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Risk of Relapse Among Opioid-Dependent Patients Treated With Extended-Release Naltrexone or Buprenorphine-Naloxone: A Randomized Clinical Trial

Arild Opheim, MSc,[1,2] Zhanna Gaulen, MSc,[1,3] Kristin Klemmetsby Solli, MSc, PhD,[4,5,6] Zill-e-Huma Latif, MD, PhD,[7] Lars T. Fadnes, MD, PhD,[1,2] Jūratė Šaltytė Benth, MSc, PhD,[8,9] Nikolaj Kunøe, MSc, PhD,[10] Lars Tanum, MD, PhD[5,11]

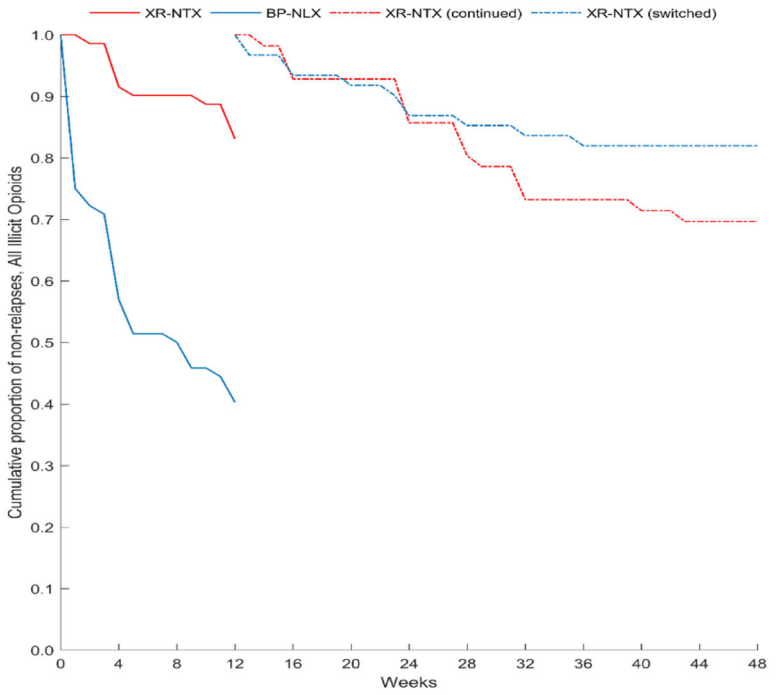
[1]Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway
[2]Institute of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[3]Department of Clinical Dentistry, University of Bergen, Bergen, Norway
[4]Norwegian Centre for Addiction Research, University of Oslo, Oslo, Norway
[5]Department of Research and Development in Mental Health Services, University Hospital, Lorenskog, Norway
[6]Vestfold Hospital Trust, Tonsberg, Norway
[7]Groruddalen Psychosis Outpatient Department, Akershus University Hospital, Oslo, Norway
[8]Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway
[9]Health Services Research Unit, Akershus University Hospital, Lorenskog, Norway
[10]Lovisenberg Diaconal Hospital, Oslo, Norway
[11]Faculty for Health Science, Oslo Metropolitan University, Oslo, Norway

Background and Objectives: Compare the risk of relapse to heroin and other illicit opioids among opioid-dependent patients receiving treatment with extended-release naltrexone (XR-NTX) or buprenorphine-naloxone (BP-NLX).
Methods: Re-analyzed data from a 12-week multicenter, open-label, randomized treatment study with a subsequent 36-week open-label follow-up study. All patients, N = 143, had completed detoxification and received at least one dose of study medication.
Results: Of 143 patients (72% men), mean age 36 years, 71 received XR-NTX and 72 BP-NLX. The risk of first relapse and the risk of any relapse to heroin and other illicit opioids were both significantly lower in the XR-NTX group compared with the BP-NLX group (hazard ratio [HR], 0.46; 95% confidence interval [CI], 0.28-0.76; $P = .002$, and HR, 0.11; 95% CI, 0.04-0.29; $P < .001$, respectively) and (HR, 0.15; 95% CI, 0.09-0.27; $P < .001$ and HR, 0.05; 95% CI, 0.03-0.09; $P < .001$, respectively). There was a stable low risk of relapse among participants receiving XR-NTX in the follow-up.
Discussion and Conclusions: Compared to BP-NLX, patients on XR-NTX had a substantially reduced risk of relapse to illicit opioids and showed a stable low risk of relapse over time in longer-term treatment.
Scientific Significance: Our data support XR-NTX as a first-line treatment option for patients with opioid addiction both in short and longer-term treatment. This is the first European study showing that XR-NTX significantly reduces the risk of first and any relapse to heroin use in opioid-dependent patients compared to BP-NLX. Our data contradict previous data from the X:BOT study, showing no significant difference in relapse risk between the groups in a 6-month randomised controlled trial. (© 2021 Authors. *The American Journal on Addictions* published by Wiley Periodicals LLC on behalf of The American Academy of Addiction Psychiatry). (Am J Addict 2021;30:453–460)

