outcomes.

We considered missing urine samples to be opioid positive and contributed to the definition of a relapse event. Thus, treatment dropouts (who stopped contributing data) were scored as having relapsed, an assumption which is likely in this population.[19–22] We did statistical analyses with SAS software (version 9.3 or higher). This study is registered with ClinicalTrials.gov, NCT02032433.

	XR-NTX group (n=283)	BUP-NX group (n=287)	Treatment effect
Inducted to study medication			
Intention-to-treat group	204 (72%)	270 (94%)	OR 0·16, 95% CI 0·09–0·28; p<0·0001
Opioid relapse, weeks 3–24			
Intention-to-treat group	185 (65%)	163 (57%)	OR 1·44, 95% CI 1·02–2·01; p=0·036
Per-protocol group	106/204 (52%)	150/270 (56%)	OR 0·87, 95% CI 0·60–1·25; p=0·44
Relapse-free-survival (weeks), range 3–24			
Intention-to-treat group	8·4 (3·0–23·4)	14·4 (5·1–23·4)	HR 1·36, 95% CI 1·10–1·68; p=0·0040
Per-protocol group	20·4 (5·4–23·4)	15·2 (5·7–23·4)	HR 0·92, 95% CI 0·71–1·18; p=0·49
Total number of weekly opioid-negative urine samples, range 0–24			
Intention-to-treat group	4 (0–19)	10 (3–20)	p<0·0001
Per-protocol group	13 (3–21)	11 (3–20)	p=0·81
Total number of self-reported opioid-abstinent days, range 0–144			
Intention-to-treat group	39 (1–144)	81 (16–144)	p<0·0001
Per-protocol group	123 (18–144)	87 (20–144)	p=0·67

Data are n (%), n/N (%), or median (IQR). XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone. OR=odds ratio. HR=hazard ratio.

Table 2: **Opioid treatment outcomes**

Role of the funding source

The authors and the study sponsor designed and implemented the study, collected and analysed the data, wrote the initial manuscript draft, and are responsible for data integrity. Indivior donated Suboxone (BUP-NX) and had access to periodic safety data only, with no input or review of this manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 30, 2014, and May 25, 2016, we randomly assigned 570 participants to receive XR-NTX (n=283) or BUP-NX (n=287; figure 1). The final study visit occurred on Jan 31, 2017. 369 participants (65%; n=175 XR-NTX, n=194 BUP-NX) completed week 28 follow-up. 430 participants (75%) completed an end-of-study visit at week 36 (figure 1). Most participants were white men, aged 25–45 years, had a primary heroin use disorder, were using by injection, were stratified as low-severity opioid use, and were single, unemployed, and Medicaid-insured (table 1).

More participants in the BUP-NX group were successfully inducted than in the XR-NTX group ($p<0·0001$; table 2). XR-NTX induction was successful in fewer participants in the early randomisation group (53%) than the late randomisation group (84%), and varied by site, ranging from 52% at a short-stay, methadone-taper unit, to 95% at an extended-stay, opioid-free programme. 204 participants inducted to XR-NTX treatment completed an average of 3·9 monthly injections (about 16 weeks treatment); 96 (47%) did not end medication early and completed the planned 24 week treatment phase. 270 participants inducted to BUP-NX treatment completed a median of 14 weeks of treatment (IQR 4·6–24·0) at a

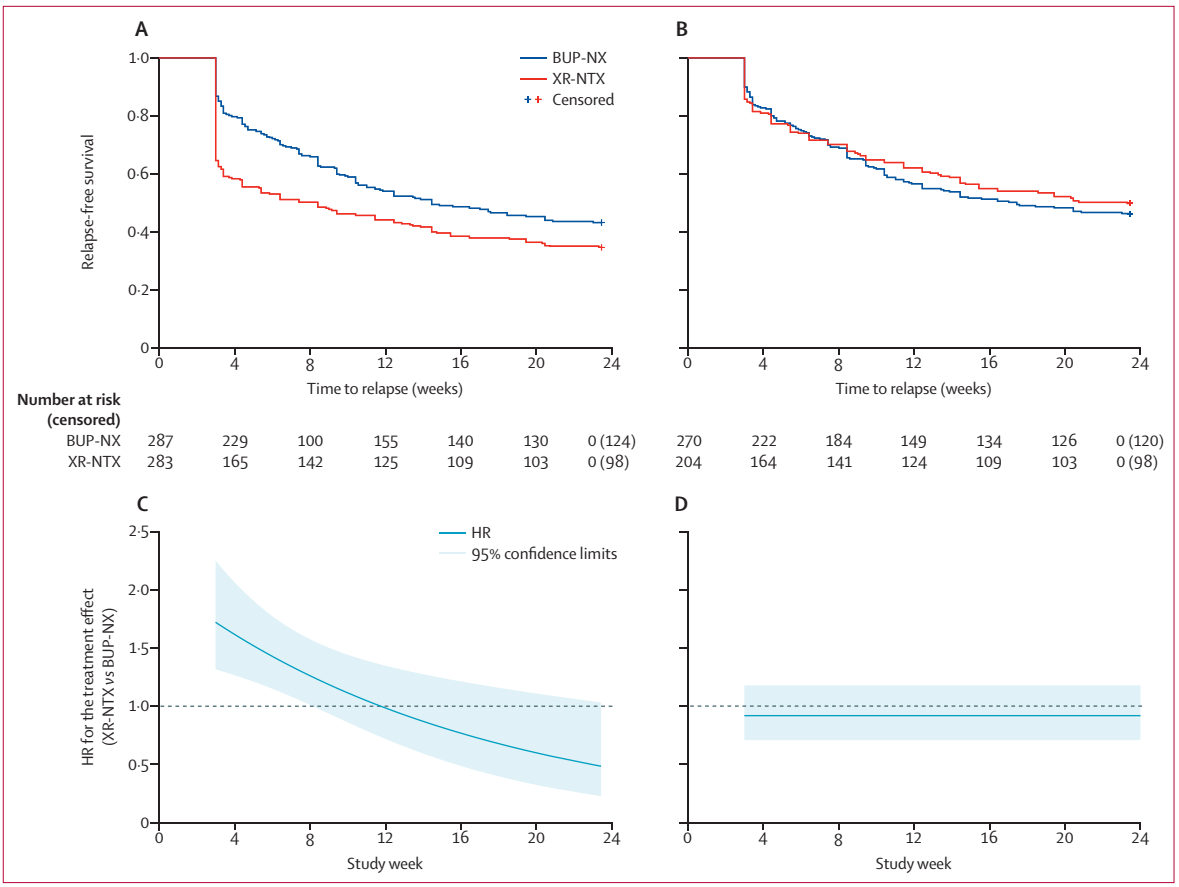


Figure 2: **Relapse-free survival and treatment effect over time for the XR-NTX and BUP-NX treatment groups**
Survival (A) and HRs and corresponding 95% CIs from the non-proportional hazards Cox model (time by treatment interaction included in the model; (C) assessed in the intention-to-treat population (n=570). Survival (B) and HRs by time (D) in the per-protocol population (n=474). XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone. HR=hazard ratio.

median maintenance dose of 16 mg/day (12–18); 115 (43%) did not end medication early and completed the planned 24 week treatment phase.

For the primary intention-to-treat sample, the proportion of opioid-relapse events was 185 (65%) of 283 participants for XR-NTX treatment versus 163 (57%) of 287 participants for BUP-NX treatment (table 2). In the survival analysis, BUP-NX treatment was favoured when compared with XR-NTX treatment (HR 1·36, 95% CI 1·10–1·68; table 2, figure 2A, C). The constancy of the relative hazard assumption was violated, as evidenced by a treatment-by-time interaction (p=0·0050). The risk of relapse was lower in the BUP-NX group than the XR-NTX group at the start of the study period, but this risk was not sustained (figure 2C). Participants in the early randomisation group had a higher risk of relapse than participants in the late randomisation group (1·32, 1·06–1·63) for both treatments, with no interaction with treatment (p=0·70). Dropout followed by missing urine data and a relapse event was a common pattern in both treatment groups: 63% (220/348) of all relapse events were defined by four consecutive missing urine samples (71% [132/185] of XR-NTX relapses and 54% [88/163] of BUP-NX relapses).

