Risk of relapse to non-opioid addictive substances among opioid dependent patients treated with an opioid receptor antagonist or a partial agonist: A randomized clinical trial

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ABSTRACT

Background and objective: First study to assess any compensatory increase in use of non-opioid illicit substances and alcohol in opioid dependent patients randomized to treatment with extended-release naltrexone (XR-NTX) or buprenorphine-naloxone (BP-NLX) and in longer term treatment with extended-release naltrexone.
Method: A multicenter, outpatient, open-label randomized clinical trial where patients received intramuscular extended-release naltrexone hydrochloride, 380 mg/month, or daily sublingual buprenorphine-naloxone 8–24/2–6 mg for 12 weeks, and an option to continue with extended-release naltrexone for an additional 36 week follow-up. The study was conducted at five urban addiction clinics and detoxification units in Norway between November 2012, and July 2016.
Results: Among the 143 patients, 106 men and 37 women, there were no significant differences between those randomized to XR-NTX or BP-NLX in the risk of first relapse to alcohol (HR 1.31; 0.68–2.53), amphetamines (HR 0.88; 0.43–1.80), benzodiazepines (HR 1.24; 0.74–2.09) or cannabis (HR 1.55; 0.83–2.89). Also in the 36-week (12–48 weeks) follow-up period we found no significant differences between patients continuing with XR-NTX compared to those switching to XR-NTX after the randomized period in risk of first relapse to any non-opioid substance. In both study periods, the mean time in the study were longer among those relapsing to non-opioid addictive substances than those who did not. There was no significant association between first relapse to illicit opioids and first relapse to non-opioid addictive substances.
Conclusion: There was no increase in the risk of relapse to non-opioid addictive substances neither in short term nor longer-term treatment with extended-release naltrexone.
Trial registration clinicaltrials.gov Identifier: NCT01717963

1. Introduction

In the last decade, opioid use has developed into a public health concern, with an estimated 32.4 million people worldwide using opioids, including heroin, opioid agonist treatment and opioids prescribed for pain conditions [24]. In the US, there has been a substantial increase in opioid use and opioid-related overdose deaths from 2000 to 2014 [17,25]. We have, in part, observed the same development in Norway, with an increase in the number of opioid-dependent individuals over the last 20 years, amounting to a high-risk population of opioid users of

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close to 10.000 [14]. In line with the WHO guidelines, OMT is the current recommended treatment to opioid users in Norway.

An alternative therapeutic approach to maintain opioid abstinence is complete detoxification and induction to antagonist medication ([4,5,15]; Kristin Klemmetsby [19,22]). Extended- release Naltrexone (XR-NTX) is an opioid antagonist that blocks the euphoric and sedative effects of opioids and offers pharmacological protection against relapse, re-dependence and overdose [1,2,6]. Several studies have confirmed the clinical efficacy of XR-NTX in reducing the use of illicit opioids and with a non-significant increase in the use of addictive non-opioid substances [8,12,16,20,23]. Others have reported, however, that patients treated with naltrexone extended release implants were more likely to use non-opioid substances like benzodiazepines, amphetamines, cocaine, and cannabis [9].

Availability of opioid agonist treatment in Norway is very high and free of charge, but it has until recently been primarily buprenorphine-based or methadone-based alternatives. The only way opioid dependent patients could get access to extended-release naltrexone was by participating in this study.

Relapse is influenced by several factors that were not considered in our study. In short, early, and late relapses seem related to different life domains and are hence different phenomena. Early relapse, 2–6 months, is more associated with depressive emotions, mental illness, unemployment, and lack of social support. Later relapses, >12 months, are more associated with the use of avoidant coping style, low self-efficacy and not considering problematic substance use as a problem [13]; motivation to quit is critical to maintaining both early and sustained remission.

Overall, the results in the literature are discrepant in terms of predictors of relapse. This discrepancy may arise from several factors, including differences in follow-up periods, definition of relapse, measurement tools and patient characteristics across studies [7].

This is the first study comparing the risk of relapse to non-opioid addictive substances among opioid-dependent patients randomized to short treatment with XR-NTX or buprenorphine-naloxone followed by longer term treatment with XR-NTX. Further, we aimed to investigate any associations between treatment retention and the type of addictive non-opioid substances used.

2. Methods

This was a 12-week multicenter, open-label, randomized treatment study with a subsequent 36-week (12–48 weeks) open-label follow-up study. All patients included in the study had received at least one dose of study medication and had at least one valid assessment after randomization (modified intention-to-treat population). Randomization was performed as a 1:1 ratio in balanced blocks receiving 380 mg extended-release naltrexone intramuscularly every fourth week or daily sublingual buprenorphine-naloxone, 8–24/2–6 mg. Allocation to treatment group was computerized using a permuted block algorithm provided by the Regional Monitoring Authority and not stratified for site or sex. Patients underwent detoxification and were in a controlled environment for a minimum of 72 h before the first XR-NTX injection. Just prior to the first injection, a dose (0.4 mg) of the short-acting opioid antagonist naloxone was administered to test if naltrexone could induce possible unacceptable withdrawal symptoms. If so happened, the XR-NTX injection would be postponed for 24 h. The patients were randomized after the end-stage of detoxification.

The initial research goal was to compare patients on BP-NLX with patients receiving XR-NTX, also in the follow-up. When only 5 patients opted to continue with BP-NLX, this group was too small for quantitative assessments, and we opted for a comparison between "continuers" (who received XR-NTX during the trial and follow-up study) and "switchers" (who received BP-NLX during the trial and XR-NTX in the follow-up study).