Address correspondence to Dr Opheim, Department of Addiction Medicine, Haukeland University Hospital, Ostre Murallmenning 7, 5021 Bergen, Norway.
E-mail: arild.opheim@helse-bergen.no

INTRODUCTION

Opioid dependence is considered a chronic relapsing disorder that carries an increased risk of repeated intoxication and overdose deaths.[1] During the past decade, opioid use has developed into a public health concern, with an estimated 16 million people worldwide experiencing this reverting illness.[2] Consequently, expanding access to addiction treatment is an essential component of a comprehensive response.[3] The most widely used therapeutic modality for the management of opioid addiction is opioid maintenance treatment (OMT), including methadone and buprenorphine. An alternative therapeutic approach to opioid dependence is complete detoxification and induction to antagonist



XR-NTX	71	56	Continued	44	35	29
BP-NLX	72	61	Switched	44	33	29

FIGURE 1. Kaplan-Meier curve presenting time to first relapse to all illicit opioids, including heroin in XR-NTX and BP-NLX groups. The first 12 weeks represent the trial period and weeks 12 to 48 represent the follow-up period, where those continuing XR-NTX are compared with those switching from BP-NLX to XR-NTX. BP-NLX = buprenorphine-naloxone; XR-NTX = extended-release naltrexone.

medication.[4] A full opioid antagonist like naltrexone, both injectable and implantable, offers pharmacological protection against relapse, re-dependence and overdose, and provides abstinence-motivated users with substantial cognitive relief from relapse-related thoughts.[5,6] An extended-release naltrexone (XR-NTX) injection lasts for 1 month, and two recent studies have shown that XR-NTX is largely comparable with buprenorphine-naloxone (BP-NLX) in treatment safety, effectiveness, and retention.[7,8] In a previous paper[7], we found that the treatment with XR-NTX was noninferior to BP-NLX based on days of use of illicit opioids and the group proportion of the total number of opioid-negative UDTs under the predefined conditions.

Lee et al[8] reported superiority for buprenorphine using the time to first relapse of illicit opioid use as the primary outcome. While the Norwegian participants were included during all stages of detoxification, the US study included all participants before detoxification.

Despite this difference in method, a comparison of outcomes between the studies seems crucial for the understanding and clinical importance of the findings.

The aim of this study was to perform a secondary analysis looking at the time to first relapse to illicit opioid use among abstinent-motivated patients who successfully completed detoxification, both in the randomized trial and the subsequent follow-up, and to compare our data with the US X:BOT study. This analysis was performed focusing on the risk of relapse to indicate a more nuanced representation of illicit opioid use than reporting days of use. This approach will provide clinicians with an added understanding of relapse in these treatment trajectories and between the treatment groups.

Further, we investigated if the risk of the first relapse could be a clinically useful outcome measure to evaluate the effectiveness of this treatment both in the randomized 12-week trial and the subsequent 36-week follow-up period.

MATERIALS AND METHODS

Methods

This study is a 12-week multicenter, open-label, randomized treatment study with a subsequent 36-week open-label follow-up study.[9] The modified intention-to-treat population included in the study ($n = 143$) had completed detoxification and received at least one dose of study medication, and had at least one valid assessment after randomization. Due to the difference in detoxification protocol between the two studies, the modified intention-to-treat population was chosen to match the per protocol population in the US X:BOT study. The modified intention-to-treat population includes all patients randomized to treatment who received at least one dose of study medication and who had at least one valid assessment after randomization. Allocation to treatment group was computerized using a permuted block algorithm provided by the regional monitoring authority and not stratified for site

or sex. Randomization was performed as a 1:1 ratio in balanced blocks to receive 380 mg XR-NTX intramuscularly every fourth week or daily sublingual BP-NLX, 8-24/2-6 mg (Fig. 1). Relapse was defined as 4 consecutive weeks of any heroin or nonstudy opioid use or 7 consecutive days of heroin or nonstudy opioid use. Relapse was censored at the end of every 4-week period. To maximize the accuracy of such retrospective interview data, we used the Time-Line Follow-Back data collecting method.[10]

