# The effectiveness, safety and feasibility of extended-release naltrexone in treatment of opioid dependence:

## A 12-month clinical study

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# Acknowledgements

getting to know the participants very well. They have been an important inspiration in my work and I have truly enjoyed working with them. I am so proud of them all!

My family and friends have not seen much of me the last couple of years. They have always been understanding, supportive and optimistic on my behalf by encouraging me to achieve my goals. Thank you for being there!

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# Abstract

**Background**: Opioid dependence is a serious and chronic disease which causes global problems. Many opioid users have major psychosocial problems and a high risk of overdose and premature death. Opioid dependence has high costs for the individual user, for their families and for society. Treatment is the most important factor to prevent harmful effects of opioid use. Opioid maintenance treatment (OMT) with opioid agonists: methadone, buprenorphine or buprenorphine-naloxone (BP-NLX), may contribute to reduced use of illegal substances and to improved health and social conditions of opioid users. However, opioid maintenance treatment is not a feasible treatment for those who want to achieve abstinence or for other reasons prefer substitution-free treatment. It is therefore important to find other safe and effective treatment options. Long-acting naltrexone given as an intramuscular injection every fourth week (XR-NTX), is a promising treatment option for opioid users. Naltrexone is an opioid antagonist that protects against overdose and blocks the euphoric effects of opioids such as heroin. In addition to reducing the craving for opioids, naltrexone can also reduce craving for alcohol. Naltrexone is not addictive, has few serious side effects and few interactions with other medications. No studies have previously compared XR-NTX with BP-NLX, the recommended substitution medication for opioid maintenance treatment in Norway. Also, there is a lack of studies of longer-term treatment outcomes with XR-NTX in clinical settings where OMT is available at no cost.

**Study aims:** *1.* Describe opioid users who volunteer for XR-NTX treatment in a clinical setting where OMT is easily available. *2.* Compare effectiveness of XR-NTX and BP-NLX during a 12-week randomised clinical trial (RCT). *3.* Evaluate effectiveness, safety and feasibility of XR-NTX in the treatment of opioid dependence during a 48-week period in a clinical setting in Norway.

**Material and method:** In a multi-site clinical trial, n=165 opioid users volunteered for study inclusion and background and demographic data were collected. A total of n=159 participants were randomised to receive either XR-NTX or BP-NLX 1:1 for a 12-week period. Following the randomised clinical trial, participants were given the opportunity to receive XR-NTX or BP-NLX based on their personal preference in a prospective follow-up study for an additional 36 weeks. A number of 117 participants selected XR-NTX and were the subject of investigation in the follow-up study. Participants received an intramuscular injection of XR-NTX every fourth week during the study. Use of opioids and craving for heroin, use of other substances, addiction-related problems, treatment satisfaction, recommendation of treatment and adverse events were assessed at the study attendances.

**Results**: At the time of study inclusion, 37% of the n=165 opioid users who volunteered for the study were not enrolled in OMT, although it was available to them. The volunteers clustered into opioid users in stable recovery and opioid users in ongoing illicit substance use. Of the n=159 participants randomised to the study, n=105 (66%) completed the 12-week RCT. The retention rates were similar in the two randomised groups in the 12-week RCT. In the follow-up study, n=58 (49.6%) of the n=117 participants completed the 36-week period. During the RCT, participants randomised to XR-NTX reported a significantly lower use of opioids and lower craving scores than participants randomised to BP-NLX. No significant differences were found between the two groups regarding use of most other drugs during the RCT. The improvements the participants achieved in the RCT were maintained or further enhanced during the follow-up. Treatment satisfaction was high among XR-NTX participants, and they would to a great extent recommend XR-NTX treatment to others. Adverse effects were most frequently reported during the induction phase of XR-NTX. No new safety concerns were revealed during the one year follow-up. One participant died in an accident, not related to the study medication.

**Discussion and conclusions**: Both opioid users in recovery and opioid users with ongoing severe substance-related problems were attracted to treatment with XR-NTX. We suggest XR-NTX may attract opioid users that prefer abstinence-based treatment and that XR-NTX may increase the overall number of opioid users in treatment. During the 12-week RCT, XR-NTX and BP-NLX showed similar results in retention, effectiveness and safety. The improvements participants achieved in the RCT were maintained or further enhanced during the following 36-week study. Due to the effectiveness and safety shown in this clinical trial during one year, XR-NTX should be considered as one of the treatment modalities available to opioid users in Norway.

# Norwegian summary

**Bakgrunn:** Opioidavhengighet er en alvorlig og kronisk lidelse som har store globale konsekvenser. Mange opioidavhengige har store psykososiale problemer og en høy risiko for overdoser og for tidlig død. Opioidavhengighet har store omkostninger både for den enkelte bruker, for deres familier og for samfunnet som helhet. Behandling er den viktigste faktoren for å hindre skadelige virkninger av opioidbruk. Legemiddelassistert rehabilitering (LAR) med opioidagonistene metadon, buprenorfin eller buprenorfin-nalokson (BP-NLX) kan bidra til å redusere bruk av illegale rusmidler og til bedrede helse- og sosiale forhold hos opioidavhengige. LAR er imidlertid ikke et aktuelt behandlingsalternativ for alle, spesielt ikke for de som foretrekker en substitusjonsfri behandling. Det er en overordnet målsetting å øke antall opioidavhengige i behandling, og å finne andre trygge og effektive behandlingsalternativer for opioidavhengighet er viktig i denne sammenheng. Langtidsvirkende naltrekson gitt som intramuskulær injeksjon hver 4. uke (XR-NTX) er et lovende behandlingsalternativ for opioidavhengighet. Naltrekson er en opioidantagonist som beskytter mot overdose og blokkerer for ruseffekt av opioider som heroin. I tillegg til å redusere craving for opioider, kan naltrekson også redusere craving for alkohol. Naltrekson er ikke vanedannende, har få alvorlige bivirkninger og få interaksjoner med andre medikamenter. Det har ikke tidligere vært utført studier som sammenligner XR-NTX med BP-NLX, det anbefalte substitusjonsmedikamentet for legemiddelassistert rehabilitering i Norge. Det er også mangel på langtidsstudier av XR-NTX i kliniske settinger hvor LAR er et lett tilgjengelig og kostnadsfritt behandlingsalternativ.

**Mål: 1**. Å beskrive opioidavhengige som frivillig velger å delta i en studie for å motta XR-NTX i en klinisk setting hvor LAR er lett tilgjengelig. **2.** Å sammenlikne effekten av XR-NTX med BP-NLX i en 12-ukers randomisert klinisk studie (RCT). **3**. Å vurdere om XR-NTX kan være et effektivt og trygt behandlingsalternativ for opioidavhengige i en klinisk setting i Norge over en 48-ukers periode.

**Materiale og metode:** I en klinisk multisenter studie ble bakgrunn og demografiske data innsamlet for n= 165 opioidavhengige som ble inkludert i en studie om XR-NTX behandling. Totalt n = 159 deltakere ble randomisert til å motta enten XR-NTX eller BP-NLX 1: 1 i en 12-ukers periode. I forlengelse av disse 12 ukene, ble alle deltakerne gitt muligheten til å fortsette i studien i ytterligere 36 uker, og kunne da fritt velge om de ønsket XR-NTX eller BP-NLX. De totalt n=117 som valgte å motta XR-NTX, var gjenstand for undersøkelse i oppfølgingsstudien. Deltakerne fikk intramuskulære injeksjoner med XR-NTX hver 4. uke i studieperioden. Ved disse studieoppfølgingene ble det innhentet data vedrørende bruk av opioider, craving for heroin, bruk av andre rusmidler, rusrelaterte problemer, behandlingstilfredshet, hvorvidt behandlingen vil bli anbefalt til andre, samt rapportert eventuelle bivirkninger eller oppståtte pasientskader.

**Resultater:** Av de totalt n = 165 opioidavhengige som ble inkludert i studien, var 37 % ikke under behandling i LAR ved studiestart, selv om dette behandlingstilbudet var tilgjengelig for dem. Blant de inkluderte deltakerne var en stor andel enten ar rehabiliterte eller hadde et pågående alvorlig rusmiddelmisbruk. Av de n = 159 deltakerne som ble randomisert til å motta enten XR-NTX eller BP-NLX, fullførte n = 105 (66 %) den 12-ukers randomiserte kliniske studien, og det var ingen forskjeller på de randomiserte gruppene når det gjaldt retensjon i behandling.  Av de n = 117 som valgte å delta i den påfølgende 36-ukers oppfølgingsstudien, fullførte n = 58 (49,6 %). Ved sammenligning av de to randomiserte gruppene i de første 12 ukene av studien, viste pasienter som ble randomisert til XR-NTX en signifikant lavere bruk av opioider og lavere craving skår enn de som ble randomisert til BP-NLX. Det var ingen forskjeller mellom gruppene når det gjaldt bruk av de flest andre rusmidler. De positive resultatene deltakerne oppnådde i de 12 første ukene, ble opprettholdt eller ytterligere forbedret i den 36-ukers lange oppfølgingsstudien. Behandlingstilfredsheten var høy blant deltakerne som ble behandlet med XR-NTX, og de ville i stor grad anbefale behandling med XR-NTX til andre. Rapporterte bivirkninger var i hovedsak relatert til første dose med langtidsvirkende naltrekson, og det ble ikke avdekket noen nye bivirkninger ved bruk av langtidsvirkende naltrekson i løpet av det året studien varte. I løpet av studien omkom en deltaker i en ulykke. Dødsfallet var ikke relatert til bruk av naltrekson.

**Diskusjon og konklusjon:** XR-NTX synes å tiltrekke seg både opioidavhengige som i stor grad var rehabiliterte og opioidavhengige som hadde et alvorlig pågående rusmiddelmisbruk. At opioidavhengige som av ulike årsaker ikke allerede var i aktiv behandling syntes å finne XR-NTX attraktivt, kan medføre at flere opioidavhengige kommer i behandling. Behandling med XR-NTX og BP-NLX viste seg å være like trygt og effektivt i løpet av den 12 uker lange RCT perioden. De positive resultatene deltakerne oppnådde de første 12 ukene ble opprettholdt eller ytterligere forsterket i løpet av de videre 36 ukene hvor alle deltakerne mottok XR-NTX. Resultatene vi har sett i studien over ett år tyder på at XR-NTX er et effektivt og trygt medikament. Vi anbefaler at XR-NTX vurderes som et behandlingsalternativ for opioidavhengige i Norge.

# List of papers

I

Solli, K.K., Tanum, L., Sharma-Haase, K., Opheim, A., Krajci, P., Latif, Z., Gaulen, Z., Kunøe, N. (2018) *Opioid users who prefer extended-release naltrexone: A descriptive study of volunteers for a treatment innovation in Norway.* Submitted for publication.

II

Tanum, L., Solli, K. K., Latif, Z. E., Benth, J. S., Opheim, A., Sharma-Haase, K., Krajci, P., Kunoe, N. (2017). The Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. JAMA Psychiatry. doi:10.1001/jamapsychiatry.2017.3206 [1].

III

Solli, K.K., Latif, Z., Opheim, A., Krajci, P., Sharma-Haase, K., Benth, J.S., Tanum, L., Kunøe, N. (2017) *Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence – a nine month follow-up study.* Submitted for publication.

Other papers co-authored by the candidate during the PhD-period, thematically related and will be referred to but which are not included in the thesis, include:

1. Kunøe N, Opheim A, Solli KK, Gaulen Z, Sharma-Haase K, Latif ZE, Tanum L. (2016) *Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway* (NTX-SBX). BMC Pharmacology and Toxicology. 2016;17(1):1-10 [2].
2. Sharma Haase K, Kunoe N, Opheim A, Gaulen Z, Nja AM, Latif ZE, Solli KK, Tanum L. (2016) *Interest in Extended Release Naltrexone among Opioid Users.* European Addiction Research. 2016;22(6):301-5 [3].

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# Abbreviations

| | |
|---|---|
| AE | Adverse events |
| BP-NLX | Buprenorphine-naloxone |
| CI | Confidence interval |
| CRF | Case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| GCP | Good clinical practice |
| GP | Medical doctor, general practitioner |
| EuropASI | The European version of the Addiction Severity Index |
| ITT | Intention-to-treat |
| MITT | Modified intention-to-treat |
| OMT | Opioid maintenance treatment |
| RCT | Randomised clinical trial |
| SAE | Serious adverse events |
| SD | Standard deviation |
| SUD | Substance use disorder |
| UDT | Urine drug test |
| VAS | Visual Analogue Scale |
| XR-NTX | Extended-release naltrexone |

# Preface

Drug rehabilitation is a multi-disciplinary field, and according to national guidelines in Norway, medicine, psychology and social work should be included. In general, medicine and psychology are far more represented in the research field than social work, and I consider this to be a big challenge. As a social worker, the possibility to contribute to the research field in drug treatment has been a great motivation. Research should, in my opinion, be an interaction with the clinical field. I believe that my 25 years of experience with working with drug users may present a valuable contribution to the research field.

In the early 1990s, abstinence-oriented treatment was the only option in treatment of opioid dependent patients. Before the introduction of OMT in Norway, we were counting the number of opioid users we thought would be able to benefit from this new approach. In the county where I worked, we ended up counting about 20. In this county today, there are approximately 350 patients in OMT. The introduction of OMT resulted in a paradigm shift in the drug addiction field. It caused changes both in regard to how we understand opioid dependence and how opioid dependence should be treated. The shift also caused changes in financial priorities. In my understanding, we lost something important during this shift. OMT is a valuable treatment option, but opioid users are a heterogeneous group and we need more than one effective treatment option to offer them.

A majority of the opioid users who are enrolled in OMT improve their quality of life during this treatment, their use of opioids decreases and the risk of overdoses is reduced. Given the extensive research on OMT, this should be the first choice when treatment is recommended. Nevertheless, not everyone wants OMT, and we owe it to them to take their preferences seriously. We need a variety of treatment approaches, so that as many as possible have a chance of obtaining a better life, regardless of their preferences for substitution medication or abstinence. Research on treatment is important. If we are able to assist only a few opioid users in gaining their preferred treatment goal by offering them a new treatment, we have partially succeeded. But of course, I hope that our research can contribute to helping as many as possible to achieve a better life!

# 1. Introduction

## 1.1. Opioid dependence

An estimated 32.4 million people around the world use opioids [4]. This number includes illegal opioids such as heroin, and opioids prescribed both in opioid maintenance treatment (OMT) and pain conditions. In Europe and in Asia, opioids are the main drug for which drug users receive treatment. While in Oceania and North America, opioids come second or third [4], suggesting opioid use is a major problem in these regions. It is estimated that Norway has a population of high-risk opioid users between 6, 200 and 10, 300 [5]. This number does not include patients that are stable in OMT.

Opioid dependence can be defined in medical terms according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). If three or more of the following criteria are present during a 12-month period: withdrawal, increased tolerance, use of larger amounts/longer periods, repeated attempts to quit/control use, amount of time spent using, physical/psychological problems related to use and activities given up to use [6].

It is estimated that one quarter of opioid users develop opioid dependence [7]. The reasons for developing and maintaining opioid dependence are multifactorial. Genetics and neurobiological factors, environmental factors, physical factors, and mental factors are contributing causes [8, 9]. Opioid dependence is a severe and debilitating problem to the opioid users, their families and society. Opioid users, in particular injection users and those not in treatment, have a higher risk of blood-borne infections such as hepatitis and HIV/AIDS [9]. In addition, their unhealthy lifestyle and risky behaviour is associated with increased mortality due to cardiovascular diseases, cancers, digestive diseases, and respiratory diseases [10, 11]. Due to the direct and indirect problems caused by drug use, they are more frequently hospitalised and are large consumers of various social services [12, 13]. Opioid users have a high burden of mental problems [11, 14], and many develop various psychosocial problems. The use of opioids and other substances may lead to cognitive impairments [15]. Opioid users often perform criminal activities to finance their illicit use of drugs [16], and many are incarcerated for shorter or longer periods [17]. Those who start using drugs at young ages often drop out of school and have little work experience. Many have different social security benefits as their income and housing problems are prevalent.

One of the reasons opioids are of such concern is that they are present in 81% of deaths caused by overdoses in Europe [13]. In the USA, there has been a 200% increase in the rate of overdose deaths involving opioids from 2000-2014 [4, 18, 19]. In overdose deaths, opioids are often found in combination with benzodiazepines (both prescribed and illicit) and alcohol [20-22].  The risk of

overdose increases when opioid users relapse to opioid use after a period of abstinence due to the loss of tolerance of opioids. The first few weeks after dropping out of treatment or after release from prison are vulnerable phases. [23-27]. Few people appear to "mature out" of opioid dependence, and mortality increases as opioid users age, due to many years of high-risk behaviour and unhealthy lifestyles [17]. The age for opioid users entering treatment in European countries in 2013 varied between 25 and 41 years, with an average 34 years. There is presently an evident trend among opioid users entering treatment in Europe: patients are aging and an increasing number are in their 40s and 50s [13].

Figure 1 shows the drug-induced mortality rates in Europe [28]. Norway and the other Northern European countries have a high number of overdose deaths, despite a significant expansion of OMT in recent years. This emphasises that development of treatment approaches should be highly prioritised.

**Figure 1 Drug-induced mortality rates in Europe**



Drug-induced mortality rates among adults (15–64): selected trends and most recent data

NB: Trends in the eight countries reporting the highest values in 2015 or 2014 and overall European trend.
EU + 2 refers to EU Member States, Turkey and Norway.
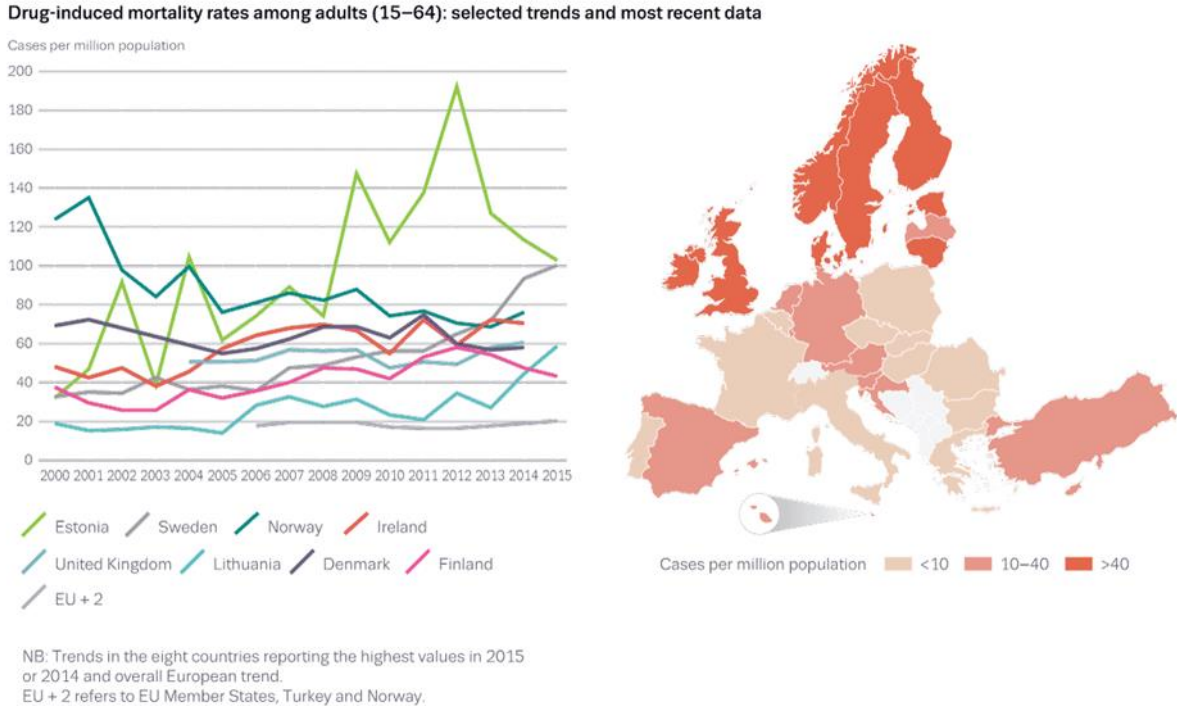
Source: EMCDDA. (2017). *European Drug Report: Trend and Developments [28]*.

## 1.2.    Treatment goal – recovery or harm reduction

The concept of recovery can be described as a process where the drug user maintains an achieved goal of abstinence and improved living conditions [29]. Abstinence-oriented treatment has the goal to eliminating drug use, to "cure the disease". Harm reduction can be understood as strategies aimed at reducing the negative consequences of drug use. Harm reduction strategies could be e.g; actions to prevent overdoses and safe needle use to prevent blood-borne infections but also strategies to reduce the level of drug use [30].

Several studies have investigated opioid users' goals upon entering treatment, and found between 50-80% of the opioid users stated abstinence from all opioids (including substitution medications) and other substances as their main treatment goal [29, 31, 32]. Opioid maintenance treatment may be seen more as harm reduction although several traditions within OMT also aim at psychosocial rehabilitation [33]. It has been suggested that some countries, among them the United Kingdom and the USA, have moved towards an abstinence-oriented drug treatment policy the last years [34].  In this perspective, OMT - which has been considered a life-long treatment - is more likely to be considered a temporary treatment option towards the main goal of abstinence. This attitude towards OMT as a temporary treatment has been expressed among both providers and opioid users [34].

An important key for an intervention to be effective is the drug users' own engagement [35, 36]. It is important that patient preferences are taken into account and that treatment options are facilitated according to the drug users' individual motivations, needs and goals [8, 34, 37]. In the debate of potential effective treatment for opioid dependence, the users' perspective has received a limited amount of attention compared to policy and professional view [31]. Treatment can be beneficial even when the ideal outcome is not attained [20]. Opioid users who enter treatment for harm reduction purposes may experience reductions in drug use and their motivation may change during time in treatment [30]. Opioid users' goals may vary between abstinence and recovery, recovery with substitution medication, or harm reduction with continued but better controlled drug use [33]. Ambivalence is a prominent feature of opioid dependence, reinforced by tolerance and physical withdrawal upon cessation of drug use  [38]. Motivation may be enhanced with the presence of a strong external force, such as licensed supervision agreements for health workers, or legal coercion for criminal offenders [39, 40].

## 1.3.    Treatment options

Being in treatment is one of the most protective factors against premature deaths among drug users [23]. As opioid dependence is a chronically relapsing disorder, long-term treatment is often required

[11]. When looking at opioid use trajectories, those who attend treatment often report 6-10 years of opioid use, and several treatment episodes might be necessary to achieve abstinence from opioids [17].  If opioid users manage to stay abstinent for five years, the likelihood of future abstinence increases substantially [11]. It has been estimated that 50-60% of drug users relapse within 6 months after treatment cessation [41]. Even so, a recent national study from England found that approximately 20% of opioid users achieved a sustained benefit from treatment [42].  A review of studies of the long-term course of opioid addiction found that the abstinence rate for opioid users decreases after treatment completion until it remains stable at approximately 30% after ten years [17]. Support from family and friends and having daily activities such as employment increases the likelihood of recovery [17, 43, 44]. Longer duration of treatment increases the likelihood that opioid users will succeed with their treatment goal, in particular, treatment durations of more than two years [42].

### 1.3.1.   Non-pharmacological treatment

Psychosocial intervention in an outpatient setting is the most common approach in Europe [13]. Outpatient treatment is provided in specialised clinics and at low-threshold services in local communities. Among the offers are regular individual counselling, therapy sessions with a spouse or a family member, group therapy, or self-help groups such as AA/NA groups [17].

Detoxification and residential programs are other approaches [17]. Detoxification may be offered on an inpatient basis, and the duration of admittance varies from a few days to a few weeks depending on the immediate physical withdrawal symptoms of the relevant substances. As detoxification by itself is not an effective treatment and high rates of relapse is common after discontinuation, outpatient follow-up or inpatient treatment is often followed by the detoxification [45]. Inpatient treatment varies in terms of content, length and intensity. Some residential treatment is based on therapeutic communities, others on 12-step treatment [17]. Low-threshold housing is also an important modality, however, this is often regarded as a harm reduction approach rather than recovery [13].

Abstinence-based approaches for opioid dependence may be effective while ongoing, but there is a major likelihood of relapse after treatment discontinuation and a high risk of overdose [25, 34]. Also, among patients who are strongly motivated for abstinence from opioids, frequent relapse to illicit opioids and overdose deaths has been observed after detoxification [46]. Despite the risk of relapse and overdoses, many opioid users prefer abstinence based treatment rather than substitution medication [15].

### 1.3.2. Opioid maintenance treatment

Opioid maintenance treatment (OMT) is the current recommended treatment for opioid dependence according to WHO guidelines [47]. Figure 2 shows the estimated coverage of OMT in Europe. In the USA, it is estimated that fewer than 1 million of the approximately 2.5 million American opioid users receive medication assisted therapies [19].

**Figure 2 Coverage of opioid substitution treatment in Europe**

Coverage of opioid substitution treatment (percentage of estimated high-risk opioid users receiving the intervention)

NB: Data displayed as point estimates and uncertainty intervals.
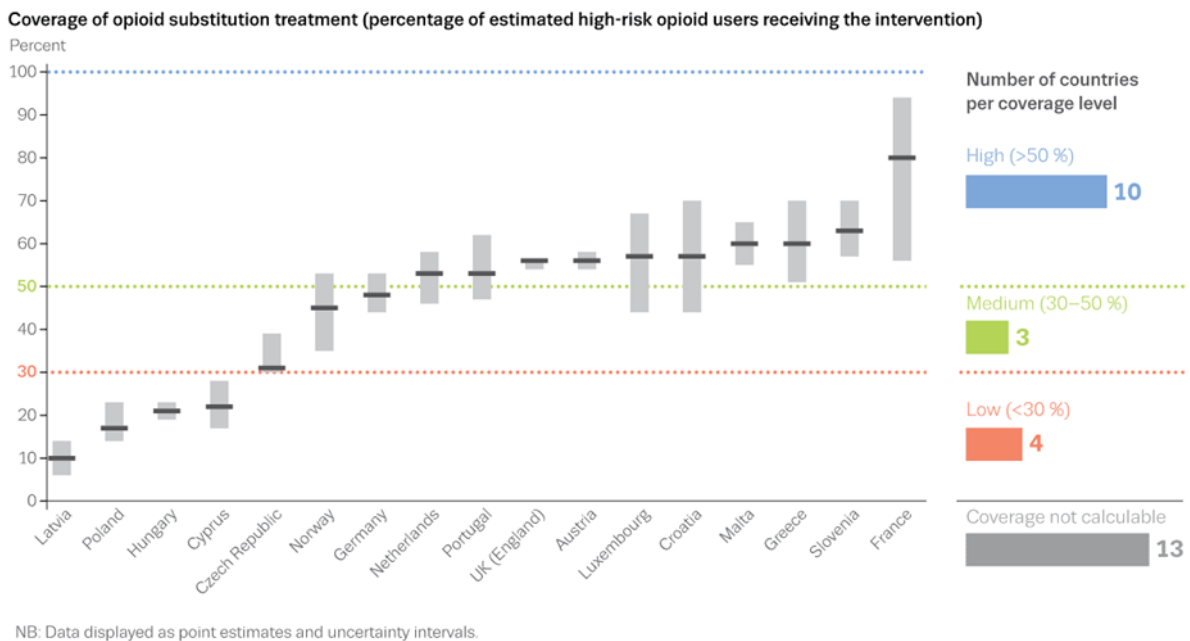
Source: EMCDDA. (2017). *European Drug Report: Trend and Developments [28]*.

OMT implies medication daily or every second day with the opioid agonist methadone [48], the partial agonist buprenorphine, or buprenorphine in combination with the antagonist naloxone [47]. It is well documented that OMT reduces overdose mortality [24, 49, 50], acute health problems [51, 52], use of opioids and other drugs, and improves opioid users' social functioning [8, 47, 53, 54]. Reduced injection drug use has been seen among patients in OMT compared to opioid users not in OMT [55]. Other studies have found reduction in criminal activity after start up in OMT [56, 57]. Based on research so far, methadone is the superior medication regarding retention in treatment [49, 53, 58]. It is recommended that OMT contains both pharmacological treatment and psychosocial interventions [47, 48].

Due to safety concerns and the risk of diversion, OMT often includes several measures of control such as daily monitored medication and weekly required urine tests. Restriction on take-home dosing can make it difficult in work situations and to travel on vacations. Maintenance therapy also involves restrictions in handling cars and machinery and may affect the licensing requirements of health care professionals [20, 59, 60]. OMT is considered a long-term treatment, often lifelong due to the chronic and relapsing nature of opioid dependence [49, 61].

Despite being the recommended treatment option, enrolment in OMT has some disadvantages, such as continued physical dependence. The control aspects can be inconvenient and prevent inclusion in work and social life. Methadone and buprenorphine may have side-effects such as gastrointestinal problems, drowsiness, hormonal changes leading to sexual dysfunction in men, and weight problems that may be bothersome to the opioid users. Substitution medication may also interfere with other drugs, such as benzodiazepines [10, 21, 22, 32, 62]. Use of other substances while on methadone is a known problem, which can increase the risk of overdose [46]. Non-adherence and drop-out from OMT is a serious problem which increases the morbidity and risk of overdoses [46, 52, 63]. A Danish study concluded that liberal OMT access with high doses of methadone and unsupervised intake do not prevent overdoses [21]. Retention rates in OMT vary widely. A review found rates between 26% - 85% at 12-month follow-ups [64].

As in many other countries, OMT is the current recommended treatment to opioid users in Norway. The treatment is free of cost for the users, and under current low-threshold treatment guidelines. The vast majority is included and very few are rejected or discharged. It is estimated that 50-60% of the population of opioid users in Norway are enrolled in OMT. Since the introduction of OMT in the late 1990s, the number of patients has been stable the last couple of years, n=7458 in 2015 [65]. Compared to other Scandinavian countries, Norway has a greater coverage of OMT [28].

Several studies have examined different aspects of OMT in Norway [24, 50-52, 65-69]. The proportion of women in OMT in Norway is about 30%, and the mean age among the patients was 43.7 in 2015. It is estimated that approximately 50% of the OMT patients use no or only a small amount of drugs. 10% of the patients use illicit opioids, 30% use cannabis, between 30-40% use benzodiazepines, 15% use amphetamines and 10% have a heavy use of alcohol [65, 66]. According to the annual report from the OMT cohort in Norway, it is estimated that approximately 90% of the patients have remained in treatment during the last year [65]. In an international context, this is a high level [64].

Due to the safety profile with the injection deterring potential of its naloxone component, buprenorphine-naloxone (BP-NLX) is the recommended option in Norway. A shift from methadone to

buprenorphine was documented during a 10-year period [66, 70]. In 2015 the mean prescribed dose in Norway was 16 mg/day for buprenorphine and 14 mg/day for buprenorphine-naloxone [65].

