Pre-treatment preference, opioid use, and life satisfaction among heroin dependent users receiving treatment with buprenorphine-naloxone or extended-release naltrexone

A 12 week randomized trial and a 36 week follow-up study

Zhanna Gaulen

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

I worked in the Department of Addiction Medicine at Haukeland University Hospital as a PhD student at the Department of Clinical Dentistry, Faculty of Medicine at the University of Bergen. My supervisor Professor Lars Tanum is affiliated with the Department of Research and Development in Mental Health, Akershus University Hospital and the Faculty of Health Sciences, Oslo Metropolitan University. My co-supervisor Professor Lars Thore Fadnes is affiliated with the Department of Global Public Health and Primary Care, Faculty of Medicine at the University of Bergen and the Department of Addiction Medicine at Haukeland University Hospital.

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Abstract in English

Background: Opioid dependence is a complex, severe and long-term chronic disease. Opioid maintenance treatment with methadone and buprenorphine-naloxone (BP-NLX) is a recognized method of reducing opioid use and the risk of overdose, as well as improving psychosocial health. For those who want to achieve abstinence and prefer treatment without opioids, naltrexone (XR-NTX) antagonist treatment is possible in a few countries. XR-NTX is an intramuscular injection given every fourth week. There are few studies on treatment preference among opioid-dependent people. No studies have previously compared XR-NTX with BP-NLX. In addition, the importance of life satisfaction as the outcome has been overlooked compared to studies in other clinical populations.

Study aims: The aims were (i) to assess the risk of relapse to illicit opioids; (ii) to compare the effect of treatment preference on adherence, illicit opioid use and risk of relapse; and (iii) to evaluate changes in life satisfaction in the RCT among participants randomized to XR-NTX and BP-NLX, and in the follow-up study among those who continued XR-NTX and switched from BP-NLX to XR-NTX.

Material and methods: In a Norwegian, multi-site, open-label clinical trial, n=159 participants with opioid use disorder were randomized to either monthly XR-NTX or daily BP-NLX for 12 weeks. Participants (n=117) in a subsequent 36-week XR-NTX follow-up study either continued XR-NTX or were switched to XR-NTX. Preference for treatment was measured prior to the study. Data on illicit opioid use, other substance use, life satisfaction measured with the Temporal Satisfaction with Life scale (TSWL), and covariates were collected every fourth week.

Results: The risk of relapse to illicit opioid use was significantly lower in the XR-NTX group compared to the BP-NLX group. Subsequently, the low risk of relapse remained stable among XR-NTX participants in the follow-up study.

Preference levels were similar across the randomized groups, with no significant associations between preference and adherence to treatment, opioid use or relapse in the RCT. In the follow-up period, among all participants, the rate of adherence was twice as high among participants with the highest preference compared to participants with the lowest preference. Opioid use was significantly higher among participants with the lowest preference than the medium or the highest preference in the switched to XR-NTX group. The risk of relapse was significantly higher among participants with the lowest or the medium preference than those with the highest preference in the continued on XR-NTX group.

TSWL scores were significantly higher in the XR-NTX group at Week 4 and Week 8 compared to the BP-NLX group in the RCT. In the follow-up period, the groups were significantly different at Week 16 and Week 48, with the higher TSWL scores in the continued on XR-NTX group. An increase in opioid use by one day was associated with lower TSWL scores. In both the low and high life satisfaction groups, TSWL scores exhibited a significant increase from baseline and at Week 12. In the follow-up period, TSWL scores exhibited a significant increase from Week 16 to Week 48 in the high Life Satisfaction group, while the low Life Satisfaction group showed persistently lower values throughout that period.

Conclusions: During treatment with XR-NTX, the risk of relapse to illicit opioid use was significantly reduced compared to the BP-NLX treatment in the RCT. Improvements were associated with the matching to the preferred treatment as well as the strength of the preference. Life satisfaction increased significantly more in the XR-NTX group than in the BP-NLX group and in the continued on XR-NTX group compared to the post RCT switched to XR-NTX group. Those participants who initially had relatively low life satisfaction showed no change with longer treatment. Frequent use of opioids was significantly associated with low or reduced life satisfaction. Our results support XR-NTX treatment as an alternative option for patients with opioid dependence who are motivated and interested in opioid-free treatment.