The primary outcomes were the risk of first relapse to and use of non-

opioid substances in the randomized 12-week period and in the 36-week follow-up study. Relapse was defined as four consecutive weeks of use of non-opioid addictive substances or seven consecutive days of non-opioid addictive substance use. Relapse was censored at the end of every 4 weeks. In order to maximize the accuracy of such retrospective data, we used the Time-Line Follow-Back data collecting method [18]. After the 12-week trial period, all patients entering the 36-week (12–48 weeks) prospective follow-up period chose XR-NTX, except 5 patients who chose to continue with BP-NLX. No patient switched from XR-NTX to BP-NLX. Due to this unexpected distribution of patients in the follow-up period, we left the original trial design and used a cohort design instead, separating the patients into one group that continued XR-NTX from the randomized phase and another group that switched to XR-NTX on entering the follow-up part. Patients randomized to BP-NLX underwent detoxification and were in a controlled environment for a minimum of 72 h before induction of XR-NTX in the follow-up study. Dropouts were defined as not attending the assessment examination within 3 days of the scheduled date, terminating the study medication, or refusing to receive an injection [11].

2.1. Inclusion and exclusion criteria

Eligible patients were opioid-dependent (per DSM-IV criteria) men and women age18–60 years. 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, while a physician examined patients for severe somatic disease. If necessary, eligible patients were referred to the detoxification unit following screening. The design of the study is described in detail elsewhere [10].

Extended-release naltrexone has not been a first-line treatment yet and more research is needed to determine naltrexone safety and benefits in pregnant women. Extended-release naltrexone could potentially be an important medication during pregnancy and lactation and is an area that warrants future studies.

2.2. Assessments

At inclusion and every four weeks, patients underwent a structured interview using the European version of the Addiction Severity Index assessing demographics, substance use and treatment, physical and mental health, work, education, criminal activity, and social functioning [10].

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 [23], we showed that the UDTs corresponded well with the patients' reports of addictive substance use, and UDTs were therefore not included in this paper.

2.3. Patients and ethics

Patients were recruited between November 1, 2012 and July 6, 2016, from outpatient clinics and detoxification units at five urban addiction clinics in Norway. Participating patients were capable of understanding and complying with the protocol and signed the informed consent before entering the study. Patients dropping out of the 12-week trial could be re-included in the follow-up study after completing another detoxification program. The procedure is described elsewhere [10,23]. All the patients were invited to enter the subsequent follow-up study where they could opt for either medication for an additional period of 36 weeks. 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.

2.4. Statistical analysis

Baseline characteristics were described as frequencies and means with standard deviations (SDs). The number and percentage of relapses as well as mean (SD) time to relapse to non-opioid substances was presented. All numbers were presented by treatment group in the trial period, and by those continuing or switching to extended-release naltrexone in the follow-up period. Risk of first relapse between the groups was compared using Cox proportional hazards model. The results were presented as hazard ratios (HR) with 95% confidence intervals (CI) and *p*-values. The difference in trend in the use of non-opioid substances in the two treatment groups was assessed by linear mixed model with fixed effects for non-linear time (in weeks), group, and the interaction between time and group. A significant interaction would imply differences in trend between the groups. Random effects for participants were included. The results were tabulated as regression coefficients and standard errors (SEs) and illustrated graphically for easier interpretation of interactions. Also, we presented the differences in mean number of weeks in the study stratified by those who relapsed to non-opioid addictive substances and those who did not with confidence intervals 95% CI and p-values. We adjusted the analyses for the use of illicit opioids last 30 days.

We used Cohen's Kappa and correlation coefficients to assess the agreement between the first relapse to heroin and other illicit opioids and the first relapse to other addictive substances like alcohol, amphetamine, benzodiazepine and cannabis.

The results with *p*-values below 0.05 were considered statistically significant in all analyses. The analyses were performed in SPSS version 25 and SAS version 9.4.

3. Results

Among the 143 patients who received at least one dose of study medication (Fig.1), and had at least one valid assessment after randomization, 106 were men (74%) and 37 women (26%). The mean age was 36 years (SD 8.3) both in the XR-NTX group and in the BP-NLX group (SD 8.9) (Table 1A). Demographic and baseline clinical characteristics of patients in Table 1A have earlier been published [16].

There were no significant differences in the risk of first relapse to the use of non-opioid addictive substances between those randomized to XR-NTX and to BP-NLX in the 12-week randomized trial. For alcohol, the number of relapses was similar between the groups, HR 1.3 (0.7–2.5), with 20 and 16 relapses in the XR-NTX and BP-NLX arm, respectively (Tables 1C and 2). The biggest difference in substance use between the XR-NTX and the BP-NLX groups were relapses to cannabis, 24 and 17, respectively.

Due to low frequencies, the use of cocaine and hallucinogens could not be further analyzed.

In the 12-week RCT, adherence to treatment in terms of time in the study was significantly longer among participants relapsing to alcohol compared to those who did not, 11.7 (CI: 11.1–12.2) and 10.1 (CI 9.5–10.7) weeks, respectively (*p* = 0.013). The same pattern was seen for those relapsing to cannabis, 11.6 (CI 11.1–12.1) weeks versus 10.0 (CI 9.4–10.6) weeks (*p* = 0.027). In contrast there was no significant difference in time in the study between those relapsing or not to amphetamines or benzodiazepines (Table 1B, Fig. 2).

In the follow-up study, there were no significant differences between the XR-NTX arms in risk of first relapse to alcohol (HR 1.0 (95% CI 0.5–1.8) (*p* = 0.920), benzodiazepines (HR 1.3 (95% CI 0.7–2.3) (*p* = 0.410), amphetamine (HR 1.0 (95% CI 0.4–1.6) (*p* = 0.579) or cannabis (HR 1.4 (95% CI 0.7–2.5) (*p* = 0.349) (Table 2, Fig. 2).

In contrast to the randomized study, we did not find any significant differences in time in the study between those relapsing or not to alcohol, amphetamines, benzodiazepines or cannabis (Table 1B, Fig. 2).