For the successfully inducted sample (n=474), the proportion of opioid-relapse events was 52% for the XR-NTX group versus 56% for the BUP-NX group, with no difference in the relative hazard of relapse over time (HR 0·92, 95% CI 0·71–1·18; table 2, figure 2B, D). The proportional hazards assumption was not violated in this Cox model and thus, the HR estimate was constant over time (figure 2D). The contrast between relapse events in the intention-to-treat and per-protocol populations was largely accounted for by high occurrence of early relapse among XR-NTX induction failures. For the XR-NTX group, induction failures relapsing on day 21 comprised 70 (25%) of the 283 participants, whereas for BUP-NX induction failures relapsing on day 21 comprised only ten (3%) of the 287 participants.

Treatment effect estimates did not vary by gender. Subgroup analyses by gender did not show a difference in success of induction for either medication or 24 week relapse for either medication between men and women

(for both intention-to-treat and per-protocol populations; data not shown).

For the intention-to-treat population, other opioid use outcomes measures (opioid relapse, relapse-free survival, opioid-negative urine samples, and opioid-abstinent days) favoured BUP-NX treatment compared with XR-NTX treatment (table 2). For the per-protocol sample, these same measures did not differ between groups (table 2).

Subjective opioid craving declined rapidly from baseline in both treatment groups (figure 3). Average opioid craving was initially less for the XR-NTX group (p=0·0012 at week 7) than for the BUP-NX group, then converged by week 24 (p=0·20; figure 3).

The proportion of participants reporting adverse events and serious adverse events did not differ between groups, with the exception of injection site reactions among XR-NTX, all of which were of minor to moderate severity (table 3). Altogether, 28 overdose events were reported among 23 participants (table 3). Eighteen (64%) of the 28 events occurred in the group randomised to XR-NTX treatment: eight in participants who had failed induction and never received XR-NTX and ten in participants who had received at least one XR-NTX injection. Ten of the 28 overdose events occurred in the group randomised to BUP-NX treatment: one in a participant who had failed induction and never received BUP-NX and nine in participants who had received at least one dose of BUP-NX (table 3). Five overdose events were fatal, two participants treated with XR-NTX and three participants treated with BUP-NX (table 3). The proportions of participants reporting any overdose event or with a fatal overdose did not differ between treatment groups (table 3).

Most overdose events occurred at times quite distal to the last dose of study medication (days 25, 33, 42, 49, 54, 66, 73, 76, 87, 88, 90, 110, 117, 141, 149, 170, 190, 227, and 318), or, for those participants who were never inducted, distal to discharge from detoxification programmes (days 10, 21, 37, 76, 86, 167, 174, 238, and 255). This outcome makes it difficult to attribute an association between study medication and overdose.

Discussion

This large multicentre, randomised, controlled, comparative effectiveness trial had five major findings. First, it was more difficult to start XR-NTX treatment than BUP-NX treatment: 28% dropped out of treatment before XR-NTX induction versus only 6% before BUP-NX induction. Second, nearly all induction failures had early relapse. Third, in the intention-to-treat population of all patients who were randomly assigned, XR-NTX had lower relapse-free survival than BUP-NX, directly related to early induction failure. Fourth, for the per-protocol population, who successfully initiated medication, XR-NTX and BUP-NX were similarly effective. Finally, fatal overdose, non-fatal overdose, and other serious

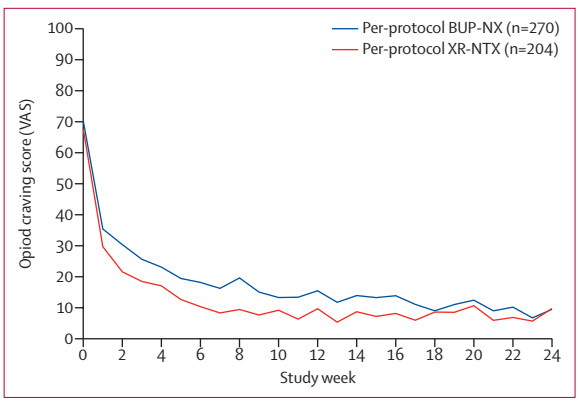


Figure 3: **Opioid craving during the trial**
Craving was self-reported with an opioid craving VAS, range 0–100. VAS=Visual Analogue Scale. XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone.

	XR-NTX group (n=283)	BUP-NX group (n=287)
Treatment-emergent adverse events		
Participants with one or more treatment-emergent adverse event*	111 (54%)	141 (52%)
Number of treatment-emergent adverse events	247	334
Study medication discontinued due to adverse event	6	8
Type of treatment-emergent adverse event		
Injection site reaction, mild or moderate	46	NA
Gastrointestinal	34	59
Psychiatric disorders	30	29
Injury, poisoning, and procedural complications	23	25
Infections and infestations	22	27
Nervous system disorders	22	28
Treatment-emergent serious adverse events		
Participants with one or more serious adverse event	29 (14%)	29 (11%)
Number of treatment-emergent serious adverse events	39	35
Type of treatment-emergent serious adverse event		
Psychiatric disorders	9	11
Infections and infestations	5	6
Pregnancy	3	4
Death	3	4
Overdose events		
Participants with one or more overdose event (all)†	15	8
Participants with one or more overdose event (per protocol)‡	9	7
Number of overdose events (all)§	18	10
Number of overdose events (per protocol)	10	9
Fatal overdose events		
Number of fatal overdose events (all)	2	3
Number of fatal overdose events (per protocol)	2	3

Data are n (%) or N. NA=not applicable. XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone. *Treatment emergent is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication. †p=0·14 (Fisher's exact). ‡p=0·31 (Fisher's exact). §Four participants reported more than one overdose event. Three of the four participants were randomly assigned to XR-NTX (two of these induction failures, one successfully inducted); each reported two overdose events. One of the four was randomly assigned to BUP-NX (successfully inducted) and reported three overdose events. None of these nine overdoses were fatal.

Table 3: **Adverse events and serious adverse events**

adverse events did not differ between treatment groups. Thus, if induction to either medication is successful, XR-NTX and BUP-NX were comparably effective and safe options. These findings afford providers, patients, and families a choice between agonist and antagonist therapies. The risk of XR-NTX induction failure should be considered, and agonist treatments for those individuals unable to complete detoxification should be encouraged.

Clinically, ease of induction is a well known limitation of naltrexone and an advantage of buprenorphine. Study sites varied in detoxification approaches and lengths of stay, but all had to wait, per protocol, for a negative-opioid urine sample before XR-NTX induction, which favoured both longer lengths of stay and non-agonist detoxification. Published strategies[23,24] to increase successful XR-NTX induction with single or minimal dosing of buprenorphine and oral naltrexone, and not dependent on a negative urine sample, might be more effective than some of the induction protocols used by our sites.

Once participants were successfully inducted to either XR-NTX or BUP-NX, they achieved similarly favourable and important clinical outcomes: relapse-free survival, overall relapse, retention in treatment, negative urine samples, days of opioid abstinence, and self-reported cravings. These findings align with results of non-inferiority from the concurrent Norwegian study,[25] which was also a randomised comparison of XR-NTX to BUP-NX treatment after a longer detoxification run-in, which minimised induction failure. Few participants in the Norwegian trial[26] were not able to induct onto either XR-NTX or BUP-NX treatment, and retention, opioid use, or adverse event outcomes did not differ between treatment groups, similar to what was observed in our per-protocol population. Forthcoming analyses from our trial will examine cost-effectiveness, individual-level clinical and genetic moderators of treatment effects, and comparative effects on other drug use, HIV risk behaviours, and cognitive function.

Importantly, this large study found no differences between treatment groups for overall death or overdose events. Overdose events and overdose fatalities were observed in both groups, nearly all of them following failed medication induction or discontinuation and dropout from either medication. These outcomes were consistent with observational analyses showing overdose risk increases substantially after discontinuation of methadone and buprenorphine.[27] Although our study was not powered to detect significant differences in overdose events and did not include a no-medication control condition, these results are similar to another large XR-NTX trial,[4] in which no overdose deaths were observed among 153 participants treated with XR-NTX over 18 months versus seven among treatment-as-usual controls. So far, no large trial has given a clear signal that XR-NTX treatment increases overdose events or death compared with placebo treatment, treatment as usual, and now, BUP-NX treatment.