Patients on BP-LNX underwent detoxification by a gradual tapering over a period of 7 days. They were in a controlled environment for a minimum of 72 hours between the last dose of BP-NLX and the XR-NTX injection. Just before the first injection, a dose (0.4 mg) of the short-acting opioid antagonist naloxone was administered to test if XR-NTX could induce possible unacceptable withdrawal symptoms. If so happened, the XR-NTX injection would be postponed for 24 hours. Upon entering the 9-month follow-up period, patients could choose between BP-NLX and XR-NTX. Of the 122 patients who entered the follow-up, only five chose to continue with BP-NLX. Due to the low number of BP-NLX patients, no meaningful clinical or statistical comparisons between the treatment groups could be performed. These five BP-NLX participants were therefore excluded from further analyses.

The primary outcome variable was the time to first relapse to heroin or other illicit opioid use in the randomized 12-week period. The secondary outcome was the risk of any relapse to heroin or other illicit opioid use in the randomized part of the study and the risk of any relapse in the 36-week follow-up study. The patients were not excluded from further analyses in case of relapse. After the 12-week trial period, all participants entering the 36-week prospective follow-up period chose XR-NTX except five participants who chose to continue with BP-LNX. No participants switched from XR-NTX to BP-LNX. Due to this distribution of participants in the follow-up period, we left the original trial design and used a cohort design instead. Patients provided written informed consent. They were not paid or compensated for taking part in the study, with the exception of reimbursement of travel expenses using public transportation.

Participants and Setting

Eligible patients were opioid-dependent (*Diagnostic and Statistical Manual of Mental Disorders* [DSM-IV], 4th edition, 2000)[11] men and women 18 to 60 years old. Criteria for exclusion were pregnancy, lactation, acute alcoholism, and severe somatic or psychiatric illness interfering with study participation, such as decompensated hepatic cirrhosis, renal failure, HIV with related symptoms, current or recurrent affective disorders with suicidal behavior and/or psychotic disorders. Women of childbearing age were required to use contraceptive methods. Study personnel screened patients for psychiatric disorders using the M.I.N.I. Interview 6.0[12], while a physician examined the patients for severe somatic disease. If necessary, eligible patients were referred to the detoxification unit following the screening. The design of the study, including sample size calculation, is described in detail elsewhere.[9] At inclusion and every 4 weeks, patients underwent a structured interview using the European version of the Addiction Severity Index. The scores of the EuropASI in the domains of physical and mental health, work, education, criminal activity, and social functioning were similar at inclusion between the treatment groups.[10,13]

In the randomized part of the study, weekly urine drug tests (UDTs) were obtained, but not in the follow-up study. In a previous paper, we showed that the UDTs corresponded well with patients' report of illicit opioid use,[7] and UDTs were therefore not included in this paper.

Patients were recruited between November 1, 2012 and July 10, 2015 from outpatient clinics and detoxification units at five urban addiction clinics in Norway. All the patients were invited to participate in the subsequent follow-up study, during which they could opt for one or the other medication for an additional period of 36 weeks. The patients were randomized after the end-stage of detoxification. The study was funded by The Research Council of Norway, The Western Norway Regional Health Trust, and The Norwegian Centre for Addiction Research and participating hospitals. The study was approved by the South-East Regional Ethical Board for Medical Research Ethics (#2011/1320), the Norwegian Medicines Agency, and by the Boards of Research Ethics at every participating hospital.