According to a linear mixed model (Table 3, supplementary), there were no overall differences between the trial groups, neither in the RCT nor in the 36-week follow-up period, in the use of alcohol, amphetamines, or cannabis, as seen from non-significant week by group interactions. The use of benzodiazepines differed between the groups in both periods (*p* = 0.046 and *p* = 0.009 for RCT and *p* = 0.049 and *p* = 0.033 for 36-week (12–48 weeks) follow up period) with the BP-NLX group, who switched to XR-NTX in the follow-up, using more (Fig. 3). In the RCT period a non-linear trend in time showed a slightly increased use of alcohol and cannabis, and a decreased use of benzodiazepines among participants in XR-NTX group. In the BP-NLX group the use of both alcohol, benzodiazepines, and cannabis initially decreased and then increased to about baseline level towards the end of RCT period. No significant time trend was identified for alcohol, amphetamines or cannabis in the follow-up period. The use of benzodiazepines was stable in the beginning and decreased slightly after week 32 in XR-NTX continued group, while in the XR-NTX switched group, the use decreased towards week 28 and then increased again towards the end of the follow-up period (Table 3, supplementary, Fig. 3).

In the RCT and in the subsequent 36-week follow-up study, we found no significant relationship between the first relapse on heroin and other illicit opioids and the first relapse on alcohol, amphetamine, benzodiazepines, or cannabis, (Fig. 2).

4. Discussion

To our knowledge, this is the first study comparing relapse to non-opioid addictive substances in opioid-dependent patients treated with either XR-NTX or BP-NLX. In this 12-week multicenter, open-label, randomized treatment study with a subsequent 36-week open-label follow-up study, we found no differences between the treatment groups in risk of relapse to alcohol, amphetamines, benzodiazepines, or cannabis, neither in the 12-week RCT period nor in the 36-week subsequent follow-up period. Further, there were no overall differences in trends in the patterns of substance use of alcohol, amphetamines, and cannabis in either of the study periods. However, there was more use of benzodiazepines in the BP-NLX group compared to the XR-NTX group. We also found an overall trend that patients relapsing to non-opioid addictive substances stayed longer in this treatment study compared to those who did not relapse to these substances, both in the 12-week trial and the subsequent 36-week follow-up.

Opioid-dependent patients who participated in this study wanted access to the novel XR-NTX treatment. They were generally motivated for opioid abstinence due to the need for breaking out from a destructive or uncontrolled opioid use, or due to a wish to stop using opioids. This motivation did not necessarily include an abstinence also from other addictive substances. In a number of clinical treatment programs, relapse to addictive illicit substances and alcohol have frequently been reasons for termination of further treatment [3]. It is important not to assume that patients who relapse on non-opioid substances were less motivated for opioid antagonist treatment than those who did not (Kristin Klemmetsby [21]). The tendency that patients who relapsed stayed longer in treatment than the abstainers, might indicate that those relapsing to other substances still preferred to stay in a treatment that prevented them from relapse to opioids. From our clinical experience with the study patients, we may propose that a number of those who relapsed may even find it more imperative to continue opioid antagonist treatment to avoid relapse also to illicit opioids and alcohol.

The increased use of benzodiazepines may reveal an unmet need for prescribed benzodiazepines in a period following induction on XR-NTX. This was most pronounced among the XR-NTX switchers, who experienced a slight increase in relapse towards the end of the follow-up period. The switchers group had a three-month shorter treatment
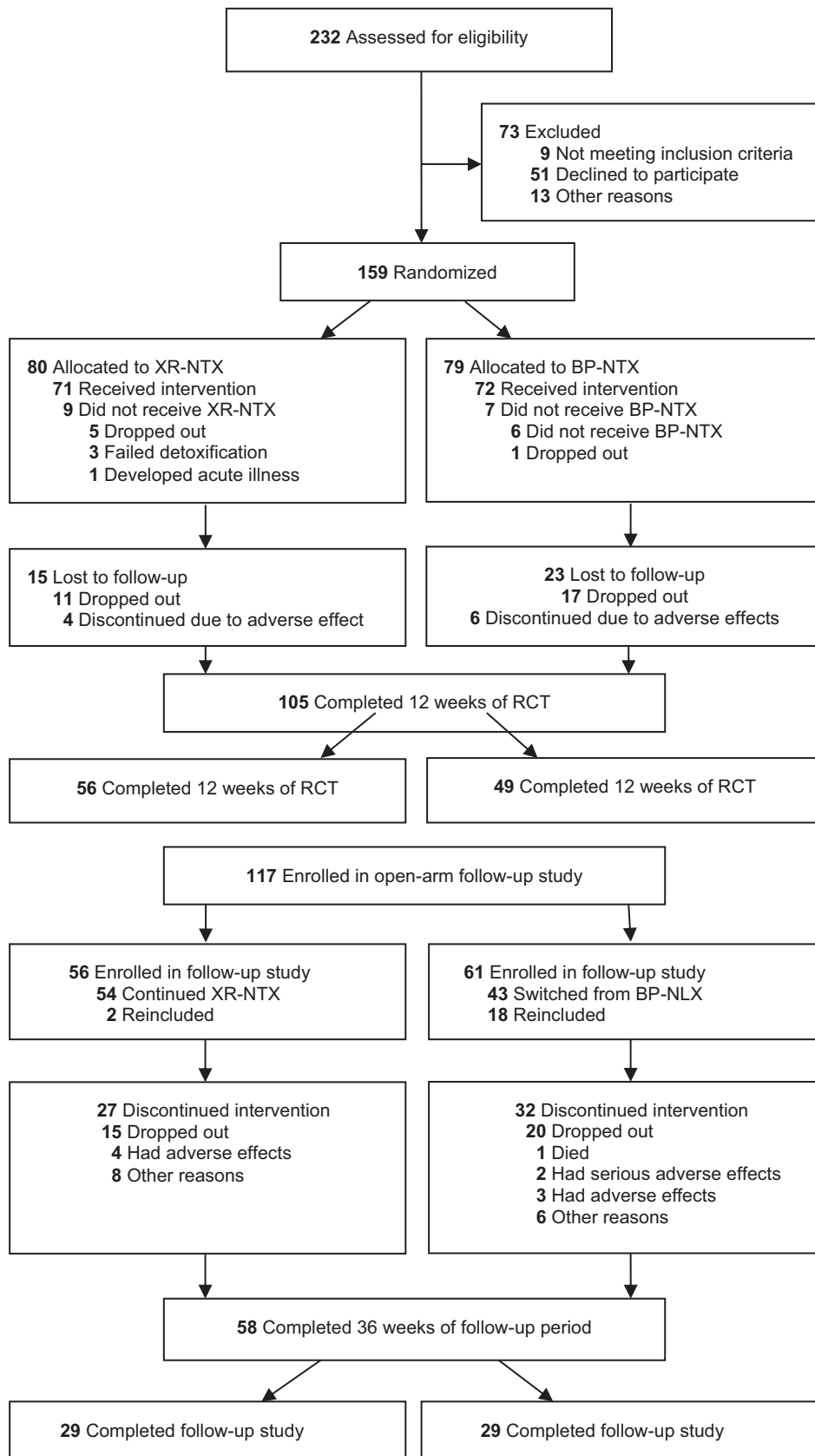
232 Assessed for eligibility