Abstract in Norwegian

Bakgrunn: Opioidavhengighet er en kompleks, alvorlig og langvarig sykdom. Legemiddelassistert rehabilitering med metadon eller buprenorfin-nalokson (BP-NLX), er en anerkjent metode for å redusere opioidbruk og risiko for overdose, samt forbedre psykososial helse. For pasienter som ønsker abstinens og foretrekker behandling uten opioider, er behandling med naltrekson (XR-NTX) antagonist mulig i noen få land. XR-NTX er en intramuskulær injeksjon gitt hver fjerde uke. Det er få studier om behandlingspreferanse blant opioidavhengige og ingen studier har sammenlignet dette hos pasienter medisinert med XR-NTX eller BP-NLX. I tillegg har betydningen av livstilfredshet som utfall hos denne pasientgruppen blitt oversett sammenlignet med studier av andre kliniske populasjoner.

Formål: Målene med studien var (i) å vurdere risikoen for tilbakefall til illegale opioider; (ii) å sammenligne effekten av behandlingspreferanser på retensjon i behandling, ulovlig opioidbruk og risiko for tilbakefall; (iii) å evaluere endringer i livstilfredshet i RCT blant deltakerne randomisert til XR-NTX og BP-NLX, og i oppfølgingsstudien blant de som fortsatte XR-NTX og byttet fra BP-NLX til XR-NTX.

Materiale og metoder: Dette er en åpen klinisk randomisert studie med flere opptaksområder. N=159 pasienter med opioidavhengighet ble randomisert til enten månedlig intramuskulær XR-NTX-injeksjoner eller daglig oral BP-NLX i 12 uker. Deltakerne (n=117) i den påfølgende 36-ukers XR-NTX oppfølgingsstudien fortsatte enten XR-NTX eller ble indusert på XR-NTX. Preferanse for behandling ble målt før studien. Data om illegal opioidbruk, annen rusmiddelbruk, og livstilfredshet målt med Temporal Satisfaction with Life-skalaen (TSWL) ble registrert hver fjerde uke.

Resultater: Risikoen for tilbakefall til illegal opioidbruk var signifikant lavere i XR-NTX-gruppen sammenlignet med BP-NLX-gruppen. Den lave risikoen for tilbakefall var stabil blant XR-NTX-deltakere også i oppfølgingsstudien.

Graden av foretrukket behandling var like på tvers av de randomiserte gruppene, uten signifikante assosiasjoner mellom preferanse og retensjon i av behandling, opioidbruk eller tilbakefall i RCT. I oppfølgingsperioden, blant alle deltakerne, var retensjon i behandling dobbelt så høy blant deltakere med høyest preferanse sammenlignet med deltakere med lavest preferanse. Opioidbruk var signifikant høyere blant deltakerne med lavest preferanse enn medium eller høyest preferanse i gruppen byttet til XR-NTX. Risikoen for tilbakefall var signifikant høyere blant deltakerne med lavest eller middels preferanse enn de med høyest preferanse i gruppen som fortsatte med XR-NTX.

I RCT-delen var TSWL-skåre signifikant høyere i XR-NTX-gruppen ved uke 4 og uke 8, sammenlignet med BP-NLX-gruppen. I oppfølgingsperioden var gruppene signifikant forskjellige ved uke 16 og uke 48, med høyere TSWL-skåre i gruppen som fortsatte med XR-NTX. En økning i opioidbruk med én dag var assosiert med lavere TSWL-skåre. Både i gruppene med lav og høy livstilfredshet, viste TSWL-skåre en betydelig økning fra baseline og ved uke 12. I oppfølgingsperioden viste TSWL-skåre en betydelig økning fra uke 16 til uke 48 i høy livstilfredshet-gruppen, mens lav livstilfredshet-gruppen viste vedvarende lavere verdier gjennom denne perioden.