A challenge to both treatment groups of this study was overall retention in treatment. Study treatment retention for 24 weeks was between 43% and 47%, which was modestly lower than retention in other 24 week trials[2–4] of either medication. A defining feature of this trial was recruitment from inpatient detoxification units, as opposed to outpatient settings. The risk of early opioid treatment dropout is likely to be greater among participants actively using heroin and initially admitted to acute detoxification units than opioid patient cohorts initiating outpatient medication treatment.[28] Detoxification admissions typically represent a spectrum of motivation and treatment-seeking; many patients are in crisis and unclear of further treatment options, while other patients are highly motivated to begin a thoughtfully considered new treatment programme. The early randomisation group in this trial, who were more recently admitted and more recently using heroin (or other opioids) than the late randomisation group, had higher overall relapse events in both treatment groups than the late randomisation group. This finding might have shown a higher risk of early dropout, leaving against medical advice, or ambivalence towards chronic medication treatment with either medication among the early randomisation group versus the late randomisation group who are more likely to be a motivated and adherent group, having already survived the initial detoxification days.

Regarding the limitations of our study, the core trial design choices, particularly the acute detoxification setting, flexible randomisation, and the varied induction protocols, which were likely to have had a substantial effect on XR-NTX induction, limit interpretation and generalisability.[16,17] An entirely outpatient study would possibly have inducted even fewer people to the XR-NTX group, and would have been consistent with standard BUP-NX induction in the USA, which is largely office-based. Alternatively, recruitment of previously detoxified people or randomisation only of participants able to immediately induct to XR-NTX treatment, the design of an earlier randomised controlled trial,[4] would have probably favoured XR-NTX treatment compared with BUP-NX treatment. Site differences in detoxification protocols and lengths of stay contributed to induction and relapse events, and showed substantial variability in standard opioid detoxification approaches. Finally, open-label, real-world effectiveness trials include more sources of bias than tightly controlled efficacy studies, including the absence of placebo control or masking, but potentially increase generalisability. The analyses of the per-protocol population might be affected by confounding because this group is defined on the basis of an after randomisation factor (induction success); however, the intention-to-treat and per-protocol populations, and both treatment groups within each population, were similar with respect to baseline demographic and clinical characteristics.

In summary, for the intention-to-treat population, XR-NTX treatment was less effective than BUP-NX treatment for the prevention of opioid relapse following admission for inpatient detoxification. This outcome was primarily due to fewer XR-NTX inductions and high occurrence of relapse among induction failures. Both medications were similar in effectiveness and safety once treatment was initiated.

Contributors

The study Clinical Trials Network (CTN) Greater New York Node (JDL, JR, EVN Jr, PN, PG, and SF), Emmes Corporation (DSt, JM), and the National Institute on Drug Abuse Center for the CTN (CCTN; DL) designed the study and wrote the protocol. All authors implemented the study protocol and contributed to data collection. Emmes (RL) and the CCTN (DL, GS) coordinated the Data Safety Monitoring Board and study monitoring. The CTN Greater New York Node (JDL, JR, EVN Jr, PN), Emmes Corporation (JM, AGM, JK, DS-B, DSa, DSt), and CCTN (DL, GS) had access to study data, and statistically analysed and interpreted the data. JDL wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Declaration of interests

All authors report grant or contract funding from the National Institute of Drug Abuse (NIDA) for this study. JDL and JR received other research support from NIDA and National Institute on Alcohol Abuse and in-kind study drug from Alkermes for another trial. EVN Jr received other research support from NIDA, Brainsway, Braeburn Pharma, and Alkermes, unpaid consulting fees from Alkermes, and consulting fees from the University of Arkansas. MF received other research support from Alkermes, US World Meds, MediaRez, and the Laura and John Arnold Foundation, and consulting fees from Alkermes and US World Meds. SR received other research support from NIDA, the Heffter Research Institute, Council on Spiritual Practices, and the Sarlo Foundation, and travel support from the Multidisciplinary Association for Psychedelic Studies. All other authors declare no competing interests.

Acknowledgments

This study was sponsored by the National Institute on Drug Abuse (NIDA). We thank all the site research teams, clinical staff, and most importantly the study participants for their effort and time. We thank the Protocol Development Committee, the Study Executive Committee, and Data Safety Monitoring Board for their support and counsel.
This research was supported by grants from the NIDA National Drug Abuse Treatment Clinical Trials Network (U10DA013046, UG1/U10DA013035, UG1/U10DA013034, U10DA013045, UG1/U10DA013720, UG1/U10DA013732, UG1/U10DA013714, UG1/U10DA015831, U10DA015833, HHSN271201200017C, and HHSN271201500065C) and K24DA022412 (EVN Jr).

References

1 Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014; **2:** CD002207.

2 Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009; **3:** CD002209.

3 Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011; **377:** 1506–13.

4 Lee JD, Friedmann PD, Kinlock TW, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med* 2016; **374:** 1232–42.

5 Jones CM, Campopiano M, Baldwin G, McCance-Katz E. National and State Treatment need and capacity for opioid agonist medication-assisted treatment. *Am J Public Health* 2015; **105:** e55–63.

6 IMS Institute for Healthcare Informatics. Use of opioid recovery medications. 2016. https://www.imshealth.com/files/web/IMSH%20Institute/Reports/Healthcare%20Briefs/IIHI_Use_of_Opioid_Recovery_Medications.pdf (accessed Aug 1, 2017).

7 Morgan JR, Schackman BR, Leff JA, Linas BP, Walley AY. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. *J Subst Abuse Treat* 2017; published online July 3. DOI:10.1016/j.jsat.2017.07.001.

8 Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006; **63:** 210–18.

9 Lee JD, McDonald R, Grossman E, et al. Opioid treatment at release from jail using extended-release naltrexone: a pilot proof-of-concept randomized effectiveness trial. *Addiction* 2015; **110:** 1008–14.

10 Alkermes Inc. Highlights of prescribing information: VIVITROL (naltrexone for extended-release injectable suspension). Revised July, 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021897s020s023lbl.pdf (accessed Aug 1, 2017).

11 Reckitt Benckiser Pharmaceuticals Inc. Highlights of prescribing information: SUBOXONE (buprenorphine and naloxone) sublingual film. Revised August, 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf (accessed Aug 1, 2017).

12 Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug Alcohol Rev* 2007; **26:** 405–10.

13 Lobmaier PP, Kunøe N, Gossop M, Katevoll T, Waal H. Naltrexone implants compared to methadone: outcomes six months after prison release. *Eur Addict Res* 2010; **16:** 139–45.

14 Mokri A, Chawarski MC, Taherinakhost H, Schottenfeld RS. Medical treatments for opioid use disorder in Iran: a randomized, double-blind placebo-controlled comparison of buprenorphine/naloxone and naltrexone maintenance treatment. *Addiction* 2016; **111:** 874–82.

15 Kelty E, Hulse G. Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. *Int J Drug Policy* 2017; **46:** 54–60.

16 Lee JD, Nunes EV, Mpa PN, et al. NIDA Clinical Trials Network CTN-0051, Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT): study design and rationale. *Contemp Clin Trials* 2016; **50:** 253–64.

17 Nunes EV, Lee JD, Sisti D, et al. Ethical and clinical safety considerations in the design of an effectiveness trial: a comparison of buprenorphine versus naltrexone treatment for opioid dependence. *Contemp Clin Trials* 2016; **51:** 34–43.

18 Sobell LC, Sobell MB. Alcohol Timeline Followback users' manual. Toronto, Canada: Addiction Research Foundation, 1995.

19 Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatry* 2011; **68:** 1238–46.

20 Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug Alcohol Dep* 2015; **150:** 112–19.

21 Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction* 2016; **111:** 695–705.

22 Hser YI, Huang D, Saxon AJ, et al. Distinctive trajectories of opioid use over an extended follow-up of patients in a multisite trial on buprenorphine + naloxone and methadone. *J Addict Med* 2017; **11:** 63–69.

23 Mannelli P, Wu LT, Peindl KS, Swartz MS, Woody GE. Extended release naltrexone injection is performed in the majority of opioid dependent patients receiving outpatient induction: a very low dose naltrexone and buprenorphine open label trial. *Drug Alcohol Depend* 2014; **138:** 83–88.

24 Sullivan M, Bisaga A, Pavlicova M, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *Am J Psychiatry* 2017; **174:** 459–67.

25 Kunøe N, Opheim A, Solli KK, et al. Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacol Toxicol* 2016; **17:** 18.

26 Tanum L, Solli KK, Latif ZE, et al. The effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry* 2017; Published online Oct 18. DOI:10.1001/jamapsychiatry.2017.3206.

27 Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017; **357:** j1550.

28 Nunes EV, Gordon M, Friedmann PD, et al. Relapse to opioid use disorder after inpatient treatment: Protective effect of injection naltrexone. *J Subst Abuse Treat* 2017; published online April 23. DOI:10.1016/j.jsat.2017.04.016.

