ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.15378

Adapting treatment length to opioid-dependent individuals' needs and preferences: a 2-year follow-up to a 1-year study of extended-release naltrexone

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ABSTRACT

Background and aims Extended-release naltrexone (XR-NTX) is an under-used treatment option for opioid dependence, today only available in a few countries in the world. Although effective, safe and feasible in short-term treatment, long-term data are scarce and there is no recommendation for required treatment length. The aims of the study were to determine the perceived need of long-term XR-NTX treatment and to examine long-term treatment outcomes. **Design** In this prospective cohort study, following a parent 1-year study of XR-NTX, participants received treatment with XR-NTX at their own discretion for a maximum of 104 weeks. **Setting and participants** Five urban, outpatient addiction clinics in Norway, comprising opioid-dependent adults aged 18–60 years (n = 50) already participating in the parent study. **Intervention** XR-NTX administered as intramuscular injections (380 mg) every 4 weeks. **Measurements** Time in the study, use of opioids and other illicit substances, opioid craving and treatment satisfaction reported every 4 weeks. **Findings** Among 58 participants who completed the 1-year parent study, 50 chose to continue the treatment with XR-NTX. Median prolonged treatment time was 44.0 weeks [95% confidence interval (CI) = 25.5–62.5], ranging from 8 to 104 weeks. Most participants (35, 70%) reported no relapse to opioid use during treatment while a subgroup (15, 30%) reported relapses to opioids during the study. Scores for mean treatment satisfaction and recommending treatment to others were very high (>9) and mean opioid craving score was very low (<1) on a scale ranging from 0 to 10. **Conclusions** Extended-release naltrexone (XR-NTX) was well tolerated in long-term treatment of opioid-dependent individuals in Norway already in XR-NTX treatment. On average, the participants chose to continue treatment for almost 1 year beyond the initial 9–12 months of treatment. Participants reported high treatment satisfaction and 70% showed no relapse to opioids during the treatment period.

Keywords Antagonist treatment, extended-release naltrexone, long-term treatment, opioid use, recovery, treatment duration, treatment of opioid dependence.

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Submitted 29 May 2020; initial review completed 10 August 2020; final version accepted 9 December 2020
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INTRODUCTION

There are three classes of medication for treatment of opioid dependence (ICD-10); full agonists, partial agonists and antagonists [1]. While agonists have been used world-wide for many years [2–5], long-acting injectable versions of the opioid antagonist naltrexone is so far only approved in the United States, Russia and Ukraine [6–9]. Administered as monthly intramuscular injections, extended-release naltrexone (XR-NTX) blocks the euphoric effects of opioids and offers a medication-assisted abstinence from opioids [10]. Studies have shown that XR-NTX is an effective, safe and feasible treatment option [8,11–17]. However, the majority of studies on XR-NTX treatment have had limited time-frames and only a few studies have reported results from 12 months or longer

[12,18,19]. To our knowledge, there are no recommendations regarding clinical treatment length with XR-NTX based on research or national guidelines [20–22].

Opioid agonist maintenance treatment (OMT), which is the current World Health Organization (WHO)-recommended treatment for opioid dependence, is recommended to be open-ended [23] and, at least in western Europe, OMT has become a long-lasting or even life-long treatment [4,24,25]. Opioid agonist treatment and XR-NTX treatment differ in a number of ways [1]. While opioid agonists maintain the opioid dependence, XR-NTX blocks the effects of opioids and supports abstinence from all opioids. Two randomized controlled trials suggested that XR-NTX is equally as effective as the opioid agonist buprenorphine–naloxone (BP-NLX) in short-term treatment with regard to retention in treatment and reduction in use of illicit opioids [26,27]. While studies of long-term treatment outcomes for opioid dependence in general are scarce, this is particularly applied to treatment with XR-NTX [5,28,29]. The discrepancy between the somewhat limited duration of most clinical XR-NTX trials and the often life-long, chronically relapsing duration of opioid dependencies is striking [29].