### 1.3.3. Naltrexone

Naltrexone is an alternative treatment that offers a medication-assisted abstinence from opioids and may prevent relapse to opioid use [71, 72]. Naltrexone is an opioid antagonist that competitively blocks the euphoric effects of opioids such as heroin. It is not addictive and cessation does not result in withdrawal. If used as prescribed, naltrexone decreases the risk of overdoses [73]. Studies have shown that naltrexone reduces both use of and craving for opioids and alcohol. Some individuals also experience reduced craving for other substances and addictive behaviour [74-82]. Naltrexone is considered well tolerated with few severe side effects [40, 80, 83-90], and there are few interactions with other drugs [8, 91]. Without addictive properties, there is no risk of diversion [53].  Naltrexone may be perceived as an attractive option to those who prefer abstinence and a substitution-free treatment [17, 37, 89].

*Oral naltrexone*

Naltrexone has been known as a treatment option for opioid dependence for almost 40 years [72, 92, 93], however, the potential advantages of naltrexone have not been utilised as expected [94, 95]. Several studies have concluded that non-compliance limits the effectiveness of oral naltrexone and those who completed treatment were mostly selected samples of well-functioning or motivated opioid users [53, 96-98].  When used as intended, oral naltrexone reduces the use of heroin and related criminal activity [47].

The tendency to drop-out of treatment seriously limits the use of oral naltrexone and might increase risk of overdose problems [99-101]. The World Health Organizations' (WHO) guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence [47] only recommends treatment with oral naltrexone to those who do not have access to OMT or to those who do not want OMT. These difficulties have motivated the development of sustained release formulations, such as implants and depot injections [86, 102-104].

*Naltrexone implants*

Naltrexone implants have up to 6 months duration. Efficacy and safety have been the subject of several studies, particularly in Australia [87, 103] and Russia [105, 106]. In Australia, a locally produced naltrexone implant has been used in a few thousand patients, although this implant is not approved by the Therapeutic Goods Administration [38, 87]. Studies of naltrexone implants showed promising results regarding retention and reduction in use of opioids. The sustained release formulation of naltrexone implants reduces the need to make a daily decision to be abstinent.

However, attempts to remove the implant have been reported [38]. Studies of naltrexone implants have been criticised for low power, poor methodological quality and insufficient evidence of safety and efficacy [53, 107]. Yet the current WHO guidelines from 2009 have found the evidence of naltrexone implants inadequate to support any recommendations [47].

*Intramuscular extended-release naltrexone*
Extended-release naltrexone (XR-NTX) administrated as an intramuscular injection every fourth week may be easier to administer than implants. XR-NTX has been effective both in laboratory and clinical settings [78, 108]. XR-NTX is approved in the USA and Russia by regulatory authorities as a treatment option for both alcohol and opioid-dependence disorders. Several studies of XR-NTX have shown promising results for feasibility, efficacy and tolerability in short-terms [78, 80, 85, 89, 109-111].

As for naltrexone implants, the WHO's 9 year old guidelines found no evidence that could support recommendation of XR-NTX [47]. However, many studies of XR-NTX have been published in the last ten years and the guidelines were not updated according to the latest results. The approval of XR-NTX in the USA was mainly based upon a RCT from Russia that showed promising results regarding retention in treatment and reduction in use of opioids [78, 84]. However, this trial has been questioned. The Russian trial compared XR-NTX with a placebo, which is ethically controversial as long as there is a well recommended treatment option such as OMT available [112]. OMT, however, is illegal in Russia, and thus the results from the study may be less generalisable to locations were OMT is extensively utilised [53].

*Tolerability and safety aspects of naltrexone*
The safety aspects of naltrexone are of particular interest, as previous studies have been the subject of criticism regarding this topic [107, 113]. Long-acting naltrexone has a favourable safety profile with few severe adverse effects [80, 85, 88]. Common side effects of naltrexone include headache, sleep disturbance, nausea, and gastrointestinal discomfort, particularly in the induction phase [61, 114]. Severe injection site reactions may occur, but are infrequently reported [86]. In order to minimise the uncomfortable symptoms in the withdrawal phase and improve the induction on naltrexone treatment in opioid dependent individuals, different approaches have been tried. One of the most controversial methods for induction on naltrexone is antagonist induced withdrawal under heavy sedation or anaesthesia [115].

Anhedonia and/or depression have been seen as possible side effects of naltrexone use due to the concern that the antagonist and blocking effect of naltrexone on the opioid receptors may block endogenous endorphins [116, 117]. However, several studies have not supported this claim, and have shown no increase in depression in opioid users treated with naltrexone [105, 114, 116-118].

On the contrary, several studies have demonstrated decreased symptoms of depression. The explanation might be that opioid users in remission experienced satisfaction with their improved situations [116, 118].

Milder psychological problems such as depression and anxiety are frequent among opioid users [117, 118] and anxiety is a common withdrawal symptom when ceasing opioids. When anxiety has been reported in some studies shortly after the induction on naltrexone, it has been suggested as a withdrawal symptom rather than being a pharmacological consequence of naltrexone. The typical findings are that increased anxiety and sleep impairment observed at naltrexone induction have declined after some time in treatment [90, 114, 116, 117].

As with discontinuation of other treatment modalities for opioid dependence, caution must be exercised when ceasing naltrexone. The users must be aware of naltrexone increasing sensitivity and decreasing tolerance, and thereby increasing the risk of overdose if the patient relapses to opioids [100]. Studies suggest that naltrexone implants mitigate the risk of overdoses compared to oral naltrexone and that rates of fatal and non-fatal overdoses among patients treated with naltrexone implants, methadone and buprenorphine were similar [103, 119, 120]. A retrospective study found no increased risk of overdoses among opioid users who have received depot naltrexone compared to other treatment modalities [121].

The lack of withdrawal effects when ceasing naltrexone may make it easier to drop out of naltrexone treatment compared to OMT [38, 80, 91, 122]. Without craving for opioids, there is a risk some naltrexone users may feel cured from their opioid dependence, think they could handle their problem on their own, and decide to terminate the naltrexone treatment prematurely [121].

*Retention and duration of treatment with naltrexone*
The majority of studies on long-acting naltrexone have had relatively limited timeframes, typically between 1-6 months [79, 89, 123]. A Russian study followed participants over a longer period and showed promising results in terms of safety and effectiveness during a 1-year follow-up trial with XR-NTX. Of the n=114 participants included in the Russian study, 62.3% completed the 1-year follow-up [84]. Also, an American study that followed a cohort of health professionals treated with XR-NTX for 96 weeks showed good results: 55% of the n=38 participants received 12 monthly injections with XR-NTX, and 36.8% received all 24 injections [40]. The two latter studies of XR-NTX, however, have some limitations regarding generalisability due to the selection of participants. A number of retrospective cohort studies showed some positive results on various addiction-related outcomes. However, improvements achieved during a relatively short period of treatment with XR-NTX seemed to wane after treatment discontinuation [14, 89, 121].

Retention in treatment with XR-NTX is a challenge, and as for OMT, it is recommended that treatment with XR-NTX is followed by psychosocial interventions [38]. Different approaches, e.g. Patient Navigation (PN), have been developed to reinforce the effects of treatment with naltrexone [124, 125]. Studies have explored whether employment based reinforcement could maintain adherence to XR-NTX in opioid users and the results were encouraging [111, 126, 127]. Contingency management has shown an effect in increasing retention rates, but may be a controversial approach [128].

Until now, there is no recommendation regarding the duration of treatment with XR-NTX [121]. When the duration of treatment is to be considered, the patients' motivation for using XR-NTX must be taken into account. Opioid users who have been in a stable recovery process for a longer period may need XR-NTX for a shorter period. Opioid users with an ongoing severe drug use may rather consider XR-NTX as an instrument of harm reduction and may need a long-term treatment. So far, the most positive outcomes from treatment with XR-NTX have been reported within samples that are particularly motivated, but promising outcome have also been seen in clinical settings [110, 129]. An American study of XR-NTX that included a retrospective follow-up approximately one year after the XR-NTX treatment had ended, found that the relapse prevention effects had waned compared to the first months of treatment [89]. The duration of treatment with XR-NTX must be adapted to the chronically relapsing nature of opioid dependence and according to the patients' needs.

### *The target group of naltrexone treatment*
In previous research, particularly in earlier studies of oral naltrexone, the overall suggestion has been that naltrexone is a treatment for a selected few [53]. A majority of previous studies of long-acting naltrexone have both included relatively few participants and the participants have represented samples of motivated or well-functioning opioid users, such as opioid users on probation or health professionals [40, 79, 80, 88, 89, 111, 130]. An American study of XR-NTX among opioid users who were under required supervision after release from prison, found no significant characteristics among the sample that could have been effect moderators [89, 131].

A number of studies of XR-NTX have also been carried out among opioid user recruited in a naturalistic setting. A recent study reported higher success rates for XR-NTX induction among users of prescribed opioids than among those using heroin [132]. Another study reported poorer adherence to treatment with XR-NTX among patients with more severe addiction-related problems [133]. Among a sample of opioid users in residential rehabilitation, users of XR-NTX showed significantly higher completion of residential treatment and early post-residential care than non-users of XR-NTX [129]. The aforementioned Russian study [78] concluded that no patient treatment

matching variables could be identified among the participants who completed the 24-week study period, and that XR-NTX was effective across various characteristics [134].

### *Studies of naltrexone in Norway*

Norwegian studies have previously examined the use of an implantable formula of naltrexone made in Australia. Initially, a couple of pilot studies were performed [135, 136] and on the basis of promising results from one of these studies, two randomised controlled studies were conducted [83, 130, 137]. In the first trial, n= 56 opioid users were randomised to receive either naltrexone implants or usual aftercare after inpatient treatment. The study found participants receiving naltrexone of 6 months duration used significantly less opioids than those in usual aftercare [83]. The second trial was performed among prison inmates, where n=46 participants were randomised to receive either naltrexone implants or methadone treatment after prison release. The study found naltrexone implants and methadone treatment to be of comparable effectiveness in terms of reduction in heroin use, although considerable attrition/statistical power problems made statistical inference difficult [138].

In a re-analysis of these data including participants from the two RCTs and a previous pilot-study, n=61 participants were offered a second naltrexone implant and 51% chose to accept [137]. The overall results from these studies suggested that the naltrexone implant was an effective treatment option in reducing opioid use, showed acceptable levels of safety and could be a feasible treatment option. However, limitations regarding these studies must be acknowledged. The number of participants was limited and the researchers described some methodological challenges [130, 139].

## 1.4. Barriers to treatment

A high number of opioid users are not in effective treatment, even though it is available. A Norwegian study found only 5-10% of the overdose deaths occurred among patients that were enrolled in the OMT program [140]. This emphasises the preventive effect of OMT, and in this perspective, it is important to understand and address the processes that prevent opioid users from entering treatment. There are a number of internal and external barriers to treatment that prevent opioid users from enrolling into effective treatment programs like OMT [141].

Internal barriers may be related to the characteristics of the individual opioid user. Substance users who have experienced natural recovery have given numerous reasons for not attending treatment. Not wanting to be stigmatised or labeled, having negative beliefs or experiences with treatment and thinking treatment would not be appropriate because their drug problems were not severe enough,

were some of the main reasons [142]. Wanting to handle their problems on their own was an additional factor [143].

Motivation and ambivalence are prominent aspects in the nature of dependence. Different psychosocial factors can affect motivation for change and reduce or increase the opioid users' ambivalence. Regulatory requirements on abstinence to retain a license can be a strong external motivation for opioid dependent health professionals. Traumatised opioid users who lack a supporting social environment may have a motivation for continued drug use. Craving and the strong reinforcing effects of opioids may affect the opioid users' impulse control and ambivalence and thus be a barrier to treatment [38].

External barriers may be structural, such as the governments' policy. For example, OMT is illegal in some countries, such as in Russia [78]. Other structural barriers such as health service funding priorities, regulatory framework, including financial matters, may also limit opioid users' access to effective treatment [141, 144]. While drug treatment is free of cost for patients in most European countries, many patients in the USA must provide most of the expenditures themselves, which results in differential availability of treatments [145].

### *Barriers to opioid maintenance treatment*
Opioid users provide various reasons for avoiding enrolling into or for ceasing currently accessible OMT programs [91, 144, 146, 147]. Internal barriers may be general dissatisfaction with and resistance towards the treatment regime with daily monitored intake and supervised urine tests and disagreements regarding the choice of and dosing of OMT medication [20, 141]. The restrictions, such as being monitored at a public pharmacy, may contribute to stigmatisation and manifestation of the patients' identities as opioid users and undermine their treatment motivation. Some may dislike the substitution medication due to the continuation of physical dependences, and others may be worried by the side effects of substitution medication and the frequent life-long perspective of OMT [148].

### *Barriers to treatment with extended-release naltrexone*
In the USA where XR-NTX is approved and available, the utilisation is still low. Administrative barriers, such as challenges in ordering and administration of the medication, high cost and lack of policy priority have been identified as possible reasons among providers and counsellors for not implementing XR-NTX [149-152]. Also counsellors and providers attitudes towards naltrexone may have an impact on the implementation. General resistance towards new treatment options among the clinicians can be decisive, as can lacking knowledge or having incorrect information about naltrexone [15, 79, 153-155].

A recent American study has examined opioid users' internal barriers to continued use of XR-NTX after 3 months in XR-NTX treatment. They found that cost and side effects were not the most frequently cited reason for ceasing XR-NTX. The main reasons were the patients felt "cured", or they would rather manage on their own [121]. A Dutch study investigating OMT patients' interest in XR-NTX found patients scepticism towards XR-NTX often were based on fear of injections or incorrect information about XR-NTX [32].

Many opioid users, including patients in OMT, identify with a long-term goal of abstinence from opioids [33, 148]. Some studies conducted in countries where XR-NTX is not yet approved, suggest that many opioid users express interest in taking long-acting naltrexone to assist them in abstinence if it was available to them [3, 32, 37, 156, 157]. The extent to which this interest translates into actual enrolment into XR-NTX treatment is not yet known.

## 1.5. Knowledge gaps

Although a number of studies have examined efficacy and safety of naltrexone in general and of XR-NTX in particular, further research that includes larger selection and several aspects are needed [8, 53, 61, 99, 139]. Both the WHO and Norwegian guidelines for the Pharmacological Treatment of Opioid Dependence express the need for more studies on the effectiveness of sustained-release formulations of naltrexone [47, 158].

Investigating possible patient treating matching factors among opioid users who volunteer for treatment with XR-NTX would be of clinical interest [53, 84, 107]. An important question is also whether there are sub groups who to a greater extent may profit from treatment with XR-NTX, and what characterises these [91].

Previous randomised controlled trials of XR-NTX have shown efficacy in settings with criminal justice offenders and in countries where OMT is illegal. It is not clear if results from these studies can be generalised to Norwegian and Western European clinical settings. Studies of XR-NTX in clinical settings where OMT is available at a low threshold may provide policy makers in Norway and Western Europe with a rationale in developing a differentiated selection of treatment modalities. It would also provide clinicians support in facilitating the best possible treatment option according to individual opioid users' needs and motivation. A question of special interest is whether opioid users with easy access to OMT are attracted to treatment with XR-NTX. It has been postulated concerns that treatment with naltrexone may prevent opioid users from enrolling into OMT [113, 159].

No studies have previously  compared XR-NTX with OMT medication [71] [1]. Two previous studies have compared OMT medications with oral naltrexone or naltrexone implants, but the number of included participants has been low [130, 138, 160].

Both short-term and longer-term treatment of XR-NTX has showed promising results [78, 80, 89, 109-111], but longer-term treatment has only been investigated to a limited extent [40, 84]. There is a discrepancy between the duration of most clinical studies on naltrexone and the often life-long, chronically relapsing duration of opioid dependence [41]. Longer-term studies of XR-NTX would increase the possibility to examine the potential of XR-NTX in the users' recovery process [17]. Whether patients will continue prolonged use of XR-NTX and whether achieved improvements will last during and after treatment, remain to be examined [38]. Both safety and effectiveness in long-term need to be more thoroughly investigated [2]. Also, there is no current evidence based recommendation regarding duration of XR-NTX treatment. The impact of XR-NTX on the long-term course of opioid use need to be assessed [17].

Due to the concern about adverse effects and increased risk of overdoses after ceasing naltrexone, thoroughly reporting incidence of serious adverse events during and after treatment is important [53]. Further examination of possible negative side effects of XR-NTX is needed, such as investigating whether use of other drugs are increasing when opioids are blocked by naltrexone.

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[1]In November 2017, shortly after our RCT study was published, an American research group presented results from an RCT comparing XR-NTX with BP-NLX (Lee et al. 2017).

## 2. Aims

The overall objectives of this thesis were to 1) describe a cohort of opioid users who volunteer for treatment with XR-NTX, 2) compare the effectiveness of XR-NTX and BP-NLX during a 12-week randomised clinical trial 3) evaluate effectiveness, safety and feasibility of XR-NTX in the treatment of opioid dependence during a 48-week period in a clinical setting in Norway.

The specific aims were:

1. To describe the characteristics; background and current life situation of opioid users volunteering to participate in a study of XR-NTX. (Paper I)
2. To investigate retention in treatment among participants A) in a 3-month RCT; comparing participants randomised to XR-NTX and BP-NLX (Paper II), and B) in a 9-month follow-up; comparing participants continuing XR-NTX and participants inducted on XR-NTX (Paper III).
3. To investigate use of opioids and craving for heroin among participants A) in a 3-month RCT; comparing participants randomised to XR-NTX and BP-NLX (Paper II), and B) in a 9-month follow-up; comparing participants continuing XR-NTX and participants inducted on XR-NTX (Paper III).
4. To investigate use of other substances and addiction-related problems among participants A) in a 3-month RCT; comparing participants randomised to XR-NTX and BP-NLX (Paper II), and B) in a 9-month follow-up; comparing participants continuing XR-NTX and participants inducted on XR-NTX (Paper III).
5. To evaluate treatment satisfaction and recommendation of treatment among participants A) in a 3-month RCT; comparing participants randomised to XR-NTX and BP-NLX (Paper II), and B) in a 9-month follow-up; comparing participants continuing XR-NTX and participants inducted on XR-NTX (Paper III).
6. To assess tolerability and safety aspects of XR-NTX among participants among participants A) in a 3-month RCT; comparing participants randomised to XR-NTX and BP-NLX (Paper II), and B) in a 9-month follow-up; comparing participants continuing XR-NTX and participants inducted on XR-NTX (Paper III).

# 3. Material and methods

## 3.1. Study designs

The Norwegian Centre of Addiction Research (SERAF) conducted a multi-site open-label randomised clinical trial (RCT) in collaboration with five hospitals in urban centres of Norway [2]. The participants were randomly assigned to receive either XR-NTX or buprenorphine-naloxone (BP-NLX) in a 1:1 ratio, for a 12-week period. The RCT period lasted from November 1, 2012 to October 23, 2015.

After the first 12 weeks, all randomised participants were offered to continue treatment with either XR-NTX or BP-NLX of their own preference for an additional 36-week study period. A very small number of participants selected BP-NLX in this follow-up, and due to this disproportional distribution, only participants who chose XR-NTX were included in the data analyses. The last patient completed participation in the follow-up study in July 6, 2016.

Paper I presents a cross-sectional study, examining the baseline characteristics of the opioid users who volunteered for study inclusion.

Paper II presents the randomised clinical trial, providing descriptive and comparative analyses of the two randomised groups in a noninferiority scenario during a 12-week period.

Paper III presents a longitudinal prospective cohort study of the participants who chose to receive XR-NTX for an additional 36 weeks after the initial 12 weeks. Descriptive and comparative analyses of the participants who continued XR-NTX treatment in the follow-up and participants who were inducted on XR-NTX in the follow-up are presented.

## 3.2. Study procedures

The study is registered at ClinicalTrials.gov ( # NCT01717963), first registered: October 28, 2012 [161], and performed according to the protocol version #3C, 12 June 2012. The study protocol is briefly summed up in a previous methodology article from the research group [2], and in the registration at ClinicalTrials.gov. The study was approved by the Regional Ethical Committee for Research South-East (#2011/1320), by the Boards of Research Ethics at the participating hospitals, and by the Norwegian Medicines Agency (EudraCT: 2011-002858-31). In addition to the original protocol, several amendments were approved and implemented during the study period, the last version of November 2016.

The study was conducted in accordance with international quality standards provided by the International Council of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to confirm compliance with Good Clinical Practice (GCP).

The calculation of sample size was partially based on results from previous research of sustained release naltrexone in Norway [83], and partially on the annual reports from the OMT cohort in Norway [2]. The findings of opioid use among these two samples were the basis of the calculated sample size. Power was set to 90% and the significance level at 5%. Further, it was assumed that both randomised groups would retain 70% of their participants at the end of Week 12. Minimum sample size was estimated in two scenarios: For the noninferiority scenario 20% was set as the margin, and this yielded a minimum sample size of n=58 in each treatment arm, n=116 in total. The superiority scenario assumed XR-NTX participants to have a mean of seven opioid negative samples out of the total twelve (7/12 or 0.58) samples, while participants receiving BP-NLX would display a mean of four opioid negative samples (4/12 or 0.33). Assuming a standard deviation of 3.0 in both groups and a significance level of 5%, the estimated sample size would be n=17 patients per medication arm or n=34 total as sufficient in order to show a significant difference between the arms with a power of 90%. The original recruitment target was a total of n=180 participants [2].

Allocation to either XR-NTX or BP-NLX was conducted by non-study personnel, computerised using a block permuted algorithm independent of site and gender and communicated by phone to study personnel in an open label manner.

To ensure consistency and quality of all the tasks that were performed during the study, the study personnel were trained in the different approaches and routines. The training included GCP course and training and certification in the structured interview; European version of the Addiction Severity Index (EuropASI) [162]. The study personnel were also trained in the use of Common Terminology Criteria for Adverse Events (CTCAE), and adverse events were coded according to these criteria. The different sites coordinated their procedures, including the registration of case report form (CRF).

The study was monitored by approved monitors from the Departments of clinical research support at the participating hospital sites. The monitors took part in the design, implementation and completion of the study. Once a year they visited the study sites, focusing on verifying the patient consents, verifying CRFs and the medical records, and verifying the study facilities.

The decisions about eligibility of the participants were taken jointly by the site investigator, the study personnel and a clinician from the OMT clinic. These were also responsible for reporting adverse

events (AE) and made decisions regarding treatment planning and possible study discontinuations for the participants.

To ensure the quality of the reported data and the performed analyses, the guidelines of CONSORT, STROBE and other recommended relevant checklists were applied [163, 164].

## 3.3. Participants

Information about the study was made available to opioid users and clinicians at OMT clinics, detoxification units and other services in the catchment area of the study hospitals. The OMT clinicians provided information to the patients and set a meeting between interested patients and the study personnel. Information about the study was also spread through the internet and in newspapers. When an initial n=30 participants were included in the study, we assumed they could activate their peer networks and spread information about the study among a larger community of opioid users and thus contribute to the recruitment [2].

All opioid users who claimed interest in the study were interviewed and underwent extensive screening and a general medical examination. Eligible patients were adults between 18 and 60 years with an opioid dependence disorder (DSM-IV). Patients with alcohol dependence were excluded from study participation, as were patients with serious somatic diseases such as acute hepatic failure or an AIDS indicator disease. Patients with less severe somatic diseases, such as those who were hepatitis C sero-positive, were eligible for participation. Patients with serious chronic or acute mental illnesses such as psychosis or suicidality were also rejected. Those with less severe mental illnesses such as depression or anxiety disorders were eligible for participation. Pregnant or breast feeding women were excluded from participation, since too little is known about XR-NTX and its effects on the fetus [165]. Female participants had to consent to using contraception during study participation [2].

In order to be eligible, the opioid users had to be registered in the national OMT program via one of the study hospitals. This guaranteed that the participants were offered psychosocial interventions and referrals to other forms of services if needed during the study period. This also guaranteed that participants who discontinued the study were taken care of and were prescribed substitution medication without any delay, if required. The clinicians at OMT cooperated with the study personnel in planning and implementation of start-up procedures, in treatment attendances and in other study related events.

Participants who dropped out of the RCT were offered re-inclusion in the follow-up study after week 12.

In paper I, the n=165 participants who volunteered for study inclusion were the subjects of investigation.

In paper II, the n=159 participants who were randomised to treatment arm (intention-to-treat) were the subjects of investigation.

In paper III, the n=117 who chose treatment with XR-NTX in the follow-up were the subjects of investigation.

## 3.4.    Screening procedures and measurements

Before inclusion, all eligible patients underwent a medical examination, a medical history was obtained and clinical lab tests (blood chemistry, haematology, hepatitis- and HIV-screening, vital signs and pregnancy test for women) were taken. Participants were screened for acute or chronic suicidality and psychotic disorders by using the MINI 6.0 interview [166]. They underwent interviews using the EuropASI; a structured manual covering demographic data, physical and mental health, education and work, drug use (measured in age at onset, usage, current use and duration of use), treatment experience and criminal behaviour [162]. Data were collected with a timeline follow back method [167].

In addition, the patients completed several self-reporting questionnaires collecting Patient-Reported Outcomes (PRO): A visual analogue scale (VAS) 1-10; assessed craving for heroin, treatment satisfaction and whether participants would recommend the treatment to others. The 25 item Hopkins Symptom Checklist [168] assessed mental health; Temporal Satisfaction With Life scale [169] assessed present satisfaction of life; McGill Pain Questionnaire [170] assessed current experience of pain; Insomnia Severity Index [171] assessed quality of sleep; and The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES-8D) [172] assessed motivation for abstinence. Europ-ASI and self-reporting questionnaires were completed at the following study attendances every fourth week throughout the study participation.

Urine drug tests (UDT) were collected every week during the RCT-period. The UDTs were analysed by study independent laboratory units.

Adverse events (AE), including adverse effects of study medication and serious adverse events (SAE), were reported at study attendances by the study personnel. The safety population in the RCT was n=143, those who took at least one dose of study medication. In the follow-up cohort, the safety-population were all participants, n=117. The AEs recorded in the study were classified using the Common Terminology Criteria for Adverse Events (CTCAE).

At the baseline interviews and during the first one and a half years of the study period, data were collected manually with paper and pencil. From summer 2014, the interviews and questionnaires were mainly computerised.

## 3.5. Interventions and start-up procedures

Before randomisation, the participant, if not abstinent from opioids, had an individually adapted tapering schedule to a maximum of 4 mg/day of buprenorphine. The inclusion and randomisation procedures were typically completed at a detoxification unit. This ensured that the opioid user, not under the influence of any drugs, could repeatedly receive information about the study procedures before entering the study. These procedures were also important to reduce the risk of drop-out between randomisation and induction on study medication.

If randomised to BP-NLX, the participant was inducted on a flexible dose of BP-NLX: Range 4-24 mg/day, target 16 mg/day [2].  When reaching a stable dose, the participants were discharged from the detoxification unit. The prescription and administration of BP-NLX were conducted by the OMT clinics, according to the national OMT guidelines.

As induction on XR-NTX may induce withdrawal symptoms, the participants who were randomised to XR-NTX were tapered off any opioids and completed a minimum of 72 hours without any opioids. Before XR-NTX was administrated, a urine drug test had to be negative on opioids before the participant was given an opioid antagonist challenge, an intramuscular test dose of 0.4 mg naloxone. If the participant did not respond with any acute withdrawal symptoms within two hours after the naloxone injection, an intramuscular injection of 380 mg Vivitrol ® was administrated. The injection was set into the gluteal muscle, alternating sides throughout the study participation. The participants were recommended to remain in an inpatient setting for a couple of days after the first injection, so they could get adequate pharmacological treatment for any withdrawal reactions to the XR-NTX injection.

The participants who were induced on XR-NTX in the follow-up study after week 12 went through the similar start-up regimen as described above.

Participants, who were randomised to XR-NTX and completed the study received a total of 13 XR-NTX injections and thus, were blocked against opioids during a 1-year period. Participants randomised to BP-NLX and who changed to XR-NTX after week 12 and participants who were re-included after week 12 received a total of 10 injections and were blocked against opioids during 9 months if completing the study.

## 3.6. Outcomes

In the exploratory analyses of baseline characteristics, outcomes were not predefined (paper I). The examined variables were participant demographics; the history of the use of heroin, substitution medication and other opioids, alcohol, amphetamines, cannabis, benzodiazepines, poly drug use and injection use; physical health such as numbers of hospitalisations, hepatitis status, and overdoses; mental health such as depression, anxiety and suicide attempts; SUD-treatment episodes; education and work; income; and criminal records.

Primary outcome variables of the 12-week RCT were retention in treatment and use of heroin and other illicit opioids, measured in days with use within the 4 weeks preceding each study attendance. Secondary outcome variables were the number of days with use of cannabis, amphetamines, cocaine, benzodiazepines, hallucinogens, and alcohol, and the degree of heroin craving, life satisfaction, treatment satisfaction, mental health, and the incidence of adverse events during the 12-week study period. Outcomes were compared between study participants allocated to BP-NLX or XR-NTX (paper II).

Outcome variables of the 36-week follow-up study were retention in treatment, use of heroin and other illicit opioids, use of other substances such as alcohol, amphetamine, cannabis, and benzodiazepines, and addiction-related problems such as injecting drug use, criminal activity, and money spent on alcohol and drugs, heroin craving and treatment satisfaction, and the incidence of adverse events including overdoses and deaths. Outcomes were compared between participants who continued XR-NTX treatment and those inducted on XR-NTX in the 36-week follow-up, and between completers and non-completers (paper III).

## 3.7. Data analyses

The collected data were entered into a GCP compliant database and de-identified before quality control and further computing.

In the descriptive and exploratory analyses, count data/categorical variables were presented as numbers and percentages. Mean (median) and 95% confidence intervals (CI) or standard deviation (SD) and range were reported on continuous variables.

In paper I, all participants who were included in the study (n=165) were subjects of the analyses. In addition to the descriptive and exploratory analyses, differences within the study participants regarding gender, age and their affiliation to the OMT program prior to inclusion were examined. If the normality assumption was violated, Wilcoxon and Mann Whitney non-parametric tests were used to explore differences between two groups. Spearman's test was used to analyse correlations between variables. A two-step cluster analysis was performed to examine the distribution of data on some variables. Missing data were excluded pairwise during the analyses.

In paper II, Intention-to-treat (ITT) analyses of efficacy endpoints including all n=159 randomised patients were performed. Differences in change in primary and secondary outcomes were assessed by linear mixed models with fixed effects for time up to second order, group variable and the interaction between the two randomised groups. Random effects for time and site were included in the models. A significant interaction would imply differences between the groups' changes throughout the follow-up period. All models were adjusted for age and gender.

Noninferiority analyses were performed by linear mixed models, where non-significant interaction between time and group was eliminated. Regression coefficients for group variables were combined with the pre-defined noninferiority margins (8 for use of heroin, 10 for use of illicit opioids, and 0.2 for opioid negative UDTs) to assess the noninferiority. The normality of residuals was assessed by inspecting the histograms. Bootstrap inference based on 1000 replications was generated in the case of skewed residuals; however, differences were negligible and hence the original results were reported.