JAMA Psychiatry | Original Investigation

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence
A Randomized Clinical Noninferiority Trial

Lars Tanum, MD, DMSci; Kristin Klemmetsby Solli, MSc; Zill-e-Huma Latif, MD; Jūratė Šaltytė Benth, PhD; Arild Opheim, MSc; Kamni Sharma-Haase, MD; Peter Krajci, MD, PhD; Nikolaj Kunøe, MSc, PhD

IMPORTANCE To date, extended-release naltrexone hydrochloride has not previously been compared directly with opioid medication treatment (OMT), currently the most commonly prescribed treatment for opioid dependence.

OBJECTIVE To determine whether treatment with extended-release naltrexone will be as effective as daily buprenorphine hydrochloride with naloxone hydrochloride in maintaining abstinence from heroin and other illicit substances in newly detoxified individuals.

DESIGN, SETTING AND PARTICIPANTS A 12-week, multicenter, outpatient, open-label randomized clinical trial was conducted at 5 urban addiction clinics in Norway between November 1, 2012, and December 23, 2015; the last follow-up was performed on October 23, 2015. A total of 232 adult opioid-dependent (per *DSM-IV* criteria) individuals were recruited from outpatient addiction clinics and detoxification units and assessed for eligibility. Intention-to-treat analyses of efficacy end points were performed with all randomized participants.

INTERVENTIONS Randomization to either daily oral flexible dose buprenorphine-naloxone, 4 to 24 mg/d, or extended-release naltrexone hydrochloride, 380 mg, administered intramuscularly every fourth week for 12 weeks.

MAIN OUTCOMES AND MEASURES Primary end points (protocol) were the randomized clinical trial completion rate, the proportion of opioid-negative urine drug tests, and number of days of use of heroin and other illicit opioids. Secondary end points included number of days of use of other illicit substances. Safety was assessed by adverse event reporting.

RESULTS Of 159 participants, mean (SD) age was 36 (8.6) years and 44 (27.7%) were women. Eighty individuals were randomized to extended-release naltrexone and 79 to buprenorphine-naloxone; 105 (66.0%) completed the trial. Retention in the extended-release naltrexone group was noninferior to the buprenorphine-naloxone group (difference, −0.1; with 95% CI, −0.2 to 0.1; $P = .04$), with mean (SD) time of 69.3 (25.9) and 63.7 (29.9) days, correspondingly ($P = .33$, log-rank test). Treatment with extended-release naltrexone showed noninferiority to buprenorphine-naloxone on group proportion of total number of opioid-negative urine drug tests (mean [SD], 0.9 [0.3] and 0.8 [0.4], respectively, difference, 0.1 with 95% CI, −0.04 to 0.2; $P < .001$) and use of heroin (mean difference, −3.2 with 95% CI, −4.9 to −1.5; $P < .001$) and other illicit opioids (mean difference, −2.7 with 95% CI, −4.6 to −0.9; $P < .001$). Superiority analysis showed significantly lower use of heroin and other illicit opioids in the extended-release naltrexone group. No significant differences were found between the treatment groups regarding most other illicit substance use.

CONCLUSIONS AND RELEVANCE Extended-release naltrexone was as effective as buprenorphine-naloxone in maintaining short-term abstinence from heroin and other illicit substances and should be considered as a treatment option for opioid-dependent individuals.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01717963

JAMA Psychiatry. 2017;74(12):1197-1205. doi:10.1001/jamapsychiatry.2017.3206
Published online October 18, 2017.

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 1284

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Lars Tanum, MD, DMSci, The Norwegian Centre for Addiction Research, The University of Oslo, PO Box 1039 Blindern, 0315 Oslo, Norway (lars.tanum@medisin.uio.no).

Substance use disorders involving opioids have a higher risk of death, poly drug use, and blood-borne infections, such as HIV and hepatitis, than other substance use disorders.[1,2] Owing to the high risk of relapse and overdose in opioid-dependent individuals, the most commonly prescribed treatment is opioid medication treatment (OMT), in which opioids with longer absorption times and half-lives are prescribed, such as the full opioid agonist methadone[3] or partial agonist buprenorphine hydrochloride.[4] Because of the injection-deterring potential of naloxone hydrochloride and the better safety profile compared with methadone, daily administration of combined buprenorphine and naloxone (buprenorphine-naloxone) is the first choice of OMT medication in a number of countries. However, the extent to which buprenorphine-naloxone deters injection in practice has been debated.[5]

Opioid medication treatment is generally found to be effective in reducing illicit opioid use, overdose mortality,[6] and associated problems, such as criminal activity[7] or injection-related incidents.[8] The disadvantages of OMT include continued physical dependence on and diversion of the prescribed opioid. The conventional alternative to OMT is follow-up counseling of drug-free patients after detoxification, which carries an increased risk of relapse to opioid use, especially soon after leaving prison or inpatient treatment programs.[9,10] The reduction or loss of opioid tolerance following both short- and long-term abstinence puts the individual at high risk of overdose if opioid use is resumed.[11]

The opioid agonist naltrexone hydrochloride has been proposed as a third alternative to maintain opioid abstinence, but in oral naltrexone treatment, low adherence, a high dropout rate, and increased mortality have been described as serious challenges.[12-14] An alternative to the oral naltrexone product now available is extended-release naltrexone, administered as monthly intramuscular injections. Extended-release naltrexone inhibits the action of heroin and other opioid agonists by a competitive blocking of the opioid receptors. This inhibition has proven effective compared with placebo both in laboratory[15] and clinical[16-19] settings, and the effectiveness is in line with previous studies on some implantable naltrexone formulations.[17,20] Moreover, contrary to OMT medications, extended-release naltrexone lacks abuse potential and should, in principle, give opioid users a prolonged period of abstinence from opioids with a high level of protection from relapse.

However, there is a lack of studies comparing extended-release naltrexone treatment with OMT. Such studies would provide novel information on differences in clinical effectiveness and adverse event profiles between the 2 treatment approaches and allow clinicians to choose the most adequate treatment for a given patient according to the individual's needs and motivation.

The aim of the present study was to compare the effectiveness of extended-release naltrexone injections administered every fourth week with daily oral buprenorphine-naloxone in reducing the use of heroin and other illicit substances in similarly motivated patients randomized to either treatment after discharge from inpatient treatment or detoxification.

Key Points

Question Are monthly intramuscular injections with extended-release naltrexone hydrochloride as effective as daily oral buprenorphine–naloxone hydrochloride in reducing the use of heroin and other illicit substances in newly detoxified, opioid-dependent individuals?

Findings In this 12-week, open-label randomized clinical trial including 159 opioid users, treatment with intramuscular extended-release naltrexone was as effective as oral buprenorphine-naloxone in reducing the use of heroin, opioids, and other illicit substances.

Meaning Maintaining short-term opioid abstinence with extended-release naltrexone should be considered an equal treatment alternative to buprenorphine-naloxone as medication-assisted treatment for opioid-dependent individuals.

Methods

This randomized clinical trial assigned 159 patients in a clinical setting to treatment with injections of extended-release naltrexone every fourth week vs daily oral buprenorphine-naloxone. The protocol, including all outcome variables, is provided in the Supplement; complete information about the protocol is available in Kunøe et al.[21]

Inclusion was stopped on July 10, 2015, and the last patient follow-up was performed on October 23, 2015. The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway, the Norwegian Medicines Agency, and the boards of research ethics at the participating hospitals. Monitoring of the study was conducted by the publicly funded Regional Monitoring Authorities at Oslo University Hospital and Haukeland University Hospital (Innovest) according to Good Clinical Practice standards. Participants provided written informed consent. They were not paid or compensated for taking part in the study, with the exception of reimbursement of travel expenses. A lottery ticket incentive was offered for every urine drug test (UDT) administered (value approximately $2 US).

Participants and Setting

Patients were recruited between November 1, 2012, and July 10, 2015, by study personnel from outpatient clinics and detoxification units at 5 urban addiction clinics in Norway: Oslo University Hospital, Akershus University Hospital, Haukeland University Hospital, Stavanger University Hospital, and Vestfold Hospital Trust. Eligible participants were opioid-dependent (according to *DSM-IV* criteria) men or women aged 18 to 60 years. Criteria for exclusion were other drug or alcohol dependence or serious somatic or psychiatric illness regarded as contraindications or in need of treatment that would interfere with study participation. Women of childbearing age could not be pregnant or lactating and agreed to use effective birth control. Participants were screened for psychiatric disorders using the Mini-International Neuropsychiatric Interview 6.0[22] and examined for serious somatic disease. Eligible

participants were referred to a detoxification unit following screening and inclusion. The study took place in an outpatient setting, and all participants were discharged from detoxification units, inpatient treatment, or prison. Ethnicity was defined by the participant.