Statistical Analysis

Baseline characteristics were described as means and SD or frequencies and percentages. The number and percentage of relapses as well as mean (SD) time to relapse to heroin and other illicit opioids was presented for each week. All numbers were presented by treatment group in the randomised controlled trial period and by those continuing or switching to XR-NTX in the follow-up period. The retention between the treatment groups was compared by the log-rank test. Since the participants may either have no relapses or one or more relapses, two types of analysis were performed. The risk of the *first* relapse between the groups was compared using the Cox regression model. To assess the differences between the groups in risk of *any* relapse, an extended Cox regression model adjusting for within-patient correlations occurring due to repeated measurements was estimated. The results were presented as hazard ratios (HR) with 95% confidence intervals (CI) and *P* values. Since the use of illicit opioids, injecting days, mental health, self-assessed problematic drug use, alcohol abuse, cannabis use, use of amphetamines and benzodiazepines, and Norwegian kroner used on drugs last 30 days prior to inclusion might be confounding characteristics; the sensitivity analyses adjusting the HRs for these variables were carried out.[23] The results with *P* values below .05 were considered statistically significant in all analyses. The analyses were performed in SPSS version 25 and SAS version 9.4 (Table 1).

TABLE 1. Demographic and baseline clinical characteristics of patients randomized to treatment with extended-release naltrexone or buprenorphine-naloxone reported as raw numbers or mean with (SD)

Characteristic	Extended-release naltrexone ($n = 71$)	Buprenorphine-naloxone ($n = 72$)
Sex (% male)	55 (78)	51 (71)
Injecting substances, raw numbers	66	66
Years with injections, mean (median)	9.9 (7.0)	9.9 (7.5)
Years of heroin use	6.2 (5.5)	7.0 (5.0)
Years of other heavy opioid use	8.4 (7.5)	8.5 (7.0)
Overdose events lifetime	4.5 (8.2)	4.4 (5.5)
Age at inclusion	35.7 (8.3)	35.9 (8.9)
Injecting days last 30 days at inclusion	9.2 (12.2)	11.4 (12.8)
Illicit opioids last 30 days at inclusion	8.2 (11.1)	14.2 (13.1)
Mental health (SCL 25) last 30 days at inclusion	47.3 (18.3)	49.8 (16.3)
Self-assessed problem drug use last 30 days at inclusion	20.1 (13.0)	21.9 (12.2)
Alcohol abuse days last 30 days at inclusion	1.0 (3.9)	1.7 (5.3)
Cannabis use last 30 days at inclusion	7.7 (11.1)	10.9 (12.7)
Amphetamines days use last 30 days at inclusion	3.3 (7.1)	5.6 (9.3)
Benzodiazepines days use last 30 days inclusion	8.4 (11.3)	12.6 (13.0)
NKR used on drugs last 30 days at inclusion	7448 (12,700)	9567 (14,113)

RESULTS

The study included 143 patients who had successfully completed detoxification, 37 women and 106 men. The mean age was 35.7 (SD, 8.3) years in the XR-NTX group and 35.9 (SD, 8.9) years in the BP-NLX group.

In the 12-week trial, the mean follow-up time for the XR-NTX group was 10.8 (SE = 0.3) weeks and 10.6 (SE = 0.3) weeks for the BP-NLX group ($P = .251$ for the log-rank test). In the 36-week prospective follow-up period, the mean follow-up time for those who continued on XR-NTX was 37.5 (SE = 1.6) weeks and 37.1 (SE = 1.6) weeks for those who switched to XR-NTX after the trial period.

The risk of the first relapse to heroin and other illicit opioids was reduced by 54% and 89% in the XR-NTX group compared to the BP-NLX group (HR, 0.46; 95% CI, 0.28-0.76; $P = .002$, and HR, 0.11; 95% CI, 0.04-0.27; $P < .001$), respectively (see Table 2 and Fig. 2). The risk of any relapse to heroin or other illicit opioids was also significantly reduced in the XR-NTX group compared to the BP-NLX group (HR, 0.15; 95% CI, 0.09-0.27; $P < .001$ and HR, 0.05; 95% CI, 0.03-0.09; $P < .001$, respectively), with a total of 14 and 11 relapses, respectively, in the XR-NTX group and 95 and 147 relapses, respectively in the BP-NLX group ($P < .001$ both groups). The pooled risk of first or any relapse to any illicit opioids strongly favored XR-NTX (HR, 0.35; 95% CI, 0.22-0.55; $P < .001$ and HR, 0.08, 95% CI, 0.05-0.12; $P < .001$, respectively) (Table 2 and Fig. 2). Adjustment for possible confounders assessed prior to inclusion did not alter the results.