In paper III, per-protocol analyses including the n=117 participants who received at least one injection of XR-NTX during the 36 weeks following the RCT-period, was performed. Descriptive analyses showed changes in drug use and addiction-related problems from the beginning of the follow-up (week 12), and at study end (week 48). A linear mixed model was performed to model changes in substance use and other variables over the time points. Random effects for time and participants nested within sites were included. Differences between participants who continued treatment with XR-NTX and participants who were inducted on XR-NTX in the follow-up, and differences between completers or non-completers were assessed by the same model with extra fixed effect for participant group and interaction between the group and time.

For analysing retention in treatment, Kaplan-Meier survival curves were plotted and log-rank tests were performed. Retention in treatment was defined as the number of days/weeks until study medication expired, and by the number of patients completing the study period.

The incidence of adverse events was reported as number of participants that experienced any adverse events among those who received at least one dose of study medication. In paper II, differences between the two randomised groups were analysed, and in paper III, differences between the participants who continued on XR-NTX and those inducted on XR-NTX in the follow-up were analysed. Fisher's exact test was used when reporting differences between the groups.

The results with p-values equal to or below 0.05 were considered significant. The noninferiority analyses in the RCT were assessed by one sided tests and in all the other conducted analyses by two-sided tests. In comparative analyses of repeated measures, p-values are reported for the mean differences between the groups.

IBM Statistical Package for Social Science (SPSS), version 24 for Windows and Statistical Analyse Software (SAS), version 9.4 were used in the data analyses.

A study independent statistician conducted most of the analyses presented in paper II and III. The data were de-identified, and the analyses were censored for any information that could disclose the group allocation. The author has performed the analyses in paper I, the descriptive analyses in paper III, the analyses of adverse events and any supplementary analyses in the thesis.

## 3.8. Author's role in the study

The author was responsible for recruiting and following up a total number of n=45 participants at two different sites. The assignments were numerous: planning participant attendances, building confidence in new relationships, schedule admissions at the detoxification units, interviewing participants, meetings and cooperation with the personnel at the OMT clinics, administrating the medication, recording all the data, and updating the CRF and the medical records. Home visits were a necessity in some cases, when participants were not able to get out of their houses due to anxiety attacks or heavy drug use.

To secure a valid database of all the sampled data when the study was completed, the author contributed in registration and cleaning of the data. The outcome in this thesis and in the enclosed papers is based on the full dataset from the study.

## 3.9. Ethics

The study was conducted in accordance with the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, World Medical Association [173].

Opioid users who expressed interest in the study were given detailed information. In particular they were informed about the possible effects and side effects of the study medications, extended-released naltrexone and buprenorphine-naloxone. Information was provided both verbally and in writing and participants were given a copy of their written informed consents according to the Helsinki declaration. By signing the consent, they agreed to participation in the RCT and in the follow-up. Participants were able to withdraw from the study at any time, and could commence opioid agonist medication as part of OMT on the day of study discontinuation if medically feasible. As participants were enrolled in the OMT program, those who discontinued the study were lost to the study investigation but not to the OMT clinics who remained responsible for their care and need for treatment.

The participants were provided a wallet-sized card that contained brief information about XR-NTX and where the date of the last administrated injection was noted. Information about XR-NTX and the study participation was registered in the participants' electronic medical records at the hospitals, in case of emergency and need of acute pain treatment.

The participants were not paid or compensated for taking part in the study, with the exception of reimbursement of travel expenses. They also received lottery tickets as incitement for providing the UDTs (approximately value $2 USD).

If the participants did not attend the scheduled appointments and did not respond to at least three attempts at communication during the ensuing week, participants were considered lost to follow-up from the study. If participants discontinued the treatment with XR-NTX, they were repeatedly informed about the increased risk of overdoses when the level of naltrexone in their blood decreased. In these situations the study personnel cooperated closely with the clinicians in OMT to prevent overdoses.

## 3.10. Role of the funding source

The study was funded by unrestricted grants from the Norwegian Research Council's Clinical Research Program (2011), the Norwegian Centre of Addiction Research (SERAF) at the University of Oslo, the Western Norway Regional Health Authority, and the participating study hospitals: Akershus

University Hospital, Haukeland University Hospital, Oslo University Hospital and Vestfold Hospital Trust. SERAF was the sponsor of the study, and hosted the regulatory and data management centre.

# 4. Results

In the results presented in this thesis, the participants were followed up to one year; from study inclusion through the 12-week RCT period and further through the 36-week follow-up. The results are presented according to the listed aims. The result section includes published and unpublished results.

## 4.1. The study sample

Figure 3 displays the flowchart of opioid users from the n=232 who were assessed for eligibility to those n=58 who completed the study after one year. The flowchart follows the participants in regard to which medication they were allocated to in the randomisation process.

Before study inclusion, n=67 of the n=232 who were screened with the intent to participate in the study, were excluded from participation. Of these, n=51 refused to participate, n=9 did not meet the inclusion criteria, n=3 failed detoxification before inclusion, and n=4 gave other reasons. The study included n=165 participants, and n=159 participants were randomised to receive either XR-NTX or BP-NLX. Between inclusion and randomisation, n=6 participants were missing; n=3 failed detoxification and n=3 gave other reasons. Of the n=159 participants randomised to the study, n=80 were assigned to XR-NTX and n=79 were assigned to BP-NLX (Figure 3).

# Figure 3 CONSORT Flowchart



N=232 Assessed for eligibility

N=67 Excluded

    N=9 Not meeting inclusion criteria
    N=51 Refused to participate
    N=3 Failed detoxification
    N= 4 Other reasons

N=165 Included in the study
    N=3 Failed detoxification
    N=3 Other reasons

N=159 Randomised in the study

N=80 Assigned to XR-NTX
N=71 Received XR-NTX
    N=9 Did not receive XR-NTX due to Drop-out (n=5), failed detoxification (n=3) and acute illness (n=1)

N=79 Assigned to BP-NLX
N=72 Received BP-NLX
    N=7 did not receive BP-NLX due to Drop-out (n=1), never received study drug (n=6)

N=15 Lost to follow-up
    N=11 Dropped-out
    N=4 Discontinued due to adverse effects

N=23 Lost to follow-up
    N=17 Dropped-out
    N=6 Discontiued due to adverse effect

N=56 Completed 12 weeks on XR-NTX

N=49 Completed 12 weeks on BP-NLX

Follow-up

N=54 Continued on XR-NTX in open-arm
N=2 Re-included in open arm XR-NTX

N= 43 Changed from BP-NLX to XR-NTX in open arm
N=18 Re-included in open arm on XR-NTX

N=27 Discontinued the study:

    N=15 Drop-out
    N=4 Due to adverse effects
    N=8 Other reasons

N=32 Discontinued the study:

    N=20 Drop-out
    N=6 Other reasons
    N=3 Due to adverse effects
    N=2 Due to serious adverse events
    N=1 Death

N=29 Completed one year in the study

N=29 Completed one year in the study

## 4.2. Participant characteristics

Table 1 presents the characteristics of the n=165 opioid users included in the study. When examining the participants' treatment experience, we found that 37.7% were not enrolled in OMT prior to study inclusion. This enabled comparative analyses based on the participants' prior affiliation to OMT.

**Table 1 Participant characteristics at study inclusion**

| | Mean / Number(percent) | 95% Confidence Intervals |
|---|---|---|
| **Gender** (n=161) | | |
| Men | 116 (72%) | - |
| Women | 45 (28%) | - |
| **Age** (n=160) | 36.0 | 34.7-37.3 |
| **Caucasian** | 142 (89.3) | |
| **Years of education** (n=159) | 11.3 | 10.9-11.7 |
| **Employment or school last 3 years** (n=160) | 43 (27%) | - |
| **Main income last 30 days** (n=159) | | |
| Employment income | 18 (11.3%) | - |
| Social security benefits | 123 (77.4%) | - |
| Acquisitive crime | 11 (7%) | - |
| **Convictions for criminal activities, lifetime** (n=149) | 4.2 | 3.1-5.3 |
| **Hepatitis C seropositive** (n=161) | 89 (53.6) | - |
| **HIV-positive** (n=165) | 4 (2.4%) | - |
| **Number of overdose attempts** (n=157) | 4.3 | 3.2-5.4 |
| **Number of suicide attempts** (n=151) | 1.4 | 1.0-1.8 |
| **Main drug problem** | | |
| Heroin | 96 (62.3%) | - |
| Substitution medication | 15 (9.7%) | - |
| Other opioids | 4 (2.6%) | - |
| Polydrug | 25 (16.2%) | - |
| **Heroin use** | | |
| Age at onset (n=154) | 21.7 | 20.7-22.8 |
| Years using (n=154) | 6.8 | 5.9-7.6 |
| **Injection use** | | |
| Age at onset (n=149) | 21.1 | 19.8-22.4 |
| Years using (n=148) | 10.1 | 8.7-11.6 |
| **Treatment** | | |
| **Affiliation to OMT** (n=154) | | |
| Enrolled in OMT prior to study inclusion | 96 (62.3%) | - |
| Not enrolled in OMT prior to study inclusion | 58 (37.7%) | - |
| **Residential detoxification** (n=157) | 5.0 | 4.2-5.8 |
| **Outpatient treatment sequences** (n=156) | 1.1 | 0.8-1.5 |
| **Times in residential treatment** (n=156) | 2.4 | 1.9-2.9 |

The comparative analyses showed that the participants enrolled in OMT at the time of study inclusion had more severe long-term addiction-related problems. These participants reported a significantly higher number of hospitalisations, a higher number of overdoses, more years with

injecting drug use and a higher number of them were Hepatitis C seropositive. Regarding their current situation, they reported significantly more days with use of substitution medication the last 30 days, which they were prescribed in OMT. They also spent significantly more money on alcohol, and reported to a less extent heroin to be their main drug problem.

Conversely, participants who were not enrolled in OMT at study inclusion had more severe current addiction-related problems. They had used more heroin in the last 30 days, and they had also spent more money on drugs in the last 30 days. They had conducted more illegal activities for profit in the last 30 days and reported to a greater extent heroin to be their main drug problem. Table 2 shows correlation analyses of the association between the types of opioid primarily used the last 30 days and various addiction-related variables. Based on the assumption that patients enrolled in OMT mainly used substitution medication and those not in OMT used heroin, the analysis confirmed the relationship between participants' addiction-related problems and their affiliation to OMT.

**Table 2 Correlation analysis of participant characteristics at study inclusion (week 0)**

| | Heroin use last 30 days | | Substitution medication last 30 days | |
|---|---|---|---|---|
| | Correlation coefficient | Significance level (2-tailed) | Correlation coefficient | Significance level (2-tailed) |
| **Heroin use last 30 days** | 1.000 | - | -0.443 | 0.000 |
| **Substitution medication last 30 days** | -0.443 | 0.000 | 1.000 | - |
| **Heroin use last 6 months** | 0.712 | 0.000 | -0.491 | 0.000 |
| **Polydrug use last 30 days** | 0.272 | 0.001 | 0.045 | 0.580 |
| **Injection use last 6 months** | 0.456 | 0.000 | -0.181 | 0.029 |
| **Injection use last 30 days** | 0.584 | 0.000 | -0.159 | 0.052 |
| **Acquisitive crime last 30 days** | 0.562 | 0.000 | -0.302 | 0.000 |
| **New in OMT** | 0.308 | 0.000 | -0.256 | 0.002 |

Another interesting finding was a majority of the opioid users reported either very high (=30 days) or very low (=0 days) on several variables such as use of heroin, substitution medication, benzodiazepines, polydrug use, and injection drug use the last 30 days. The participants also reported very high or very low on variables concerning experienced drug problems, problems with physical health, vocational problems, and mental problems in the last 30 days. This clustered

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distribution was seen regardless of the participants' affiliation to OMT prior to study inclusion. The clustered distribution was observed in histograms and a two-step cluster analysis confirmed the observation. Examples of this cluster distribution are showed in Figure 4.

**Figure 4 – Distribution of variables at study inclusion**
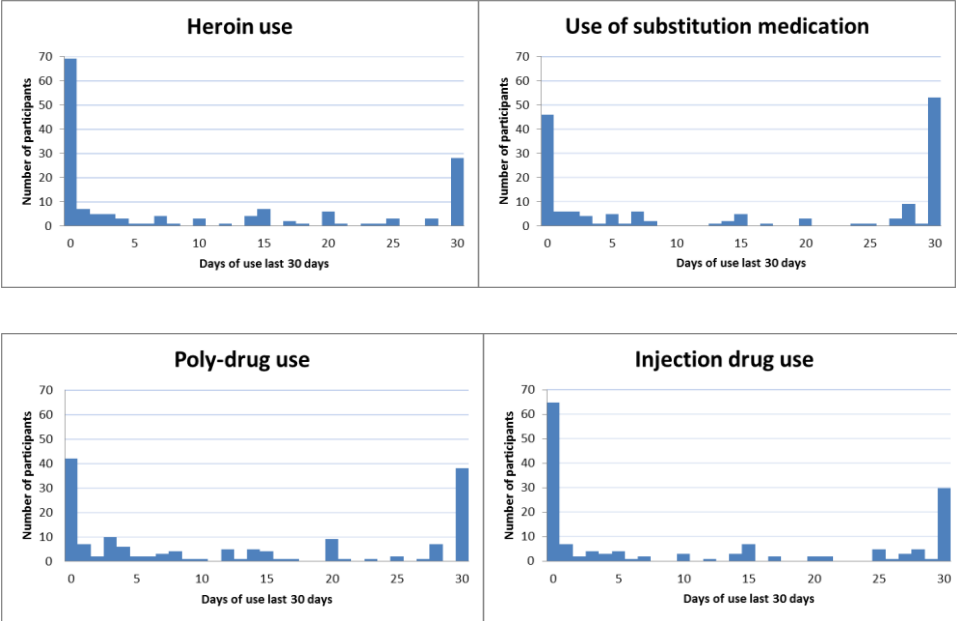


The distribution of days of use of heroin, substitution medication, polydrug, and injections among participants within the last 30 days before study inclusion.

When examining the baseline characteristics between the two randomised groups in the RCT, participants randomised to XR-NTX showed less use of heroin and other illicit opioids during the last 30 days, but not the last 6 months. On the other variables, there were no differences between the randomised groups.

## 4.3. Retention in treatment

Figure 5 displays retention in treatment for all randomised participants, n=159, from the time of randomisation to the end of the study one year later where n=58, approximately 37% of the ITT-population completed the study. Immediately after randomisation n=16 participants dropped out, n=9 in the XR-NTX-group and n=7 in the SB-NLX-group, and a total of n=143 took the first dose of study medication.

In Figure 5, the dark blue line shows the participants who were allocated to BP-NLX, n=79. A number of n=49 in the BP-NLX group completed the 12-week RCT. Of the RCT completers in the BP-NLX group, n=43 changed from BP-NLX to XR-NTX in the follow-up, and n=18 of those who were randomised to BP-NLX and dropped out of the RCT, were re-included in the follow-up. Of those n=61 initially randomised to BP-NLX who took at least one dose of XR-NTX in the follow-up, n=29 completed the study at week 48.

The light blue line shows the participants who were randomised to XR-NTX in the RCT, n=80. At week 12, n=56 had completed the RCT, and n=54 of them chose to continue with XR-NTX in the follow-up. Of those who dropped out of the RCT, n=2 participants were re-included in the follow-up study. Of those n=56 initially randomised to XR-NTX and who continued the follow-up, n=29 completed the 1-year study.

A total of n=134 opioid users took at least one dose of XR-NTX during the 48 weeks of the study; n=71 in the RCT, and n=63 were inducted on XR-NTX in the follow-up. Approximately 43% of the n=134 completed the study at week 48.

In the RCT, n=105 (66%) participants completed the 12 weeks. Mean days of retention was similar in the two randomised groups: 69.3 in the XR-NTX group and 63.7 days in the BP-NLX group. Of the non-completers, n=24 were randomised to XR-NTX and n=30 were randomised to BP-NLX.

According to the protocol, participants were offered XR-NTX or BP-NLX free of choice in the follow-up. However, only n=5 participants chose BP-NLX: n=2 randomised to XR-NTX and n=3 randomised to BP-NLX, and none of them completed the study. Due to this disproportional distribution, no comparative analyses were conducted between the randomised groups. A total of n=117 participants chose XR-NTX in the follow-up study, and n=58 (49.6%) completed the 9-month follow-up. Among participants who continued XR-NTX treatment from the RCT, n=28 completed the follow-up, and among participants who were inducted on XR-NTX in the follow-up, n=30 completed the follow-up. The mean number of weeks in treatment for the follow-up was 25.5. For the total 1-year study, the mean number of weeks in treatment was 37.5.

**Figure 5 Retention in treatment during 48 weeks**
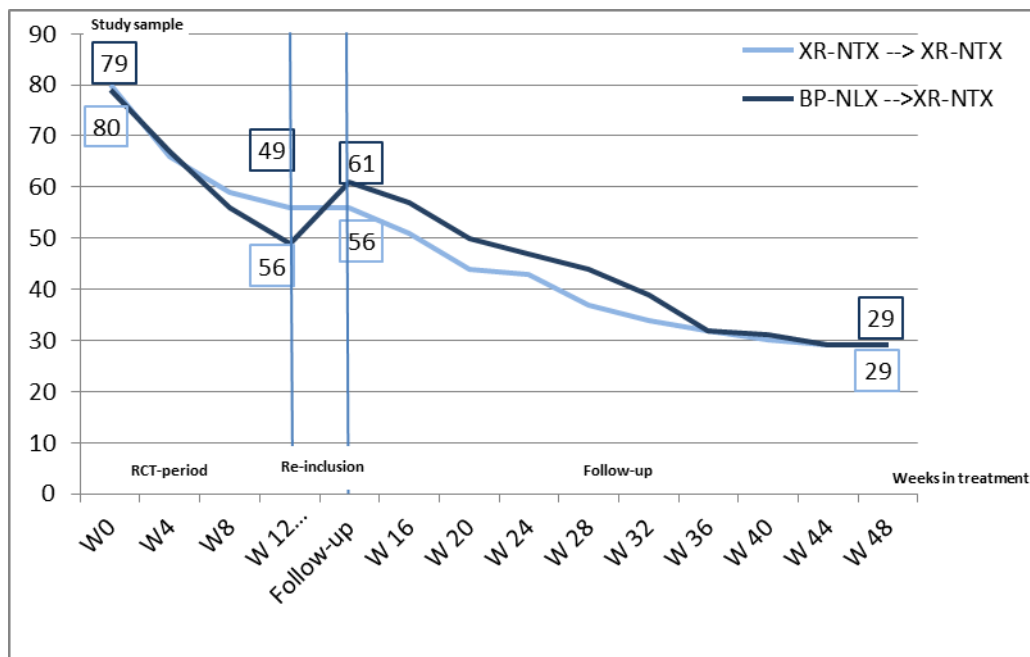


The Figure shows retention in treatment during the 12-week RCT and the 36-week follow up. The increase in number of participants after week 12 is drop-outs who were re-included in the study and inducted on XR-NTX in the follow-up. Participants are followed according to the medication they were allocated to in the RCT.

During the 1-year follow-up, non-completers gave various reasons for terminating the study. Of those n=143 who took the first dose of study medication, n=28 dropped out of the RCT-period, n=11 in the XR-NTX group and n=17 in the BP-NLX group. Another n=10 discontinued the study due to experiencing adverse effects; n=4 in the XR-NTX group and n=6 in the BP-NLX group (Figure 3).

In the follow-up, n=59 of the total n=117 participants discontinued the study. Drop-outs were the most common reason, n=35, while n=7 discontinued due to adverse events, n=2 due to serious adverse events, n=1 died and another n=14 provided other reasons. Other reasons provided were; "wanting to manage on their own without XR-NTX", or disliking the effect of XR-NTX when using other substances.

## 4.4.    Use of opioids and craving for heroin

During the 12 first weeks, participants showed a substantial decrease in use of heroin and other opioids (Table 3). The analyses of opioid negative UDT's showed that the XR-NTX group were noninferior compared to the BP-NLX group. Superiority analysis showed significantly less use of heroin (p=0.003) and less use of other illicit opioids (p=0.06) in the XR-NTX-group compared to the BP-NLX-group during the RCT.

In the follow-up, there was a further reduction in days of use of opioids. Participants showed a significant reduction in use of heroin from week 12 to week 44 (p=0.036), but to week 48, the reduction was non-significant (p=0.527). In use of other illicit opioids, there was a significant reduction from week 12 to week 32 (p=0.049), but not to week 48 (p=0.271). Half of the participants were abstinent from all opioids during the follow-up, and opioids were infrequently used (Table 3). None of the participants returned to daily opioid use during the study period.

There was a non-significant difference between participants continuing XR-NTX and participants inducted on XR-NTX in use of heroin and other opioids during the follow-up. Non-completers reported significantly more use of heroin from week 24 (p=0.049) to week 40 (p=0.019) and more use of other opioids in week 12 (p=0.020) and week 16 (p=0.031) compared to the completers.

Craving was measured on a VAS, and participants responded to the statement: "I need heroin" with scores from 0 (not at all) to 10 (very much so). In the RCT, the participants reported significantly lower craving scores from week 0 to week 12 (p<0.001).

In the follow-up, participants showed a non-significant reduction in craving between week 12 and week 48 (p=0.550). When comparing participants inducted on XR-NTX and those continuing XR-NTX treatment, the latter group showed significantly lower craving scores from week 12 (p=0.015) to week 20 (p=0.040). Completers showed significantly less craving scores than non-completers from week 20 (p=0.041) to week 36 (p=0.033).

## 4.5.     Use of other substances and addiction-related problems

The last 30 days before study inclusion, participants reported at least one day with use of the following substances: 58% used cannabis, 62% used benzodiazepines, 43% used amphetamines, and 20% have had heavy use of alcohol. The range of days using was 1-30 days. From inclusion to week 12, there was a non-significant reduction among participants in use of other substances or in addiction-related problems (Table 3). Except for use of benzodiazepines, where the XR-NTX group reported significantly less days with use (p=0.040), there were no differences between the randomised groups in the RCT.

At follow-up, participants reported a significant reduction in money spent on drugs from week 12 to week 48 (p=0.029). No significant changes were reported on the other variables among the participants between week 12 and week 48, however, polydrug use was significantly reduced from week 12 to week 32 (p=0.020).

When comparing participants who continued XR-NTX and those inducted on XR-NTX in the follow-up, the latter groups reported significantly more heavy alcohol use (p=0.044) and significantly more days working (p=0.031) at week 48. Non-completers reported significantly more polydrug use (p=0.046) and cannabis use (p=0.025) than completers at week 40.

**Table 3 Number of days with substance use and addiction-related problems**

| | Mean (95% Confidence interval) | | | |
|---|---|---|---|---|
| | Inclusion (n=159) | Completers RCT Week 12 (n=105) | Follow-up Week 28 (n=81) | Completers Follow-up Week 48 (n=58) |
| Heroin-days last 4 weeks | 9.9 (7.9-11.8) | 2.4 (1.2-3.6) | 0.3 (0.1-0.4) | 0.5 (0.0-1.1) |
| Other opioids – days last 4 weeks | 16.0 (13.8-18.1) | 7.5 (5.2-9.8) | 0.4 (0.0-1.1) | 0.4 (0.1-0.7) |
| Polydrug – days last 4 weeks | 13.0 (11.0-15.0) | 6.5 (4.6-8.3) | 5.1 (3.4-6.9) | 4.2 (2.3-6.1) |
| Cannabis – days  last 4 weeks | 9.3 (7.4-11.2) | 6.3 (4.5-8.2) | 8.6 (6.2-11.0) | 8.4 (5.7-11.2) |
| Amphetamines – days last 4 weeks | 4.4 (2.3-4.7) | 2.9 (1.5-4.2) | 2.9 (1.5-4.3) | 3.4 (1.7-5.2) |
| Benzodiazepines- days last 4 weeks | 10.3 (8.3-12.2) | 7.3 (5.3-9.2) | 6.5 (4.3-8.6) | 5.7 (3.3-8.1) |
| Heavy alcohol use – days last 4 weeks | 3.5 (2.6-5.7) | 3.2 (2.1-4.4) | 3.1 (1.9-4.2) | 2.6 (1.5-3.7) |
| Injection use – days last 4 weeks | 10.6 (8.6-12.7) | 4.5 (2.8-6.3) | 2.8 (1.7-4.4) | 4.1 (1.7-6.5) |
| Money spent on drugs last 4 weeks (Nkr) | 8588 (6365-10811) | 3306 (1855-4757) | 1266 (710-1821) | 1705 (978-2433) |
| Money spent on alcohol last 4 weeks (Nkr) | 421 (241-600) | 304 (188-420) | 388 (208-568) | 341 (147-535) |
| Acquisitive crime – days last 4 week | 5.8 (4.2-7.5) | 1.5 (0.4-2.5) | 1.7 (0.5-2.9) | 1.3 (0.3-2.4) |
| Work – days  last 4 weeks | 2.8 (1.5-4.0) | 4.3 (2.5-6.1) | 4.4 (2.2-6.5) | 5.7 (2.9-8.5) |

Mean and confidence intervals are descriptive numbers, not adjusted for repeated measures or site effect.

## 4.6.       Treatment satisfaction and recommendation of treatment

Every fourth week from inclusion and throughout the study the participants were asked how satisfied they were with the treatment the last 4 weeks, using a Visual Analog Scale (VAS) from 0: very dissatisfied, to 10: very satisfied. In the RCT, the XR-NTX group scored significantly higher on treatment satisfaction than the BP-NLX group.

Participants reported a non-significant increase in treatment satisfaction in the follow-up (p=0.198) (Table 4). When comparing participants who continued XR-NTX to participants inducted on XR-NTX in the follow-up, the latter reported significantly lower treatment satisfaction from week 12 (p=0.000) to week 32 (p=0.009), but the differences was non-significant between week 36 (p=0.124) and week 48 (p=0.278). Non-completers reported significantly lower treatment satisfaction from week 16 (p=0.009) to week 40 (p<0.001).

**Table 4 Treatment satisfaction in the follow-up study**

|  | Week 12 Mean (SD) | Week 28 Mean (SD) | Week 48 Mean (SD) |
|---|---|---|---|
| Participants continuing XR-NTX | 8.78 (2.15) | 9.39 (1.29) | 9.61 (0.79) |
| Participants inducted on XR-NTX | 3.96 (3.36) | 8.82 (2.39) | 9.28 (1.71) |
| Completers | 6.6 (3.87) | 9.46 (1.28) | 9.52 (0.88) |
| Non-completers | 6.06 (3.55) | 7.95 (3.07) | - |

Mean and standard deviation are descriptive numbers, not adjusted for repeated measures or site effect.

At every study attendance the participants were asked if they would recommend their treatment to opioid users who were in the same situation as themselves. On a VAS, participants scored from 0: not at all, to 10: very much so. In the RCT, participants randomised to XR-NTX would to a greater extent recommend their treatment to others than participants randomised to BP-NLX.

In the follow-up, all participants reported whether they would recommend XR-NTX to others (Table 5). There was a non-significant increase in the scores among the participants in the follow-up (p=0.517). When comparing the participants who continued XR-NTX treatment and those inducted on XR-NTX in the follow-up, the latter group reported significantly lower scores from week 12 (p<0.001) to week 24 (p=0.041). At week 48, the difference was non-significant (p=398). The non-completers reported significantly lower scores from week 12 (p=0.008) to week 40 (p=0.026), compared to the completers.

**Table 5 Recommendation of treatment in the follow-up study**

|  | Week 12 Mean (SD) | Week 28 Mean (SD) | Week 48 Mean (SD) |
|---|---|---|---|
| Participants continuing XR-NTX | 9.38 (1.31) | 9.7 (0. 81) | 9.75 (0.59) |
| Participants inducted on XR-NTX | 7.54 (2.74) | 9.25 (1.81) | 9.67 (0.76) |
| Completers | 8.92 (1.98) | 9.68 (0.74) | 9.71 (0.68) |
| Non-completers | 7.94 (2.59) | 8.75 (2.55) | - |

Mean and standard deviation are descriptive numbers, not adjusted for repeated measures or site effect.

## 4.7. Tolerability and safety aspects of XR-NTX

During the 12-weeks RCT, a total of n=65 participants of those n=143 who took at least one dose of study medication (45.5%), reported one or more AE. In the 36-week follow-up, n=62 of the total n=117 participants (53%) reported any AEs. Of the total of n=134 opioid users who took at least one

dose of XR-NTX during the study, n=80 (60%) reported one or more AEs. Withdrawal-like symptoms were reported most frequently. Other reported AEs were injection site problems, insomnia, headache, psychological reactions (typically depression or anxiety), infections (including n=4 pneumonia), non-serious injuries, and pain conditions in the back and in a knee. The withdrawal-like symptoms and the injection site problems were considered related to XR-NTX. It varied whether the other adverse events were assessed to be related to XR-NTX. Except for the reported withdrawal-like symptoms (p=0.001), there were no significant differences between the two randomised groups regarding reported AEs during the RCT-period.

In the follow-up, participants who continued on XR-NTX and participants who were inducted on XR-NTX were compared. Those who were inducted on XR-NTX in the follow-up, reported significantly more withdrawal-like symptoms (p=0.016) than those who continued on XR-NTX. There were no other significant differences regarding AEs between the two groups during the follow-up.

Thus, starting up with XR-NTX entailed a greater risk of experiencing withdrawal-like AEs. Typical reported withdrawal-like symptoms were nausea, chills, shivering, diarrhoea, sneezing and muscle-cramps.

Discontinuation due to AEs was reported among n=10 participants in the RCT, n=4 in the XR-NTX group, and n=6 in the BP-NLX group. Among participants in the follow-up, n=7 discontinued due to AE; n=4 of those who continued on XR-NTX, and n=3 of those who were inducted on XR-NTX. The type of reported AEs among those who discontinued varied; psychological reactions, insomnia, headache, increased craving for heroin, seizure, injection-site problems, need for pain treatment, weight loss and withdrawal-like symptoms, the latter being the most prevalent.

In the RCT, n=9 participants reported serious adverse events (SAE), and respectively, n=5 in the follow-up. One participant randomised to BP-NLX reported a non-fatal overdose on opioids in the RCT period. No opioid overdoses among participants treated with XR-NTX were reported during the study. In the follow-up, n=3 participants reported non-opioid, non-fatal overdoses: of them, n=2 were due to Gamma Hydroxybutyrate (GHB). The other SAEs were infections, surgeries, a withdrawal related incident, and acute pain condition. A majority of these events required prolonged hospitalisations. All participants recovered without sequelae. Two of the reported SAEs were serious injection-site reactions requiring surgery, and these two participants discontinued the study. Except for the related incident and the two serious injection-site reactions, the other SAEs were not considered related to XR-NTX. There were no deaths among the participants in the RCT period, but one participant died during the follow-up.