73 Excluded
   9 Not meeting inclusion criteria
  51 Declined to participate
  13 Other reasons

159 Randomized

80 Allocated to XR-NTX
  71 Received intervention
    9 Did not receive XR-NTX
      5 Dropped out
      3 Failed detoxification
      1 Developed acute illness

79 Allocated to BP-NTX
  72 Received intervention
    7 Did not receive BP-NTX
      6 Did not receive BP-NTX
      1 Dropped out

15 Lost to follow-up
  11 Dropped out
   4 Discontinued due to adverse effect

23 Lost to follow-up
  17 Dropped out
   6 Discontinued due to adverse effects

105 Completed 12 weeks of RCT

56 Completed 12 weeks of RCT

49 Completed 12 weeks of RCT

117 Enrolled in open-arm follow-up study

56 Enrolled in follow-up study
  54 Continued XR-NTX
   2 Reincluded

61 Enrolled in follow-up study
  43 Switched from BP-NLX
  18 Reincluded

27 Discontinued intervention
  15 Dropped out
   4 Had adverse effects
   8 Other reasons

32 Discontinued intervention
  20 Dropped out
   1 Died
   2 Had serious adverse effects
   3 Had adverse effects
   6 Other reasons

58 Completed 36 weeks of follow-up period

29 Completed follow-up study

29 Completed follow-up study

Fig. 1. CONSORT flowchart.

Table 1

Demographic and Baseline Clinical Characteristics of Patients Randomized to Treatment with Extended-Release Naltrexone or Buprenorphine-Naloxone (**1 A**). Mean duration of follow-up in weeks stratified by those who relapsed or not (**1B**).

1 A

Characteristics	Extended-Release Naltrexone	Buprenorphine-Naloxone
	(*n* = 71)	(*n* = 72)
Male, n (%)	55 (78)	51 (71)
Injecting substances, raw numbers	66	66
Years with injections, mean (SD)	9.9 (7.0)	9.9 (7.5)
Mean years of heroin use (SD)	6.2 (5.5)	7.0 (5.0)
Years (SD) of other heavy opioid use	8.4 (7.5)	8.5 (7.0)
Overdose events lifetime, mean (SD)	4.5 (8.2)	4.4 (5.5)
Age at inclusion, mean (SD)	35.7 (8.3)	35.9 (8.9)
Injecting days last 30 days at inclusion, mean (SD)	9.2 (12.2)	11.4 (12.8)
Illicit opioids last 30 days at inclusion, mean (SD)	8.2 (11.1)	14.2 (13.1)

1B

Substances	12-week trial period		36-week prospective follow-up	
	Mean (95% CI)	p-value	Mean (95% CI)	p-value
Alcohol				
No relapse	10.1 (9.5; 10.7)	**0.013**	37.2 (34.6; 39.7)	0.645
Relapse	11.7 (11.1; 12.2)		38.0 (33.7; 42.2)	
Amphetamines				
No relapse	10.2 (9.6; 10.8)	0.262	36.9 (34.3; 39.4)	0.626
Relapse	11.5 (10.8; 12.1)		39.0 (34.9; 43.1)	
Benzodiazepines				
No relapse	10.1 (9.4; 10.8)	0.455	38.8 (36.1; 41.5)	0.199
Relapse	11.0 (10.4; 11.6)		35.4 (31.8; 38.9)	
Cannabis				
No relapse	10.0 (9.4; 10.6)	**0.027**	36.7 (34.0; 39.3)	0.253
Relapse	11.6 (11.1; 12.1)		38.9 (35.1; 42.8)	

1C

Substances	12-week trial period			36-week subsequent follow-up		
	Total	BP-NLX	XR-NTX	Total	XR-NTX-s	XR-NTX-c
	(N = 143)	(N = 72)	(N = 71)	(N = 117)	(N = 61)	(N = 56)
Alcohol	36 (25.2)	16 (22.2)	20 (28.2)	41 (35.0)	22 (36.1)	19 (33.9)
Amphetamines	30 (21.0)	16 (22.2)	14 (19.7)	33 (28.2)	19 (31.1)	14 (25.0)
Benzodiazepines	57 (39.9)	27 (37.5)	30 (42.3)	46 (39.3)	22 (36.1)	24 (42.9)
Cannabis	41 (28.7)	17 (23.6)	24 (33.8)	40 (34.2)	19 (31.1)	21 (37.5)
Cocaine	5 (3.5)	3 (4.2)	2 (2.8)	5 (4.3)	4 (6.6)	1 (1.8)
Hallucinogens	0	0	0	2 (1.7)	2 (3.3)	0