The 36-week follow-up study period included 117 patients receiving XR-NTX. There was no significant difference in time to first relapse to heroin or other illicit opioids between those continuing with XR-NTX treatment and those switching to XR-NTX after week 12. Among those who continued to use XR-NTX, there were 27 relapses to heroin compared with 29 relapses among those switching to XR-NTX. In both groups, there were 18 relapses to other illicit opioids in the 36-week follow-up (see Supporting Information). However, in the group switching to XR-NTX, there were more relapses to other illicit opioids during the first four weeks compared to the group continuing on XR-NTX (HR, 0.45; 95% CI, 0.22-0.94; $P = .034$) despite the equal number of relapses in the two groups throughout the study period (Table 2). On the other hand, this difference between the groups became insignificant after adjustment for the use of illicit opioids, injecting days, mental health, self-assessed problematic drug use, alcohol abuse, cannabis use, use of amphetamines and benzodiazepines, and money (Norwegian kroner) used on drugs assessed prior to baseline. Patients receiving XR-NTX and BP-NLX displayed a similar retention time in the study, with 56 of the 71 patients in the XR-NTX group and 49 of the 72 in the BP-NLX group completing the trial. The mean follow-up time for those who continued on XR-NTX was 37.5 (SE = 1.6) weeks and 37.1 (SE = 1.6) weeks for those who switched to XR-NTX after the randomized period ($P = .642$ for the log-rank test).

DISCUSSION

This study showed that opioid-dependent patients who had successfully completed detoxification and were randomized to treatment with XR-NTX had a substantially reduced risk of relapse to heroin and other illicit opioids compared to those randomized to BP-NLX. The overall risk of relapse to any illicit opioids was about three times in favor of treatment with

TABLE 2. Cox regression for risk of first relapse and risk of any relapse, to heroin, other illicit opioids and all illicit opioids, in the trial period and in the 36-week follow-up

	First relapse		Any relapse	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Trial period				
• Heroin				
◦ BP-NLX	1		1	
◦ XR-NTX	0.46 (0.28; 0.76)	**.002**	0.15 (0.09; 0.27)	**<.001**
• Other illicit opioids				
◦ BP-NLX	1		1	
◦ XR-NTX	0.11 (0.04; 0.29)	**<.001**	0.05 (0.03; 0.09)	**<.001**
• All illicit opioids				
◦ BP-NLX	1		1	
◦ XR-NTX	0.35 (0.22; 0.55)	**<.001**	0.08 (0.05; 0.12)	**<.001**
36-week follow-up				
• Heroin				
◦ Switched to XR-NTX	1		1	
◦ Continued XR-NTX	0.78 (0.41; 1.50)	.455	1.06 (0.62; 1.83)	.830
• Other illicit opioids				
◦ Switched to XR-NTX	1		1	
◦ Continued XR-NTX	0.27 (0.07; 1.04)	.057	0.45 (0.22; 0.94)	**.034**
• All illicit opioids				
◦ Switched to XR-NTX	1		1	
◦ Continued XR-NTX	0.70 (0.36; 1.38)	.305	0.85 (0.54; 1.34)	.480

Bolded data indicate statistical significance $P \leq .05$.
CI = confidence interval; HR = hazard ratio.