The hospital guidelines for reporting adverse events, entails that any events occurring within 3 months after treatment closure are to be reported. The study procedure has been in adherence to these guidelines. No additional adverse events were reported within 3 months after discontinuation of the study.

# 5. Methodological considerations

The study presented in this thesis and in the enclosed papers have some methodological limitations that need to be considered. The results from the study should be interpreted in view of limitations discussed in the following sections.

Criticism has been raised about how treatment results in studies of SUD in general are evaluated [41]. Despite opioid dependence being considered as a chronic and relapsing disease, treatment is usually organised in limited time periods, and results are primarily measured in terms of recovery [9]. The concept of opioid dependence has changed during the years. There has been a movement from treatment in residential settings to outpatient settings and the focus on harm reduction has largely increased. In our study, the main outcomes are retention in treatment and use of opioids and other substances. Consistent measurements such as used in our study, may be a too rigid way of evaluating whether an approach can be effective. In this perspective, it is relevant to discuss the effectiveness in regard to the participants' treatment goal. The findings in this study could indicate that some of the participants' goals were recovery, while other had more harm reduction purposes.

## 5.1. Study designs

Prior to the start-up of the study, a comprehensive study protocol was prepared. The protocol was indicative of the research work carried out during the study, including how the analyses were conducted and the results were presented in the papers, with one exception: In the follow-up, participants could choose the medication based on their own preference. While n=117 chose to either continue on or to be inducted on XR-NTX, only n=5 chose to either continue on or change to BP-NLX. Due to this disproportional distribution, no comparative analysis could be conducted between the two groups. The protocol was considered to be sufficiently robust to generate information of clinical and scientific value [2].

### 5.1.1. The cross-sectional study

A cross-sectional study is a study that is carried out at one point of time. In the present study, the baseline point of time was defined as just prior to study inclusion (paper I). The baseline data, which were collected with the timeline follow-back method, were reported in the last 30 days prior to study inclusion. The baseline data were collected before the participants were allocated to receive either XR-NTX or BP-NLX. This cross-sectional study provides the opportunity to investigate and identify any specific characteristics among the study participants, independent of the medication they were randomised to in the RCT. The number of participants included in the cross-sectional study was

n=165. Opioid users, who were screened for participation but for different reasons were not included in the study, were not a subject of investigation in this study.

A cross-sectional study is exploratory and suitable for measuring prevalence. A cross-sectional study limits the ability to draw causal inferences, but can be useful for developing hypothesis. The finding in regard to the participants' affiliation to OMT prior to study inclusion was a result of examining the baseline data, and led to the conduction of ad-hoc analyses, comparing the identified groups. The study did not assess the participants' motivation for joining the study in particular, but one hypothesis developed was that the participants not in treatment prior to study inclusion were attracted to a substitution-free treatment with XR-NTX rather than to OMT. Our findings were confirmed by a correlation analysis, but the results must be interpreted with caution, and should be repeated and verified in other studies.

Another finding when examining the baseline data was the observation of the clustered distribution of several variables. This lead to a hypothesis that we could identify two clusters among the participants: those in recovery and those with severe ongoing addiction-related problems. However, this finding must be interpreted with caution, and a two-step cluster analysis was conducted as a control measure. The cluster analysis recognised two clusters and suggested they had a fair quality. When imputing only a few of the clustered variables, the quality of the clusters was considered good. The more variables imputed in the analysis, the less obvious were the clusters.

Given the explorative nature of this study and the large number of variables that was collected at baseline, it is necessary to be critical of which variables to use in the analyses. The risk of a Type 1 error may otherwise be high, as significant results may be attributable to chance. A significance level of 5% implies that in comparisons, one in twenty significant results may be false [174].

A Type 2 error may occur if the sample size is too small, and hence the power is too low. This may lead to a situation where actual differences between groups are not detected. In this study, several differences were detected between the participants who were enrolled in OMT prior to study inclusion and those who were not. However, these differences must be interpreted with caution, and may advantageously be verified in further research among a larger sample. A larger sample may also reveal additional differences between the groups [174].

### 5.1.2. The XR-NTX vs. BP-NLX randomised clinical trial

The great advantage of a RCT is that if differences in outcome are found, this can be attributed to the intervention and not to differences between the randomised groups. The participants are allocated to the different interventions by randomisation and the groups are followed in the same way. A RCT

requires that those randomised are treated equally except for the intervention. The endpoints should be registered in the same way and with the same quality. It is a goal to uphold the similarity between the two groups throughout the whole study, except for the randomised medication. Following this, the only factor that should differ between the groups is the intervention.

In accordance with the Cochrane Handbook, sequence generation, allocation concealment, blinding, and complete data outcomes are important factors to reduce the risk of bias and secure the best quality of a RCT [175, 176].

The sequence generation was conducted by non-study personnel, computerised using a block permuted logarithm, and communicated to the study personnel by phone. The generation was independent of gender and site, and thus the risk of selection bias was considered low [177].

Concealment of allocation (hidden randomisation) implies that the participant must have met the inclusion criteria and consented to participate before being allocated [177]. If not, this could have an impact on his/her participation in the study. The allocation in the present study was independent of the clinicians and the study personnel. As OMT was available for all study participants, we suggest the motivation for study participation was to obtain XR-NTX. Some of the participants may have been disappointed when they were allocated to BP-NLX, and there is a risk that this affected their adherence in the RCT [15]. However, to minimalise this risk, all participants were offered XR-NTX after week 12.

Blinding of the participants is important to avoid performance bias, and the use of placebo is a possibility that can be considered in a RCT. Hence, as long as there is a substitution medication for opioid dependence that is effective and so far considered one of the best possible treatment options (best practice), ethical considerations entailed that buprenorphine should be the alternative to XR-NTX in this trial. The use of placebo has been criticised in previous studies of naltrexone [112, 178]. Blinding could still be an alternative, but besides some substantial practical challenges in masking placebo injections and placebo BP-NLX, we presumed that participants would de-mask and quickly recognise their respective treatment due to their long experiences with opioid use. There are some disadvantages in not masking, such as the expected effects of the medication could affect the two groups, and there may also be performance bias, detection bias and bias in the analyses. However, our conclusion was that masking or use of placebo was inexpedient. Through comprehensive previous research, including blinded placebo-controlled studies, the efficacy of XR-NTX has been established, and an open-label study may increase generalisability [78, 80, 89, 105]. When examining the effectiveness of XR-NTX, masked studies are less important [15].

Except for the analyses of adverse events, a study-independent statistician performed most of the analyses in the RCT. The dataset was de-identified and allocation was masked, and this implies a reduced risk of detection bias in the analyses.

Complete data outcome is important to avoid attrition bias. One challenge in a RCT is non-compliance, the number of randomised participants lost to follow-up. This is in general a problem in studies of people with SUD [79], and withdrawal symptoms in the initial phase of XR-NTX may increase the drop-out rate in studies of XR-NTX in particular [80]. Intention-to-treat (ITT) analysis is a strategy where all the randomised participants are included in all the analyses. The strictest form of ITT is to also include participants who were included but not randomised to the study. The number of included participants in this study was n=165; n=1 was a failure inclusion, and n=5 participants were lost to follow-up between inclusion and randomisation. The number of randomised participants was n=159 and these were the subjects of investigation in the RCT, with an exception for the analyses of adverse events.

The advantage of ITT analyses is that the randomised allocation is followed and the treatment effect in clinical practise can be estimated. Hence, this requires that all participants are followed up; otherwise the analyses may be equivocal. In our study, the attrition rates among the participants who dropped out from the study between randomisation and the first medication dose were almost equal (n=9 in the XR-NTX group and n=7 in the BP-NLX group). This may to a lesser degree influence the results compared to a situation where the attrition was skewed due to major attrition in one of the randomised groups. In ITT analyses there may be missing data which have to be accounted for and treated with an accurate method.

Modified intention-to-treat (MITT) is an alternative strategy, where the ITT-number is modified by specific criteria. In the present trial MITT was used in analysis of adverse events and the specific criteria where participants who took at least one dose of study medication. The most interesting safety aspect was to explore the adverse effects of XR-NTX, and secondly to compare it with the adverse effects of BP-NLX. Hence, AE is reported by the number of participants who experienced any AE and it was considered most relevant to use MITT. Of the n=159 who were randomised to the study, n=143 took at least one dose of study medication and those were the subject of the analysis of AEs. Although ITT analyses are considered the best option, a meta-analysis comparing ITT and MITT in n=72 RCTs found comparable estimates of treatment effect and the conclusion was that MITT analyses did not bias trial results [179].

A need for noninferiority studies comparing retention in treatment with XR-NTX and substitution medication has been emphasised [180]. A noninferiority trial tests whether a new treatment is not

acceptably less efficacious than an established treatment [178]. According to this, the sample size was estimated with a 20% noninferiority margin [2]. When there is an available treatment option such as OMT where effectiveness has been documented in several studies, it is considered expedient to examine whether XR-NTX is no worse than BP-NLX.

Although a RCT is the gold standard in comparing two different treatment modalities, it may turn out to have some performance bias. Self-determination and patients own engagements in treatment are important principles in the treatment of opioid users [35, 148]. According to these principles, a number of participants are likely not to participate in a RCT due to the random allocation, or they will withdraw from participation if not allocated to the preferred medication arm [15, 130]. We suggested participants preferred XR-NTX over BP-NLX in our study. On the contrary, a previous Norwegian study comparing naltrexone implants and methadone suggested methadone was the preferred medication [130]. Methadone had at that time a limited availability in Norway. Although these kinds of problems may bias the result in a RCT, it may contribute to reflect how the treatment options would be accepted in a clinical setting. The recently published American X:BOT study [123]comparing XR-NTX with BP-NLX, also discussed this problem, as XR-NTX was not as widespread and known treatment option among opioid users as BP-NLX. A possible solution to minimise this problem could be to randomise participants in two sequences; first, participants could be allocated either to a "free-of-choice" group or to a group that would be randomised. Secondly, the two groups could either choose between the two treatment options or be randomised to one of them [15]. This may to a higher degree reflect the participants' needs and preferences and contribute to increased retention in the study. However, to be able to provide useful results with this method, a large cohort would be required.

In the RCT period the participants randomised to BP-NLX were in contact with the OMT clinics more frequently due to daily intake of BP-NLX. This increased the likelihood of BP-NLX patients receiving counselling more frequently than the XR-NTX patients, and  this may have had an impact on their adherence in the study [53]. The 12-week duration of the RCT is short in regard to the chronic nature of opioid dependence. However, the duration was considered appropriate according to the aim of comparing the effectiveness of XR-NTX and BP-NLX.

### 5.1.3.    The longitudinal prospective cohort study

A study is defined as longitudinal when individuals are followed over time and the data are collected at different time points during the follow-up [181]. In this prospective study, we followed the cohort of opioid users who received XR-NTX during a 36-week period and recorded the study variables and outcomes as the study progressed.

One advantage of cohort studies is the ability of measuring changes in outcome and determining variable patterns over time. Considering the short duration of the RCT, the longitudinal cohort study could provide us with a greater understanding of the effectiveness, safety and feasibility of XR-NTX. Any limitations in the RCT, e.g. in regard to attrition, may also have impact on the following cohort study. However, by re-including participants who dropped out of the RCT, this problem is minimised.

According to the protocol, participants were able to choose between XR-NTX and BP-NLX in the follow-up, and the intention was to perform comparative analyses between the two groups. However, only n=5 participants chose BP-NLX in the follow-up and none of them completed the study. Due to this disproportional distribution, no comparative analyses were performed. The lack of a comparative control group is considered a limitation to the study. If comparing the study cohort (XR-NTX) and a control group (BP-NLX), we would to a greater degree be able to assess whether results were attributed to the impact of XR-NTX. The aims of the study were to investigate the effectiveness, safety and feasibility of XR-NTX in a clinical setting in the long-term. In regard to these aims, comparative analyses between participants who continued on XR-NTX and participants who were inducted on XR-NTX in the follow-up, and between completers and non-completers, were performed. The present design was considered appropriate to achieve the aims of the follow-up study.

The subjects of investigation in the follow-up were the n=117 participants who received at least one dose of XR-NTX after week 12. All of these n=117 participants were also the target group when examining adverse events.

A longitudinal study is in particular vulnerable to drop-out and missing data, thus appropriate methods of analysis are needed to deal with missing data and to estimate treatment effect for those who dropped out [182]. If treatment with XR-NTX was systematically followed by counselling, it would probably provide better results [111]. Psychosocial treatment was not a mandatory part of the study. However, some participants presented a need for and received supplementary treatment. If the participants were satisfied with the way their presented psychosocial needs were met, they may have remained longer in the study. A cohort study is exposed to bias to a greater extent than a RCT. This will be discussed in the further sections. The participants who volunteered to receive XR-NTX in this longitudinal study may model what will happen in a clinical setting if XR-NTX were an available treatment option to all opioid users in Norway [15].

## 5.2. Sample and selection bias

Selection bias implies that the study sample in some way differs from the population it is supposed to represent. The bias can often be connected to the population from which the sample was collected, the recruitment process, or the drop-outs. Selection bias may reduce the representativeness and influence the treatment outcome.

The sample size was calculated to have enough power to detect differences between the two randomised groups in a noninferiority scenario. As many previous studies of naltrexone have had low retention rates, the importance of good power estimation is underlined [128]. The sample size calculation should secure enough power in the analyses to produce more accurate estimates of the results. Although we were not able to reach the n=180 recruitment target, the number of opioid users who participated in the study should be high enough to avoid Type 2 error, that are more likely to be found if the sample size is small and without enough power [174].

The study sample is not random. It is not likely that they represent an average and independently selected sample of opioid users, as we suggest the participants were attracted to the study by the option to receive XR-NTX. However, as we managed to recruit both participants who were enrolled in OMT prior to study inclusion and not, this may imply that we have certain representativeness within the study sample concerning OMT affiliation.

The different sites may have had different approaches in the recruitment process, which may have caused selection bias. The volunteering opioid users who were considered eligible were included in the study, but it was not necessarily random which opioid users who volunteered for the study. The majority of the study participants were recruited by clinicians in OMT. Whether the clinician introduced the study to their patients or not may have been influenced by the clinicians' attitudes towards XR-NTX and their previous experience with the project. A selection process took place prior to the eligibility process, and many opioid users were never given information about the study.

The randomised groups showed significantly different scores regarding use of opioids the last 30 days prior to inclusion. Participants randomised to XR-NTX reported fewer days with opioid use than those randomised to BP-NLX. When comparing the use of opioids the last 6 months before inclusion, there were no differences between the two groups. Reduction in drug use prior to treatment entry has been seen in previous research [56, 183]. We have no explicit explanation for the observed differences between the groups at baseline, but it is not evident that abstinence prior to treatment entry is a predictor of treatment entry, completion or outcome [183]. To minimise the risk of bias, the differences in baseline values were taken into account when estimating the linear mixed models.

## 5.3.  Information bias

If information collected in the study is not correct or if variables are misclassified, we refer to this as information bias.

A large number of data from the study were based on patient reported outcomes (PRO). The veracity of this kind of data are of frequent concern. PROs may be influenced by participants being under the influence of drugs or having cognitive difficulties that may lead to recall-bias. Participants may also have an interest in exaggerating or undermining the reported data. These factors may reduce the reliability and validity of the data, but different precautions can be made in order to minimise this risk, e.g.  standardised questionnaires, procedure manuals and staff training [184]. In our study, personnel were skilled and trained for the tasks, and the timeline follow-back method we used is considered useful to reduce recall-bias. Participants were informed about research data being kept separate from medical records in order to increase the confidentiality and reduce the participants concerns about information leading to personal consequences. Although PROs have some limitations, they have been shown to be reliable if conditions are well prepared [184].

As a multi-centre study, several clinicians and study personnel were involved in the recruitment process and the follow-up. Despite being trained and coordinated in the use of Europ-ASI and the other reported assessments, this may be a potential source of error variance. Besides possible differences in reporting and registration of data, the relationship between the participant and the personnel can be decisive. The personnel had different professional backgrounds and different levels of clinical experiences. This may have had an influence on the opioid users' treatment process and their participation in the study. Some of the questions were personal and challenging to answer and a trusting relationship between the participant and personnel would be beneficial in order to obtain truthful answers.

## 5.4.  Attrition bias

Attrition bias refers to bias caused by study participants' loss to follow-up. Attrition is a well-known problem in studies of drug users  [64] - and this leads to a high number of missing data when the data are not completed for all the participants at all time points [179]. Due to attrition and missing data, the results may be less valid and to a lesser extent generalisable for the population of opioid users they are supposed to represent.

In a randomised trial, the use of ITT-analysis is recommended as the best method to prevent attrition bias [179]. Results may be skewed by attrition bias if one of the randomised groups presents a higher

drop-out rate, and this may violate the internal validity. The distribution of the missing data was about equal in the two randomised groups in our study, and this reduced the attrition bias caused by missing data. To reduce the problem of attrition it is important that the methods of statistical analyses are capable of handling missing data. We applied linear mixed model approach, which handles missing data in an appropriate method and is considered a suitable approach for assessing longitudinal data.

It is commonly assumed that the non-completers will be among those who are most dissatisfied with the treatment and least likely to adhere to the treatment, and thus would be more likely to report lower on measures of value. In the present study, it is possible that the non-completers used more opioids than the completers, at least after they discontinued the study. Poor compliance which leads to missing data may have resulted in no differences being revealed when the two groups were compared [128]. This phenomenon, the failure to detect an effect or a result that is present, is categorised as a Type 2 error.

## 5.5.  Confounding factors

Confounding factors are associated both with the outcome and the independent variable (exposure) and can increase variance and introduce bias to the results. A confounding factor cannot be caused by the exposure or the outcome. A mediator, however, is a factor that may be affected by the independent variable, and may in turn affect the outcome. Both confounders and mediators may lead to an overestimation or underestimation of a treatment effect.

Cohort studies may in general be prone to confounding due to differential loss to follow-up. A RCT, however, is not prone to this due to the randomisation process, and as seen in the present study, there were similar losses in both groups during the 12 weeks of the RCT [63].

If the study objects were sampled from a special group of opioid users, this may have had a confounding effect that may have reduced the generalisability of the study. When looking at previous research of naltrexone, particularly motivated groups, e.g. health workers, have shown good results regarding retention in treatment [40], and thus the participants' motivation could be regarded as a confounder.

Previous research in the naltrexone field has identified craving scores and longer duration of opioid dependence as potential confounders regarding craving for opioids when using long-acting

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naltrexone [74]. High craving scores prior to XR-NTX induction seem to influence on craving scores after induction on XR-NTX.

Gender and age are in general often regarded as confounding factors in analyses [174]. In our study, the mean age was lower among participants compared to the average OMT patient. This may have impact on the results of the analyses. However, in the mixed model approaches, analyses were adjusted for age and gender.

Participants' treatment preferences and disappointment over not being randomised to the preferred medication may be a confounder (Figure 6) [63]. Even if substitution medication was available to all the participants, they volunteered for this study where they had the possibility to receive XR-NTX. As XR-NTX was not available to opioid users in general in Norway, it was likely that the participants joined the study with the intent of obtaining XR-NTX. The very low proportion of participants who chose BP-NLX in the open-arm supports this assumption. We suggest they were particularly motivated to receive XR-NTX and if they were randomised to BP-NLX they may have become disappointed. This may have negatively affected the results regarding adherence, continued opioid use and treatment satisfaction in the RCT [185]. This could have been controlled if the participants were asked which medication they preferred most in the RCT or if the participants were randomised in two sequences, as described above in section 5.1.3 [15, 130]. In the recently published American X:BOT study where participants were allocated to either XR-NTX or BP-NLX, both medications were approved by the authorities and available to opioid users in general [123]. Although structural barriers to treatment may limit American opioid users' access to treatment in general, it is likely that the two medications were about equally attractive and hence less of a confounding factor compared to our study.

**Figure 6 Confounders and mediators**
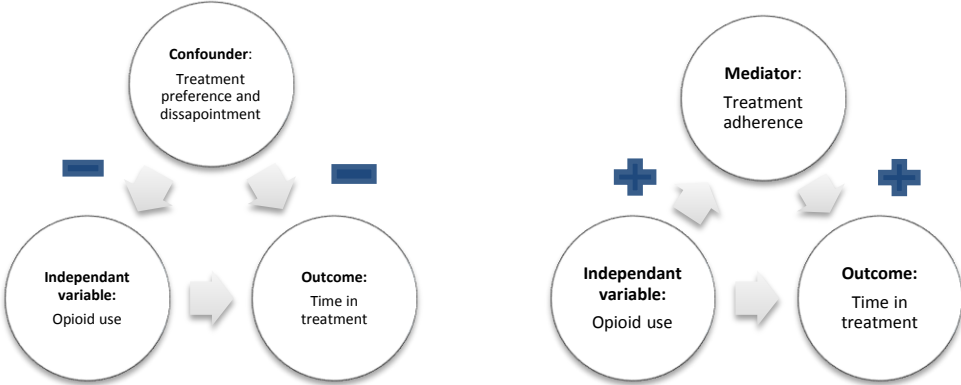
Placebo effects may also be a confounder. In our study, participants were given information about the ability of XR-NTX to reduce craving. The participants' expectations of experiencing reduced craving may have had an impact on how they in fact perceived and reported craving. The attention the participants received when they were followed up in the study may have had a positive impact on their self-esteem. Improved self-esteem may lead to improved sense of mastering and changes in drug use and addiction-related problems. An effect such as this is known as the "Hawthorn effect", when participants change their behaviour due to awareness of being observed [186].

## 5.6. Internal and external validity

Validity is an expression of the degree to which a study or a specific test is capable of measuring what it is intended to measure. It is a goal to minimise the systematic errors and bias to increase the internal validity. External validity rests on internal validity, and implies that the results from a study can be generalised to other situations or populations [174].

A randomised controlled trial is considered to have high internal validity, but as described previously, there are possible sources of bias that may have had an impact on the validity, e.g. the present RCT was not blinded [175].

A longitudinal cohort study is to a greater extent exposed to bias as described above, and this may lower the internal validity. The lack of a control group, the attrition rate of approximately 50%, and the possibility of Type 1 and 2 errors are among factors that may bias the results from the follow-up study. Thus, the results should be interpreted with caution, and the study may advantageously be repeated to strengthen the reliability of the results.

The sample size (power) and the population the sample is representing can affect the external validity of a study. The sample size is estimated according to a noninferiority scenario in the RCT, considered to have sufficient power to provide reliable results. The external validity in the present study is considered good due to the naturalistic, clinical setting. It is likely that the results can be generalised to other high-income countries with similar context and conditions as Norway, such as those with equivalent health care systems and regulatory frameworks regarding OMT [187].

## 5.7. Strengths

This is the first study comparing XR-NTX with BP-NLX. The noninferiority design provides a valuable contribution to consider the effectiveness and safety of XR-NTX compared to the well-documented effects of BP-NLX. An US study (X:BOT) also comparing XR-NTX and BP-NLX was started after our study and overlapped in time [123]. The X:BOT study presented results comparable to our RCT results and had a larger sample size (n=570). As discussed above in section 5.6, corresponding results from other studies may strengthen the validity of our study.

The naturalistic clinical setting of our study is a strength, where all the participants had access to OMT, but still volunteered for XR-NTX. The inclusion criteria entailed that few opioid users were excluded from the study, and the participants were found to be a heterogeneous group which did not differ from the general population of opioid users in Norway.

The mandatory enrolment in OMT implied that the participants could obtain substitution medication if discontinuing the study. This also ensured that the participants had access to ancillary services if needed, both during the study and after study discontinuation. Hence, participants who discontinued the study were not completely lost to follow-up and any adverse events that occurred after study discontinuation were reported and taken care of.

This study is also the first study in Norway and in Western Europe of XR-NTX treatment of opioid users. Although the medication is approved in Russia and in the USA, there are many societal and policy aspects that differ between these countries and Western Europe, which may have affected the treatment outcomes. The clinical setting of the RCT, where the participant characteristics to a great extend correspond with the national OMT population in Norway, is also considered as beneficial compared to RCT conducted among criminal justice offenders or in countries where OMT is illegal [78, 89].

## 5.8. Ethical considerations

The study was conducted according to the Helsinki declaration and the participants gave their written informed consent before study inclusion [173]. An informed consent entails voluntariness and that information is comprehended. The consent was obtained in a process, where information about the study was repeated both in outpatient settings and inpatient before study inclusion and randomisation. It was important that the patients were not under the influence of drugs when the information was provided so they could obtain a full understanding of what study participation entailed. The participants were able to withdraw from the study at any time.

Research in vulnerable groups is challenging. Drug users are often regarded as vulnerable due to the nature of opioid dependence. The drug users' motives and behaviour are often affected by ambivalence and craving for drugs. Their cognitive abilities may be weakened and their autonomy may be reduced due to the impact of drugs [188]. The amount of addiction-related problems often makes them outcasts in our society. They are often not regarded as trustworthy and they frequently lack confidence in other people. The relationship between the client and the clinician is an important factor to succeed in treatment and one of the key points regarding the clients' engagement in the treatment process [35]. This aspect may also be important regarding the relation between the participant and the researcher.

In qualitative research, reflexivity is a known concept. Reflexivity implies that we recognise and consider the importance of our own experiences, viewpoint and opinions in the research [189]. Even though a researcher should have a neutral and open-minded orientation towards the research topic, we must be aware of and acknowledge that our attitudes and actions may be biased. The participants in this study met different study personnel with different backgrounds and expertise. The differences in clinical experience among the study personnel, could affected how they handled the meetings with the participants. When the participants met with study personnel regularly every fourth week for a year and answered personal questions, it is likely that relationships similar to the one between patient and clinician that we see in traditional treatment processes were developed. Study personnel (being experienced clinicians) may have indirectly affected the participants' treatment outcomes, by using their skills as clinicians in interactions with the participants. It is impossible not to interact with the participants, and if the study personnel kept a distance to participants, they could feel rejected and thus discontinue the study.

As XR-NTX is not currently approved and available for purchase in Norway, the manufacturer supplied the study medication with XR-NTX at no cost. This being an investigator-initiated trial, a contract was designed which implied that the manufacturer provided the study with XR-NTX without restrictions. Neither the manufacturer nor any of the funding organisations had access to the data or editorial control.

# 6. Discussion of results

*Quote from a participant:*

*"I've been without any illicit drugs for years now! Back to work, my daughter is staying with me every other week, and I got a lot of new friends who have never had anything to do with drugs. I met this really nice guy, and we were going away for the weekend. I had to take my methadone with me, and when he saw it, he said: What is that? Are you an opioid addict! That's when I realised that OMT no longer matched who I was. Every day I woke up and felt withdrawal symptoms, like I was stuck in this drug addict identity!"*

In this chapter, the main results of this thesis, presented in chapter 4, will be discussed further in relation to existing research.

## 6.1. Participant characteristics

The participant characteristics presented at baseline were within the range of reported characteristics of the Norwegian OMT cohort [67]. The data showed that the use of substances and addiction-related problems among the study sample did not differ much from the opioid users in Norway who were enrolled in OMT [16, 67]. The study participants did not have strong external motivation such as being on parole or being health workers in risk of losing their jobs as seen in previous studies of XR-NTX [40, 89]. The characteristics of the study sample were in compliance with findings presented in other studies of naltrexone that includes a clinical sample of opioid users [123, 133, 134].

The mean age among the study participants was approximately eight years younger than the average OMT patient in Norway [140]. The OMT population in Norway is aging. While the proportion of patients over 50 years is increasing, the proportion of patients under the age of 30 is stable [140]. It seemed that XR-NTX attracted opioid users who were somewhat younger than the average OMT patients. Innovations are more likely to be adopted and implemented among younger people [190], and this may contribute to explain the differences in age seen between the study sample and the general OMT population in Norway.

Unlike in countries such as Russia and the USA, where legal framework and financial and insurance restrictions may prevent opioid users' access to OMT, all of the participants in our study had free access to OMT. XR-NTX is not yet approved in Europe and only available in Norway through our study, thus we suggest that the opioid users' participation in the study was motivated by the option to receive XR-NTX. The disproportional distribution of participants who chose BP-NLX supports this

suggestion. A Norwegian survey has previously suggested opioid users would be interested in receiving XR-NTX if it was available to them, and findings in our study confirm this interest in practice [3]. The naturalistic setting of our study may give us a realistic insight in how XR-NTX may attract opioid users in a clinical setting in countries with similar regulations and drug policy as Norway. The differences in study prerequisites between our study and the Russian and American studies of XR-NTX may influence the basis of comparisons [84, 89, 123].

Thirty-seven percent of the participants were not enrolled in OMT prior to study inclusion. This may suggest we recruited opioid users whom for different reasons did not consider OMT as a relevant treatment option. Opioid users not in effective treatment such as OMT have a higher risk of overdoses [23]. Our findings confirmed that participants currently not enrolled in OMT had more ongoing, severe addiction-related problems. It can be presumed they were at a higher risk of overdoses than those who were enrolled in OMT prior to study inclusion. This finding was very encouraging and implies that XR-NTX may be an effective alternative in increasing the total number of opioid users in treatment and thereby reduce the number of overdoses among opioid users.

Participants enrolled in OMT prior to study inclusion reported a more severe history of addiction-related problems. However, as seen in many previous studies, both health and psychosocial factors were improved while in OMT [49, 53]. Studies have found that many patients in OMT express a main goal of abstinence [32, 33, 148]. In a survey conducted by our research group, more than half of the respondents reported high interest in stopping opioid use [3]. Half of the respondents also reported high interest in receiving a drug to reduce craving for opioids. The results from this survey may reflect the motivation for receiving XR-NTX among the study participants. Based on a clinical impression, we suggest some of the participants who have accomplished recovery with OMT, wanted XR-NTX in a transitional phase to achieve their main goal of abstinence. Discontinuing substitution medication is risky even if patients are very motivated. Few succeed in detoxification from OMT and many relapse to opioid use [46]. XR-NTX may offer a medication-assisted abstinence and be perceived by the patients as a support in a transition phase towards medication-free abstinence.

The analyses of the baseline data identified two sub-groups among the participants. One group was those who reported frequent use of heroin and other illicit drugs and scored high on variables indicating severe ongoing addiction-related problems. The other group was those who reported infrequent use of illicit drugs and low scores on addiction-related problems. The bimodal distribution that we identified suggests that the participants were at different stages in their drug use trajectories: those who were already in recovery and those who had ongoing, severe drug use. This pattern was seen independent of their affiliation to OMT prior to study inclusion. However, those who used

substitution medication most frequently were more likely to be enrolled in OMT than those who used heroin most frequently. This observed pattern may indicate that the two identified groups had different motivation for joining the study and obtaining XR-NTX. Those who were in recovery may have wanted XR-NTX to assist them to maintain an achieved abstinence. Among those who had ongoing severe addiction-related problems, the motivation for joining the study may have been to start a recovery process or the purpose may have been related to harm reduction.