Table 1 (*continued*)

1C						
Substances	12-week trial period			36-week subsequent follow-up		
	Total	BP-NLX	XR-NTX	Total	XR-NTX-s	XR-NTX-c
	(N = 143)	(N = 72)	(N = 71)	(N = 117)	(N = 61)	(N = 56)
	Mean survival time (SE)					
Alcohol	10.2 (0.3)	10.4 (0.4)	10.0 (0.4)	24.6 (1.3)	24.9 (1.8)	24.4 (2.0)
Amphetamines	10.5 (0.3)	10.4 (0.4)	10.6 (0.4)	26.8 (1.2)	26.5 (1.7)	27.2 (1.8)
Benzodiazepines	8.5 (7.7)	9.2 (0.6)	7.9 (0.6)	22.6 (1.4)	23.9 (1.9)	21.0 (2.1)
Cannabis	9.5 (0.4)	10.0 (0.5)	8.9 (0.6)	23.9 (1.4)	25.2 (1.8)	22.5 (2.1)

Descriptive statistics for relapse and mean time to first relapse. In the 12-week trial period, participants were randomized to allocated treatment with either medications BP-NLX or XR-NTX. In the follow-up period, two groups using XR-NTX were compared, either switching from BP-NLX to XR-NTX (XR-NTX-s) or those continuing on XR-NTX (XR-NTX-c) (1C).

Table 2

Cox regression model to quantify differences in risk of first relapse between XR-NTX compared to BP-NLX in the 12-week trial period, and similarly in the follow-up period between those who switched to XR-NTX from BP-NLX compared to those continuing XR-NTX from start of treatment.

Substances	12-week trial period		36-week prospective follow-up	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Alcohol	1.3 (0.7; 2.5)	0.419	1.0 (0.5; 1.8)	0.92
Amphetamines	0.9 (0.4; 1.8)	0.719	1.0 (0.4; 1.6)	0.579
Benzodiazepines	1.2 (0.7; 2.1)	0.411	1.3 (0.7; 2.3)	0.41
Cannabis	1.6 (0.8; 2.9)	0.167	1.4 (0.7; 2.5)	0.349

Kaplan-Meier curves are presented in the following Fig. 1.

period on XR-NTX than those randomized to XR-NTX, which might have influenced their need of benzodiazepines. In the switch group, most patients were disappointed with being initially randomized to BP-NLX for three months, since they joined the study to get access to treatment with XR-NTX.

The heterogenous group of patients in our study did not differ much from the general population of opioid-dependent patients in Norway and we consider the naturalistic clinical setting, and the heterogeneity of the patients make it easier to generalize the study findings.

A limitation in this study is the lack of blinding, but a placebo design with this population risks "self-unmasking" by use of illicit opioids and in so doing reduce the potential benefit of masking and risk re-occurring illicit opioid use by the patients.

Opioid dependence is a chronic illness, requiring longitudinal comprehensive care. Future research directions should explore how to optimally initiate extended-release naltrexone and reduce drop-out rates and patients′ willingness to re-start extended-release naltrexone treatment. Also, further research should try to establish appropriate duration of treatment with extended-release naltrexone and find the best combination of medication and psychosocial interventions.

5. Limitations and strengths

The sample size (statistical power) was considered to have sufficient power to answer the primary objectives. However, the sample size is not calculated for other substances and could be slightly lower for those with slightly lower precision in the estimates.

The lack of urine drug tests in the follow-up is a weakness. Though, analyses performed in the randomized clinical trial during the first 12 weeks showed a high correlation between the reported use of illicit substances and urine analysis results.

The high availability of opioid agonist treatment in Norway makes it likely that most participants in this study were mainly motivated to receive the novel medication extended-release naltrexone and not buprenorphine-naloxone. This makes it difficult to know whether extended-release naltrexone would be equally effective in individuals with lower motivation for opioid abstinence. It is likely, however, that our study results can be generalized to other high-income countries with equivalent health care systems and regulatory frameworks regarding opioid agonist treatment, as in Norway. We managed to recruit patients both enrolled in opioid agonist treatment preceding study inclusion, and those who were not. This, we think, may infer a certain degree of representativeness within the study concerning opioid agonist treatment affiliation.

The trial is conducted in a relatively naturalistic, clinical setting which improves the external validity, but it might not be generalizable to all settings with people with opioid dependence.

6. Conclusions

Our findings showed that XR-NTX treatment did not significantly increase non-opioid substance use or interfere with adherence to treatment or early discontinuation. These findings may be related to the patients′ treatment goal or desire to stay in a treatment that protects them from relapse to opioids.