Procedure, Outcomes, and Masking

After detoxification, participants were randomly assigned (1:1) to commence either individually dosed buprenorphine-naloxone, 4 to 24 mg/d (target dose, 16 mg/d) given orally daily in a controlled environment or extended-release naltrexone, 380 mg, given intramuscularly every fourth week for the following 12 weeks. Allocation to treatment group was computerized using a permuted block algorithm provided by the regional monitoring authority and not stratified for site or sex. Following induction into either medication regimen, participants were asked to attend standard drug counseling, but no behavioral interventions could be initiated. At baseline (inclusion) and every 4 weeks thereafter, patients underwent a structured interview using the European version of the Addiction Severity Index covering drug use, physical and mental health, work, education, and criminal activity.[23-25]

Primary outcome variables were comparison of retention in the study, the proportion of total number of UDTs without illicit opioids, and number of days of use of heroin and other illicit opioids. The weekly UDTs were analyzed using specific chromatographic methods and calculated as the number of opioid-negative urine drug screens divided by the total number of attended tests (group proportion) in accordance with recently revised Cochrane guidelines.[26] Missing UDTs were considered as testing positive for opioids in all participants. Since a number of participants were abusing illicit opioids other than heroin at the time of inclusion, we discriminated between such use.

Secondary outcome variables were number of days of use of cannabis, amphetamines, cocaine, benzodiazepines, hallucinogens, alcohol, the number of days of injecting (intravenous) drugs, the degree of heroin craving (visual analog scale, 0-10, with 0 indicating none; 10, very strong), thoughts about heroin (visual analog scale, 0-10, with 0 indicating none; 10, constant or very frequent), life satisfaction (Temporal Satisfaction with Life Scale–Present items, 5-35; with 5 indicating very low; 35, very high),[27] satisfaction with treatment (visual analog scale, 0-10; with 0 indicating very low; 10, very high), and mental health (Hopkins Symptom Checklist-25 of anxiety and depression, 25-100, with 25 indicating very low; 100, very high).[28,29]

Data on heroin, other illicit opioids, and substance use were collected every fourth week by an interview using the timeline follow-back technique, where participants reported the number of days of use within the 28 days preceding each interview.[30] Retention in treatment was defined as the number of days until dropout from study medication and by the number of patients completing the study at week 12.

Participants who completed this randomized clinical trial were invited to continue or cross over to either treatment for up to 48 weeks. These data will be described in a subsequent publication.

Statistical Analysis

Minimum sample size was estimated in 2 scenarios. For the noninferiority scenario with a power of 90% and significance level of 5%, we assumed that both groups would retain 70% of their participants at the end of week 12 and set 20% as the noninferiority margin; this yielded a minimum sample size of 58 in each group (116 total).

The superiority scenario assumed extended-release naltrexone participants to have a mean of 7 opioid-negative samples out of the total 12 (0.58) samples, while participants receiving buprenorphine-naloxone would display a mean of 4 opioid-negative samples (0.33). Assuming an SD of 3.0 in both groups and a significance level of 5%, the estimated sample size would be 17 patients per medication arm (34 total) as sufficient to show a significant difference between the arms with a power of 90%. Intention-to-treat analyses of efficacy end points were performed with all randomized participants.

Differences in primary and secondary outcomes were assessed by linear mixed models with fixed effects for time, group, and the interaction between the 2 variables. Random effects for time and site were included in the models. A significant interaction implied differences between the groups' changes throughout the follow-up. The models were also adjusted for age and sex.

Noninferiority analyses were performed by linear mixed models, where a nonsignificant interaction between time and group was eliminated. Regression coefficients for group variables were combined with the predefined noninferiority margins (8 for heroin, 10 for illicit opioids, and 0.2 for opioid-negative UDTs).

The normality of residuals was assessed by inspecting the histograms. Bootstrap inference based on 1000 replications was generated in the case of skewed residuals; however, differences were negligible and the original results were reported. Adverse events were compared using Fisher exact test. Retention in treatment was assessed by a log-rank test.

The results at $P < .05$ were considered significant in all superiority analyses. The noninferiority analyses were assessed by 1-sided test at the same significance level. Statistical analyses were conducted by a study-independent statistician blinded to the names of the study medications. The analyses were performed in SPSS, version 24 (SPSS Corp) and SAS, version 9.4 (SAS Institute).

Results

Patient Characteristics

Men and women displayed similar age distributions (mean [SD], 36.2 [8.9] and 35.6 [7.9] years, respectively), years of heavy heroin use (mean, 6.7 [5.5] and 6.9 [5.3], respectively), years of heavy use of other illicit opioids (mean, 2.8 [5.5] and 3.0 [7.6], respectively), age at onset of injection use (mean, 21.2 [7.8] and 21.0 [8.6] years, respectively), and other social characteristics corresponding to data from the national registry on opioid-dependent substance users in Norway. All

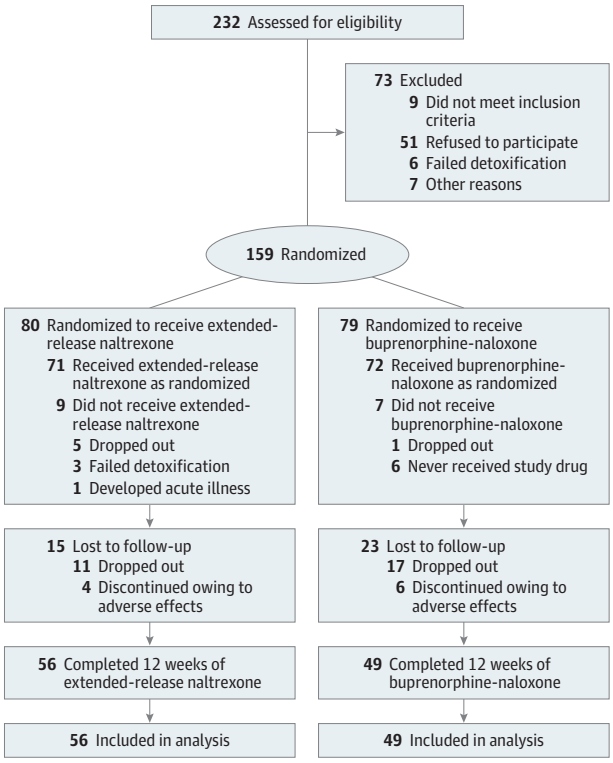
Table 1. Lifetime and Baseline Clinical Characteristics of Participants Randomized Into Treatment Groups[a]

Lifetime Characteristic	Extended-Release Naltrexone[b] (n = 80)	Buprenorphine-Naloxone[b] (n = 79)
Age, mean (SD), y	36.4 (8.8)	35.7 (8.5)
Sex, No. (%)		
Male	61 (76.3)	54 (68.4)
Female	19 (23.6)	25 (31.6)
White, No. (%)	72 (90.0)	70 (88.6)
Injecting (intravenous) users, No. (%)	72 (90.0)	64 (81.0)
HIV positive, No. (%)	2 (2.5)	2 (2.5)
Hepatitis C seropositive, No. (%)	44 (55.0)	42 (53.2)
Years of substance use, mean (SD)		
Heavy opioid use	8.9 (7.8)	9.6 (10.5)
Heroin	6.9 (5.8)	6.7 (5.2)
Other illicit opioids	2.4 (5.1)	3.2 (7.0)
Cannabis	9.0 (7.3)	10.2 (9.0)
Amphetamines	6.7 (7.3)	6.3 (6.6)
Cocaine	1.4 (3.1)	1.7 (2.8)
Benzodiazepines	5.1 (6.0)	5.9 (8.7)
Alcohol for intoxication	3.5 (4.8)	2.9 (4.1)
Use during past 30 d (baseline), mean (SD)		
Heroin	7.6 (11.0)	12.0 (12.9)
Other illicit opioids	8.2 (11.1)	14.5 (13.2)
Cannabis	8.2 (11.1)	10.2 (12.6)
Amphetamines	3.4 (7.4)	5.4 (9.1)
Cocaine	0.2 (0.7)	1.3 (3.9)

[a] Intention-to-treat sample, 159.

[b] Naltrexone, naloxone, and buprenorhine were all administered as the hydrochloride form.