Konklusjon: Under behandling med XR-NTX var risikoen for tilbakefall til illegal opioidbruk signifikant redusert sammenlignet med BP-NLX-behandlingen i RCT-perioden. Forbedringer var assosiert med matching til den foretrukne behandlingen, samt styrken i preferansen til pasientene. Livstilfredsheten økte betydelig mer i XR-NTX-gruppen enn i BP-NLX-gruppen og i den fortsettende XR-NTX gruppen sammenlignet med den post RCT induserte på XR-NTX gruppen. De deltakerne som i utgangspunktet hadde relativt lav livstilfredshet viste ingen endring med lengre behandling. Hyppig bruk av opioider var signifikant assosiert med lav eller redusert livstilfredshet. Behandling med langtidsvirkende naltrekson bør være et tilgjengelig tilbud for pasienter med opioidavhengighet som er motivert og interessert i opioidfri behandling.

List of Publications

Opheim, A., Gaulen, Z., Solli, K.K., Latif, Z.-e., Fadnes, L.T., Benth, J.Š., Kunøe, N. & Tanum, L. (2021). Risk of relapse among opioid-dependent patients treated with extended-release naltrexone or buprenorphine-naloxone: A randomized clinical trial. The American Journal on Addictions, 30: 453-460. doi.org/10.1111/ajad.13151

Gaulen Z, Brenna I.H., Fadnes L.T., Šaltytė Benth J, Solli K.K., Kunoe N., Opheim A., & Tanum L. (2021). The predictive value of degree of preference for extended-release naltrexone for treatment adherence, opioid use and relapse. European Addiction Research. 2021 Sep 24:1-12. doi.org/10.1159/000518436

Gaulen, Z., Šaltytė Benth J., Fadnes L.T., Brenna I.H., & Tanum L. (2021). Life satisfaction among individuals with opioid use disorder receiving extended-release naltrexone: A 12-week randomized controlled trial and a 36-week follow-up. Journal of substance abuse treatment. doi.org/10.1016/j.jsat.2021.108656

Other papers co-authored with the candidate during the study and PhD-period that are thematically related and will be referenced to, but are not included in the thesis:

Solli K.K., Kunoe N., Latif Z.E.H., Sharma-Haase K., Opheim A., Krajci P., Gaulen Z., Šaltytė Benth J., Tanum L. (2019). Availability of extended-release naltrexone may increase the number of opioid-dependent individuals in treatment: Extension of a randomized clinical trial. Eur Addict Res 25 (6): 303-9. doi.10.1159/000501931

Sharma Haase K., Kanøe N., Opheim, A., Gaulen, Z., Nja, A.L.M., Latif, Z.E. H., Solli, K.K., & Tanum, L. (2016). Interest in extended-release naltrexone among opioid users. European Addiction Research, 22 (6): 301-5 (3).

Kunøe, N., Opheim, A., Solli, K.K., Gaulen, Z., Sharma-Haase, K., Latif, Z.E.H., & 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, 17(1), 1-10. doi.10.1186/s40360-016-0061-1

Index of Tables and Figures

Abbreviations

Abbreviations used in the dissertation and the papers are presented below.

Abbreviation	Explanation
BP-NLX	Buprenorphine-Naloxone
CI	Confidence Interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EuropASI	European version of the Addiction Severity Index
HR	Hazard Ratios
ICD-10	International Classification of Diseases
ITT	Intention-to-treat
LS	Life satisfaction
MINI	International Neuropsychiatric Interview 6.0
MITT	Modified intention-to-treat
OMT	Opioid Maintenance Treatment
PPI	Present Pain intensity
QoL	Quality of life
RCT	Randomized Controlled Trial
SAE	Serious adverse events
SCL-25	Hopkins Symptom Checklist-25
SD	Standard Deviation
SE	Standard Error
SUD	Substance use dependence
TSWLS	Temporal Satisfaction With Life Scale
X:BOT	Extended-Release Naltrexone vs Buprenorphine for Opioid Treatment
XR-NTX	Extended-Release Naltrexone

Contents

1. INTRODUCTION

1.1 Opioid dependence

Heroin and the opioid prescription analgesics oxycodone, codeine and morphine have a greater risk and cause of addiction than any other substance [1]. This is because opioids are highly addictive, tolerance is achieved within a few days, and withdrawal is severe [1]. The risks of dependence and overdose are especially high among those who do not receive treatment [2]. Statistics from the US show that today's opioid dependence and overdoses are associated with the over-prescription of opioid pain relievers, the purity of heroin, and the administration of the strong illicit synthetic opioid fentanyl [3].