Previous studies focusing on the patients' motivation for treatment showed that 50–80% of the participants stated their main treatment goal to be long-term abstinence from all opioids (including prescribed opioid agonists) and other illicit substances [30–32]. XR-NTX could be an adequate alternative for this group of abstinence-motivated patients [5].

It has been postulated that longer duration of treatment, in particular treatment lasting more than 2 years, increases the likelihood of attaining patients' treatment goals [33]. An important key for an intervention to be effective is the users' engagement and that treatment is facilitated according to the patients' preferences, needs and goals [34,35]. However, previous studies of XR-NTX have not taken into account participants' need or preference for treatment duration [36]. According to the chronic nature of opioid dependence, relapses are frequent and a longer-term treatment period or subsequent treatment episodes are often necessary before patients manage to achieve their treatment goals [29]. Another aspect is that abstinence achieved during a relatively short period of treatment with XR-NTX seemed to wane after treatment discontinuation, according to some cohort studies [11,20,37]. Thus, there is a need to explore patients' preferences on XR-NTX treatment duration.

The objectives of this study were to investigate the participants' perceived need and preference to remain in XR-NTX treatment over time and to assess the efficacy of long-term treatment. We aimed to explore (1) for how long the participants chose to receive XR-NTX treatment, (2) the use of opioids, other illicit substances and alcohol, (3) opioid craving, (4) treatment satisfaction and participants' willingness to recommend XR-NTX treatment to others and (5) reported adverse events during the time in treatment.

METHODS

Design

This prospective 2-year cohort study was a prolonged follow-up to a previous 3-month randomized clinical trial comparing XR-NTX with BP-NLX [26] and a subsequent 9-month follow-up study of XR-NTX [12,38–41]. At the conclusion of the 9-month follow-up study, participants were offered continued treatment with XR-NTX up to a period of 104 weeks. The participants were free to discontinue the XR-NTX treatment whenever they wanted within the 2-year period. Participants who chose to discontinue the treatment before maximum treatment time (104 weeks) would not be re-enrolled into the study.

Participants and setting

Among the 58 participants who completed the parent 12-month study, 50 agreed to prolong the treatment period with XR-NTX up to 104 weeks. Recruitment for the parent study took place at outpatient clinics and detoxification units at five urban hospitals in Norway. Eligible patients were opioid-dependent (DSM-IV) adults aged 18–60 years. Exclusion criteria were serious somatic or psychiatric illness regarded as contraindications for study participation, such as acute renal or hepatic failure, severe cancer, psychosis or high risk of suicide. Women could not be pregnant or lactating and agreed to use effective birth control [12,26,39].

The study took place in a naturalistic outpatient setting with clinical visits every fourth week. Participants had to be enrolled into an OMT program prior to study inclusion but did not receive any OMT medications during the study participation. Enrolment in an OMT program ensured the participants' access to agonist treatment should they need to after XR-NTX cessation. The first participant entered the prolonged study in May 2014, and the last participant completed the study in February 2018.

Study interventions

Participants received intramuscular injections with extended-release naltrexone, 380 mg, once every fourth week, in line with the medication regimen in the parent study. Counselling was not mandatory, but participants were offered psychosocial follow-up by clinicians according to their individual needs and preferences.

Measurements and outcomes

Every 4 weeks during their time in treatment, the participants reported substance use, opioid craving, treatment satisfaction and recommendation of XR-NTX treatment to others. We used the same inventories as in the parent study [12,26,39], and only actual assessments were used in the analyses. The primary outcome variable was time in XR-NTX treatment, defined as the number of weeks participants chose to receive XR-NTX injections. If they wanted to end the treatment, they were asked about the reason for this. Participants were not excluded if they relapsed to opioid use or used other illicit substances while in the study.

Secondary outcome variables were use of opioids or other illicit substances such as cannabis, amphetamines, benzodiazepines and alcohol for intoxication within the 4 weeks preceding each interview. The assessment of substances was based on: 0 = no use; 1 = yes, on 1 or 2 days in 4 weeks; 2 = yes, weekly; and 3 = yes, daily or almost daily.

The degrees of opioid craving, satisfaction with treatment and recommendation of treatment to others were assessed using a validated visual analog scale (0–10).