Figure 1. CONSORT Flowchart for Inclusion of Participants



Screening, randomization, and follow-up. Naltrexone, naloxone, and buprenorhine were all administered as the hydrochloride form.

women and 85.0% of the men were white. Four participants were HIV positive, and 86 (54.1%) tested seropositive for hepatitis C. The mean daily dose of buprenorphine-naloxone during the study was 11.2 mg (range, 6-24 mg). Other characteristics are reported in **Table 1**.

Retention in Treatment

Among the 232 participants assessed for eligibility, 165 were included in the study and 159 were randomized to treatment with extended-release naltrexone (80 [50.3%]) or buprenorphine-naloxone (79 [49.7%]). Reasons for exclusion of 73 individuals were refusal to participate (51 [69.9%]), not meeting inclusion criteria (9 [12.3%]), failed detoxification (6 [8.2%]), and other reasons (7 [9.6%]) (**Figure 1**). Among the randomized participants, 143 agreed to commence their medication: 71 (49.7%) in the extended-release naltrexone group and 72 (50.3%) in the buprenorphine-naloxone group.

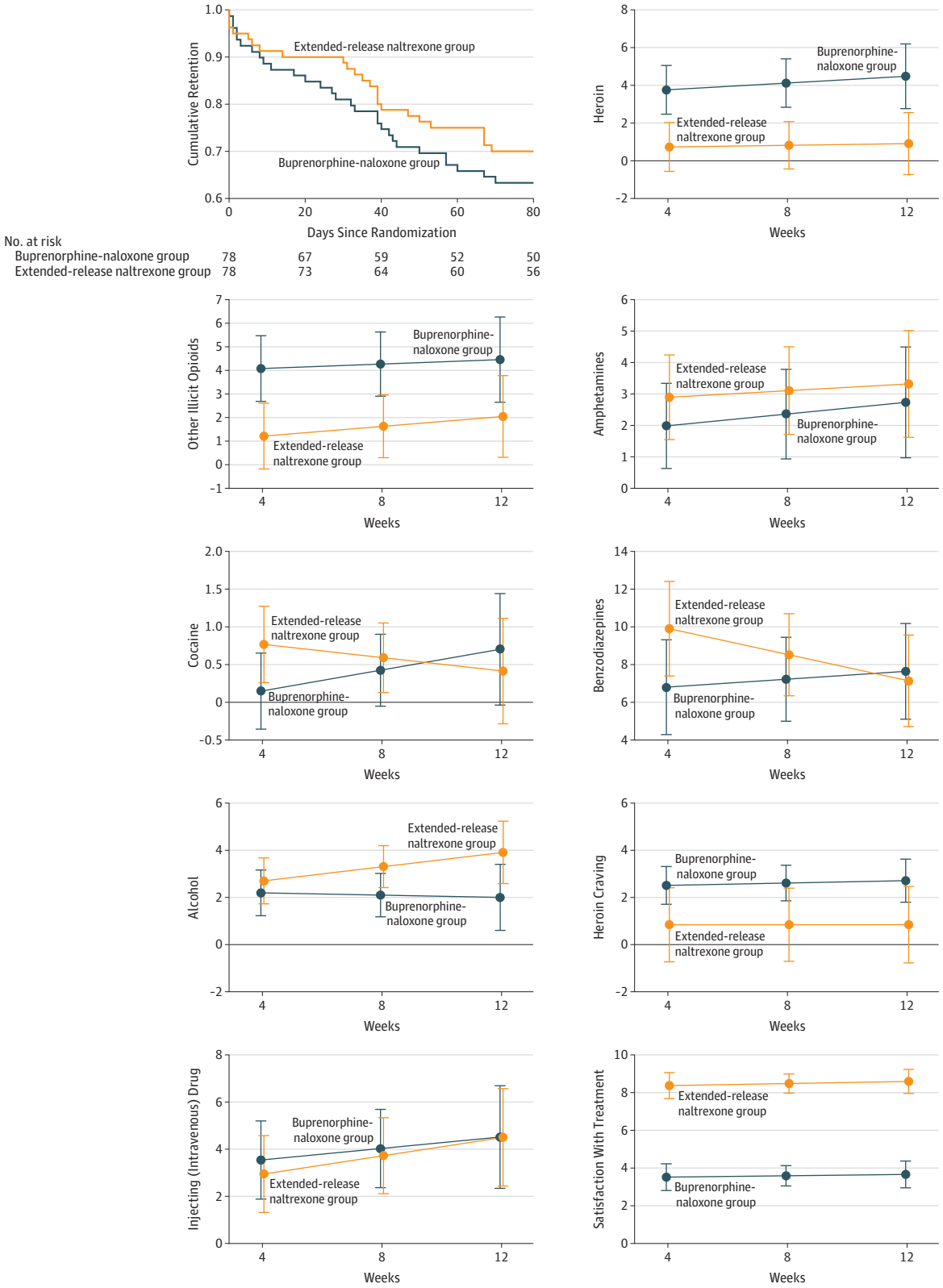
Participants receiving extended-release naltrexone and buprenorphine-naloxone displayed a similar retention time in the study (mean [SD], 69.3 [25.9] and 63.7 [29.9] days, respectively; $P = .33$) (**Figure 2**). The proportion of participants retained in the extended-release naltrexone group was noninferior to the buprenorphine-naloxone group (difference, −0.1; 95% CI, −0.2 to 0.1; $P = .04$).

After 12 weeks (84 days), 105 (66.0%) participants had attended all scheduled follow-up appointments and taken their medication as prescribed. Fifty-three participants dropped out: 24 in the extended-release naltrexone group and 29 in the buprenorphine-naloxone group.

Primary Outcomes

Treatment with extended-release naltrexone was noninferior to buprenorphine-naloxone regarding the group proportion of the total number of opioid-negative UDTs (mean [SD], 0.9 [0.3] and 0.8 [0.4], respectively; mean difference, 0.1 with 95% CI, −0.04 to 0.2; $P < .001$). Regarding days of use of heroin (mean difference, −3.2 with 95% CI, −4.9 to −1.5; $P < .001$) and other illicit opioids (mean difference, −2.7 with 95% CI, −4.6 to −0.9; $P < .001$), extended-release naltrexone treatment showed noninferiority to buprenorphine-naloxone under the predefined conditions. Assessing superiority of 1 treatment over the other showed no significant differences between the treatment groups in the proportion of negative UDTs ($P = .18$). However, extended-release naltrexone participants used significantly less heroin at all time points and less other illicit opioids at weeks 4 and 8, even though the pattern of use was not significantly different between groups ($P = .64$ for heroin, $P = .71$ for illicit opioids).

Figure 2. Survival Curves for Retention in Treatment and Estimated Mean Number of Days for the Use of Heroin, Other Illicit Opioids, and Major Secondary Outcomes



Visual analog scales were used to assess heroin craving (0-10, with 0 indicating none; 10, very strong) and satisfaction with treatment (0-10, with 0 indicating very low; 10, very high). Naltrexone, naloxone, and buprenorhine were all administered as the hydrochloride form. Error bars indicate 95% CIs.

Table 2. Days of Use of Heroin and Other Illegal Substances Assessed at Weeks 4, 8, and 12[a]