Despite a significant expansion of the Norwegian opioid maintenance treatment (OMT) program and a decline in methadone-related deaths over the past twenty years [4], 83% of deaths in 2021 were opioid-related. Deaths from morphine, codeine, and oxycodone account for 26% of all causes of mortality, followed by heroin (23%), synthetic opioids (17%), and methadone (17%). The average age of those who die from overdose is increasing from 36 years in 2006 to 45 years in 2021. The potential for overdose increases with a low treatment rates, relapse periods, intravenous and intramuscular opioid use, and also during the first few weeks after release from prison or treatment [5-9].

The substance use interaction model, or epidemiological triangle, suggests that three key features contribute to dependence on the use of psychoactive substances, including opioids [10]. One of the features is the environment in which people live (Fig. 1.1). External factors such as cultural acceptance, friends and family may cause or allow the transmission of addiction [11-15]. The risk of early onset of drug or alcohol use is increased by adverse childhood experiences such as physical or emotional abuse, domestic violence, substance use or mental illness in the family [16].

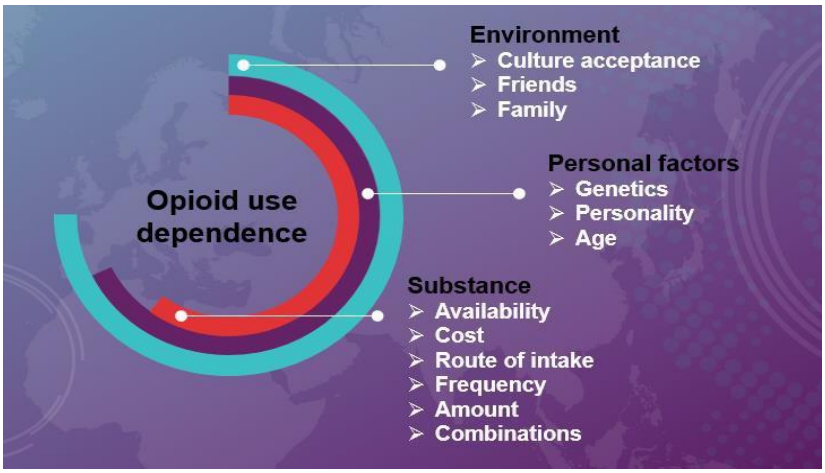

Figure 1.1 The substance use interaction model includes three key features influencing the development of substance use dependence on any psychoactive substance (figure is based on graphics created by SlideModel.com).

The second feature is personal factors: genetics, personality and age [17]. Based on studies with twins, genetics correlates with the heritability of substance use dependence and, when combined with environmental factors, accounts for 40–60% of the risk of dependence [18]. Furthermore, the risk of developing dependence may be higher in people born with impulsivity, hyperactivity or novelty-seeking temperament [19]. In addition, there is a strong correlation between dependence and age of onset. For example, 45-50% of people who start drinking before the age of 14 are at risk of developing alcohol use dependence at any point in their lives [20]. The third feature is the substance itself: the range of substances available, their cost, route of administration, frequency and amount of substances used each time, as well as their various combinations [21].

When substance withdrawal leads to strong cravings and physical illness, this is called withdrawal symptoms and is one of the first signs of addiction. Other symptoms of dependence include feelings of compulsion, difficulty controlling substance use, tolerance, lack of interest in other activities, and continued use despite harmful consequences. As a result, substance dependence may be diagnosed if a person meets

the diagnostic criteria defined by the International Classification of Diseases [22, 23] or the Diagnostic and Statistical Manual of Mental Disorders [24] within 12 months. Not all people develop dependence on psychoactive substances, but the longer they are used, the higher the risk [25-27]. The *UN World Drug Report 2021* estimated that approximately 16 million people worldwide suffer from opioid dependence [28].