Research ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics Southeast 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, according to Good Clinical Practice standards. Before inclusion in the parent study, participants provided a written informed consent. The treatment carried no cost for the participants. They were not paid or compensated for taking part in the study, with the exception of reimbursement of travel expenses for using public transportation.

Statistical analyses

The analyses performed in this extension study were not pre-registered and should be considered as exploratory. By means of an exploratory approach, a growth mixture model (GMM) was estimated to identify potential homogeneous subgroups of participants following distinct trajectories in opioid use. The number of groups was determined by applying the Bayesian information criterion, where the smaller value means a better model, and requiring reasonable group sizes, non-overlapping 95% confidence intervals (CI) for trajectories and average within-group probabilities of 0.80 or higher. Baseline characteristics of the identified subgroups were compared by independent-samples median test or χ^2 test, as appropriate.

Time in treatment was assessed by a Kaplan–Meier analysis, and subgroups with distinct trajectories identified by GMM were compared by log-rank test. The development in the use of substances (four-category ordinal variables) was assessed by generalized linear mixed models with fixed effects for time, measured in weeks. Linear mixed models with time as a fixed effect were estimated to assess the development in continuous variables, opioid craving, treatment satisfaction and treatment recommendation. The time and time-squared were included into the models where the development exhibited a non-linear pattern (opioids, cannabis, amphetamines, alcohol, opioid craving and treatment satisfaction and recommending XR-NTX). If the non-linear part was negligible, only linear time was entered the model (benzodiazepines). All models included random effects for participants nested within the study center. The regression models were estimated for the total sample first and then stratified by subgroups identified by GMM. For stratified analyses, the additional fixed effects for subgroup as well as interaction between subgroup and time were included. All models were adjusted for age and sex. The results were presented graphically as either odds for more use of certain substance or average value with 95% confidence interval (CI). Results with *P*-values below 0.05 were considered statistically significant. The analyses were performed using SPSS software version 24 (IBM, Armonk, NY, USA), SAS statistical package version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 16 (StataCorp, College Station, TX, USA).

RESULTS

Of the 50 participants who chose to prolong treatment with XR-NTX, 24 had been in XR-NTX treatment for 12 months and 26 for 9 months (Fig. 1). The mean age was 36 years, and 82% were men. Patients' characteristics were representative of the full patient group enrolled into the parent study [12,26,38,40,41].

The median time in this 2-year prolonged treatment study was 44.0 weeks (95% CI = 25.5–62.5), ranging from 8 to 104 weeks. Nearly half the participants continued treatment for more than 1 year, while 30% [15] and 54% [27] ended treatment after 24 weeks and 52 weeks, respectively. At the end of the study (104 weeks), 18% [9] were still in treatment.

The use of illicit opioids was very low throughout the study. However, the growth mixture model identified two subgroups of participants with distinct patterns of opioid use. The average within-group probabilities were above 0.95 and 95% CI non-overlapping, indicating homogeneous groups. There were no differences between the groups concerning which study medication the participants received in the parent randomized controlled trial (RCT). In the 'no-relapse' group [35], 24 reported no opioid