	Extended-Release Naltrexone		Buprenorphine-Naloxone		Extended-Release Naltrexone vs Buprenorphine-Naloxone	
Time Point	No. of Participants	Mean (SD)[b]	No. of Participants	Mean (SD)[b]	Mean Difference (95% CI)[c]	*P* Value[c]
Heroin Use						
Week 4	63	0.8 (1.5)	65	3.7 (7.4)	−3.0 (−4.9 to −1.2)	.001
Week 8	59	0.8 (1.9)	55	4.4 (9.1)	−3.3 (−5.1 to −1.5)	<.001
Week 12	57	1.1 (2.3)	50	4.1 (8.4)	−3.6 (−6.0 to −1.2)	.003
Other Illicit Opioids Use						
Week 4	63	1.2 (2.2)	65	4.2 (7.9)	−2.9 (−4.8 to −0.9)	.004
Week 8	59	1.8 (4.7)	55	4.0 (8.5)	−2.6 (−4.6 to −0.7)	.007
Week 12	57	2.0 (5.0)	50	4.4 (8.7)	−2.4 (−4.9 to 0.1)	.06
Cannabis Use						
Week 4	63	6.7 (9.8)	65	5.3 (9.4)	1.4 (−1.8 to 4.7)	.38
Week 8	59	6.4 (8.9)	55	4.8 (8.5)	1.6 (−1.3 to 4.6)	.28
Week 12	57	7.5 (9.7)	50	5.1 (9.6)	1.8 (−1.5 to 5.1)	.27
Amphetamine Use						
Week 4	63	2.9 (6.0)	65	2.0 (5.3)	9 (−1.0 to 2.8)	.35
Week 8	59	3.4 (7.0)	55	1.9 (5.4)	8 (−1.2 to 2.7)	.46
Week 12	57	3.4 (7.5)	50	2.1 (5.7)	0.6 (−1.9 to 3.0)	.64
Cocaine Use						
Week 4	63	0.8 (3.2)	65	0.1 (0.3)	0.6 (−0.1 to 1.3)	.09
Week 8	59	0.5 (1.8)	55	0.7 (3.4)	0.2 (−0.5 to 0.8)	.62
Week 12	57	0.5 (1.8)	50	0.6 (2.9)	−0.3 (−1.3 to 0.7)	.58
Benzodiazepine Use						
Week 4	63	1.1 (11.2)	65	6.9 (1.3)	3.1 (−0.5 to 6.7)	.09
Week 8	59	8.0 (11.3)	55	6.6 (9.4)	1.3 (−1.8 to 4.4)	.41
Week 12	57	6.7 (9.5)	50	7.3 (1.4)	−0.5 (−4.0 to 3.0)	.78
Alcohol Use for Intoxication						
Week 4	63	3.0 (4.4)	65	2.3 (3.8)	0.5 (−0.9 to 1.9)	.47
Week 8	59	2.9 (4.6)	55	1.9 (3.1)	1.2 (−0.1 to 2.5)	.06
Week 12	57	4.4 (7.3)	50	2.1 (3.6)	1.9 (−0.02 to 3.8)	.05

[a] Hallucinogens were used once or twice by 5 participants receiving extended-release naltrexone hydrochloride and 4 receiving buprenorphine–naloxone hydrochloride.

[b] Means and SDs are descriptive numbers, not adjusted for repeated measurements or for site effects.

[c] Results of linear mixed model for difference between groups; adjusted for repeated measurements and site effect; random effect for time included.

Secondary Outcomes

There were no significant differences between the treatment groups in the pattern of use of amphetamine (*P* = .73), cocaine (*P* = .13), alcohol (*P* = .21), cannabis (*P* = .78), or injecting drugs (*P* = .68) (Figure 2). However, participants receiving extended-release naltrexone had a significant reduction in days of benzodiazepine use (*P* = .04), while the buprenorphine-naloxone group remained stable. There were no significant differences between groups at different time points. Hallucinogens were used once or twice by 5 participants receiving extended-release naltrexone and 4 receiving buprenorphine-naloxone (**Table 2**).

At all time points, participants receiving extended-release naltrexone reported significantly less heroin craving and thoughts about heroin (Table 2) than did buprenorphine-naloxone participants. Satisfaction with treatment was significantly higher among extended-release naltrexone participants and they would also recommend their treatment to others to a higher extent compared with buprenorphine-naloxone participants. Life satisfaction was significantly higher among extended-release naltrexone participants at weeks 4 and 8, but not at week 12. The Hopkins Symptom Checklist-25 scores showed no significant differences between the groups. Correcting the analyses for sex and age did not change the results.

Adverse Events

More adverse events were reported by extended-release naltrexone than buprenorphine-naloxone participants (49 [69.0%] vs 25 [34.7%]; *P* < .001), but only 10 participants discontinued treatment owing to adverse events: 4 in the extended-release naltrexone group and 6 in the buprenorphine-naloxone group. A number of events were related to induced or experienced withdrawal symptoms, such as nausea, chills, shivering, diarrhea, and sneezing, and were more frequent among the extended-release naltrexone participants (28 [39.4%] vs 10 [13.9%] events).

There were no deaths, but 6 (8.5%) extended-release naltrexone and 3 (4.2%) buprenorphine-naloxone participants

Table 3. Reported AEs Among 143 Participants Taking at Least 1 Dose of Study Medication[a]

Outcome	No. (%)		P Value[b]
	Extended-Release Naltrexone (n = 71)	Buprenorphine-Naloxone (n = 72)	
Deaths	0	0	
Nonserious AE	43 (60.6)	22 (30.6)	<.001
Serious AE[c]	6 (8.5)	3 (4.2)	.33
Pneumonia-related	2 (2.8)	0	
Withdrawal-related	3 (4.2)	0	
Acute pain	1 (1.4)	1 (1.4)	
Opioid overdose	0	1 (1.4)	
Planned surgery	0	1 (1.4)	
Insomnia	8 (11.3)	3 (4.2)	.13
Anxiety and depression symptoms	12 (16.9)	6 (8.3)	.14
Injection site problems	4 (5.6)	0	
Withdrawal-related AE[d]	28 (39.4)	10 (13.9)	<.001

Abbreviation: AE, adverse event.

[a] Naltrexone, naloxone, and buprenorhine were all administered as the hydrochloride form.

[b] Determined with Fisher exact test; empty cells indicate not applicable.

[c] Two participants reported 2 serious AEs each.

[d] Thirty-seven participants reported 2 or more withdrawal-related events.

reported a serious adverse event (**Table 3**). All recovered completely and maintained their study medication.

Discussion

To our knowledge, this is the first study comparing the effectiveness of extended-release naltrexone injections with that of daily oral buprenorphine-naloxone, the standard OMT in Norway and other countries. Treatment with extended-release naltrexone was as effective as buprenorphine-naloxone in maintaining retention in treatment and reducing the use of heroin, other illicit opioids, and the use of other illicit substances except cannabis; injecting behavior; and craving for opioids. The main clinical implication of these findings is that extended-release naltrexone seems to be as safe and effective as buprenorphine-naloxone treatment for maintaining short-term abstinence from heroin, opioids, and other illicit substances in opioid-dependent individuals newly detoxified and/or discharged from inpatient treatment or prison. Since we discriminated between heroin and other illicit opioids, mainly oral formulations, our data also seem to be clinically relevant for the growing number of individuals who are addicted to prescribed opioids.

Induction into extended-release naltrexone treatment required full detoxification to a greater extent than into the buprenorphine-naloxone treatment. The Norwegian guidelines for detoxification of opioid users turned out to be insufficient for study detoxification and frequently produced adverse effects related to withdrawal symptoms on induction of extended-release naltrexone and, to some extent, buprenorphine-naloxone. We therefore changed our detoxification strategy during the first year of the study in accordance with the most recent literature at the time of our study,[31-33] which reduced the number of new adverse events related to induction of treatment. Serious adverse events were equally distributed between the groups and were not directly related to the given treatment, which explains why there were no dropouts among participants reporting a serious adverse event.

Satisfaction with treatment and willingness to recommend their treatment to others were significantly higher among extended-release naltrexone participants. This finding may be due to the perception of being protected against relapse of opioid use and possible overdose and better opportunities to return to work or educational activities when not having to meet daily or every second day for supervised intake of an opioid agonist. However, the high availability of OMT in Norway[34] makes it likely that the majority of participants were mainly motivated to receive the novel extended-release naltrexone treatment and not buprenorphine-naloxone. As treatment preference has been shown to be important for treatment satisfaction and adherence in other settings,[35,36] it is difficult to know whether extended-release naltrexone would be equally effective in individuals with lower motivation for opioid abstinence.

There was only 1 reported overdose in the study, which is much lower than most reports on the first 12 weeks after discharge from treatment or prison.[9,37,38] This low rate may reflect the high motivation for treatment and good response to regular follow-up by the same study worker in this group of participants.

The rather low reported mean use of opioids the last 30 days before inclusion is probably due to the fact that a number of participants included in the study had already completed detoxification or had sustained abstinence for varying periods of time (prison or inpatient treatment), while others were still actively using opioids at study enrollment.

The doses of buprenorphine-naloxone used in the study were adjusted to community-based practice representing treatment as usual. Our mean daily dose of 11.2 mg therefore corresponded fairly well with the 2016 National OMT Report mean dose of 13 mg/d.[39]

Limitations

One limitation of the present study is the lack of blinding. However, previous blinded placebo-controlled studies in clinical[16,17] and laboratory[15] settings seem sufficient to prove efficacy for the extended-release naltrexone medication. Owing to an increased risk of overdose in newly detoxified opioid users, the use of placebo and/or masking of medications were considered unethical. In addition to substantial practical challenges

in managing 4 different medication arms, we regard most patients as capable of demasking or recognizing their respective treatments quickly, given their long experience with opioid use. Since we wanted to perform the study in a naturalistic setting, attempts to demask the treatment could easily be a disturbing element interfering with a true-effectiveness assessment. We therefore question the value of such a scheme in clinical trials for opioid dependence.