We collected more specified data about our participants than what is available through the annual report of the national OMT cohort in Norway. In the annual report, it is estimated that approximately 50% of the OMT patients have a good control of their drug use [65]. Although this estimate is not fully comparable to our results, we consider our results to be within the range of the OMT population in Norway. There is no evidence that the study participants are different from the OMT population concerning being at different stages in their drug use trajectories or concerning motivation for treatment.

Considering the nature of XR-NTX, we suggest that the main goal for the participants was abstinence from opioids. It is also likely that all of them wanted to achieve better control of their use of other substances. XR-NTX seems to match the goals and needs of those who prefer abstinence from opioids. Yet, complete abstinence from drugs is not necessary for engagement and the patient's engagement in treatment is important to succeed [35]. Harm reduction can be a start of the process to achieve abstinence [30]. Recovery may be defined as a process where drug use and addiction-related problems are improved and does not necessarily imply abstinence [148]. However, improvements are difficult to measure and outcomes other than abstinence are seldom regarded as successful results [29].

XR-NTX is an unknown treatment option in Norway, and observing other opioid users having positive treatment outcomes may have had an impact on the recruitment process [154].  As we predicted in the protocol [2], the recruitment was easier when some of the participants had positive experiences with XR-NTX and contributed to spread information about the study. In an American study, opioid users in detoxification units were asked what kind of follow-up treatment they preferred to be engaged in to prevent relapse: methadone, buprenorphine, XR-NTX, or none. XR-NTX was the alternative most patients chose, although only a few of them have had previous experience with this medication [37].

The numbers of users of prescribed opioids have increased rapidly around the world in recent years [19, 191]. Compared to heroin users, users of prescribed opioids may to a lesser extent be a marginalised group [155, 192]. As we discriminated between heroin and other opioids and found

decreased use of both kinds, we suggest that our findings may be relevant for both heroin users and for those who are addicted to other opioids such as prescribed opioids.

## 6.2. Retention in treatment

During the 12 first weeks of the study, the retention in treatment was similar among participants randomised to XR-NTX and BP-NLX. High retention is a good measurement of utility and clinical efficacy [128]. The results indicate that XR-NTX was as effective as BP-NLX in maintaining opioid users in treatment.

While the paper presenting results from our RCT was published in October 2017, an American RCT comparing XR-NTX and BP-NLX during a 24-week period was published in November 2017 [123]. The American study experienced substantial hurdles when initiating XR-NTX, and a large proportion of participants randomised to XR-NTX failed to start medication. When analysing participants who were successfully inducted to study medication (per-protocol population), retention in treatment was similar in the two groups, and this result corresponds to results from our study [123].

Besides the above-mentioned American study, no other studies have previously compared XR-NTX and BP-NLX. This implies that retention in treatment in our study cannot be directly compared to other studies, as the treatments, samples, and setting are very different. While BP-NLX is a well-documented approach and widely used in OMT programs in many countries, XR-NTX has a limited distribution in only a few countries. This makes comparisons between our study and other studies challenging and not completely equivalent [15]. However, some studies have examined retention in treatment with XR-NTX [40, 78, 80, 89] and other studies have examined retention in treatment with BP-NLX [49, 53]. In a review of retention in medication-assisted treatment for opioid dependence (including studies of methadone, buprenorphine and naltrexone), RCTs of 3 months' durations presented retention rates between 19% and 94.1% [64]. The result from our RCT is within the range of findings in this review.

Retention rates usually decrease as time in treatment increases. While the retention rate was approximately 50% in the 9-month follow-up, 43% of the n=134 participants who took at least one dose of XR-NTX in the study completed the study at week 48. Two studies found retention rates of 55% [40], respectively 62.3% [84] after one year in treatment with XR-NTX. Differences in study designs, the availability of OMT medication, and the selection of participants may limit the comparison between these two studies and our study. Studies of 12 months follow-up in treatment of opioid dependence presented retention rates between 26% and 85% [64]. Thus, findings from our long-

term study are within the range of findings in other studies. In the annual Norwegian OMT status report, however, it is estimated that approximately 90% of the patients remained in treatment during a year [65]. In an international context, this result is very good. However, the estimate in this report is not fully comparable to the result from our study.

A number of participants failed to complete the detoxification before the initial XR-NTX injection. Previous studies of XR-NTX have showed drop-out rates of 30% during the detoxification phase prior to the initial XR-NTX injection [193]. There may be different reasons for drop-outs in this phase, experiencing painful withdrawal symptoms being the most frequent [194]. In the newly published American RCT they reported a high number of participants who did not complete the detoxification and failed to take the initial XR-NTX injection [123]. The analyses of the ITT-population in the American study showed BP-NLX to be more effective than XR-NTX, and the researchers emphasised induction failures among participants randomised to XR-NTX as the most prominent factor in regard to this [123].

Another reason for participants dropping out in an early phase of the study may be the disappointment of not being randomised to the preferred study medication [15]. Participants reaction to which medication they expected (or hoped) to receive, may influence the retention rate [185]. When looking at the number of participants in our study who dropped out before taking their first dose of study medication, there were no differences between the two randomised groups. Psychosocial interventions have been recommended, in particular in the withdrawal phase prior to the first XR-NTX injection where drop-out is most common [194]. Retention was not reimbursed with systematic psychosocial treatment approaches in our study.

Due to experiencing unpleasant withdrawal symptoms and/or adverse effects in regard to the initial injection of XR-NTX, a number of participants in the study rejected taking the second XR-NTX injection. This has also been seen in previous studies of XR-NTX [38, 121]. With the intention to facilitate a more optimal detoxification approach, a naltrexone assisted detoxification regimen has been developed. It has showed promising results both in regard to improve the XR-NTX induction and in regard to the numbers of patients who continued with a second injection of XR-NTX [132].

Differences in outcome regarding XR-NTX and BP-NLX must be expected when examining the two groups separately, due to the differences in administration and the effects of the medicaments. Compared to BP-NLX, it is more time consuming and difficult to start up with XR-NTX. While BP-NLX can be easily initiated in outpatient settings, the initial XR-NTX injection requires detoxification and several days without any opioids, preferably in an inpatient setting [132]. This regime is also required if a patient has dropped out of treatment and wants to be re-included in XR-NTX treatment after a

period with opioid use. Episodes of illicit opioid use during OMT treatment are not uncommon, and if BP-NLX is discontinued, a re-start can be rapidly initiated. This is more complicated with XR-NTX, because a new detoxification is needed [15]. A delay in re-medication of XR-NTX with the intention to obtain a euphoric effect of opioids may easily result in discontinuation of the treatment. In an ordinary clinical setting, this may pose a problem regarding retention in treatment with a poorer outcome for XR-NTX compared to BP-NLX.

The participants' individual reasons for discontinuing the study have not been fully investigated. However, reasons for drop-out have been investigated in previous studies and the findings are consistent with the clinical impression in our study. Among the reasons stated were the thought of feeling cured and wanting to manage on their own [121]. Experiencing a lack of craving when using XR-NTX and knowing that discontinuation of XR-NTX does not entail withdrawal effects can make it too easy to terminate the medication. This may lead to thoughts of being able to manage themselves, and to premature discontinuation of XR-NTX. The thought of feeling cured may undermine participants' adherence to XR-NTX in long-term [38].


## 6.3.    Use of opioids and craving for heroin

During the 12-week period of the RCT, all participants showed a substantial reduction in use of opioids and reduced craving for heroin. Participants randomised to XR-NTX reported significantly less use of opioids and lower craving scores than those randomised to BP-NLX. Although the majority of the participants were already in treatment prior to study inclusion, their use of opioids decreased when entering the study. These improvements were continued and further enhanced in the 36-week follow-up.  No significant differences were found between participant who continued XR-NTX and those inducted on XR-NTX in the follow-up. Non-completers reported significantly more use of opioids and higher craving scores on several time points during the follow-up, compared to completers.

It is well-documented that OMT contributes to decreasing the use of illicit opioids and craving for heroin among opioid users [49, 53]. Likewise, a number of studies have showed decreased use of opioids and reduction in craving during treatment with XR-NTX [40, 77, 80, 84, 123, 128]. Hence, the results from our study were consistent with previous research regarding opioid use and craving for heroin among opioid users in treatment with XR-NTX or in OMT.

Testing the opioid blockade is a well-known phenomenon among opioid users who receive XR-NTX, and it is likely that some of the episodes of opioid use seen in our study can be attributed to this phenomenon [77, 195].

When comparing craving scores for heroin between the two randomised groups in the RCT, we see that the participants randomised to XR-NTX had a greater reduction in craving than those randomised to BP-NLX. Being maintained on substitution medication implies that the opioid receptors are activated by opioids and thus, craving should be unlikely. Our results suggest that XR-NTX in a higher degree is able to prevent craving. However, when informed about the study medication before study inclusion, participants were told that XR-NTX would reduce the craving for heroin. As the study medication was not masked, participants may be biased by this information and this may have affected their scores. The aforementioned dissatisfaction with not being randomised to the preferred study medication may have had a modifying effect on the craving scores in the BP-NLX group [15]. The craving scores among participants in the RCT align with results in craving among the per-protocol population in the newly published American RCT [123].

Although craving among the non-completers was significantly higher than completers in the follow-up, both groups reported an apparently low score. Hence the non-completers reported an anti-craving effect almost at the same level as the completers, and it is not obvious that this factor affected their discontinuation of treatment with XR-NTX.

## 6.4.    Use of other substances and addiction-related problems

During the 12-week RCT, participants showed a reduction in use of most other substances and their addiction-related problems were improved. The majority of improvements participants achieved during the RCT period were maintained or further enhanced in the 36-week follow-up.

Several studies have found that OMT reduces the use of other illicit drugs, and improves addiction-related problems [49, 53]. However, in varying degrees, continued use of drugs is not uncommon among patients in OMT [46]. At study inclusion, the participants reported a higher use of other drugs than reported among the average OMT patients [65, 66], even if a majority of the participants already were enrolled in OMT prior to study start. This suggests that the study participants who were enrolled in OMT were not sufficiently able to benefit from this treatment.

Several studies of XR-NTX have shown improved outcomes regarding the use of alcohol, illicit drugs, and addiction-related problems; hence the results in the present study are in accordance to these studies [40, 78, 84, 85, 89].

There have been concerns about XR-NTX leading to increased use of other substances when the opioid users experience the opioid blockade from XR-NTX [103]. As in another study of XR-NTX, the findings in our study do not support such concerns [84]. In the follow-up, participants inducted on XR-NTX had a significantly higher heavy alcohol use compared to participants who continued XR-NTX. The numbers however, were very small: 0.6 days with heavy alcohol use compared to 0.3 days the last 4 weeks. Although the use of other substances was reduced and kept at a low level during the study period, a small increase in substance-use was observed at some points. We suggest that one reason for this observed variability may be an expression of the participants' disappointment with the lack of progression in their recovery process. The study cohort displayed a severe abundance of addiction-related problems at study inclusion, and few were employed. At the study attendances, participants expressed readiness to start working, but due to lack of qualifications, finding a job was difficult for many of them. The number of days working was increased during the study, but not as much as we could wish for. We suggest the participants would benefit greatly from receiving ancillary services focusing on employment based reinforcements, which they did not systematically receive during the study.

## 6.5. Treatment satisfaction and recommendation of treatment

Participants were to a great extent satisfied with XR-NTX during the one year in treatment. This is consistent with findings in other studies [40, 83]. During the first 12 weeks, participants randomised to XR-NTX reported a significant higher treatment satisfaction than participants randomised to BP-NLX. This result may imply that the participants who received XR-NTX were satisfied with benefits such as the increased degree of freedom due to no daily monitored intake, the cessation of physical dependence, and being protected against relapse. However, the differences in treatment satisfaction between the two randomised groups may also be a result of the BP-NLX-group being disappointed with the result of the randomisation.

In the follow-up, participants who were inducted on XR-NTX were less satisfied with XR-NTX the first months in treatment, compared to those who continued XR-NTX treatment. This corresponds with the clinical impression, where participants express that a certain adaption period is necessary before they were fully satisfied with the XR-NTX treatment. Treatment satisfaction among the completers showed an average higher score than among the non-completers. It is likely that dissatisfaction with treatment may have had an impact on the non-completers' adherence to the study.

In the RCT, those who were randomised to XR-NTX recommended their treatment to a higher extent than those who were randomised to BP-NLX. To a great extent, participants using XR-NTX in the

study would recommend XR-NTX to other opioid users, and this finding is in accordance with a previous study [121]. Even though the completers displayed a higher score than the non-completers, the mean score of the non-completers was 8.7 of 10 in week 28. This suggests that even if the participants did not adhere to XR-NTX themselves, they considered XR-NTX an appropriate treatment option to other opioid users.

Meeting treatment preferences is important for treatment satisfaction and treatment adherence [34, 37]. A differentiated selection of available treatment modalities increases the likelihood of recruiting and keeping opioid users in treatment, therefore XR-NTX could be a useful supplement to the existing selection.

## 6.6. Tolerability and safety aspects of XR-NTX

During the 1-year follow-up, the reported adverse events were both in extent and theme, similar to findings in other studies of XR-NTX [78, 79, 84, 121]. Except for the reported adverse effects associated with the initial XR-NTX injection there were no significant differences in reported adverse events among participants in the 12-week RCT period or in the 36-week follow-up.

Few serious adverse events were reported and no new safety concerns were revealed during the 1-year follow-up. Except for one participant who was hospitalised due to severe withdrawal symptoms after the initial injection with XR-NTX and the two participants who experienced serious injection-site reactions requiring surgery, none of the other serious advents were assessed as definite related to XR-NTX. One participant died in an accident, not related to XR-NTX. There were no significant differences between the two randomised groups regarding reported SAE in the RCT. Neither were there any significant differences between the participants who continued XR-NTX and the participants who were inducted to XR-NTX in the follow-up.

Before randomisation, participants were tapered to a maximum of 4 mg of BP-NLX [2]. This implied that those randomised to BP-NLX could rapidly be inducted to a stable dose on BP-NLX, while those randomised to XR-NTX continued tapering and completed the necessary days without opioids. This procedure explains why BP-NLX participants to a lesser degree reported adverse effects in the initial phase of the study. Detoxification from opioids causes withdrawal symptoms such as anxiety, nausea, diarrhea, chills, and insomnia, with a peak on days 2-4 after ceasing opioids [45, 155]. Both in the RCT and in the follow-up, participants frequently reported withdrawal-like symptoms after their initial XR-NTX injection. This is in accordance with findings in other studies [40, 89]. It is difficult to differentiate the withdrawal symptoms from opioids and some of the side-effects of an initial XR-NTX

dosing [45], as naltrexone can displace both exogenous (abused) opioids and natural opioid receptor functioning.

According to the study protocol, the participants had to be abstinent from opioids for at least 72 hours before a test dose with naloxone was distributed. If the participant did not react to this test dose, XR-NTX was administrated [2]. The majority of the study participants were admitted for inpatient detoxification during the randomisation and induction on study medication. Many reported withdrawal symptoms and cravings while they were tapering and some dropped out before the initial dose of XR-NTX was administered. We experienced that the longer period without opioids before the initial XR-NTX injection, the fewer adverse effects were reported. According to this clinical observation, the study participants were strongly recommended to wait more than 72 hours before taking the test-dose. Some waited as long as 7-10 days, and as the study progressed, fewer participants reported AEs related to the initial XR-NTX injection. However, some participants initially wanted to wait for more than 72 hours, but due to craving and fear of dropping out, they chose to take the first dose of XR-NTX even if the likelihood of experiencing unpleasant withdrawal symptoms were increased.

The trajectory of treatment may be influenced by the detoxification procedures, and improving these procedures may decrease the number of adverse effects and increase the likelihood of a successful start on a treatment such as XR-NTX [155]. In the American X:BOT study, the challenges in regard to detoxification were emphasised as the most important barrier to the utilisation of XR-NTX [123]. If XR-NTX is to be implemented as an additional treatment option to opioid users, the start-up regime should consider following the recommendation which resulted in most successful start-ups on XR-NTX. This regime included a 7-day increasing daily dose of oral naltrexone, followed by the first injection with XR-NTX [132]. The rationale for using naltrexone in a withdrawal phase is that faster transition to abstinence increases the number of opioid users completing the withdrawal phase [45].

No opioid overdoses were reported among the participants while using XR-NTX during the study, but one participant in the BP-NLX group reported a non-fatal opioid overdose in the RCT. The American X:BOT study reported 19 overdose events and 5 fatal overdose events among the per-protocol population of n=474, and no significant differences between the study groups [123]. The risk of overdoses after discontinuation of substitution medication is at the highest the first four weeks after treatment discontinuation [63]. After a period of abstinence from opioids, such as after release from prison, drop-out from residential treatment or discontinuation of XR-NTX, the risk of overdoses increases due to the loss of tolerance of opioids [24, 26, 100]. It is important that users of XR-NTX are thoroughly informed about this increased risk and continue to be followed-up by clinicians after the

medication is discontinued. This practice was implemented in our study, and study personnel cooperated closely with the clinicians to prevent harmful consequences of treatment discontinuation. Follow-up from clinicians also entailed that AEs were reported until 3 months after the study discontinuation. This implied that the time period with the highest risk of overdoses was monitored, but still, no overdoses were reported among the study participants within this period.

For some participants, experiencing adverse effects was the reason for discontinuation of the study. This has also been seen in previous studies [40, 121]. However, the types of reported AE varied among those who discontinued the study and the majority of the AEs were not considered severe. The individually perceived disadvantages are suggested to be the most important factors in regard to treatment discontinuation. Of the reported SAEs, only 3 were considered related to XR-NTX and only two of these SAEs caused the participants to discontinue the study.

# 7. Implications

## 7.1. Clinical implications

Based on our findings in this study, XR-NTX is considered to be a valuable supplement to the existing treatment modalities. The benefits of XR-NTX may have important clinical implications that can represent an improvement in treatment of opioid users.

As XR-NTX is not addictive and has few interactions with other drugs, the risk of diversion is low. Thus there is no need for a monitoring regime as in OMT [8]. In combination with monthly injections instead of daily intake, this makes it easier for the patients to participate in daily activities and maintaining work or school. Some opioid users are treatment-resistant, some because they are not able to attend the often required daily attendances in OMT. Once monthly injections with XR-NTX may be easier to adhere to for those who are hard to reach and difficult to include in other treatment options.

In regard to the available research, users of OMT are often discouraged from ceasing substitution medication. Even in particularly motivated patients there is a high risk of relapse and overdoses after discontinuing substitution medication, [46]. We suggest XR-NTX could be a valuable treatment option in a transition phase to those who want to cease substitution medication. Also, opioid users who are released from prison are likely to utilise XR-NTX and thus be protected against relapse and overdoses in the vulnerable phase after release [89, 138]. We suggest XR-NTX is a promising treatment alternative to opioid users who prefer a substitution-free treatment and want to achieve abstinence.

Before induction on XR-NTX, the manufacturer recommends 7-10 days of abstinence from opioids to reduce withdrawal symptoms [196]. However, the reinforcing effects of opioids cause many to fail to complete the necessary days of abstinence. Withdrawal symptoms may be an important hindrance for the utilisation of XR-NTX and several studies have been aiming to identify the most effective detoxification regimen [45, 80, 132, 197]. Recently published research has recommended a tapering regime that reduces the discomfort when starting on XR-NTX [132]. This method should form the basis for the detoxification phase that initiates the treatment with XR-NTX. Whether the detoxification takes place in an outpatient or inpatient setting may be significant in regard to whether the opioid user succeeds in completing the detoxification and induction on XR-NTX, and inpatient detoxification is recommended [123, 197] . Reimbursement with systematic psychosocial supplementary treatment may be an important factor to achieve a successful introduction to XR-NTX [194].

The participants were asked about the reasons for discontinuing the study but their answers were only broadly categorised. More detailed information about the reasons would provide better knowledge that could be basis for improvements regarding facilitating treatment with XR-NTX [121]. Some opioid users have prematurely discontinued XR-NTX because they felt cured and wanted to manage on their own [121]. To avoid this, it is important to systematically add psychosocial treatment such as motivational interviewing to the XR-NTX treatment. In recovered patients, XR-NTX may be considered an "insurance policy", preventing relapse [9]. Abstinent opioid users may relapse to opioids when they are influenced by alcohol, but since XR-NTX may affect both craving and the impact of opioids and alcohol, the risk of impaired assessment capacity is reduced while using XR-NTX [38].

## 7.2. Implications for policy

An important objective for policy makers is developing strategies to reduce the number of overdoses among drug users and prevent other harmful effects of opioid use on society. As previously described, opioid users are among those with the highest risk of overdoses and they account for the majority of expenditures directly or in-directly related to the effects of drug use. Being in treatment prevents overdoses and it is an overall important objective to increase the numbers of opioid users in effective treatment.

Our findings suggest that XR-NTX has the ability to attract opioid users who for different reasons are not currently in treatment. This is an encouraging finding, and suggests that XR-NTX could contribute to increasing the overall numbers of opioid users in treatment. An important effect of this may be reduced numbers of overdoses, as overdoses most frequently occur among opioid users not in treatment.

It is in general profitable for the society to have opioid users in pharmacological treatment compared to no treatment [198]. The monthly distribution of XR-NTX and the lack of need for monitoring and control measures imply that the amounts of money spend on distribution and monitoring will be decreased compared to BP-NLX [199]. It is not known yet what the costs of XR-NTX will be for clinical use in Norway and in Western Europe, but in regard to our study's ability to recruit opioid users not in treatment, the likelihood of savings for the society is present.

Harm reduction and recovery are two different objectives in drug policy. We suggest both are important perspectives in policy making, and that approaches addressing both these objectives

should be further developed. Both OMT and XR-NTX are treatment options that may be utilised in recovery and for harm reduction purposes.

There has been expressed concern about naltrexone preventing opioid users from enrolling into OMT [113, 159]. As seen in the present study, some patients enrolled in OMT volunteered for treatment with XR-NTX. It is not known whether those would continue or discontinue OMT if XR-NTX was not available to them through the study. The easy access to OMT opioid users in Norway suggests that the opioid users' treatment preferences were decisive when they volunteered for XR-NTX. Also, the results from our study showed that the participants used somewhat more drugs than the average OMT patient, suggesting that they were among the patients who to a lesser degree benefit from treatment with OMT. It is not yet known whether some opioid users who preferred XR-NTX would have better treatment outcome in OMT and it is a relevant question whether it is an ethical responsibility to offer opioid users to replace effective OMT treatment with XR-NTX. However, we do know that many opioid users prefer a substitution-free treatment even if the prognoses of achieving continued abstinence are worse compared to treatment with OMT. We also know that approximately 50% of the opioid users are not in treatment at all. If OMT and XR-NTX were prescribed and distributed in the same clinics, opioid users could choose the medications in regard to the treatment option they preferred and found most suitable in regard to their individual needs and motivation. We suggest these two treatment options may be complementary rather than opposing.

Introduction and implementation of novel approaches can be a protracted and complicated matter [200]. When new treatment modalities are being implemented, it is important that information about the innovations efficacy is made known to the organisation. It is also important that the innovation correspond with the established values in the organisation [201]. Observed positive results from the concrete treatment option is an advantage [154]. Larger treatment centres with appropriate infrastructure, general experience with the use of medication in treatment, and available medical staff are preconditions when implementing new approaches such as XR-NTX [151, 154, 202]. Contrary to the USA, OMT in Norway is free of cost and a part of the governments' health system. This implies that there is a well-functioning infrastructure that easily should be able to include new treatment options such as XR-NTX [151, 154]. The managers of the OMT clinics in Norway meet annually, and new treatment modalities may easily be implemented through this unified organisation. An example of this is the successful change from methadone to buprenorphine in Norway during a ten years' period [66].

Barriers to utilisation of XR-NTX may be expressed in other ways in Norway and in other Western European countries compared to the USA, in regard to the differences in health policy and funding of

the health care system. It is important to try out methods for integrating this novel treatment into existing treatment modalities and to identify relevant barriers for utilisation [88].

## 7.3. Implications for research

In November 2017, an American research group presented results from a RCT including n=570 participants randomised to either XR-NTX or BP-NLX. To a great extent, the per-protocol analyses from this study confirmed the findings in our study, but still, many questions remain. Although much research has been conducted suggesting effectiveness and safety of XR-NTX, there are in particular questions regarding the feasibility in naturalistic clinical settings that need to be answered.

A key question is the recommended duration of treatment with XR-NTX. Although participants seem to benefit from treatment with XR-NTX, very few studies have investigated the effectiveness in long-term treatment (more than one year). The length of treatment required to achieve the necessary stability to manage without XR-NTX is not known. Neither is it known if achieved improvements will continue after treatment is completed. While being in treatment protects against the harmful effects of opioids, opioid dependence is a chronic disease and relapse is common after treatment completion [155]. Long-term treatment is recommended and longer treatment periods provide better treatment outcomes [9, 122]. Being abstinent for five years has shown to increase the likelihood of further sustained abstinence [11]. Opioid users, who have been successfully recovered for years through OMT, may need XR-NTX for a shorter period, while those who continue drug use during the treatment with XR-NTX may need a life-long duration of treatment with XR-NTX. These different alternatives need to be examined more thoroughly. In the continuation of the 1-year follow-up in the present study, completers were offered continued treatment with XR-NTX of a non-specified duration. We suggest data from this prolongation will provide important information in assessing the duration of treatment with XR-NTX.

Mental, physical and societal factors may have an impact on sustained abstinence and recovery. Possible changes in mental and somatic health symptoms and status, related to the continued XR-NTX induced abstinence from opioids need to be assessed. Furthermore, what necessary types and levels of reimbursements may contribute to improving the treatment outcomes of XR-NTX? As recommended by the WHO [203], medication-assisted treatment such as OMT should include psychosocial support, and this also applies to treatment with XR-NTX. Maintaining abstinence long-term is important, and there is a need for studies that explore effective auxiliary services to achieve this [124].

Although previous research has suggested that XR-NTX may be more effective among particularly motivated or well-functioning groups of opioid users, other research including ours has shown promising results among opioid users with a wide range of characteristics. XR-NTX is however, not a suitable treatment option for all opioid users. In regard to providing the best recommendation to clinicians, there is a need to explore whether any sub-groups of opioid users can utilise XR-NTX to a greater extent. The number of prescription opioid users is increasing, and research regarding differences in treatment preferences and treatment outcomes between heroin users and those dependent on prescription opioids are still meagre [17, 54]. The participants in our study who were enrolled in OMT prior to study inclusion were using either methadone or buprenorphine (with or without naloxone) when entering the study. Some of them also used heroin or other illicit opioids occasionally or more frequently. Participants not enrolled in OMT prior to study inclusion mainly used heroin, but some were prescribed opioids or used illegally purchased substitution medication. We did not examine whether there were any differences in retention in treatment regarding which opioid the participants used prior to inclusion. How the use of different kinds of opioids may interfere on the utilisation of XR-NTX, need further examination [88].

In American studies, it has been emphasised that the cost of XR-NTX is one of the most important barriers to implementation and utilisation [151, 198, 202, 204]. It must, however, be taken into consideration that funding of the health care system in the USA differs from many other countries, such as Norway and in Western Europe. Since there are few longitudinal studies of XR-NTX in real-world settings, there is a need for research disclosing the cost effectiveness in long-term use of XR-NTX.

## 8. Conclusions

During this clinical study we found XR-NTX to be an effective and safe treatment option. The study participants were considered representative of opioid users in Norway, although they were somewhat younger than the average OMT population. We found that a relatively large proportion of the participants were not enrolled in available OMT programs prior to study inclusion, and suggest that XR-NTX in particular attracted opioid users who preferred an abstinence-based treatment option. In the naturalistic clinical study, both opioid users in recovery and opioid users with current, severe addiction-related problems were attracted to medication-assisted abstinence with XR-NTX. When comparing XR-NTX with BP-NLX, we suggest that XR-NTX is noninferior to BP-NLX in retaining opioid users in treatment and in use of opioids during a 3 months period. A decrease in use of other illicit drugs and improved addiction-related problems was seen among both groups of randomised participants. The improvements regarding drug use and addiction-related problems were maintained among the patients treated with XR-NTX during the one year in the study. Treatment satisfaction with XR-NTX was high, and both completers and non-completers would to a great degree recommend XR-NTX to other opioid users. No new safety aspects were revealed during the one year, and few serious adverse events were reported. A majority of the reported adverse effects were associated with withdrawal from opioids and the initial injection of XR-NTX. All of the participants recovered and only a minority of them discontinued XR-NTX due to the adverse effects.

It is important to underline that XR-NTX does not represent a replacement to OMT, but a potential alternative for those who for different reason do not consider substitution medication a relevant treatment option. A high number of opioid users have abstinence as a main goal, and a broader treatment selection implies that the treatment process can be better tailored to the individual opioid users' preferences and needs.

# References

1.      Tanum, L., Solli, K.K., Latif, Z.E., Benth, J.S., Opheim, A., Sharma-Haase, K., Krajci, P., and Kunoe, N., *Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial.* JAMA Psychiatry, 2017. **74**(12): p. 1197-1205.

2.      Kunøe, N., Opheim, A., Solli, K.K., Gaulen, Z., Sharma-Haase, K., Latif, Z.E., and Tanum, L., *Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX).* BMC Pharmacology and Toxicology, 2016. **17**(1): p. 1-10.

3.      Sharma Haase, K., Kunoe, N., Opheim, A., Gaulen, Z., Nja, A.M., Latif, Z.E., Solli, K.K., and Tanum, L., *Interest in Extended Release Naltrexone among Opioid Users.* European Addiction Research, 2016. **22**(6): p. 301-305.

4.      UNODC, *World Drug Report 2015*, in *United Nations publication*. 2015, United Nations Office on Drug and Crime: Vienna.

5.      Norwegian Institute for Alcohol and Drug Research, *The Drug Situation in Norway 2014 (Annual Report to the EMCDDA)*, O. Hordvin, Editor. 2015, Norwegian Institute for Alcohol and Drug Research: Oslo.

6.      *Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed.* 2000, Washington, DC: American Psychiatric Association.

7.      Ward, J., Hall, W., and Mattick, R.P., *Role of maintenance treatment in opioid dependence.* Lancet, 1999. **353**(9148): p. 221-226.

8.      Bart, G., *Maintenance medication for opiate addiction: the foundation of recovery.* Journal of Addictive Diseases, 2012. **31**(3): p. 207-225.

9.      McLellan, A.T., Lewis, D.C., O'Brien, C.P., and Kleber, H.D., *Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation.* JAMA, 2000. **284**(13): p. 1689-1695.

10.     Khademi, H., Kamangar, F., Brennan, P., and Malekzadeh, R., *Opioid Therapy and its Side Effects: A Review.* Archives of Iranian medicine, 2016. **19**(12): p. 870-876.