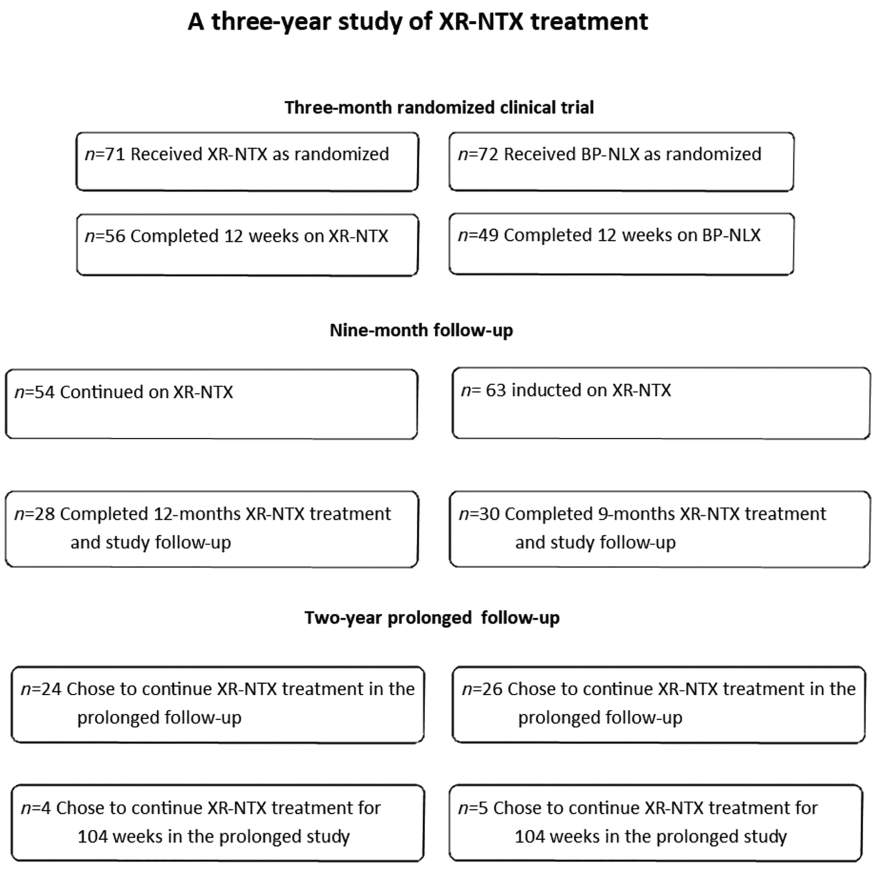

Figure 1 Study flow-chart

use at all, while 11 reported a few single days of use during the study participation. In the 'relapse' group [15], participants reported more frequently single days with use [6] or daily/almost daily use over longer periods [9].

Participants in the no-relapse group had used other illicit opioids significantly longer prior to study inclusion ($P = 0.023$), but no other differences between the groups in baseline characteristics were found (Table 1). The median time in treatment did not differ between the groups [48.0 weeks (95% CI = 24.8–71.2) in the no-relapse group and 40.0 weeks (95% CI = 29.9–50.1) in the relapse group, $P = 0.345$; see Fig. 2].

The proportional odds assumption was met for all substance use variables. Overall, there was a weak non-significant linear trend (Fig. 3a) towards less use of opioids throughout the study period ($P = 0.085$ and 0.045 for time components), with no differences in trend between the groups. The odds for more use of opioids were, however, significantly higher for the relapse group than the no-relapse group throughout the study ($P < 0.001$) (Fig. 3b).

Use of other illicit substances and alcohol is displayed in Fig. 3c–j. There was a significant trend towards less use of cannabis (Fig. 3c, $P = 0.028$ and $P = 0.456$ for time components) and benzodiazepines (Fig. 3g, $P < 0.001$). The odds for more use of benzodiazepines were significantly higher in the opioid relapse group throughout the study ($P = 0.009$) (Fig. 3h). However, the trend in use of benzodiazepines (Fig. 3h) showed a more pronounced reduction in odds for use in the relapse group than in the no-relapse group ($P = 0.039$).

Alcohol use showed no significant trend during the study period (Fig. 3i). However, participants in the no-relapse group exhibited stable and somewhat decreasing odds for more use of alcohol, while participants in the relapse group increased their alcohol use at first, but then rapidly decreased it to essentially no use towards the end of the study period. These differences were significant (Fig. 3j, $P = 0.030$ and $P = 0.015$ for first- and second-order interactions).

Opioid craving scores remained low during the study, with a mean score <1 on a scale ranging from 0 to 10 (Fig. 4a).

The scores for treatment satisfaction and recommending XR-NTX to other opioid-dependent individuals remained very high throughout the study, with mean scores >9 and >9.5 respectively, on a scale ranging from 0 to 10 (Fig. 4b,c).

When asked why they wanted to discontinue the XR-NTX treatment before 104 weeks, 29 participants

Table 1 Life-time and baseline characteristics of all participants and stratified by subgroups identified by growth mixture model.