Conclusions

Maintaining short-term abstinence from illicit opioids and other substances with extended-release naltrexone was as effective and safe as buprenorphine-naloxone. Extended-release naltrexone should be an available treatment option for opioid-dependent individuals

ARTICLE INFORMATION

Accepted for Publication: August 25, 2017.

Published Online: October 18, 2017. doi:10.1001/jamapsychiatry.2017.3206

Author Affiliations: The Norwegian Centre for Addiction Research, The University of Oslo, Oslo, Norway (Tanum, Solli, Sharma-Haase, Kunøe); Department.of Research and Development in Mental Health Service, Akershus University Hospital, Lorenskog, Norway (Tanum, Latif); Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway (Benth); Health Services Research Unit, Akershus University Hospital, Lorenskog, Norway (Benth); Department of Addiction Medicine, Haukeland University Hospital, Haukeland, Norway (Opheim); Faculty of Medicine & Odontology, The University of Bergen, Bergen, Norway (Opheim); Department of Addiction Medicine, Vestfold Hospital Trust, Tonsberg, Norway (Sharma-Haase); Department of Addiction Medicine, Oslo University Hospital, Oslo, Norway (Krajci).

Author Contributions: Dr Kunøe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tanum, Kunøe.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Tanum, Solli, Šaltytė Benth, Kunøe.
Critical revision of the manuscript for important intellectual content: Solli, Latif, Šaltytė Benth, Opheim, Sharma-Haase, Krajci, Kunøe.
Statistical analysis: Solli, Šaltytė Benth, Kunøe.
Obtained funding: Tanum, Opheim, Kunøe.
Administrative, technical, or material support: Tanum, Solli, Latif, Opheim, Sharma-Haase, Krajci, Kunøe.
Study supervision: Tanum, Krajci, Kunøe.

Conflict of Interest Disclosures: None reported.

Funding/Support: The study was supported by unrestricted grants from the Research Council of Norway and the Western Norway Regional Health Authority. Financial support was also received from the Norwegian Centre for Addiction Research, University of Oslo, and from Akershus University Hospital.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication; however, Alkermes Inc was allowed to comment on the manuscript before submission for publication.

Additional Contributions: All data analyses were conducted by study-independent statistician Jūratė Šaltytė Benth, PhD (Akershus University Hospital and University of Oslo). Zhanna Gaulen, MSc (Department of Addiction Medicine, Haukeland University Hospital), Anne-Lill Mjoelhus Njaa, MSc (Center for Alcohol and Drug Research, Stavanger University Hospital), and Linn Wergeland Digranes, BSc (Department of Addiction Medicine, Akershus University Hospital), contributed to data collection. There was no financial compensation. Alkermes Inc supplied extended-release naltrexone for the study. We thank all study site personnel for their efforts, as well as all participating patients.

REFERENCES

1. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. *N Engl J Med*. 2014;370(22):2063-2066.

2. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284(13):1689-1695.

3. Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. *JAMA*. 1965;193:646-650.

4. *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. Geneva, Switzerland: World Health Organization; 2009.

5. Duke AN, Correia CJ, Walsh SL, Bigelow GE, Strain EC. Acute effects of intramuscular and sublingual buprenorphine and buprenorphine/naloxone in non-dependent opioid abusers. *Psychopharmacology (Berl)*. 2010;211(3):303-312.

6. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2(2):CD002207.

7. Bukten A, Røislien J, Skurtveit S, Waal H, Gossop M, Clausen T. A day-by-day investigation of changes in criminal convictions before and after entering and leaving opioid maintenance treatment: a national cohort study. *BMC Psychiatry*. 2013;13:262.

8. Skeie I, Brekke M, Gossop M, et al. Changes in somatic disease incidents during opioid maintenance treatment: results from a Norwegian cohort study. *BMJ Open*. 2011;1(1):e000130.

9. Bukten A, Stavseth MR, Skurtveit S, Tverdal A, Strang J, Clausen T. High risk of overdose death following release from prison: variations in mortality during a 15-year observation period. *Addiction*. 2017;112(8):1432-1439.

10. Chutuape MA, Jasinski DR, Fingerhood MI, Stitzer ML. One-, three-, and six-month outcomes after brief inpatient opioid detoxification. *Am J Drug Alcohol Abuse*. 2001;27(1):19-44.

11. Strang J, McCambridge J, Best D, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. *BMJ*. 2003;326(7396):959-960.

12. Degenhardt L, Larney S, Kimber J, Farrell M, Hall W. Excess mortality among opioid-using patients treated with oral naltrexone in Australia. *Drug Alcohol Rev*. 2015;34(1):90-96.

13. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev*. 2011;4.

14. Roozen HG, de Waart R, van den Brink W. Efficacy and tolerability of naltrexone in the treatment of alcohol dependence: oral versus injectable delivery. *Eur Addict Res*. 2007;13(4):201-206.

15. Sullivan MA, Vosburg SK, Comer SD. Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. *Psychopharmacology (Berl)*. 2006;189(1):37-46.

16. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet*. 2011;377(9776):1506-1513.

17. Krupitsky E, Zvartau E, Blokhina E, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Arch Gen Psychiatry*. 2012;69(9):973-981.

18. Lee JD, Friedmann PD, Kinlock TW, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med*. 2016;374(13):1232-1242.

19. Lee JD, McDonald R, Grossman E, et al. Opioid treatment at release from jail using extended-release naltrexone: a pilot proof-of-concept randomized effectiveness trial. *Addiction*. 2015;110(6):1008-1014.

20. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. *Arch Gen Psychiatry*. 2009;66(10):1108-1115.

21. Kunøe N, Opheim A, Solli KK, et al. Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacol Toxicol*. 2016;17(1):18.

22. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22-33.

23. McLellan AT, Luborsky L, Cacciola J, et al. New data from the Addiction Severity Index: reliability

and validity in three centers. *J Nerv Ment Dis*. 1985;173(7):412-423.

24. Kokkevi A, Hargers C. EUROPASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *Eur Addict Res*. 1995;1(4):208-210.

25. Kokkevi A. Psychosocial assessment in substance abuse and dependence. *Curr Opin Psychiatry*. 2001;14(3):167-172.

26. Cochrane Drugs and Alcohol. CDAG resources for authors http://cda.cochrane.org/cdag-resources-authors. Accessed January 7, 2016.

27. Pavot W, Diener E, Suh E. The Temporal Satisfaction With Life Scale. *J Pers Assess*. 1998;70(2):340-354.

28. Joukamaa M, Lehtinen V, Karlsson H, Rouhe E. SCL-25 and recognition of mental disorders reported by primary health care physicians. *Acta Psychiatr Scand*. 1994;89(5):320-323.

29. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974;19(1):1-15.

30. Sobell LC, Sobell MB, Litten RZ, Allen JP. *Timeline Follow-Back: a Technique for Assessing Self-Reported Alcohol Consumption*. Totowa, NJ: Humana Press; 1992.

31. Sullivan M, Bisaga A, Pavlicova M, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *Am J Psychiatry*. 2017;174(5):459-467.

32. Sigmon SC, Bisaga A, Nunes EV, O'Connor PG, Kosten T, Woody G. Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice. *Am J Drug Alcohol Abuse*. 2012;38(3):187-199.

33. Mannelli P, Wu LT, Peindl KS, Swartz MS, Woody GE. Extended release naltrexone injection is performed in the majority of opioid dependent patients receiving outpatient induction: a very low dose naltrexone and buprenorphine open label trial. *Drug Alcohol Depend*. 2014;138:83-88.

34. EMCDDA. *European Drug Report: Trend and Developments*. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction; 2015.

35. Sullivan MA, Rothenberg JL, Vosburg SK, et al. Predictors of retention in naltrexone maintenance for opioid dependence: analysis of a stage I trial. *Am J Addict*. 2006;15(2):150-159.

36. Nunes EV, Krupitsky E, Ling W, et al. Treating opioid dependence with injectable extended-release naltrexone (XR-NTX): who will respond? *J Addict Med*. 2015;9(3):238-243.

37. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend*. 2009;105(1-2):9-15.

38. UNODC. *World Drug Report 2015*. Vienna: United Nations Office on Drug and Crime; 2015.

39. Waal H, Bussesund K, Clausen T, Skeie I, Håseth A, Lillevold P. The annual OMT status survey for 2016. Statusrapport 2016-Er kvalitetsforbedring nå viktigere enn kapasitetsutvikling? Oslo, Norway: Norwegian Centre for Addiction Research; 2017.