11.     Hser, Y.I., Hoffman, V., Grella, C.E., and Anglin, M.D., *A 33-year follow-up of narcotics addicts.* Archives of General Psychiatry, 2001. **58**(5): p. 503-508.

12.     Skeie, I., Brekke, M., Lindbaek, M., and Waal, H., *Somatic health among heroin addicts before and during opioid maintenance treatment: a retrospective cohort study.* BMC Public Health, 2008. **8**: p. 43.

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

14.     Ngo, H.T.T., Tait, R.J., and Hulse, G.K., *Hospital psychiatric comorbidity and its role in heroin dependence treatment outcomes using naltrexone implant or methadone maintenance.* Journal of Psychopharmacology, 2011. **25**(6): p. 774-782.

15.     Nunes, E.V., Lee, J.D., Sisti, D., Segal, A., Caplan, A., Fishman, M., Bailey, G., Brigham, G., Novo, P., Farkas, S., and Rotrosen, J., *Ethical and clinical safety considerations in the design of an effectiveness trial: A comparison of buprenorphine versus naltrexone treatment for opioid dependence.* Contemporary clinical trials, 2016. **51**: p. 34-43.

16.     Skjaervo, I., Skurtveit, S., Clausen, T., and Bukten, A., *Substance use pattern, self-control and social network are associated with crime in a substance-using population.* Drug and Alcohol Review, 2017. **36**(2): p. 245-252.

17.     Hser, Y.I., Evans, E., Grella, C., Ling, W., and Anglin, D., *Long-term course of opioid addiction.* Harvard Review of Psychiatry, 2015. **23**(2): p. 76-89.

18.     Rudd, R.A., Aleshire, N., Zibebell, J.E., and Gladden, M., *Increases in Drug and Opioid Overdose Deaths - United States, 2000-2014*, in *Morbidity and Mortality Weekly Report*. 2016, US Department of Health and Human Services/Centers for Disease Control and Prevention. p. 1378-1382.

19.     Volkow, N.D., Frieden, T.R., Hyde, P.S., and Cha, S.S., *Medication-assisted therapies--tackling the opioid-overdose epidemic.* The New England journal of medicine, 2014. **370**(22): p. 2063-2066.

20.     Lofwall, M.R. and Walsh, S.L., *A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world.* Journal of addiction medicine, 2014. **8**(5): p. 315-326.

21.     Tjagvad, C., Skurtveit, S., Linnet, K., Andersen, L.V., Christoffersen, D.J., and Clausen, T., *Methadone-Related Overdose Deaths in a Liberal Opioid Maintenance Treatment Programme.* European Addiction Research, 2016. **22**(5): p. 249-258.

22.     Jones, J.D., Mogali, S., and Comer, S.D., *Polydrug abuse: a review of opioid and benzodiazepine combination use.* Drug and Alcohol Dependence, 2012. **125**(1-2): p. 8-18.

23.     Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., and McLaren, J., *Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies.* Addiction, 2011. **106**(1): p. 32-51.

24.     Clausen, T., Anchersen, K., and Waal, H., *Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study.* Drug and Alcohol Dependence, 2008. **94**(1-3): p. 151-157.

25.     Strang, J., McCambridge, J., Best, D., Beswick, T., Bearn, J., Rees, S., and Gossop, M., *Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study.* Bmj, 2003. **326**(7396): p. 959-960.

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

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

28.     EMCDDA, *European Drug Report: Trend and Developments*. 2017, European Monitoring Centre for Drugs and Drug Addiction: Lisbon.

29.     Laudet, A.B., *What does recovery mean to you? Lessons from the recovery experience for research and practice.* Journal of Substance Abuse Treatment, 2007. **33**(3): p. 243–256.

30.     Single, E., *Defining harm reduction.* Drug and Alcohol Review, 1995. **14**(3): p. 287-290.

31.     McKeganey, N., Morris, Z., Neale, J., and Robertson, M., *What are drug users looking for when they contact drug services: abstinence or harm reduction?* Drugs: Education, Prevention and Policy, 2004. **11**(5): p. 423-435.

32.     Zaaijer, E.R., Goudriaan, A.E., Koeter, M.W., Booij, J., and van den Brink, W., *Acceptability of Extended-Release Naltrexone by Heroin-Dependent Patients and Addiction Treatment Providers in the Netherlands.* Substance Use and Misuse, 2016. **51**(14): p. 1905-1911.

33.     Neale, J., Nettleton, S., and Pickering, L., *What is the role of harm reduction when drug users say they want abstinence?* International Journal of Drug Policy, 2011. **22**(3): p. 189-193.

34.     Neale, J., Nettleton, S., and Pickering, L., *Does recovery-oriented treatment prompt heroin users prematurely into detoxification and abstinence programmes? Qualitative study.* Drug and Alcohol Dependence, 2013. **127**(1-3): p. 163-169.

35.     Jackson, L.A., Buxton, J.A., Dingwell, J., Dykeman, M., Gahagan, J., Gallant, K., Karabanow, J., Kirkland, S., LeVangie, D., Sketris, I., Gossop, M., and Davison, C., *Improving psychosocial health and employment outcomes for individuals receiving methadone treatment: a realist synthesis of what makes interventions work.* BMC Psychology, 2014. **2**(1): p. 26.

36.     Vogel, M., Dursteler, K.M., Walter, M., Herdener, M., and Nordt, C., *Rethinking retention in treatment of opioid dependence-The eye of the beholder.* International Journal of Drug Policy, 2017. **39**: p. 109-113.

37.     Uebelacker, L.A., Bailey, G., Herman, D., Anderson, B., and Stein, M., *Patients' Beliefs About Medications are Associated with Stated Preference for Methadone, Buprenorphine, Naltrexone, or no Medication-Assisted Therapy Following Inpatient Opioid Detoxification.* Journal of substance abuse treatment, 2016. **66**: p. 48-53.

38.     Woody, G.E., *Antagonist models for treating persons with substance use disorders.* Current psychiatry reports, 2014. **16**(10): p. 489.

39.     Hser, Y.I., Maglione, M., Polinsky, M.L., and Anglin, M.D., *Predicting drug treatment entry among treatment-seeking individuals.* Journal of substance abuse treatment, 1998. **15**(3): p. 213-220.

40.     Earley, P.H., Zummo, J., Memisoglu, A., Silverman, B.L., and Gastfriend, D.R., *Open-label Study of Injectable Extended-release Naltrexone (XR-NTX) in Healthcare Professionals With Opioid Dependence.* Journal of addiction medicine, 2017. **11**(3): p. 224-230.

41.     McLellan, A.T., McKay, J.R., Forman, R., Cacciola, J., and Kemp, J., *Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring.* Addiction, 2005. **100**(4): p. 447-58.

42.     Eastwood, B., Strang, J., and Marsden, J., *Effectiveness of treatment for opioid use disorder: A national, five-year, prospective, observational study in England.* Drug and Alcohol Dependence, 2017. **176**: p. 139-147.

43.     Peles, E., Sason, A., Tene, O., Domany, Y., Schreiber, S., and Adelson, M., *Ten Years of Abstinence in Former Opiate Addicts: Medication-Free Non-Patients Compared to Methadone Maintenance Patients.* Journal of Addictive Diseases, 2015. **34**(4): p. 284-295.

44.     Scherbaum, N. and Specka, M., *Factors influencing the course of opiate addiction.* International Journal of Methods in Psychiatric Research, 2008. **17 Suppl 1**: p. 39-44.

45.     Gowing, L., Ali, R., and White, J.M., *Opioid antagonists with minimal sedation for opioid withdrawal.* Cochrane Database of Systematic Reviews, 2017. **5**.

46.     Magura, S. and Rosenblum, A., *Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored.* The Mount Sinai journal of medicine, 2001. **68**(1): p. 62-74.

47.     WHO, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Denpendence*. 2009, World Health Organization.

48.     Dole, V.P. and Nyswander, M., *A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride.* JAMA, 1965. **193**.

49.     Mattick, R.P., Breen, C., Kimber, J., and Davoli, M., *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.* Cochrane Database of Systematic Reviews, 2014. **2**.

50.     Clausen, T., Waal, H., Thoresen, M., and Gossop, M., *Mortality among opiate users: opioid maintenance therapy, age and causes of death.* Addiction, 2009. **104**(8): p. 1356-1362.

51.     Skeie, I., Brekke, M., Gossop, M., Lindbaek, M., Reinertsen, E., Thoresen, M., and Waal, H., *Changes in somatic disease incidents during opioid maintenance treatment: results from a Norwegian cohort study.* BMJ Open, 2011. **1**(1).

52.     Skeie, I., Brekke, M., Clausen, T., Gossop, M., Lindbaek, M., Reinertsen, E., Thoresen, M., and Waal, H., *Increased somatic morbidity in the first year after leaving opioid maintenance treatment: results from a Norwegian cohort study.* European Addiction Research, 2013. **19**(4): p. 194-201.

53.     Connery, H.S., *Medication-assisted treatment of opioid use disorder: review of the evidence and future directions.* Harvard Review of Psychiatry, 2015. **23**(2): p. 63-75.

54.     Nielsen, S., Larance, B., Degenhardt, L., Gowing, L., Kehler, C., and Lintzeris, N., *Opioid agonist treatment for pharmaceutical opioid dependent people.* Cochrane Database of Systematic Reviews, 2016(5).

55.     Gjersing, L. and Bretteville-Jensen, A.L., *Is opioid substitution treatment beneficial if injecting behaviour continues?* Drug and Alcohol Dependence, 2013. **133**(1): p. 121-126.

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

57.     Bukten, A., Skurtveit, S., Gossop, M., Waal, H., Stangeland, P., Havnes, I., and Clausen, T., *Engagement with opioid maintenance treatment and reductions in crime: a longitudinal national cohort study.* Addiction, 2012. **107**(2): p. 393-399.

58.     Mattick, R.P., Breen, C., Kimber, J., and Davoli, M., *Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence.* Cochrane Database of Systematic Reviews, 2009(3).

59.     Havnes, I.A., Clausen, T., and Middelthon, A.L., *'Diversion' of methadone or buprenorphine: 'harm' versus 'helping'.* Harm Reduction Journal, 2013. **10**: p. 24.

60.     Wright, N., D'Agnone, O., Krajci, P., Littlewood, R., Alho, H., Reimer, J., Roncero, C., Somaini, L., and Maremmani, I., *Addressing misuse and diversion of opioid substitution medication: guidance based on systematic evidence review and real-world experience.* Journal of public health, 2016. **38**(3): p. 368-374.

61.     Ayanga, D., Shorter, D., and Kosten, T.R., *Update on pharmacotherapy for treatment of opioid use disorder.* Expert opinion on pharmacotherapy, 2016. **17**(17): p. 2307-2318.

62.     Larney, S., Zador, D., Sindicich, N., and Dolan, K., *A qualitative study of reasons for seeking and ceasing opioid substitution treatment in prisons in New South Wales, Australia.* Drug and Alcohol Review, 2016. **36**(3): p. 305-310.

63.     Sordo, L., Barrio, G., Bravo, M.J., Indave, B.I., Degenhardt, L., Wiessing, L., Ferri, M., and Pastor-Barriuso, R., *Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies.* Bmj, 2017. **357**: p. 1550.

64.     Timko, C., Schultz, N.R., Cucciare, M.A., Vittorio, L., and Garrison-Diehn, C., *Retention in medication-assisted treatment for opiate dependence: A systematic review.* Journal of addictive diseases, 2016. **35**(1): p. 22-35.

65.     Waal, H., Bussesund, K., Clausen, T., Skeie, I., Håseth, A., and Lillevold, P., *The annual OMT status survey for 2015 (In Norwegian only: Statusrapport 2015-Mot grensene for vekst og nytte?).* 2016, Norwegian Centre for Addiction Research.

66.     Riksheim, M., Gossop, M., and Clausen, T., *From methadone to buprenorphine: changes during a 10 year period within a national opioid maintenance treatment programme.* Journal of Substance Abuse Treatment 2014. **46**(3): p. 291-294.

67.     Waal, H., Bussesund, K., Clausen, T., Skeie, I., Håseth, A., and Lillevold, P., *The annual OMT status survey for 2016 (In Norwegian only: Statusrapport 2016-Er kvalitetsforbedring nå viktigere enn kapasitetsutvikling?).* 2017, Norwegian Centre for Addiction Research.

68.     Bernard, J.P., Havnes, I., Slordal, L., Waal, H., Morland, J., and Khiabani, H.Z., *Methadone-related deaths in Norway.* Forensic science international, 2013. **224**(1-3): p. 111-6.

69.     Clausen, T., *The Norwegian OMT program– benefits and challenges.* Norsk Farmaceutisk Tidsskrift, 2014(122(10)): p. s 39- 42.

70.     Blindheim, M. and Johannessen, A., *National clinical guideline for opioid maintenance treatment. (In Norwegian only: Nasjonal retningslinje for legemiddelassistert rehabilitering ved opioidavhengighet)*, N.D.o. Health, Editor. 2010: Oslo.

71.     Lobmaier, P., Kornor, H., Kunoe, N., and Bjorndal, A., *Sustained-release naltrexone for opioid dependence.* Cochrane Database of Systematic Reviews, 2008(2): p. Cd006140.

72.     Martin, W.R., Jasinski, D.R., and Mansky, P.A., *Naltrexone, an antagonist for the treatment of heroin dependence. Effects in man.* Archives of General Psychiatry, 1973. **28**(6): p. 784-791.

73.     Kunøe, N., Lobmaier, P., Ngo, H.T., and Hulse, G., *Injectable and implantable sustained release naltrexone in the treatment of opioid addiction.* British Journal of Clinical Pharmacology, 2014. **77**(2): p. 264-271.

74.     Hulse, G.K., Ngo, H.T., and Tait, R.J., *Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone.* Biological psychiatry, 2010. **68**(3): p. 296-302.

75.     Herbeck, D.M., Jeter, K.E., Cousins, S.J., Abdelmaksoud, R., and Crèvecoeur-MacPhail, D., *Gender differences in treatment and clinical characteristics among patients receiving extended release naltrexone.* Journal of Addictive Diseases, 2016. **35**(4): p. 305-314.

76.     Sideroff, S., Charuvastra, V., and Jarvik, M., *Craving in heroin addicts maintained on the opiate antagonist naltrexone.* The American Journal of Drug and Alcohol Abuse, 1978. **5**.

77.     Sullivan, M.A., Bisaga, A., Mariani, J.J., Glass, A., Levin, F.R., Comer, S.D., and Nunes, E.V., *Naltrexone treatment for opioid dependence: does its effectiveness depend on testing the blockade?* Drug and Alcohol Dependence, 2013. **133**(1): p. 80-85.

78.     Krupitsky, E., Nunes, E.V., Ling, W., Illeperuma, A., Gastfriend, D.R., and Silverman, B.L., *Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial.* Lancet, 2011. **377**(9776): p. 1506-1513.

79.     Coviello, D.M., Cornish, J.W., Lynch, K.G., Boney, T.Y., Clark, C.A., Lee, J.D., Friedmann, P.D., Nunes, E.V., Kinlock, T.W., Gordon, M.S., Schwartz, R.P., Nuwayser, E.S., and O'Brien, C.P., *A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers.* Substance Abuse, 2012. **33**(1): p. 48-59.

80.     Comer, S.D., Sullivan, M.A., Yu, E., Rothenberg, J.L., Kleber, H.D., Kampman, K., Dackis, C., and O'Brien, C.P., *Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial.* Archives of General Psychiatry, 2006. **63**(2): p. 210-8.

81.     Bosco, D., Plastino, M., Colica, C., Bosco, F., Arianna, S., Vecchio, A., Galati, F., Cristiano, D., Consoli, A., and Consoli, D., *Opioid antagonist naltrexone for the treatment of pathological gambling in Parkinson disease.* Clinical Neuropharmacology, 2012. **35**(3): p. 1118-1120.

82.     Mouaffak, F., Leite, C., Hamzaoui, S., Benyamina, A., Laqueille, X., and Kebir, O., *Naltrexone in the Treatment of Broadly Defined Behavioral Addictions: A Review and Meta-Analysis of Randomized Controlled Trials.* European Addiction Research, 2017. **23**(4): p. 204-210.

83.     Kunøe, N., Lobmaier, P., Vederhus, J.K., Hjerkinn, B., Hegstad, S., Gossop, M., Kristensen, O., and Waal, H., *Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial.* The British journal of psychiatry, 2009. **194**(6): p. 541-546.

84.     Krupitsky, E., Nunes, E.V., Ling, W., Gastfriend, D.R., Memisoglu, A., and Silverman, B.L., *Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness.* Addiction, 2013. **108**(9): p. 1628-1637.

85.     Garbutt, J.C., Kranzler, H.R., O'Malley, S.S., Gastfriend, D.R., Pettinati, H.M., Silverman, B.I., Loewy, J.W., and Ehrich, E.W., *Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. .* JAMA, 2005. **293**: p. 1617-1625.

86.     Gastfriend, D.R., *Intramuscular extended-release naltrexone: current evidence.* Annals of the New York Academy of Sciences, 2011. **1216**: p. 144-166.

87.     Hulse, G.K., Morris, N., Arnold-Reed, D., and Tait, R.J., *Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone.* Archives of General Psychiatry, 2009. **66**(10): p. 1108-1115.

88.     Korthuis, P.T., Lum, P.J., Vergara‑Rodriguez, P., Ahamad, K., Wood, E., Kunkel, L.E., Oden, N.L., Lindblad, R., Sorensen, J.L., Arenas, V., Ha, D., Mandler, R.N., and McCarty, D., *Feasibility and safety of extended‑release naltrexone treatment of opioid and alcohol use disorder in HIV clinics: a pilot/feasibility randomized trial.* Addiction, 2017. **112**(6): p. 1036-1044.

89.     Lee, J.D., Friedmann, P.D., Kinlock, T.W., Nunes, E.V., Boney, T.Y., Hoskinson, R.A., Jr., Wilson, D., McDonald, R., Rotrosen, J., Gourevitch, M.N., Gordon, M., Fishman, M., Chen, D.T., Bonnie, R.J., Cornish, J.W., Murphy, S.M., and O'Brien, C.P., *Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders.* The New England Journal of Medicine, 2016. **374**(13): p. 1232-1242.

90.     Maremmani, I., Rovai, L., Maremmani, A.G.I., Bacciardi, S., Rugani, F., Massimetti, E., Gazzarrini, D., Pallucchini, A., and Janiri, L., *Antagonist opioid medications in mental illness: State of art and future perspectives.* Heroin addiction and related clinical problems, 2015. **188**: p. 394.

91.     Woody, G.E., *Advances in the treatment of opioid use disorders.* F1000Research, 2017. **6**: p. 87.

92.     NAS-NRC, *Clinical evaluation of naltrexone treatment of opiate-dependent individuals: Report of the national research council committee on clinical evaluation of narcotic antagonists*, in *Archives of General Psychiatry*. 1978, National Research Council Committee on Clinical Evaluation of Narcotic Antagonist. p. 335-340.

93.     Ling, W., Mooney, L., and Wu, L.T., *Advances in opioid antagonist treatment for opioid addiction.* The Psychiatric clinics of North America, 2012. **35**(2): p. 297-308.

94.     Nunes, E.V., Rothenberg, J.L., Sullivan, M.A., Carpenter, K.M., and Kleber, H.D., *Behavioral therapy to augment oral naltrexone for opioid dependence: a ceiling on effectiveness?* The American Journal of Drug and Alcohol Abuse, 2006. **32**(4): p. 503-517.

95.     Ling, W., Mooney, L., Zhao, M., Nielsen, S., Torrington, M., and Miotto, K., *Selective review and commentary on emerging pharmacotherapies for opioid addiction.* Substance abuse and rehabilitation, 2011. **2**: p. 181-188.

96.     Minozzi, S., Amato, L., Vecchi, S., Davoli, M., Kirchmayer, U., and Verster, A., *Oral naltrexone maintenance treatment for opioid dependence.* Cochrane Database of Systematic Reviews, 2011. **4**.

97.     Roozen, H.G., de Waart, R., and van den Brink, W., *Efficacy and tolerability of naltrexone in the treatment of alcohol dependence: oral versus injectable delivery.* European Addiction Research, 2007. **13**(4): p. 201-206.

98.     Cornish, J.W., Metzger, D., Woody, G.E., Wilson, D., McLellan, A.T., Vandergrift, B., and O'Brien, C.P., *Naltrexone pharmacotherapy for opioid dependent federal probationers.* Journal of substance abuse treatment, 1997. **14**(6): p. 529-534.

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

100.    Digiusto, E., Shakeshaft, A., Ritter, A., O'Brien, S., and Mattick, R.P., *Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD).* Addiction, 2004. **99**(4): p. 450-60.

101.    Gibson, A.E., Degenhardt, L.J., and Hall, W.D., *Opioid overdose deaths can occur in patients with naltrexone implants.* The Medical journal of Australia, 2007. **186**(3): p. 152-153.

102.    Bigelow, G.E., Preston, K.L., Schmittner, J., Dong, Q., and Gastfriend, D.R., *Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: Dose–effects and time-course.* Drug and Alcohol Dependence, 2012. **123**(1–3): p. 57-65.

103.    Hulse, G.K., Tait, R.J., Comer, S.D., Sullivan, M.A., Jacobs, I.G., and Arnold-Reed, D., *Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants.* Drug and Alcohol Dependence, 2005. **79**(3): p. 351-357.

104.    Chiang, C.N., Hollister, L.E., Gillespie, H.K., and Foltz, R.L., *Clinical evaluation of a naltrexone sustained-release preparation.* Drug and Alcohol Dependence, 1985. **16**(1): p. 1-8.

105.    Krupitsky, E., Zvartau, E., Blokhina, E., Verbitskaya, E., Wahlgren, V., Tsoy-Podosenin, M., Bushara, N., Burakov, A., Masalov, D., Romanova, T., Tyurina, A., Palatkin, V., Slavina, T., Pecoraro, A., and Woody, G.E., *Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence.* Archives of General Psychiatry, 2012. **69**(9): p. 973-981.

106.    Tiihonen, J., Krupitsky, E., Verbitskaya, E., Blokhina, E., Mamontova, O., Fohr, J., Tuomola, P., Kuoppasalmi, K., Kiviniemi, V., and Zwartau, E., *Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial.* The American journal of psychiatry, 2012. **169**(5): p. 531-536.

107.    Larney, S., Gowing, L., Mattick, R.P., Farrell, M., Hall, W., and Degenhardt, L., *A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence.* Drug and Alcohol Review, 2014. **33**(2): p. 115-128.

108.    Sullivan, M.A., Vosburg, S.K., and Comer, S.D., *Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin.* Psychopharmacology 2006. **189**(1): p. 37–46.

109.    Cousins, S.J., Denering, L., Crevecoeur-MacPhail, D., Viernes, J., Sugita, W., Barger, J., Kim, T., Weimann, S., and Rawson, R.A., *A demonstration project implementing extended-release naltrexone in Los Angeles County.* Substance Abuse, 2016. **37**(1): p. 54-62.

110.    Crits-Christoph, P., Markell, H.M., Gibbons, M.B., Gallop, R., Lundy, C., Stringer, M., and Gastfriend, D.R., *A Naturalistic Evaluation of Extended-Release Naltrexone in Clinical Practice in Missouri.* Journal of substance abuse treatment, 2016. **70**: p. 50-57.

111.    DeFulio, A., Everly, J.J., Leoutsakos, J.M., Umbricht, A., Fingerhood, M., Bigelow, G.E., and Silverman, K., *Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial.* Drug and Alcohol Dependence, 2012. **120**(1-3): p. 48-54.

112.    Wolfe, D., Carrieri, M.P., Dasgupta, N., Wodak, A., Newman, R., and Bruce, R.D., *Concerns about injectable naltrexone for opioid dependence.* Lancet, 2011. **377**(9776): p. 1468-1470.

113.    Degenhardt, L., Gibson, A., Mattick, R.P., and Hall, W., *Depot naltrexone use for opioid dependence in Australia: large-scale use of an unregistered medication in the absence of data on safety and efficacy.* Drug and Alcohol Review, 2008. **27**(1): p. 1-3.

114.    Mysels, D.J., Cheng, W.Y., Nunes, E.V., and Sullivan, M.A., *The association between naltrexone treatment and symptoms of depression in opioid-dependent patients.* The American Journal of Drug and Alcohol Abuse, 2011. **37**(1): p. 22-26.

115.    Gowing, L., Ali, R., and White, J.M., *Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal.* Cochrane Database of Systematic Reviews, 2010(1).

116.    Dean, A.J., Saunders, J.B., Jones, R.T., Young, R.M., Connor, J.P., and Lawford, B.R., *Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence.* Journal of psychiatry & neuroscience, 2006. **31**(1): p. 38-45.

117.    Miotto, K., McCann, M., Basch, J., Rawson, R., and Ling, W., *Naltrexone and dysphoria: fact or myth?* The American Journal on Addictions, 2002. **11**(2): p. 151-160.

118.    Krupitsky, E., Zvartau, E., Blokhina, E., Verbitskaya, E., Wahlgren, V., Tsoy-Podosenin, M., Bushara, N., Burakov, A., Masalov, D., Romanova, T., Tyurina, A., Palatkin, V., Yaroslavtseva, T., Pecoraro, A., and Woody, G., *Anhedonia, depression, anxiety, and craving in opiate dependent patients stabilized on oral naltrexone or an extended release naltrexone implant.* The American Journal of Drug and Alcohol Abuse, 2016. **42**(5): p. 614-620.

119.    Kelty, E. and Hulse, G., *Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opiate use.* Addiction, 2012. **107**(10): p. 1817-24.

120.    Kelty, E. and Hulse, G., *Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone.* International Journal of Drug Policy, 2017. **46**: p. 54-60.

121.    Williams, A.R., Barbieri, V., Mishlen, K., Levin, F.R., Nunes, E.V., Mariani, J.J., and Bisaga, A., *Long-term follow-up study of community-based patients receiving XR-NTX for opioid use disorders.* The American Journal on Addictions, 2017. **26**(4): p. 319-325.

122.    Bartu, A., Freeman, N.C., Gawthorne, G.S., Allsop, S.J., and Quigley, A.J., *Characteristics, retention and readmissions of opioid-dependent clients treated with oral naltrexone.* Drug and Alcohol Review, 2002. **21**(4): p. 335-340.

123.    Lee, J.D., Nunes, E.V., Jr., Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C.C., King, J., Lindblad, R., Liu, D., Matthews, A.G., May, J., Peavy, K.M., Ross, S., Salazar, D., Schkolnik, P., Shmueli-Blumberg, D., Stablein, D., Subramaniam, G., and Rotrosen, J., *Comparative effectiveness of extended-release naltrexone versus*

buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet, 2017. **391**(10118): p. 309-318.

124.    Silverman, K., DeFulio, A., and Sigurdsson, S.O., *Maintenance of reinforcement to address the chronic nature of drug addiction.* Preventive medicine, 2012. **55 Suppl**: p. 46-53.

125.    Farabee, D., Hillhouse, M., Condon, T., McCrady, B., McCollister, K., and Ling, W., *Injectable pharmacotherapy for opioid use disorders (IPOD).* Contemporary clinical trials, 2016. **49**: p. 70-77.

126.    Everly, J.J., DeFulio, A., Koffarnus, M.N., Leoutsakos, J.M., Donlin, W.D., Aklin, W.M., Umbricht, A., Fingerhood, M., Bigelow, G.E., and Silverman, K., *Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: a randomized controlled trial.* Addiction, 2011. **106**(7): p. 1309-18.

127.    Jarvis, B.P., Holtyn, A.F., DeFulio, A., Dunn, K.E., Everly, J.J., Leoutsakos, J.M.S., Umbricht, A., Fingerhood, M., Bigelow, G.E., and Silverman, K., *Effects of incentives for naltrexone adherence on opiate abstinence in heroin‐dependent adults.* Addiction, 2017. **112**(5): p. 830-837.

128.    Johansson, B.A., Berglund, M., and Lindgren, A., *Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review.* Addiction, 2006. **101**(4): p. 491-503.

129.    Leslie, D.L., Milchak, W., Gastfriend, D.R., Herschman, P.L., Bixler, E.O., Velott, D.L., and Meyer, R.E., *Effects of injectable extended-release naltrexone (XR-NTX) for opioid dependence on residential rehabilitation outcomes and early follow-up.* The American Journal on Addictions, 2015. **24**(3): p. 265-270.

130.    Lobmaier, P.P., Kunøe, N., and Waal, H., *Treatment research in prison: Problems and solutions in a randomized trial.* Addiction Research & Theory, 2010. **18**(1): p. 1-13.

131.    Friedmann, P.D., Wilson, D., Nunes, E.V., Hoskinson Jr, R., Lee, J.D., Gordon, M., Murphy, S.M., Bonnie, R.J., Chen, D.T., Boney, T.Y., and O'Brien, C.P., *Do patient characteristics moderate the effect of extended-release naltrexone (XR-NTX) for opioid use disorder?* Journal of Substance Abuse Treatment, 2017. **85**(61-75).

132.    Sullivan, M., Bisaga, A., Pavlicova, M., Choi, C.J., Mishlen, K., Carpenter, K.M., Levin, F.R., Dakwar, E., Mariani, J.J., and Nunes, E.V., *Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine.* The American journal of psychiatry, 2017. **174**(5): p. 459-467.

133.    Cousins, S.J., Radfar, S.R., Crevecoeur-MacPhail, D., Ang, A., Darfler, K., and Rawson, R.A., *Predictors of Continued Use of Extended-Released Naltrexone (XR-NTX) for Opioid-Dependence: An Analysis of Heroin and Non-Heroin Opioid Users in Los Angeles County.* Journal of Substance Abuse Treatment, 2016. **63**: p. 66-71.

134.    Nunes, E.V., Krupitsky, E., Ling, W., Zummo, J., Memisoglu, A., Silverman, B.L., and Gastfriend, D.R., *Treating Opioid Dependence With Injectable Extended-Release Naltrexone (XR-NTX): Who Will Respond?* Journal of Addiction Medicine, 2015. **9**(3): p. 238-243.

135.    Waal, H., Christophersen, A.S., Frogopsahl, G., Olsen, L.H., and Morland, J., *Naltrexone implants--a pilot project (In Norwegian only: Implantasjon av naltreksonkapsler).* Tidsskrift for den Norske Laegeforening, 2003. **123**(12): p. 1660-1661.

136.    Waal, H., Frogopsahl, G., Olsen, L., Christophersen, A.S., and Morland, J., *Naltrexone implants -- duration, tolerability and clinical usefulness. A pilot study.* European Addiction Research, 2006. **12**(3): p. 138-144.

137.    Kunøe, N., Lobmaier, P., Vederhus, J.K., Hjerkinn, B., Hegstad, S., Gossop, M., Kristensen, Ø., and Waal, H., *Retention in naltrexone implant treatment for opioid dependence.* Drug and Alcohol Dependence, 2010. **111**(1–2): p. 166-169.