	No-relapse group (n = *35*)		*Relapse group* (n = *15*)	
Life-time characteristics	*Mean (SD)*, n *(%)*	*Median (min–max)*	*Mean (SD)*, n *(%)*	*Median (min–max)*
Age, mean (SD)	35.4 (8.8)	33 (22–60)	37.3 (9.5)	37 (22–51)
Women, *n* (% of total study sample)	4 (8)		5 (10)	
Hepatitis C seropositive, *n* (% of total in the group)	13 (37.1)		10 (66.7)	
Injecting users, *n* (% of total in the group)	28 (80)		14 (93.3)	
Injecting use, age at onset, mean (SD)	22.8 (7.4)	20 (14–45)	23.0 (7.8)	19 (14–34)
Years of injecting use, mean (SD)	8.5 (9.3)	5 (0–40)	12.1 (11.6)	8 (0–35)
Substance use, age at onset, mean (SD)				
Heroin	24.0 (7.5)	21 (15–43)	21.8 (5.6)	22 (13–33)
Other illicit opioids	23.7 (8.3)	23.5 (8–41)	25.7 (10.2)	26 (14–46)
Cannabis	14.7 (3.1)	14 (10–27)	14.8 (2.3)	14 (12–20)
Amphetamines	17.7 (4.6)	17 (11–35)	17.9 (4.2)	18 (14–30)
Benzodiazepines	20.5 (7.5)	19 (10–45)	20.3 (6.9)	17 (14–35)
Alcohol for intoxication	13.1 (2.6)	13 (6–17)	14.7 (2.8)	14 (12–23)
Years of substance use, mean (SD)				
Heroin	6.8 (5.7)	5 (0–27)	6.8 (4.0)	6 (0–14)
Other illicit opioids[a]	3.4 (7.1)	0.5 (0–32)	0.8 (2.1)	0 (0–7)
Cannabis	11.2 (7.9)	11 (0–33)	12.2 (9.2)	13 (0–28)
Amphetamines	6.2 (6.5)	4.5 (0–27)	8.1 (8.4)	5 (0–28)
Benzodiazepines	5.9 (8.7)	3 (0–37)	3.5 (2.5)	4 (0–10)
Alcohol for intoxication	5.8 (6.4)	4 (0–23)	2.2 (3.2)	1 (0–10)

[a]$P = 0.023$ for independent-samples median test. SD = standard deviation.

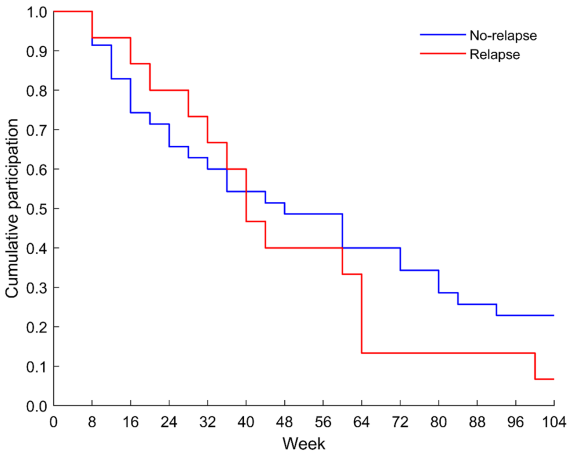

Figure 2 Time in treatment with extended-release naltrexone. Number at baseline was 50, declining to 9 at week 104. [Colour figure can be viewed at wileyonlinelibrary.com]

stated that they felt strong enough to stay abstinent without XR-NTX, four expressed a desire to get high, three reported that they were tired of being in treatment, five were reported as dropouts and we have missing data on the last nine participants.

XR-NTX was well tolerated, and only five participants reported transient adverse events: sleep disturbance, gastrointestinal discomfort and different types of infections. None of the adverse events were considered as serious or related to the study medication and none led to discontinuation of the study medication or ending of the study. No serious adverse events were reported among the participants during the first 3 months after study completion.