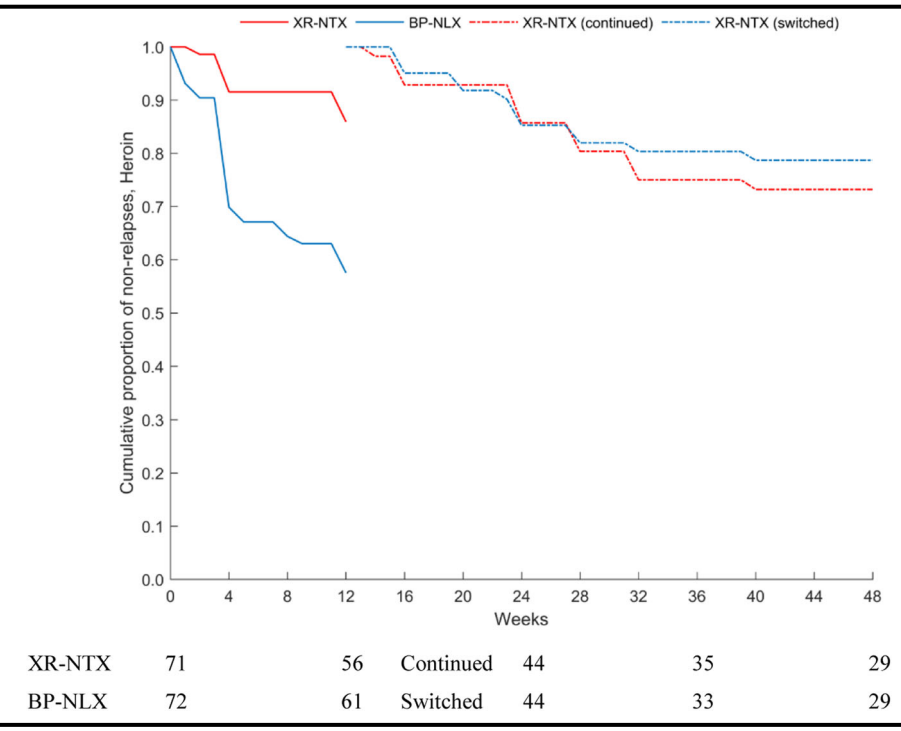


FIGURE 2. Kaplan-Meier curve presenting time to first relapse to heroin in XR-NTX and BP-NLX groups. The first 12 weeks represent the trial period and weeks 12 to 48 represent the follow-up period, where those continuing XR-NTX are compared with those switching from BP-NLX to XR-NTX. BP-NLX = buprenorphine-naloxone; XR-NTX = extended-release naltrexone.

XR-NTX. Our finding of low relapse rate to heroin and other illicit opioids found in the XR-NTX group is consistent with other treatment studies of XR-NTX.[14-16]

Treatment with XR-NTX reduces the use of illicit opioid use more than does placebo or treatment referral, but the need to withdraw from opioids before initiating XR-NTX limits its use. Approximately 37% of the study participants withdrawing from opioids before XR-NTX induction did not start treatment.[17-19] Morgan et al[20] notes that XR-NTX patients more often discontinued therapy compared to BP-NLX patients. This illustrates that the retention of opioid-dependent patients on XR-NTX medication is a challenge. In order not to limit the impact of a new opioid addiction medication like XR-NTX, methods for improving retention rates are vital. It is further critically important to determine the method that best could successfully increase retention on XR-NTX medication, and at the same time, minimize withdrawal symptoms and risk of potential relapse.[21] In our study,[22] we found that 49.6% of the participants completed the 36-week follow-up with XR-NTX, which is within the range of findings in studies of OMT.

In our previous study, the objective was to determine whether treatment with XR-NTX would be as effective as daily BP-NLX in maintaining abstinence from heroin and other illicit substances in newly detoxified patients. The outcome was assessed in terms of days of use of illicit opioids and confirmed by weekly UDTs, and the results from these primary analyses were in accordance with the secondary analyses in this study, but here the differences between the groups were more accentuated. However, our secondary analyses are not in line with the findings in the US X:BOT study that reported an even relapse rate ($P = .44$) between the two treatments after 24 weeks, even in their per protocol population. Since the risk of relapse may increase with time, we also compared our data to the number of relapses after 12 weeks in the X:BOT study, analyzed and given to us by the X:BOT study group for this purpose (see the "Acknowledgments" section). This 12-week analysis (data withheld) showed a similar robust difference in relapse rate in XR-NTX-treated patients between the studies as the previously published 24-week data. The substantial difference in relapse risk between the studies therefore could not be attributed to the difference in treatment time.[8] We cannot explain this difference between the United States and Norwegian studies regarding the risk of relapse on XR-NTX treatment, and further pooled analyses should be performed on data from the two studies. Since these studies may influence clinicians in their choice of clinical treatment for opioid-dependent patients and their attitude toward XR-NTX and BP-NLX, it seems important to further investigate this reported clinical discrepancy in effectiveness.

It was only through participating in this study patients could get access to XR-NTX medication, and certainly, most of the patients joined this study because they were motivated to receive treatment with nonopioid medication such as XR-NTX to avoid the stigma and schemes associated with the available opioid-based medication. This is an important consideration in clinical practice when deciding on treatment in collaboration with patients with opioid dependence. To optimize future treatment with XR-NTX, it seems vital to capture the patients' perspectives on enablers and barriers to longer-term abstinence from opioids. For opioid-dependent patients, who could successfully complete detoxification and are striving for abstinence from opioids, XR-NTX could be offered as a first-line treatment.