The study shows that many had at least one episode trying heroin, but that for those receiving extended-release naltrexone the risk of continued use was significantly less compared to those using buprenorphine-based opioid agonist therapy without increasing the use of non-opioid drugs. Changes in addictive behaviors in general are complex phenomena not readily captured by dichotomous classification. This suggests that it might not be useful to think binary of relapse versus non-relapse, but rather that people make steps in a wanted direction and sometimes take a misstep before continuing in the direction of preference. Extended-release naltrexone could thus be a safety net in such situations.
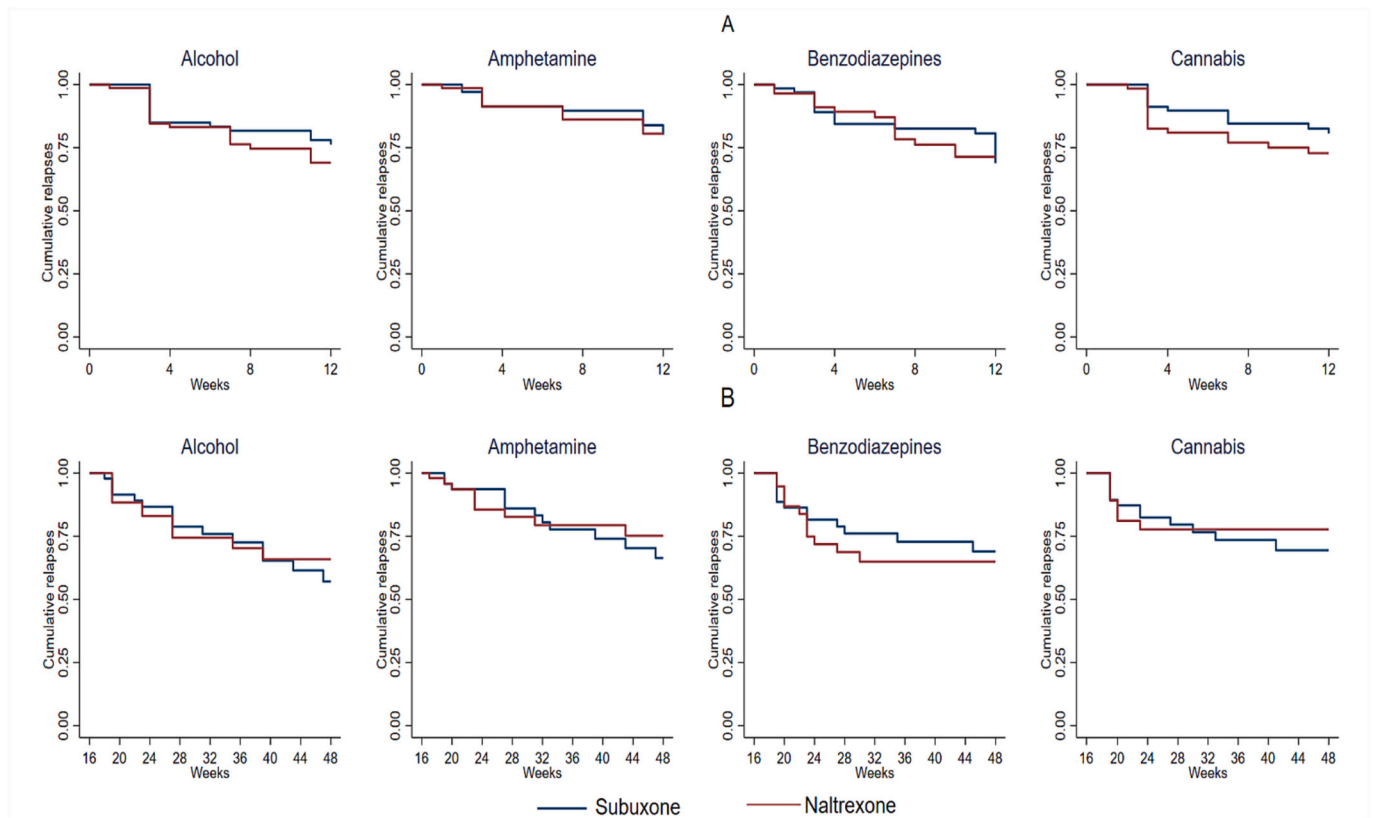
Fig. 2. Differences in risk of first relapse to non-opioid addictive substances between XR-NTX (red lines) and BP-NLX (blue lines) in the 12-week trial period (0–12 weeks) and in the follow-up period (16–48 weeks) between those who switched to XR-NTX (blue lines) compared to those continuing on XR-NTX (red lines) from start of treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Results of linear mixed model for use of addictive substances adjusted for use of illicit opioids last 30 days at inclusion. The results are illustrated in Fig. 2.

Substances	RCT		Follow-Up	
	Regr.coeff. (SE)	p-value	Regr.coeff. (SE)	p-value
Alcohol				
Week	−0.49 (0.22)	**0.028**	0.04 (0.13)	0.758
Week x Week	0.04 (0.02)	**0.025**	−0.001 (0.002)	0.608
Group	−0.18 (0.86)	0.836	−1.00 (2.55)	0.694
Week x Group	0.38 (0.33)	0.245	0.01 (0.19)	0.955
Week x Week x Group	−0.02 (0.03)	0.4	0.0002 (0.003)	0.953
Amphetamines				
Week	−0.59 (0.28)	**0.036**	−0.05 (0.21)	0.8
Week x Week	0.05 (0.02)	**0.013**	0.001 (0.003)	0.688
Group	−1.20 (1.08)	0.265	−4.49 (4.29)	0.296
Week x Group	0.79 (0.37)	**0.033**	0.40 (0.30)	0.186
Week x Week x Group	−0.06 (0.03)	**0.035**	−0.007 (0.005)	0.112
Benzodiazepines				
Week	−1.02 (0.34)	**0.003**	−0.56 (0.31)	0.068
Week x Week	0.08 (0.03)	**0.001**	0.01 (0.005)	0.062
Group	−0.33 (1.55)	0.829	−11.41 (5.51)	**0.038**
Week x Group	1.00 (0.50)	**0.046**	0.76 (0.39)	**0.049**
Week x Week x Group	−0.10 (0.04)	**0.009**	−0.01 (0.006)	**0.033**
Cannabis				
Week	−1.01 (0.37)	**0.004**	0.26 (0.29)	0.378
Week x Week	0.08 (0.03)	**0.005**	−0.002 (0.004)	0.641
Group	−1.60 (1.54)	0.299	1.79 (5.92)	0.763
Week x Group	0.87 (0.45)	0.052	0.02 (0.42)	0.965
Week x Week x Group	−0.06 (0.04)	0.078	−0.003 (0.007)	0.692