DISCUSSION

In this 2-year prolonged follow-up to a previous 1-year study of XR-NTX, the participating opioid-dependent individuals chose to continue XR-NTX treatment for median 44 weeks. Opioid use was low during the study. Only 15 participants were identified as a relapse group, while 35 were identified as a no-relapse group. Use of other illicit substances and alcohol was also low during the study. Throughout the study, participants reported low craving scores and high treatment satisfaction and they would, to a high degree, recommend XR-NTX to others. When asked why they wanted to discontinue XR-NTX, the majority of participants stated that they felt strong enough to stay abstinent without XR-NTX. Only a few non-serious adverse events were reported during the study.

To our knowledge, this is the first study reporting outcomes from long-term treatment with XR-NTX up to 3 years, and the first study focusing on the participants' preferences regarding treatment length.

The average treatment length in our study, 44 weeks in addition to the previous 36 or 48 weeks in the parent study, corresponds well to previous findings on treatment trajectories across various treatment modalities, indicating that opioid-dependent individuals are more likely to

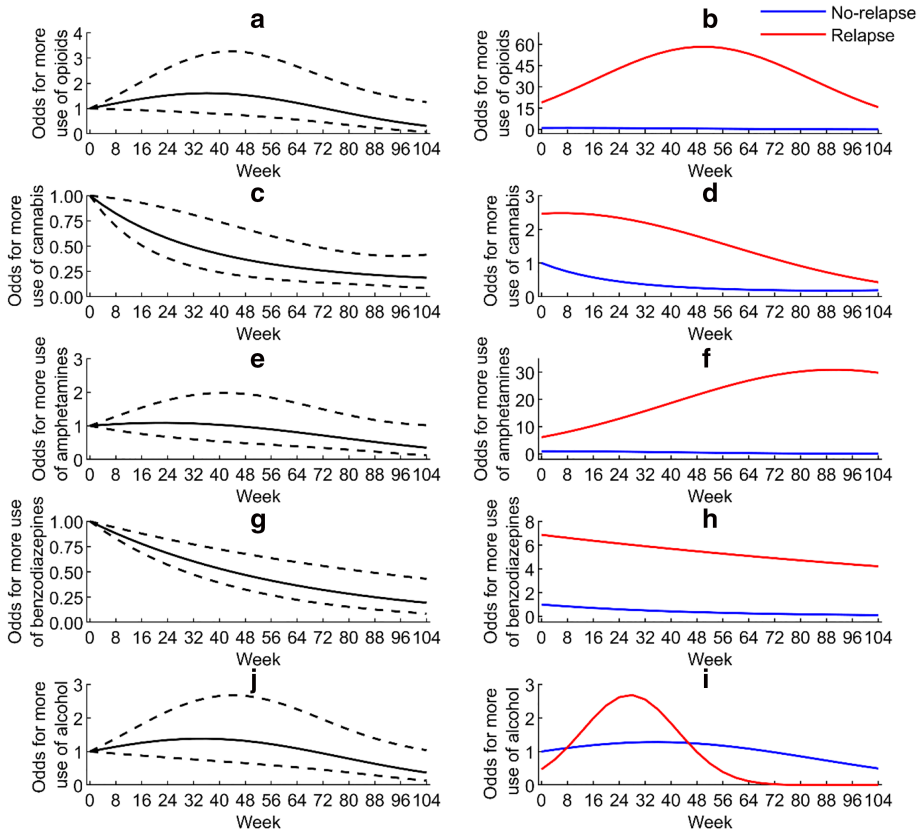

Figure 3 Odds for substance use among study participants. Odds for more substance use among all participants (left), and odds for more substance use in no-relapse group and relapse group 2 (right) with 95% confidence interval. Number at baseline was 50, declining to 9 at week 104. [Colour figure can be viewed at wileyonlinelibrary.com]