Our main hypothesis for the better outcome on XR-NTX in Norway is the difference in the healthcare system between the two countries. The Norwegian OMT program is publicly funded with a choice of medication carrying no additional cost to the patient. The Norwegian patients entered the study primarily to get the novel XR-NTX treatment. Maybe the US patients were interested in joining the X:BOT study in order to get OMT for their dependence, and not particularly abstinent-minded or seeking an antagonist treatment. This might have influenced the results in favor of XR-NTX in Norway. The aspect of motivation for opioid abstinence should be taken into consideration in clinical practice when deciding on treatment for individuals with opioid dependence. For opioid-dependent individuals who could successfully complete detoxification and who are motivated for longer-term abstinence from opioids, XR-NTX could be offered as a first-line treatment.

Another issue raised by this study is whether relapse to opioids is a clinically meaningful assessment to guide clinicians in their choice of treatment. In our first paper, we reported a moderate superiority of XR-NTX over BP-NLX in the number of days of illicit opioid use, but the magnitude of the difference between groups was far less than the robust differences in relapse rates. The robust difference between groups may, at least in part, be due to how the relapse was defined, and a slightly modified definition of relapse would probably have resulted in a more moderate difference between the groups. We therefore question the use of relapse rate as meaningful guidance to clinicians in medication treatment choices for patients with opioid dependence. Actually, a high number of our patients that relapsed only once were highly motivated for opioid abstinence and completed the full study length.

Our inclusion and exclusion criteria of patients corresponded well with those used in the US X:BOT study, making the comparison valid for this population of opioid-dependent individuals. The US X:BOT study had many dropouts due to failed detoxification, which led to the superiority of BP-NLX over XR-NTX in the ITT population analyses. The per protocol population, however, showed an equal relapse rate between the treatment groups. In contrast, our patients were included at all stages of detoxification, but the majority after having completed detoxification.

The low relapse rate of heroin and other illicit opioids on XR-NTX treatment was continued throughout the 36-week follow-up period. The lack of difference in relapse rate between those continuing with XR-NTX and those switching to XR-NTX indicated that the relapse rate to any opioids was low already from the first weeks of treatment and continued to remain stable over time. When adjusted for current symptoms of anxiety or depression, there was practically no relapse to opioids after 24 weeks among participants with low or no symptoms of anxiety or depression.[14] The effects of XR-NTX in reducing the risk of relapse to heroin and other illicit opioids were upheld by those continuing and those who switched to XR-NTX.

Extended-release formulations of buprenorphine could have been a more relevant comparator for XR-NTX than oral daily BP-NLX since this formulation may provide protection against diversion and improve patient compliance However, extended-release buprenorphine was not approved in Europe until 2019, and such a comparison have not yet been systematically evaluated. Further research should conduct a comparative effectiveness study of XR-NTX versus extended-release buprenorphine.[17]

Limitations

The lack of blinding in our study represents a limitation; however, the effect sizes are beyond what usually could be expected from placebo effects. Another limitation is that the reported opioid use was not confirmed by UDT in the follow-up part of the study. However, in the 12-week period, reported use of opioids corresponded well with the UDTs results.[7] Another consideration is the possible reduced generalizability to opioid-dependent patients at large since XR-NTX was available only through participation in the study, and BP-NLX was accessible in OMT programs. The patients in this study were probably more motivated toward opioid abstinence than the average population of opioid-dependent individuals, and this may have influenced the outcome. However, in the randomized part of the study, such a motivation not to use illicit opioids should also be relevant for those randomized to 12 weeks of BP-NLX.

CONCLUSIONS

In line with our descriptive data, relapse analyses showed that XR-NTX was clearly more efficacious in preventing relapse to heroin and other illicit opioid use compared to BP-NLX, in contrast to the US X:BOT study showing an equal rate of relapse between treatments. The low relapse rate for XR-NTX patients continued throughout the follow-up period. Our data indicate that XR-NTX should be proposed as a first-line treatment option for abstinence-motivated patients with opioid addiction. Further, the level of motivation for XR-NTX should be taken into consideration when deciding on treatment modality in clinical practice.

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Clinical Trial Registration

clinicaltrials.gov Identifier: NCT01717963.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.