138.    Lobmaier, P.P., Kunøe, N., Gossop, M., Katevoll, T., and Waal, H., *Naltrexone Implants Compared to Methadone: Outcomes Six Months after Prison Release.* European Addiction Research, 2010. **16**(3): p. 139-145.

139.    Lobmaier, P.P., Kunoe, N., Gossop, M., and Waal, H., *Naltrexone depot formulations for opioid and alcohol dependence: a systematic review.* CNS Neuroscience & Therapeutics, 2011. **17**(6): p. 629-636.

140.    Waal, H., Bussesund, K., Clausen, T., Skeie, I., Håseth, A., and Lillevold, P., *The annual OMT status survey for 2014 (In Norwegian only: Statusrapport 2014-En aldrende LAR-populasjon).* 2015, Norwegian Centre for Addiction Research.

141.    Deering, D.E., Sheridan, J., Sellman, J.D., Adamson, S.J., Pooley, S., Robertson, R., and Henderson, C., *Consumer and treatment provider perspectives on reducing barriers to opioid substitution treatment and improving treatment attractiveness.* Addictive Behaviours, 2011. **36**(6): p. 636-42.

142.    Sobell, L.C., Ellingstad, T.P., and Sobell, M.B., *Natural recovery from alcohol and drug problems; methodological review of the research with suggestions for future directions.* Addiction, 2000. **95**(5): p. 749-764.

143.    Cunningham, J.A., Sobell, L.C., Sobell, M.B., Agrawal, S., and Toneatto, T., *Barriers to treatment: why alcohol and drug abusers delay or never seek treatment.* Addictive Behaviors, 1993. **18**(3): p. 347-53.

144.    Harris, J. and McElrath, K., *Methadone as social control: institutionalized stigma and the prospect of recovery.* Qualitative health research, 2012. **22**(6): p. 810-824.

145.    Mark, T.L., Lubran, R., McCance-Katz, E.F., Chalk, M., and Richardson, J., *Medicaid coverage of medications to treat alcohol and opioid dependence.* Journal of substance abuse treatment, 2015. **55**: p. 1-5.

146.    Ridge, G., Gossop, M., Lintzeris, N., Witton, J., and Strang, J., *Factors associated with the prescribing of buprenorphine or methadone for treatment of opiate dependence.* Journal of substance abuse treatment, 2009. **37**(1): p. 95-100.

147.    Vanderplasschen, W., Naert, J., Vander Laenen, F., and De Maeyer, J., *Treatment satisfaction and quality of support in outpatient substitution treatment: opiate users' experiences and perspectives.* Drugs: Education, Prevention and Policy, 2015. **22**(3): p. 272-280.

148.  Notley, C., Blyth, A., Maskrey, V., Craig, J., and Holland, R., *The experience of long-term opiate maintenance treatment and reported barriers to recovery: a qualitative systematic review.* European Addiction Research, 2013. **19**(6): p. 287-298.

149.  Alanis-Hirsch, K., Croff, R., Ford, J.H., 2nd, Johnson, K., Chalk, M., Schmidt, L., and McCarty, D., *Extended-Release Naltrexone: A Qualitative Analysis of Barriers to Routine Use.* Journal of substance abuse treatment, 2016. **62**: p. 68-73.

150.  Thomas, C.P., Wallack, S.S., Lee, S., McCarty, D., and Swift, R., *Research to practice: Adoption of naltrexone in alcoholism treatment.* Journal of Substance Abuse Treatment, 2003. **24**(1): p. 1-11.

151.  Aletraris, L., Edmond, M.B., and Roman, P.M., *Adoption of injectable naltrexone in US substance use disorder treatment programs.* Journal of studies on alcohol and drugs, 2015. **76**(1): p. 143-151.

152.  Robertson, A.G. and Swartz, M.S., *Extended-release naltrexone and drug treatment courts: Policy and evidence for implementing an evidence-based treatment.* Journal of Substance Abuse Treatment, 2017. **85**: p. 101-104.

153.  Wallack, S.S., Thomas, C.P., Martin, T.C., Chilingerian, J., and Reif, S., *Substance abuse treatment organizations as mediators of social policy: slowing the adoption of a congressionally approved medication.* The journal of behavioral health services & research, 2010. **37**(1): p. 64-78.

154.  Abraham, A.J., Rieckmann, T.R., McNulty, T., Kovas, A.E., and Roman, P.M., *Counselor attitudes toward the use of naltrexone in substance abuse treatment: A multi-level modeling approach.* Addictive Behaviors, 2011. **36**(6): p. 576-583.

155.  Veilleux, J.C., Colvin, P.J., Anderson, J., York, C., and Heinz, A.J., *A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction.* Clinical psychology review, 2010. **30**(2): p. 155-166.

156.  Ahamad, K., Milloy, M.J., Nguyen, P., Uhlmann, S., Johnson, C., Korthuis, T.P., Kerr, T., and Wood, E., *Factors associated with willingness to take extended release naltrexone among injection drug users.* Addiction Science & Clinical Practice, 2015. **10**: p. 12.

157.  Jones, H.E., *Acceptance of naltrexone by pregnant women enrolled in comprehensive drug addiction treatment: an initial survey.* The American Journal on Addictions, 2012. **21**(3): p. 199-201.

158.  *National Guidelines for Pharmacological Treatment to Opioid Dependent*, D.o. Health, Editor. 2010, Department of Health: Oslo.

159.  Hall, W., Degenhardt, L., Gibson, A., and Mattick, R.P., *Authors reply to Brewer: 'Depot naltrexone use for opioid dependence in Australia: large-scale use of an unregistered medication in the absence of data on safety and efficacy'.* Drug and Alcohol Review, 2008. **27**(4): p. 448-449.

160.  Mokri, A., Chawarski, M.C., Taherinakhost, H., and Schottenfeld, R.S., *Medical treatments for opioid use disorder in Iran: a randomized, double-blind placebo-controlled comparison of buprenorphine/naloxone and naltrexone maintenance treatment.* Addiction, 2016. **111**(5): p. 874-82.

161.    Tanum, L., *Naltrexone vs Buprenorphine-Naloxone for Opioid Dependence in Norway*. 2012: ClinicalTrials.Gov.

162.    Kokkevi, A. and Hartgers, C., *EuropASI: European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence.* European Addiction Research, 1995. **1**(4): p. 208-210.

163.    Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gotzsche, P.C., Devereaux, P.J., Elbourne, D., Egger, M., and Altman, D.G., *CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials.* International journal of surgery, 2012. **10**(1): p. 28-55.

164.    von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotzsche, P.C., and Vandenbroucke, J.P., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.* International journal of surgery, 2014. **12**(12): p. 1495-1499.

165.    Farid, W.O., Dunlop, S.A., Tait, R.J., and Hulse, G.K., *The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: Review of human and animal data.* Current Neuropharmacology, 2008. **6**(2): p. 125-150.

166.    Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., and Dunbar, G.C., *The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.* The Journal of Clinical Psychiatry, 1998. **59 Suppl 20**.

167.    Sobell, L.C., Sobell, M.B., Litten, R.Z., and Allen, J.P., *Timeline follow-back: a technique for assessing self-reported alcohol consumption*. 1992, Totowa, NJ: Humana Press.

168.    Derogatis, L.R., Lipman, R.S., Rickels, K., Uhlenhuth, E.H., and Covi, L., *The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory.* Behavioral Science, 1974. **19**: p. 1-15.

169.    Pavot, W., Diener, E., and Suh, E., *The Temporal Satisfaction With Life Scale.* Journal of Personality Assessment, 1998. **70**(2): p. 340-354.

170.    Melzack, R., *The short-form McGill pain questionnaire.* Pain, 1987. **30**(2): p. 191-197.

171.    Bastien, C.H., Vallières, A., and Morin, C.M., *Validation of the Insomnia Severity Index as an outcome measure for insomnia research.* Sleep Medicine, 2001. **2**(4): p. 297-307.

172.    Miller, W.R. and Tonigan, J.S., *Assessing drinkers' motivation for change: The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES).* Psychology of Addictive Behaviors, 1996. **10(2)**(Special Section: Project MATCH Assessment Strategies ): p. 81-89.

173.    WMA. *WMA declaration of Helsinki: Ethical principles for medical research involving human subjects*. 2013 13.07.2017; Available from: http://www.webcitation.org/6wsyQO5Tu

174.    Aalen, O.O., Frigessi, A., Moger, T.A., Scheel, I., Skovlund, E., and Veierød, M.B., *Statistiske metoder i medisin og helsefag*. 2006, Oslo: Gyldendal akademisk.

175.    Jorgensen, L., Paludan-Muller, A.S., Laursen, D.R., Savovic, J., Boutron, I., Sterne, J.A., Higgins, J.P., and Hrobjartsson, A., *Evaluation of the Cochrane tool for assessing risk of bias in*

*randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews.* Systematic reviews, 2016. **5**: p. 80.

176.     Higgins, J.P.T. and Green, S., *Cochrane Handbook for Systematic Reviews of Interventions* T.C. Collaboration, Editor. 2011: www.handbook.cochrane.org. .

177.     Dettori, J., *The random allocation process: two things you need to know.* Evidence-Based Spine-Care Journal, 2010. **1**(3): p. 7-9.

178.     Hahn, S., *Understanding noninferiority trials.* Korean Journal of Pediatrics, 2012. **55**(11): p. 403-407.

179.     Dossing, A., Tarp, S., Furst, D.E., Gluud, C., Wells, G.A., Beyene, J., Hansen, B.B., Bliddal, H., and Christensen, R., *Modified intention-to-treat analysis did not bias trial results.* Journal of Clinical Epidemiology, 2016. **72**: p. 66-74.

180.     Bart, G., *Promise of extended-release naltrexone is a red herring.* Lancet, 2011. **378**(9792): p. 663; author reply 663-4.

181.     Kirkwood, B.R. and Sterne, J.A.C., *Essential medical statistics*. 2nd ed. ed. 2003, Malden: Blackwell.

182.     Saha, C. and Jones, M.P., *Type I and Type II error rates in the last observation carried forward method under informative dropout.* Journal of Applied Statistics, 2016. **43**(2): p. 336-350.

183.     Rosengren, D.B., Downey, L., and Donovan, D.M., *"I already stopped": abstinence prior to treatment.* Addiction, 2000. **95**(1): p. 65-76.

184.     Del Boca, F.K. and Noll, J.A., *Truth or consequences: the validity of self-report data in health services research on addictions.* Addiction, 2000. **95 Suppl 3**: p. 347-360.

185.     Hser, Y.I., Evans, E., Huang, D., Weiss, R., Saxon, A., Carroll, K.M., Woody, G., Liu, D., Wakim, P., Matthews, A.G., Hatch-Maillette, M., Jelstrom, E., Wiest, K., McLaughlin, P., and Ling, W., *Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial.* Addiction, 2016. **111**(4): p. 695-705.

186.     *Oxford Living Dictionaires*, in *Oxford Dictionaires*. 2017: https://en.oxforddictionaries.com/definition/hawthorne_effect.

187.     Calabria, B., Degenhardt, L., Briegleb, C., Vos, T., Hall, W., Lynskey, M., Callaghan, B., Rana, U., and McLaren, J., *Systematic review of prospective studies investigating "remission" from amphetamine, cannabis, cocaine or opioid dependence.* Addictive Behaviors, 2010. **35**(8): p. 741-749.

188.     Ruyter, K., Solbakk, J.H., and Waal, H., *(In Norwegian only) Etiske prinsipper, erfaringer og ettertanker* in *Rusmiddelbrukeren og forskeren*. 2009, Norwegian Centre for Addiction Research (SERAF).

189.     Malterud, K., *Reflexivity and metapositions: strategies for appraisal of clinical evidence.* Journal of evaluation in clinical practice, 2002. **8**(2): p. 121-126.

190.     Rogers, E.M., *Diffusion of Innovations, 5th Edition*. 2003: Free Press.

191. Ling, W., Mooney, L., and Hillhouse, M., *Prescription opioid abuse, pain and addiction: clinical issues and implications.* Drug and Alcohol Review, 2011. **30**(3): p. 300-305.

192. Dreifuss, J.A., Griffin, M.L., Frost, K., Fitzmaurice, G.M., Potter, J.S., Fiellin, D.A., Selzer, J., Hatch-Maillette, M., Sonne, S.C., and Weiss, R.D., *Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study.* Drug and Alcohol Dependence, 2013. **131**(1): p. 112-118.

193. Mogali, S., Khan, N.A., Drill, E.S., Pavlicova, M., Sullivan, M.A., Nunes, E., and Bisaga, A., *Baseline characteristics of patients predicting suitability for rapid naltrexone induction.* The American Journal on Addictions, 2014. **24**(3): p. 258-264.

194. Ramsey, S.E., Rounsaville, D., Hoskinson, R., Park, T.W., Ames, E.G., Neirinckx, V.D., and Friedmann, P., *The Need for Psychosocial Interventions to Facilitate the Transition to Extended-Release Naltrexone (XR-NTX) Treatment for Opioid Dependence: A Concise Review of the Literature.* Substance abuse : research and treatment, 2016. **10**: p. 65-68.

195. Kunøe, N., Lobmaier, P., Vederhus, J.K., Hjerkinn, B., Gossop, M., Hegstad, S., Kristensen, Ø., and Waal, H., *Challenges to antagonist blockade during sustained‑release naltrexone treatment.* Addiction, 2010. **105**(9): p. 1633-1639.

196. Silverman, B.L. and Akerman, S.C., *Antagonist Treatment for Opioid Use Disorder.* The American Journal of Medicine, 2016. **130**(3): p. 117.

197. Sigmon, S.C., Bisaga, A., Nunes, E.V., O'Connor, P.G., Kosten, T., and Woody, G., *Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice.* The American Journal of Drug and Alcohol Abuse, 2012. **38**(3): p. 187-199.

198. Murphy, S.M. and Polsky, D., *Economic Evaluations of Opioid Use Disorder Interventions.* Pharmacoeconomics, 2016. **34**(9): p. 863-887.

199. Baser, O., Chalk, M., Fiellin, D.A., and Gastfriend, D.R., *Cost and utilization outcomes of opioid-dependence treatments.* The American journal of managed care, 2011. **17 Suppl 8**: p. 235-248.

200. Garner, B.R., *Research on the diffusion of evidence-based treatments within substance abuse treatment: a systematic review.* Journal of substance abuse treatment, 2009. **36**(4): p. 376-399.

201. Knudsen, H.K., Ducharme, L.J., Roman, P.M., and Link, T., *Buprenorphine diffusion: the attitudes of substance abuse treatment counselors.* Journal of Substance Abuse Treatment, 2005. **29**(2): p. 95-106.

202. Cousins, S.J., Crèvecoeur-MacPhail, D., Kim, T., and Rawson, R.A., *The Los Angeles County hub-and-provider network for promoting the sustained use of extended-release naltrexone (XR-NTX) in Los Angeles County (2010–2015).* Journal of Substance Abuse Treatment, 2017. **85**: p. 78-83.

203. WHO and UNODC, *Principles of Drug Dependent Treatment-Discussion Paper*. 2008, World Health Organization and United Nations Office on Drugs and Crime.

204. Murphy, S.M., Polsky, D., Lee, J.D., Friedmann, P.D., Kinlock, T.W., Nunes, E.V., Bonnie, R.J., Gordon, M., Chen, D.T., Boney, T.Y., and O'Brien, C.P., *Cost-Effectiveness of Extended Release*

*Naltrexone to Prevent Relapse among Criminal-Justice-Involved Persons with a History of Opioid Use Disorder.* Addiction, 2017. **112**(8): p. 1440-1450.

# Papers I-III

# Paper I

# Paper II

# Paper III

# Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a nine-month follow-up study

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**Running head:** Extended-release naltrexone

# Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a nine-month follow-up study

**Keywords**: Extended-release naltrexone, opioid use, treatment innovation, treatment of opioid dependence, recovery, craving, antagonist treatment

## Abstract

***Background and aims:*** This is a nine-month follow-up study of a previously published randomized clinical trial (RCT) comparing extended-release naltrexone (XR-NTX) to buprenorphine-naloxone (BP-NLX) over three months. The aims were to estimate the effectiveness, safety and feasibility of XR-NTX treatment over nine months among opioid dependents who continued on or were inducted on XR-NTX treatment after the initial three-month RCT. ***Design:*** In this trickle style, prospective nine-month cohort study, people with opioid dependence who participated in the preceding three-month RCT were followed every fourth week. Differences between groups were assessed by linear mixed models. ***Setting:*** Five urban, outpatient addiction clinics in Norway. ***Participants:*** Opioid-dependent men and women aged 18-60 years who continued on (n=54) or were inducted on (n=63) XR-NTX. ***Intervention:*** XR-NTX administrated as intra-muscular injections (380 mg) every fourth week. ***Measurements:*** Data on retention, use of heroin and other illicit substances, opioid craving, treatment satisfaction, addiction-related problems, and adverse events were reported every fourth week. ***Findings:*** Half of the n=117 participants (49.6%) completed the study, while n=35 were lost to follow-up and n=24 discontinued due to other reasons. No differences were observed between those who continued on and those inducted on XR-NTX in this follow-up. Participants showed non-significant reductions between weeks 12 and 48 in the use of heroin (mean reduction -2.7, CI:-5.5-0.3, p=0.053) and other opioids (mean reduction -2.2, CI:-6.1-1.7, p=0.271). A total of n=57 (48.7%) participants reported full opioid abstinence. The lack of urine drug testing is a limitation. Two participants reported serious adverse events that required surgery for injection site reactions. No opioid overdoses were reported. ***Conclusions:*** During this nine-month follow-up study with extended-release naltrexone for opioid dependence, 49.6% of participants completed treatment and 48.7% were abstinent from opioids. The treatment did not raise any new safety concerns.

## Introduction

Treatment is the most important factor to prevent overdose death and other harmful effects of opioid abuse (1). Opioid agonist maintenance treatment (OMT) is the WHO-recommended option (2). Despite the effectiveness of OMT (3) and its availability in many countries, it is utilized only by half of people with opioid dependence in Europe (4). As OMT maintains opioid dependence, it risks not engaging users who identify with a long-term goal of abstinence from all opioids (5-7).

Naltrexone is an opioid antagonist that competitively blocks euphoric effects of heroin and other opioids, thereby preventing relapse of opioid abuse and overdose deaths when used as prescribed (8-11). It also reduces the craving for opioids and alcohol (12, 13). Sustained-release formulations of naltrexone, both implantable and injectable, have shown promising results in maintaining abstinence from opioids and acceptable retention rates in studies with durations up to 6 months (14-19). An injectable form of extended-release naltrexone (XR-NTX) administrated once monthly is approved in the USA and in Russia (14, 20, 21). Two recently published randomized clinical trials (RCT) compared the effectiveness of XR-NTX to buprenorphine-naloxone, and showed similar retention, effectiveness and safety between the two medication groups (22, 23).

The data on long-term use of XR-NTX are limited (3, 24). In a Russian trial, 62.3% of n=114 participants completed one-year follow-up (9). In an American study, 55% of n=38 health professionals received 12 XR-NTX injections (25). In comparison, a review found retention rates between 26-85% at 12-month follow-ups for patients in opioid agonist treatment (24).

Sustained-release formulations of naltrexone are considered well-tolerated with few serious side effects (11, 21, 26, 27). Severe injection site reactions that require surgery may occur, but are not frequently reported (21). Studies of sustained-release formulations of naltrexone have been criticised for the lack of post-treatment reporting of adverse events, including overdoses (28, 29). A recent study found no significant differences in rates of overdoses among people with opioid dependence treated with opioid agonist treatment or naltrexone implants, including after treatment cessation (30).

Previous research on XR-NTX has mainly been conducted in countries where OMT has a limited availability due to structural barriers, e.g. in Russia, where OMT medication is illegal, or in populations where access is limited because the patients are responsible for treatment costs (3, 14, 25, 31). To evaluate the clinical potential of XR-NTX in settings where OMT is available at no cost, studies with longer follow-ups are needed (3, 32, 33).

The overall purpose of the study was to assess the effectiveness, safety and feasibility of longer-term treatment with XR-NTX in a clinical setting. We aimed to: (1) estimate and compare the proportion of participants who continued XR-NTX with those inducted on XR-NTX after an initial three-month RCT and their retention in XR-NTX treatment during a nine-month period; (2) compare frequency of opioid use between participants who continued XR-NTX and those inducted on XR-NTX; and (3) between completers and non-completers; (4) compare frequency of use of other substances and psychosocial problems between participants who continued XR-NTX and those inducted on XR-NTX; (5) estimate and compare craving scores and treatment satisfaction between participants who continued XR-NTX and those inducted on XR-NTX; and (6) between completers and non-completers; and

(7) estimate and compare reported adverse events between participants who continued XR-NTX and those inducted on XR-NTX.

According to the study protocol, participants could choose between receiving BP-NLX or XR-NTX in the nine-month follow-up period. Of the n=122 participants who entered the follow-up, only n=5 chose further treatment with BP-NLX while n=117 chose XR-NTX. While OMT is available at no cost in Norway, XR-NTX was only available through this study. The opportunity to receive XR-NTX was likely the most important motivating factor for study participation (23). Due to the low number of BP-NLX participants, no meaningful statistical or clinical comparisons could be carried out, meaning the n=117 participants receiving XR-NTX would be the natural focus of investigation. Participants who preferred BP-NLX were followed up at their sites' OMT clinics according to the national OMT guidelines.

## Methods

In the aforementioned Norwegian multi-centre RCT, n=159 people with opioid dependence were randomised to receive XR-NTX or BP-NLX in a 1:1 ratio (23). Retention rates were non-inferior in the two groups and n=105 completed the three-month study (Figure 1). Superiority analysis showed significantly lower use of illicit opioids and lower craving scores in the XR-NTX group. No significant differences were found between the treatment groups regarding most other illicit substance use. In the XR-NTX group, more adverse events were reported (23).

### Design
This nine-month, cohort study was conducted following the three-month RCT in a prospective, trickle-style design as each participant completed the RCT (34). Participants consented to participate in the follow-up at conclusion of the RCT. In order to estimate effectiveness, safety and feasibility of XR-NTX in longer-term, participants continuing XR-NTX (n=54) and participants inducted on XR-NTX (n=63) were compared with regard to retention in treatment, substance use, adverse events and on other relevant outcomes (see below) every fourth week during the nine-month study period (23).

### Setting
In the period from November 2012 to July 2015, opioid-dependent individuals were recruited for study participation in the RCT from five urban hospitals in Norway. RCT participants were offered to continue participation in the follow-up at week 12. Participants, who dropped-out of any treatment arm during the RCT period and were motivated for re-inclusion, could be re-included in the study at week 12. The follow-up study was completed when the last patient completed participation in July 2016.

### Participants
Eligible participants were opioid-dependent men and women aged 18-60 years. Exclusion criteria were alcohol dependence, or serious somatic or psychiatric illnesses regarded as contra-indications for study participation. Women could not be pregnant or breastfeeding and had to accept the use of contraception during the study.

### Measurements and outcomes
Participants were interviewed every fourth week using the Addiction Severity Index, European version (35), and self-reported craving for opioids and treatment satisfaction. Data

were collected using the time-line follow-back method (36). Any adverse events that occurred during the study period and for up to three months after study discontinuation were reported.

Outcomes were: retention in treatment, measured in numbers of weeks in treatment and the number of participants completing the study; the number of participants abstinent from opioids during the study; the use of heroin and other illicit opioids, the use of cannabis, amphetamines, and benzodiazepines; heavy alcohol use; injection use; acquisitive crime and work, measured in number of days within the four weeks preceding each study attendance; money spent on drugs and alcohol within the four weeks preceding each study attendance, measured in Norwegian crowns (NOK); craving for heroin and treatment satisfaction within the four weeks preceding each study attendance measured by a Visual Analogue Scale (VAS) with scores from 0-10; and the number of reported adverse events (34).

Outcomes were compared between the participants continuing XR-NTX treatment (n=54) and the participants inducted on XR-NTX (n=63) and between completers and non-completers.

**Study intervention**
After week 12, participants chose medication based on their preferences. Those who preferred XR-NTX are referred to in this paper. Participants already receiving XR-NTX in the RCT continued their treatment. Participants who changed from BP-NLX to XR-NTX and those who were re-included on XR-NTX in the follow-up were referred to a detoxification unit at week 12. After a minimum of 72 hours without any intake of opioids and if passing a 0.4 mg naloxone challenge test, participants were given an injection of 380 mg XR-NTX (Vivitrol ®). To relieve withdrawal symptoms such as vomiting, chills and insomnia in the detoxification phase, participants were prescribed adequate pharmacological treatment. Participants were discharged from the detoxification units 1-7 days after the initial medication dose. Following induction, participants received a XR-NTX injection in an outpatient setting every fourth week throughout the study period. Counselling was not mandatory, but was offered to all participants at the study site as part of standard ancillary services.

**Research ethics**
The study was approved by the South-East Regional Ethical Board for Medical Research Ethics (#2011/1320) and by the Norwegian Medicines Agency.

All participants were given oral and written information about the study including possible effects and side-effects of study medication before assigning the written informed consent (37). Except for travel expenses, participants were not paid or compensated for taking part in the study.

The participants were able to withdraw from the study at any time. Participants who failed to attend study follow-up and did not respond to at least three attempts at communication during the ensuing week, were reported as lost to follow-up in the study. Participants were informed of the increased risk of overdoses after discontinuing XR-NTX. All participants were required to accept enrolment into the local OMT program to ensure adequate follow-up and rapid access to opioid agonist treatment in the event of drop-out from the study.

**Statistical analyses**
Statistical analyses were performed on data from n=117 participants who received at least one injection of XR-NTX during weeks 12-48. Data were described as means and confidence

intervals (CI) or frequencies and percentages. Kaplan-Meier survival curves were plotted and log-rank test performed to assess retention in treatment.

Nine-month changes in substance use, addiction-related outcomes and treatment satisfaction were assessed by linear mixed models with fixed effects for time up to third order to describe non-linear pattern. Random effects for time and participants nested within sites were included. Differences between participants continuing XR-NTX treatment and participants inducted on XR-NTX as well as differences between completers and non-completers were assessed by the same models with extra fixed effects for participant group and interaction between the group and time. A significant interaction would imply a difference in change between the groups. The results were presented as observed means and mean differences with the corresponding 95% CI and p-values derived from linear mixed models.

Differences in the number and type of adverse effects between the participants who continued on XR-NTX and those inducted on XR-NTX in the follow-up study were described using Fisher's exact test.

Results with p-values <0.05 were considered significant and all tests were two-sided. Statistical analyses were performed using IBM SPSS Statistics, version 24 and SAS version 9.4.

## Results

Of the n=143 participants who received at least one dose of study medication in the RCT, n=117 (81.8%) chose XR-NTX treatment in the follow up study; n=54 continued on XR-NTX, n=43 changed from BP-NLX to XR-NTX, while n=20 re-presented for XR-NTX after having previously dropped out of the RCT (Figure 1).

**<Figure 1 about here>**

Among the n=117 participants, n=89 were men and n=28 were women. The mean age was 35.6 years. Prior to study inclusion, 63.2% of the participants reported heroin as their primary problem substance, 12.0% reported other opioids and 24.8% reported poly-drug use including opioids (Table 1).

**<Table 1 about here>**

### Retention
After nine months, n=58 participants (49.6%) had attended all scheduled visits and received XR-NTX injections as prescribed (Figure 2). The mean number of weeks in treatment was 25.5 (CI: 23.3-27.7). There were no differences in retention between participants continuing XR-NTX and those inducted on XR-NTX.

**<Figure 2 about here >**

Non-completers (n=59) conveyed different reasons for discontinuing the study: n=35 (59.3%) were lost to follow-up, n=14 (23.7%) wanted to manage without any medication or disliked the effect of XR-NTX, n=7 (11.9%) reported adverse events (see below), n=2 (3.4%) reported serious adverse events and n=1 (1.7%) died in an accident.

**Use of opioids**
Participants reported a significant reduction in use of heroin between weeks 12 and 44 (p=0.036), but the reduction to week 48 (p=0.053) was non-significant. Between weeks 12 and 32, there was a significant reduction in use of other opioids (p=0.049), but no significant reduction was detected between week 12 and later assessments. A total of n=57 (48.7%) participants reported no use of opioids during the study.

**<Table 2 about here>**

There were no significant differences in use of heroin or other illicit opioids between participants who continued with XR-NTX and participants inducted on XR-NTX (Table 2). Non-completers reported significantly more use of heroin from week 24 (p=0.049) to week 40 (p=0.019) and more use of other opioids in week 12 (p=0.049) and week 16 (p=0.031) compared to the completers (Figure 3).

**<Figure 3 about here>**

**Other outcome measures**
Between weeks 12 and 48, participants spent significantly less money on drugs (p=0.029). There were non-significant changes among the participants between weeks 12 and 48 in use of other illicit substances and in other addiction-related problems. When comparing participants who continued XR-NTX treatment and those inducted on XR-NTX, there were significant differences in heavy alcohol use and in days of work between weeks 12 and 48 (table 2).

Participants reported a non-significant reduction in heroin craving between weeks 12 and 48. Participants inducted on XR-NTX scored significantly higher on craving from week 12 (p=0.015) to week 20 (p=0.040) than those continuing XR-NTX. Non-completers scored significantly higher on craving from week 20 (p=0.042) to week 36 (p=0.033) compared to completers (Figure 3).

There was a non-significant increase in treatment satisfaction between weeks 12 and 48. Participants continuing XR-NTX scored significantly higher than those inducted on XR-NTX from week 12 (p<0.001) to week 32 (p=0.009). Completers scored significantly higher than non-completers in week 16 (p=0.009) to week 40 (p<0.001) (Figure 3).

**Safety and tolerability**
A total of n=62 (53%) participants reported at least one non-serious adverse event (Table 3). Participants inducted on XR-NTX reported n=37 and participants who continued on XR-NTX; reported n=25 adverse events (p=0.198).

A total of n=37 participants reported 2-15 different adverse events, most frequently withdrawal-like symptoms reported by the participants who were inducted on XR-NTX in the follow-up. Other adverse events were infections, non-serious injuries, and various pain conditions. Injection site problems and withdrawal-like symptoms were considered to be related to XR-NTX.

Adverse events caused n=7 participants to discontinue treatment due to: withdrawal-like symptoms (n=2), psychological reactions (n=2), need for opioid agonist pain treatment (n=1), seizure (n=1), and insomnia (n=1).

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Five participants reported a serious adverse event requiring hospitalisation; two due to infections, one planned surgery and two serious injection-site reactions requiring surgery. All participants recovered completely and except for those who experienced the injection-site reactions, all continued XR-NTX treatment. One participant died of internal injuries after an accident. No opioid overdoses were reported. No serious adverse events, including no overdose fatalities were reported among the participants during the first three months following their completion of the study.