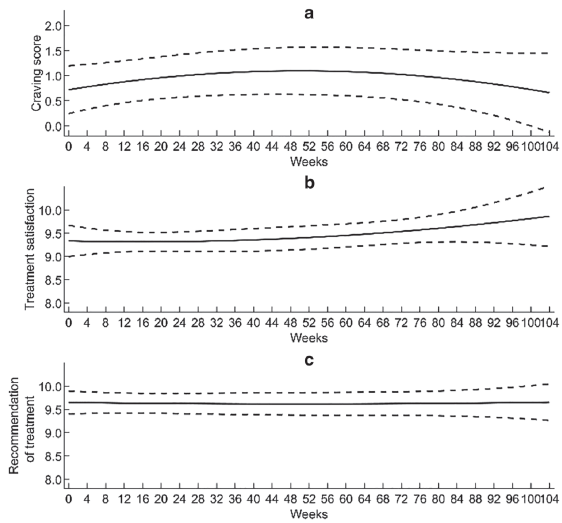

Figure 4 Opioid craving score, treatment satisfaction and recommendation of treatment. Visual analog scales were used to assess: (a) heroin craving (0–10, with 0 indicating none and 10, very strong), (b) treatment satisfaction (0–10, with 0 indicating low and 10, very high) and (c) recommendation of treatment to others (0–10, with 0 indicating not at all and 10, very much so). Figures display mean and 95% confidence interval. At baseline, craving score was reported by 47 participants and 50 reported treatment satisfaction and recommendation of treatment, numbers declining towards 9 at week 104.

succeed with their treatment goal when the treatment duration is at least 2 years [33].

Time in treatment did not differ between the identified two subgroups of participants. This finding indicates that preferred treatment time is not necessarily related to whether or not a patient used opioids but may rather be related to other aspects, such as the participants' treatment goal. We would emphasize that relapse to opioid use should not be an exclusion criterion for long-term XR-NTX treatment in clinical practice.

Opioid dependence is a chronic and relapsing disease, and it is reasonable that treatment should match these features. OMT is often regarded as a life-long treatment, while XR-NTX has been mainly used for limited time-periods. Length of XR-NTX treatment should be tailored according to the individuals' needs and preferences [21], and not restricted due to administrative time limitations. Insurance policies, high cost and lack of policy priority has been identified as administrative hindrances for the utilization of XR-NTX [42,43]. The participants in our study received XR-NTX free of cost, were not excluded from the study if they relapsed to opioid use or used other illicit substances and they could discontinue the treatment at their own discretion within the 2-year period. Few restrictions and high treatment satisfaction increased the likelihood of

treatment duration being correlated with participants' needs and preferences.

Our study suggests that many abstinence-motivated opioid-dependent individuals need and prefer longer-term treatment with XR-NTX to be prepared for post-treatment abstinence from opioids. The majority of participants stated that they felt strong enough to stay abstinent from opioids without XR-NTX as the reason for discontinuing the treatment. Missing data on this variable is a limitation of the study; however, the available data suggest that treatment discontinuation correlated with the participants' readiness to stay abstinent from opioids.

Similar to the findings in the parent study [12,26], participants reported low use of opioids, other illicit substances and alcohol. Craving scores were low, and they reported high scores on treatment satisfaction and on recommendation of XR-NTX to others. These findings also confirm XR-NTX as an effective and feasible option in long-term treatment. The participants' willingness to recommend XR-NTX treatment to other opioid-dependent individuals underscores the fact that the participants themselves perceived XR-NTX to be an effective treatment option, even if they relapsed to opioid use.

The safety and efficacy of short-term treatment with XR-NTX is well documented [8,11,12,18,26,27], but documentation on long-term treatment is lacking. In our study we found a very high tolerability, with very few and transient non-serious adverse effects, and none of the participants terminated treatment due to tolerability issues. Our data suggest that XR-NTX is also safe and well tolerated in long-term treatment.

The patients' characteristics corresponded well with the total sample of the parent study [12,26]. When entering the parent study, a limited number of participants were already in recovery in OMT and not using illicit substances, while a majority reported ongoing illicit substance use and serious addiction-related problems [38]. While opioid-dependent individuals already in recovery in OMT may need XR-NTX in a shorter transition phase to obtain medication-free abstinence over time, those who have an ongoing opioid addiction and addiction-related problems are likely to need longer-term treatment.