Ethics approval

Role of funding source
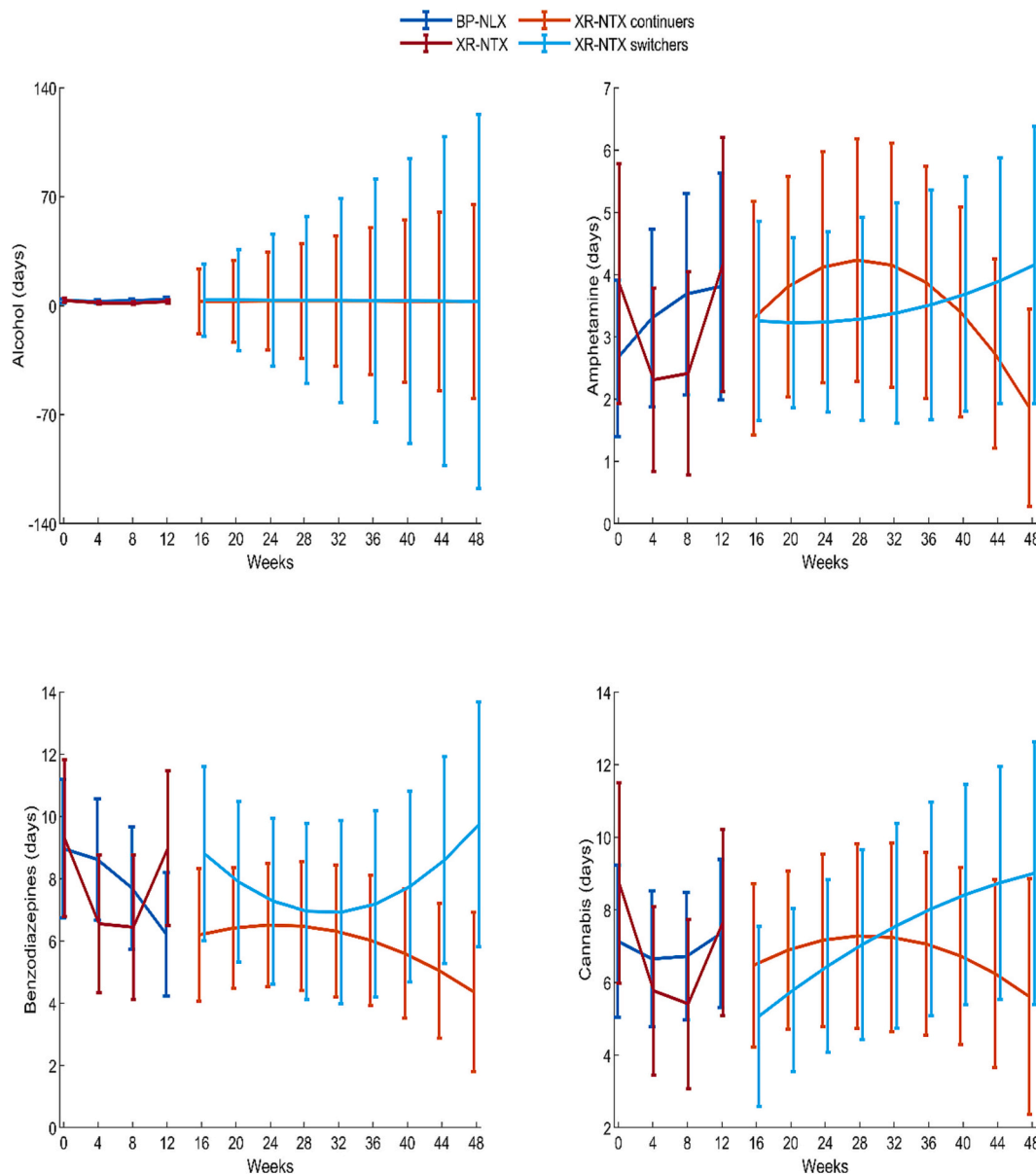
CRediT authorship contribution statement

Fig. 3. Estimated mean days of use of non-opioid addictive substances, alcohol, amphetamines, benzodiazepines and cannabis, last 4 weeks in the 2 treatment groups with 95% CI, 12-week clinical trial and 36-week follow-up. Results of linear mixed model.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2023.107360.

References

[1] G.E. Bigelow, K.L. Preston, J. Schmittner, Q. Dong, D.R. Gastfriend, Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: dose–effects and time-course, Drug Alcohol Depend. 123 (1–3) (2012) 57–65, https://doi.org/10.1016/j.drugalcdep.2011.10.018.

[2] I.H. Brenna, A. Marciuch, B. Birkeland, M. Veseth, B. Røstad, E.-M. Løberg, Weimand, B. J. J. o. S. A. T, 'Not at all what I had expected': Discontinuing treatment with extended-release naltrexone (XR-NTX): A qualitative study, 2021, p. 108667.

[3] H.H. Brorson, E. Ajo Arnevik, K. Rand-Hendriksen, F. Duckert, Drop-out from addiction treatment: A systematic review of risk factors, Clin. Psychol. Rev. 33 (8) (2013) 1010–1024, https://doi.org/10.1016/j.cpr.2013.07.007.

[4] S.D. Comer, P. Mannelli, D. Alam, A. Douaihy, N. Nangia, S.C. Akerman, M.A.J.T.A. J.O.A. Sullivan, Transition of patients with opioid use disorder from Buprenorphine to extended-release naltrexone: a randomized clinical trial assessing two transition regimens 29 (4) (2020) 313–322.