**<Table 3 about here>**


## Discussion

Of the n=143 participants who took at least one dose of study medication in the three-month RCT, n=117 (81.8%) chose to continue on XR-NTX or be inducted on XR-NTX in the nine-month follow-up study. Only n=5 participants (3.5%) chose to either continue on BP-NLX or transition from XR-NTX to BP-NLX in the follow-up. As BP-NLX is available in Norway at no cost in the OMT programs while XR-NTX was not registered for use and only available for study participants, it is likely that study participation was motivated by the possibility to obtain XR-NTX (23). Half of the participants (49.6%) completed the study. Participants showed a non-significant reduction in use of opioids and 48.7% reported abstinence from all opioids. There were no significant changes in substance use and addiction-related problems during the follow-up, with the exception of a significant reduction in money spent on drugs. Participants reported a sustained reduction in craving for heroin and increased treatment satisfaction. Adverse events were reported by 53% of the participants and the majority of these were related to withdrawal symptoms during induction on XR-NTX.

Retention rates reported in studies of medication-assisted treatment for opioid dependence vary considerably (24). Two studies of XR-NTX reported retention rates of 55% and 62.3% after one year in treatment (9, 25). In our study half of the participants completed the follow-up with XR-NTX, while 40.6% (58/143) completed both the RCT and the follow-up study, in total a 48-week period. Differences in study designs, the availability of OMT medication, and the selection of participants limit comparison between our study and previous studies of XR-NTX. The study design did not include any mandatory supplementary interventions. We suggest that implementing such interventions could improve retention in treatment. In contrast to the findings from a longer-term study in Russia, we found no differences in the retention rates between participants who continued on XR-NTX from the RCT phase and those inducted on XR-NTX in the follow-up study (9).

Participants reported less use of illicit opioids and less craving for heroin during the course of the study. Nearly half of the participants reported no opioid use. In the other half of participants, their opioid use remained at a low level (Table 2), consistent with other studies of sustained-release naltrexone (9, 11, 15, 16, 19, 22, 26, 38, 39).

Similar to the preceding RCT phase (23) and other XR-NTX studies (19, 25), the majority of the adverse events were withdrawal-related and reported following the first administration of XR-NTX (21). While we administered the first XR-NTX injection after a minimum 72 hours of complete abstinence from any opioids, other studies have recommended a longer period of abstinence (9, 40, 41). No opioid overdoses were reported during the study or within three

months after study discontinuation. This may reflect the effectiveness of XR-NTX in blocking the opioid receptors and thereby preventing overdoses (20) as well as being an indication of the participants' high motivation for an opioid-free treatment. The safety profile of XR-NTX in our study corresponded with previous findings in other longer-term studies (9, 25).

The naturalistic setting of the study may provide additional knowledge about the utilization of XR-NTX outside a study context. We regard the generalizability from this study to be acceptable to locations where the health care system and the regulatory framework regarding OMT correspond to the system in Norway or in other Western European countries.

This study has several limitations: the open-label design without blinding and the loss of a relevant control group may reduce the validity of the study and limit our ability to draw conclusions regarding efficacy (42). However, we considered the observational design appropriate to achieve the objectives of this study, which was to assess the longer-term clinical effectiveness, safety and feasibility of XR-NTX. The lack of urine drug testing (UDT) is a limitation, thus self-reported drug use could not be confirmed. In the RCT, reported use of drugs corresponded with UDT results at an acceptable level (23). Attrition due to high drop-out rates is a weakness of this study, as often seen in longer-term studies (32).

In summary, the improvements participants obtained during the three-month RCT were maintained during the following nine-month treatment with XR-NTX.
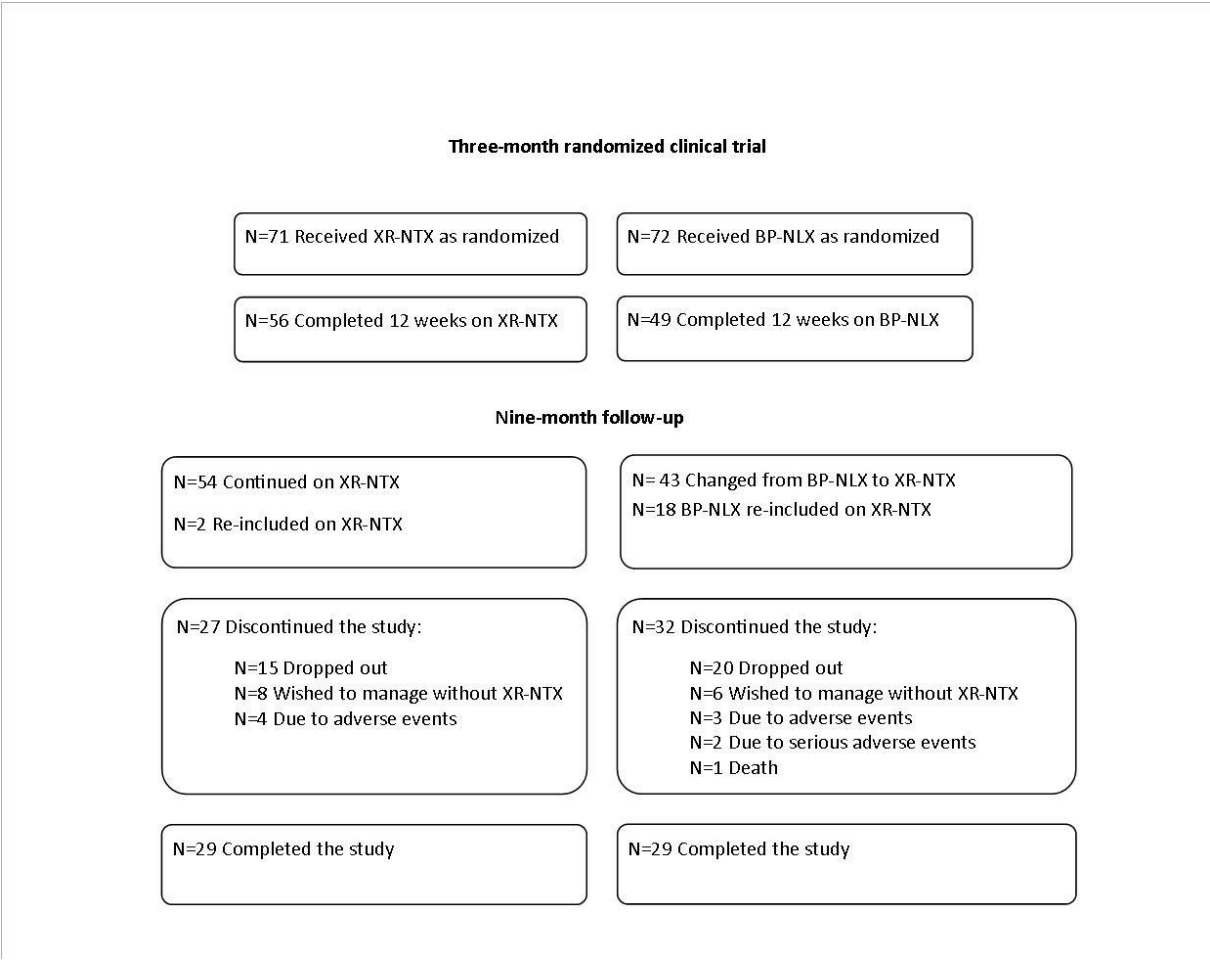
# References

1.      Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011;106(1):32-51.
2.      WHO. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Denpendence. World Health Organization; 2009.
3.      Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harvard review of psychiatry. 2015;23(2):63-75.
4.      EMCDDA. European Drug Report: Trend and Developments. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2015.
5.      Larney S, Zador D, Sindicich N, Dolan K. A qualitative study of reasons for seeking and ceasing opioid substitution treatment in prisons in New South Wales, Australia. Drug Alcohol Rev. 2016.
6.      Vanderplasschen W, Naert J, Vander Laenen F, De Maeyer J. Treatment satisfaction and quality of support in outpatient substitution treatment: opiate users' experiences and perspectives. Drugs: Education, Prevention and Policy. 2015;22(3):272-80.
7.      Notley C, Blyth A, Maskrey V, Craig J, Holland R. The experience of long-term opiate maintenance treatment and reported barriers to recovery: a qualitative systematic review. European addiction research. 2013;19(6):287-98.
8.      Herbeck DM, Jeter KE, Cousins SJ, Abdelmaksoud R, Crèvecoeur-MacPhail D. Gender differences in treatment and clinical characteristics among patients receiving extended release naltrexone. Journal of addictive diseases. 2016;35(4):305-14.
9.      Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. Addiction. 2013;108(9):1628-37.
10.     Sullivan MA, Bisaga A, Mariani JJ, Glass A, Levin FR, Comer SD, et al. Naltrexone treatment for opioid dependence: does its effectiveness depend on testing the blockade? Drug and alcohol dependence. 2013;133(1):80-5.
11.     Kunøe N, Lobmaier P, Ngo HT, Hulse G. Injectable and implantable sustained release naltrexone in the treatment of opioid addiction. British Journal of Clinical Pharmacology. 2014;77(2):264-71.
12.     Maremmani I, Rovai L, Maremmani AGI, Bacciardi S, Rugani F, Massimetti E, et al. Antagonist opioid medications in mental illness: State of art and future perspectives. stress. 2015;188:394.
13.     NAS-NRC. Clinical evaluation of naltrexone treatment of opiate-dependent individuals: Report of the national research council committee on clinical evaluation of narcotic antagonists. National Research Council Committee on Clinical Evaluation of Narcotic Antagonist; 1978. Report No.: 0003-990X Contract No.: 3.
14.     Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377(9776):1506-13.
15.     Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. Archives of general psychiatry. 2009;66(10):1108-15.
16.     Kunøe N, Lobmaier P, Vederhus JK, Hjerkinn B, Hegstad S, Gossop M, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. The British journal of psychiatry : the journal of mental science. 2009;194(6):541-6.
17.     DeFulio A, Everly JJ, Leoutsakos JM, Umbricht A, Fingerhood M, Bigelow GE, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. Drug and alcohol dependence. 2012;120(1-3):48-54.

18.	Crits-Christoph P, Markell HM, Gibbons MB, Gallop R, Lundy C, Stringer M, et al. A Naturalistic Evaluation of Extended-Release Naltrexone in Clinical Practice in Missouri. J Subst Abuse Treat. 2016;70:50-7.

19.	Lee JD, Friedmann PD, Kinlock TW, Nunes EV, Boney TY, Hoskinson RA, Jr., et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. The New England journal of medicine. 2016;374(13):1232-42.

20.	Bigelow GE, Preston KL, Schmittner J, Dong Q, Gastfriend DR. Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: Dose–effects and time-course. Drug and alcohol dependence. 2012;123(1–3):57-65.

21.	Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. Annals of the New York Academy of Sciences. 2011;1216:144-66.

22.	Lee JD, Nunes EV, Jr., Novo P, Bachrach K, Bailey GL, Bhatt S, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. The Lancet. 2017.

23.	Tanum L, Solli KK, Latif ZE, Benth JS, Opheim A, Sharma-Haase K, et al. The Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. JAMA Psychiatry. 2017.

24.	Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. Journal of addictive diseases. 2016;35(1):22-35.

25.	Earley PH, Zummo J, Memisoglu A, Silverman BL, Gastfriend DR. Open-label Study of Injectable Extended-release Naltrexone (XR-NTX) in Healthcare Professionals With Opioid Dependence. Journal of addiction medicine. 2017.

26.	Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Archives of general psychiatry. 2006;63(2):210-8.

27.	Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BI, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. . JAMA. 2005;2005;293:1617-25.

28.	Wolfe D, Carrieri MP, Dasgupta N, Wodak A, Newman R, Bruce RD. Concerns about injectable naltrexone for opioid dependence. The Lancet. 2011;377(9776):1468-70.

29.	Larney S, Gowing L, Mattick RP, Farrell M, Hall W, Degenhardt L. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. Drug Alcohol Rev. 2014;33(2):115-28.

30.	Kelty E, Hulse G. Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. International Journal of Drug Policy. 2017;46:54-60.

31.	Nunes EV, Krupitsky E, Ling W, Zummo J, Memisoglu A, Silverman BL, et al. Treating Opioid Dependence With Injectable Extended-Release Naltrexone (XR-NTX): Who Will Respond? Journal of addiction medicine. 2015;9(3):238-43.

32.	Hser YI, Evans E, Grella C, Ling W, Anglin D. Long-term course of opioid addiction. Harvard review of psychiatry. 2015;23(2):76-89.

33.	McLellan AT, McKay JR, Forman R, Cacciola J, Kemp J. Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring. Addiction. 2005;100(4):447-58.

34.	Kunøe N, Opheim A, Solli KK, Gaulen Z, Sharma-Haase K, Latif ZE, et al. Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). BMC Pharmacology and Toxicology. 2016;17(1):1-10.

35.	Kokkevi A, Hartgers C. EuropASI: European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence. European addiction research. 1995;1(4):208-10.

36.	Sobell LC, Sobell MB, Litten RZ, Allen JP. Timeline follow-back: a technique for assessing self-reported alcohol consumption. Totowa, NJ: Humana Press; 1992.

37.	WMA. WMA declaration of Helsinki: Ethical principles for medical research involving human subjects https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/2013 [updated 13.07.2017. Available from: http://www.webcitation.org/6wsyQO5Tu

38.	Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. Archives of general psychiatry. 2012;69(9):973-81.

39.	Lobmaier PP, Kunøe N, Gossop M, Katevoll T, Waal H. Naltrexone Implants Compared to Methadone: Outcomes Six Months after Prison Release. European addiction research. 2010;16(3):139-45.

40.	Cousins SJ, Denering L, Crevecoeur-MacPhail D, Viernes J, Sugita W, Barger J, et al. A demonstration project implementing extended-release naltrexone in Los Angeles County. Substance abuse. 2016;37(1):54-62.

41.	Sullivan M, Bisaga A, Pavlicova M, Choi CJ, Mishlen K, Carpenter KM, et al. Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine. The American journal of psychiatry. 2017:appiajp201616050548.

42.	Nunes EV, Lee JD, Sisti D, Segal A, Caplan A, Fishman M, et al. Ethical and clinical safety considerations in the design of an effectiveness trial: A comparison of buprenorphine versus naltrexone treatment for opioid dependence. Contemporary clinical trials. 2016;51:34-43.

*Figure 1: Flow chart for participants included in the study*



**Three-month randomized clinical trial**

N=71 Received XR-NTX as randomized

N=72 Received BP-NLX as randomized

N=56 Completed 12 weeks on XR-NTX

N=49 Completed 12 weeks on BP-NLX

**Nine-month follow-up**

N=54 Continued on XR-NTX

N=2 Re-included on XR-NTX

N= 43 Changed from BP-NLX to XR-NTX

N=18 BP-NLX re-included on XR-NTX

N=27 Discontinued the study:

    N=15 Dropped out
    N=8 Wished to manage without XR-NTX
    N=4 Due to adverse events

N=32 Discontinued the study:

    N=20 Dropped out
    N=6 Wished to manage without XR-NTX
    N=3 Due to adverse events
    N=2 Due to serious adverse events
    N=1 Death

N=29 Completed the study
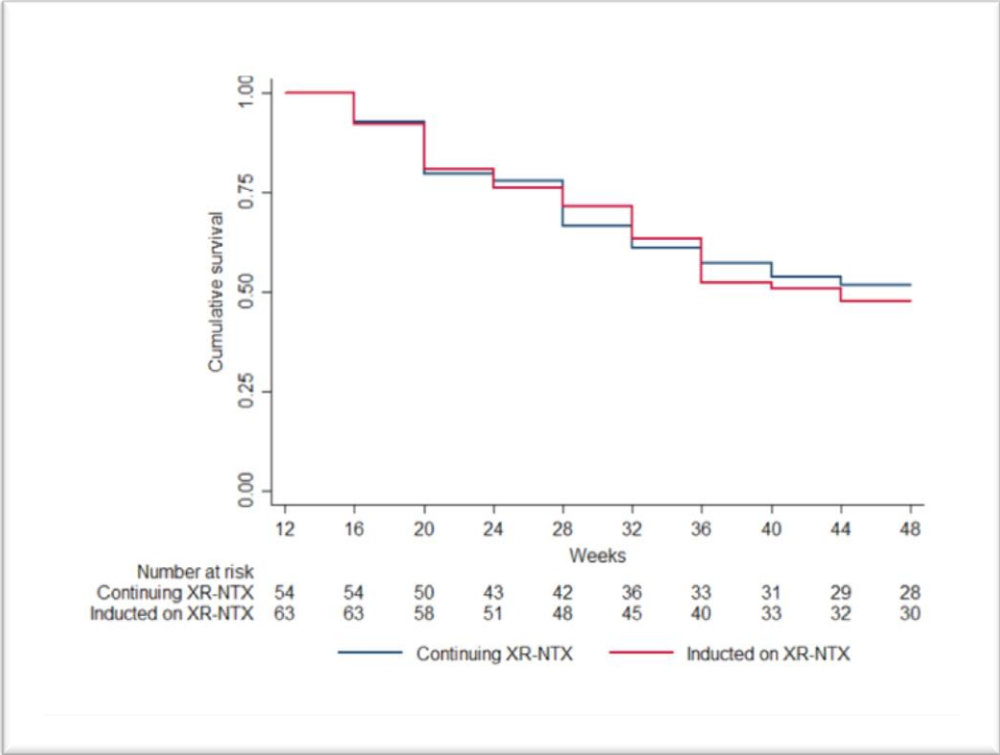
N=29 Completed the study

*This flowchart displays the participant flow from the randomised groups in the preceding RCT (23) to inclusion and end of the present nine-month follow-up study. The left side are participants randomized to XR-NTX and the right side are participants randomized to BP-NLX.*

**Table 1 – Lifetime characteristics of participants**

| Lifetime characteristics | Mean (number) | CI (percent) |
|---|---|---|
| Age in years | 35.6 | 34.1-37.1 |
| Women/men | 28/89 | 24%/76% |
| HIV positive | 2 | 1.7% |
| Hepatitis C seropositive | 61 | 52.1% |
| Injecting use, age at onset | 20.7 | 19.1-22.2 |
| Years of injecting use | 10.0 | 8.3-11.7 |
| Substance use, age at onset | | |
| Heroin | 22.0 | 20.8-23.2 |
| Other illicit opioids | 19.6 | 17.5-21.6 |
| Cannabis | 15.0 | 14.4-15.7 |
| Poly-drug | 17.8 | 16.7-18.9 |
| Benzodiazepines | 18.7 | 17.4-20.0 |
| Amphetamine | 17.2 | 16.3-18.2 |
| Alcohol for intoxication | 13.5 | 12.7-14.2 |
| Years of substance use | | |
| Heroin | 6.7 | 5.8-7.7 |
| Other illicit opioids | 2.3 | 1.3-3.4 |
| Cannabis | 10.1 | 8.5-11.7 |
| Poly-drug | 9.9 | 8.6-11.2 |
| Benzodiazepines | 5.3 | 3.9-6.7 |
| Amphetamine | 6.7 | 5.4-8.0 |
| Heavy alcohol use | 3.9 | 2.9-4.9 |

*Characteristics of the n=117 people with opioid dependence who received XR-NTX in the study. Data collected at the time of inclusion in the RCT, week 0.*

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**Figure 2 - Retention in treatment for the n=117 participants who received XR-NTX in the follow-up study\***



*Kaplan-Meier survival curves for n=54 participants who continued XR-NTX treatment in this follow-up study, and the n=63 participants inducted on XR-NTX.*

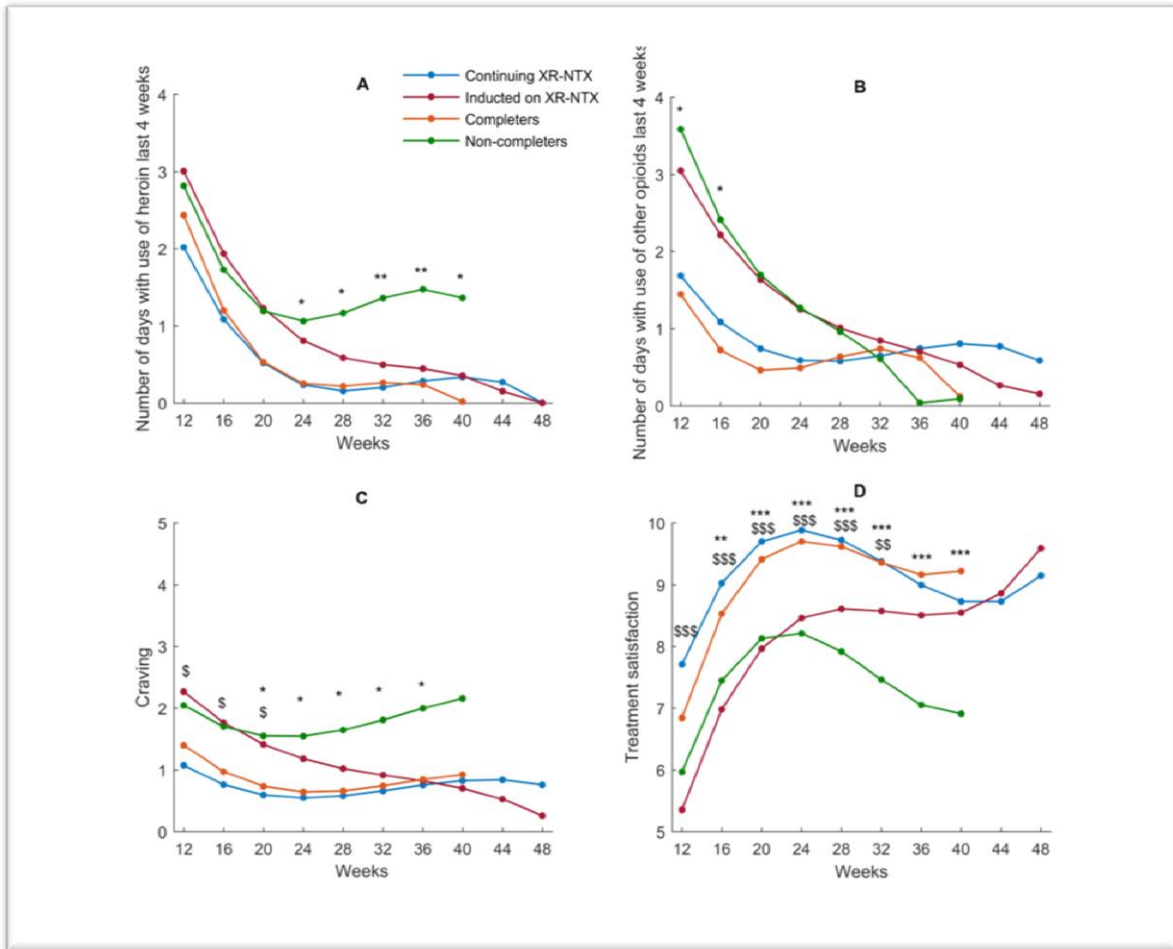*Table 2 – Substance use and addiction-related problems*

| Time point | Participants continued XR-NTX treatment | | Participants inducted on XR-NTX | | Participants continued XR-NTX treatment vs Participants inducted on XR-NTX | |
|---|---|---|---|---|---|---|
| | No. of participants | Mean (95% CI) [1] | No. of participants | Mean ( 95% CI) [1] | Mean difference (95% CI)[2] | P value |
| **Heroin use** | | | | | | |
| Week 12 | 54 | 0.9 (0.3-1.5) | 63 | 4.7 (2.5-6.9) | -1.0 (-2.3; 0.3) | 0.141 |
| Week 48 | 28 | 0.1 (0.0-0.2) | 30 | 0.8 (-0.3-1.9) | 0.3 (-0.5; 1.0) | 0.479 |
| **Other illicit opioids use** | | | | | | |
| Week 12 | 54 | 1.2 (-0.2-2.5) | 63 | 3.6 (1.6-5.6) | -1.4 (-3.1; 0.4) | 0.129 |
| Week 48 | 28 | 0.2 (-0.1-0.4) | 30 | 0.6 (0.0-1.2) | 0.7 (-0.1; 1.6) | 0.088 |
| **Poly-drug use** | | | | | | |
| Week 12 | 54 | 6.0 (3.5-8.4) | 63 | 9.5 (6.5-12.4) | -1.0 (-3.8; 1.9) | 0.496 |
| Week 48 | 28 | 3.0 (0.7-5.2) | 30 | 5.3 (2.3-8.3) | 0.3 (-2.9; 3.4) | 0.874 |
| **Cannabis use** | | | | | | |
| Week 12 | 54 | 7.2 (4.5-9.8) | 63 | 7.3 (4.6-10.0) | 1.2 (-2.1; 4.5) | 0.467 |
| Week 48 | 28 | 6.4 (2.7-10.0) | 45 | 10.3 (6.2-14.4) | -1.0 (-6.0; 4.1) | 0.704 |
| **Amphetamine use** | | | | | | |
| Week 12 | 54 | 3.7 (1.6-5.8) | 63 | 3.3 (1.3-5.3) | 0.2 (-2.3; 2.7) | 0.894 |
| Week 48 | 28 | 2.6 (-0.2-5.4) | 30 | 4.2 (1.9-6.4) | -0.6 (-3.4; 2.3) | 0.690 |
| **Benzodiazepine use** | | | | | | |
| Week 12 | 54 | 7.2 (4.4-9.9) | 63 | 8.6 (6.0-11.2) | -1.1 (-3.9; 1.8) | 0.469 |
| Week 48 | 28 | 3.9 (1.0-6.8) | 30 | 7.3 (3.5-11.2) | -0.9 (-4.8; 3.0) | 0.659 |
| **Heavy alcohol use** | | | | | | |
| Week 12 | 54 | 1.2 (-0.1-2.4) | 63 | 0.3 (0.0-0.5) | 0.3 (-0.6; 1.1) | 0.503 |
| Week 48 | 28 | 0.3 (-0.1-0.6) | 30 | 0.6 (0.0-1.2) | -0.9 (-1.8; -0.02) | **0.044** |
| **Injection use** | | | | | | |
| Week 12 | 54 | 4.5 (2.3-6.7) | 63 | 7.0 (4.0-10.0) | -1.0 (-3.9; 1.9) | 0.491 |
| Week 48 | 28 | 2.4 (-0.7-5.5) | 30 | 6.0 (2.2-9.9) | 1.2 (-2.2; 4.6) | 0.499 |
| **Acquisitive crime** | | | | | | |
| Week 12 | 54 | 1.1 (-0.2-2.5) | 63 | 2.5 (0.8-4.3) | -0.02 (-1.9; 1.9) | 0.983 |
| Week 48 | 28 | 1.4 (-0.4-3.3) | 30 | 1.2 (0.0-2.5) | 0.6 (-1.4; 2.6) | 0.529 |
| **Work** | | | | | | |
| Week 12 | 54 | 4.0 (1.7-6.4) | 63 | 3.8 (1.5-6.1) | 1.2 (-1.9; 4.2) | 0.454 |
| Week 48 | 28 | 3.2 (0.1-6.4) | 30 | 7.9 (3.5-12.2) | -5.1 (-9.8; -0.5) | **0.031** |
| **Money spent on drugs** | | | | | | |
| Week 12 | 54 | 1951 (1183-2720) | 63 | 5098 (2336-7860) | -395 (-2070; 1281) | 0.644 |
| Week 48 | 28 | 655 (146-1164) | 30 | 2650 (1407-3892) | -659 (-2464; 1146) | 0.474 |
| **Money spent on alcohol** | | | | | | |
| Week 12 | 54 | 432 (229-634) | 63 | 276 (85-467) | -50 (-297; 197) | 0.690 |
| Week 48 | 28 | 363 (42-685) | 30 | 320 (72-567) | -20 (-408; 369) | 0.921 |

Comparing number of days with substance use and addiction-related problems during the last 4 weeks between participants continuing XR-NTX treatment and participant inducted on XR-NTX in the follow-up.

[1] Mean and confidence intervals (CI) are descriptive numbers, not adjusted for repeated measurements or site effect.

[2] Mean differences with corresponding 95% confidence intervals and p-values are derived from linear mixed models, adjusted for intra-participant and intra-site correlations.

***Figure 3 –Estimated mean number of days of use of A) heroin, B) other opioids, and C) mean craving scores and D) mean treatment satisfaction***



A and B: mean number of days with use of heroin (A) and other opioids (B) last 4 weeks.
C and D: Visual analogue scale were used to assess craving (C) (0-10 with 0 indicating none and 10 indicating very strong) and treatment satisfaction (D) (0-10 with 0 indicating very low and 10 indicating very high)
* Significant differences between Completers and Non-completers, p<0.05
** Significant differences between Completers and Non-completers, p<0.01
*** Significant differences between Completers and Non-completers, p<0.001
$ Significant differences between "Continuing XR-NTX" and "Inducted on XR-NTX", p<0.05
$$ Significant differences between "Continuing XR-NTX" and "Inducted on XR-NTX", p<0.01
$$$ Significant differences between "Continuing XR-NTX" and "Inducted on XR-NTX", p<0.001

### Table 3 – Adverse events

| | Participants continuing XR-NTX in the follow-up study N=54 | Participants inducted on XR-NTX in the follow-up study N=63* | P-value ** |
|---|---|---|---|
| **Adverse events** | | | |
| **Withdrawal-like symptoms** (e.g. nausea, chills, diarrhoea, muscle-cramps) | 7 (13%) | 21 (33.3%) | 0.016 |
| **Injection-site problems** | 5 (9.3%) | 2 (3.2%) | 0.246 |
| **Psychological reactions** (e.g. anxiety, depression) | 5 (9.3%) | 8 (12.7%) | 0.769 |
| **Headache** | 5 (9.3%) | 7 (11.1%) | 0.771 |
| **Insomnia** | 2 (3.7%) | 6 (9.5%) | 0.284 |
| **Weight-problems** | 3 (5.6%) | 2 (3.2%) | 0.661 |
| **Other non-serious adverse events** | 13 (24.1%) | 18 (28.6%) | 0.676 |
| **Discontinued study due to adverse events** | 4 (7.4%) | 3 (4.8%) | 0.702 |
| **Serious adverse events** | | | |
| **Serious adverse events*** | 1 (1.9%) | 4 (6.4%) | 0.372 |
| **Discontinued study due to serious adverse events** | 0 | 2 (3.2%) | 0.499 |
| **Non-opioid non-fatal overdoses**** | 0 | 3 (4.8%) | 0.248 |
| **Opioid overdoses** | 0 | 0 | - |
| **Death***** | 0 | 1 (1.6%) | 1 |

*Adverse events reported among the n=117 participants receiving XR-NTX. Several participants are registered with multiple adverse events.*
*\*Includes n=20 participants who were re-included and started XR-NTX in the follow-up.*
*\*\* Fisher's exact test*
*\*\*\*No serious adverse events were reported during the first three months after the study discontinuation*
*\*\*\*\*Gamma hydroxybutyrate(GHB)*
*\*\*\*\*\*One participant died in an accident*