Participants' abstinence from or use of opioids identified early in the study was very likely to be maintained throughout their study period. The relatively low number of participants in the study may have prevented us from identifying groups with clear changes in patterns of opioid use, as seen in other studies [36,44,45]. However, the fact that a number of participants continued their opioid use during the study emphasizes the importance of XR-NTX treatment being reinforced by psychosocial interventions [17,46–48], as recommended for OMT [23,49]. The participants who used opioids chose to continue XR-NTX treatment, although they could have received agonist treatment if they wanted to. These participants may have had a treatment goal other than abstinence, more in line with a harm reduction approach and a controlled use of opioids. This finding may be useful in clinical practice, meaning that XR-NTX could attract opioid users with different kinds of motivation, and clinicians should be attentive to the pattern of opioid use early in the treatment process and tailor the treatment strategy accordingly concerning treatment length and content. Some participants clearly expressed an unmet need for psychosocial follow-up, and we suggest that this lack of follow-up is the reason behind some of the treatment dropouts. However, we did not systematically record whether or not the participants needed or received psychosocial follow-up during the study. This is a limitation of the study, as psychosocial approaches may reinforce the process of recovery.

The lack of urine drug testing (UDT) is another limitation of the study, as participants' reports of substance use could not be confirmed. In the parent study, however, the UDTs corresponded well with the information provided by the participants [12,26].

Study participants who decided to end treatment with XR-NTX before 104 weeks were not allowed to re-start treatment. Thus, this study does not reflect a real-life clinical setting where patients may choose to stop the medication, regret their decision and be allowed to re-start the medication [36]. Some participants regretted ending XR-NTX treatment before the end of the study, and requested re-inclusion in the study. However, re-inclusion was not a part of the study design, and thus participants who relapsed to opioid use were recommended to consider initiating agonist treatment in OMT. Opioid users in general are often in need of several treatment episodes before achieving long-term abstinence [29]. It is therefore important that clinical practice facilitate a possible re-start on XR-NTX for those who express this need.

Further research should investigate post-treatment efficacy and patients' willingness to re-start XR-NTX treatment after discontinuation, as induction of XR-NTX is challenging [27]. It is also important to explore factors that enable or prevent opioid users from achieving recovery and to maintain abstinence from opioids after treatment discontinuation. Increased knowledge of such factors may guide clinicians to tailor individual treatment trajectories in a more effective way.

CONCLUSIONS

Extended-release naltrexone seems to be effective, well tolerated and feasible in long-term treatment up to 3 years. Clinicians should be attentive to patients' needs and preferences and XR-NTX treatment should be individually tailored with regard to duration and content.

Trial registration

Clinicaltrials.gov no. NCT01717963, first registered: 28 October 2012. Protocol version no. 3C, 12 June 2012.

Declaration of interests

This work was supported by unrestricted grants from the Research Council of Norway (grant no. 204725–3) 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. Extended-release naltrexone (Vivitrol®) was provided to this investigator-initiated study by the manufacturer Alkermes, Inc. The sponsors and the manufacturer did not possess any editorial control or access to study data. The authors declare that they have no competing interests.

Acknowledgements

This work was supported in part by unrestricted grants from the Research Council of Norway (grant no. 204725–3). The Norwegian Centre for Addiction Research, University of Oslo and Akershus University Hospital provided financial support for the study. The manufacturer Alkermes, Inc., at no cost and in accordance with an IIT agreement, provided extended-release naltrexone (Vivitrol®) for use in the study. The sponsors and the manufacturer had no editorial control or access to study data. We would like to thank all patients in the study, the study sites and the staff members.

Author contributions

Kristin Solli: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization. **Arild Opheim:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; validation; visualization. **Zill-E-Huma Latif:** Data curation; investigation; project administration. **Peter Krajci:** Data curation; investigation; project administration; supervision. **Jūratė Benth:** Formal analysis; methodology; software; visualization. **Nikolaj Kunøe:** Conceptualization; funding acquisition; methodology; project administration. **Lars Tanum:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; visualization.

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