[5] S.D. Comer, M.A. Sullivan, E. Yu, J.L. Rothenberg, H.D. Kleber, K. Kampman, C. P. O'Brien, Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial, Arch. Gen. Psychiatry 63 (2) (2006) 210–218, https://doi.org/10.1001/archpsyc.63.2.210.

[6] Z. Gaulen, I.H. Brenna, L.T. Fadnes, J.Ś. Benth, K.K. Solli, N. Kunoe, L.J.E.A. R. Tanum, The predictive value of degree of preference for extended-release naltrexone for treatment adherence, Opioid Use, Relapse. 28 (1) (2022) 56–67.

[7] C. Guliyev, E. Ince-Guliyev, K. Ögel, Predictors of relapse to alcohol and substance use: are there any differences between 3 and 12 months after inpatient treatment? J. Psychoactive Drugs 54 (4) (2022) 358–367.

[8] E. Krupitsky, E.V. Nunes, W. Ling, D.R. Gastfriend, A. Memisoglu, B.L. Silverman, Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness, Addiction 108 (9) (2013) 1628–1637, https://doi.org/10.1111/add.12208.

[9] N. Kunøe, P. Lobmaier, J.K. Vederhus, B. Hjerkinn, M. Gossop, S. Hegstad, H. Waal, Challenges to antagonist blockade during sustained-release naltrexone treatment, Addiction 105 (9) (2010) 1633–1639, https://doi.org/10.1111/j.1360-0443.2010.03031.x.

[10] N. Kunøe, A. Opheim, K.K. Solli, Z. Gaulen, K. Sharma-Haase, Z.E. Latif, L. Tanum, Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX), BMC Pharmacol. Toxicol. 17 (1) (2016) 1–10, https://doi.org/10.1186/s40360-016-0061-1.

[11] Z.E. Latif, J. Saltyte Benth, K.K. Solli, A. Opheim, N. Kunoe, P. Krajci, L. Tanum, Anxiety, depression, and insomnia among adults with opioid dependence treated with extended-release naltrexone vs buprenorphine-naloxone: A randomized clinical trial and follow-up study, JAMA Psychiatry (2018), https://doi.org/10.1001/jamapsychiatry.2018.3537.

[12] J.D. Lee, E.V. Nunes Jr., P. Novo, K. Bachrach, G.L. Bailey, S. Bhatt, J. Rotrosen, Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial, Lancet 391 (10118) (2017) 309–318, https://doi.org/10.1016/S0140-6736(17)32812-X.

[13] F.D. Moe, C. Moltu, J.R. McKay, S. Nesvåg, J. Bjornestad, Is the relapse concept in studies of substance use disorders a 'one size fits all'concept? A systematic review of relapse operationalisations, Drug. Alcohol. Rev. 41 (4) (2022) 743–758.

[14] Norwegian Institute for Alcohol and Drug Research, The Drug Situation in Norway 2014 (Annual Report to the EMCDDA), 2015. Retrieved from Oslo:.

[15] E.V. Nunes, A. Bisaga, E. Krupitsky, N. Nangia, B.L. Silverman, S.C. Akerman, M.A. J.A. Sullivan, Opioid Use and Dropout from Extended-Release Naltrexone in a Controlled Trial: Implications for Mechanism, 2019.

[16] A. Opheim, Z. Gaulen, K.K. Solli, Z.E.H. Latif, L.T. Fadnes, J.Š. Benth, L. Tanum, Risk of relapse among opioid-dependent patients treated with extended-release naltrexone or buprenorphine-naloxone: A randomized clinical trial, Am. J. Addict. 30 (5) (2021) 453–460.

[17] R.A. Rudd, N. Aleshire, J.E. Zibebell, M. Gladden, Increases in Drug and opioid Overdose Deaths - United States, 2000–2014, 2016. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm?s_cid=mm6450a3_w.

[18] L.C. Sobell, M.B. Sobell, R.Z. Litten, J.P. Allen, Timeline Follow-Back: a Technique for Assessing Self-Reported Alcohol Consumption, Humana Press, Totowa, NJ, 1992.

[19] K.K. Solli, N. Kunoe, K. Sharma-Haase, A. Opheim, P. Krajci, Z. Gaulen, L.J.E.A. R. Tanum, Availability of extended-release naltrexone may increase the number of opioid-dependent individuals in treatment: extension of a randomized clinical, Trial. 25 (6) (2019) 303–309.

[20] K.K. Solli, Z.E. Latif, A. Opheim, P. Krajci, K. Sharma Haase, L. Tanum, N. Kunoe, Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a nine-month follow-up to a three-month randomized trial, Addiction 113 (10) (2018) 1840–1849, https://doi.org/10.1111/add.14278.

[21] K.K. Solli, A. Opheim, Z.E.H. Latif, P. Krajci, J.Š. Benth, N. Kunoe, L. Tanum, Adapting treatment length to opioid-dependent individuals' needs and preferences: A 2-year follow-up to a 1-year study of extended-release naltrexone, Addiction 116 (8) (2020) 2084–2093.

[22] J.V. Strang, N. Degenhardt, L. Hickman, M., et al., Opioid use disorder, Nature 6, Article number: 3 (2020).

[23] L. Tanum, K.K. Solli, Z.E. Latif, J.S. Benth, A. Opheim, K. Sharma-Haase, N. Kunoe, Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: A randomized clinical noninferiority trial, JAMA Psychiatry 74 (12) (2017) 1197–1205, https://doi.org/10.1001/jamapsychiatry.2017.3206.

[24] UNODC, World Drug Report 2015, 2015. Retrieved from Vienna: http://www.unodc.org/wdr2015/.

[25] N.D. Volkow, T.R. Frieden, P.S. Hyde, S.S. Cha, Medication-assisted therapies–tackling the opioid-overdose epidemic, N. Engl. J. Med. 370 (22) (2014) 2063–2066, https://doi.org/10.1056/NEJMp1402780.