Although opioid use affects about 1% of the world's population, the overall burden of opioid dependence on opioid users, their families and society is enormous because of its complexity and severity [28]. A 33-year follow-up from the United States showed that people with opioid dependence can be trapped in cyclical periods of heavy use, abstinence and relapse, with periods of possible treatment and/or incarceration [29]. Moreover, those who inject drugs are exposed to blood-borne infections, mainly HIV and hepatitis B and C [30]. The *World Drug Report 2021* estimates that 11 million people worldwide inject drugs every year and are at risk of contracting these infections [28].

In addition to physiological side effects, opioid users often suffer from comorbid mental health problems [29, 31] and many develop various psychological problems [32-36]. This includes mental disorders such as anxiety and depression, schizophrenia [37, 38] and post-traumatic stress disorder [36, 39]. Personality disorders such as antisocial personality [35, 40] are common mental health disorders among individuals with substance dependence [41, 42].

There is also an increased risk of personal social problems with family and employment among people with opioid dependence, especially among those who inject drugs [42]. They are often stigmatized not only by society, family and friends [43], but also by social and healthcare services [44, 45]. Considering all this, it is not surprising that life satisfaction among people with opioid dependence is low compared to the general population [46].

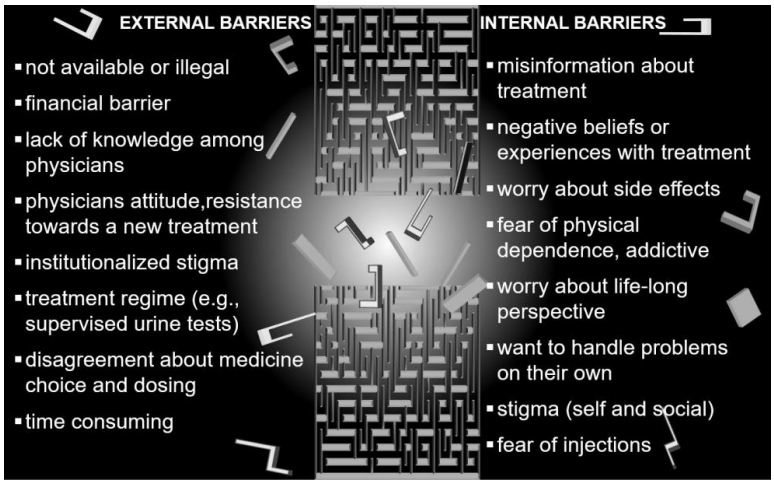

Figure 1.2 Internal and external barriers to accessing opioid dependence treatments (figure is based on graphics created by SlideModel.com).

To prevent the physiological and psychological adverse effects of opioid use, some people seek public health services but face economic and social barriers [47]. The main internal and external barriers to accessing opioid dependence treatment are shown in Fig. 1.2.

Stigma [44, 48], time-consuming or time commitment [49], and treatment regimen [47, 50] have been barriers to the treatment of opioid dependence. Other barriers to treatment, such as misinformation, unavailability and disbelief in treatment effects, have been associated with both pharmacological approaches: opioid agonist maintenance treatment and extended-release naltrexone antagonist treatment (later referred to as XR-NTX) [47-49, 51-59]. Globally, less than 10% of opioid-dependent people receive the treatment they need [28, 60].

1.2 Opioid dependence treatment goals

Overcoming barriers and seeking professional help is an important first step towards achieving individual goals. Treatment approaches for opioid dependence vary widely across countries in terms of access to treatment, availability of medication options,

dosages, levels of control and levels of psychosocial support [50]. One approach is harm prevention to reduce the negative consequences of opioid use such as crime, death from overdose and blood-borne viruses. Another approach takes a recovery perspective and includes social factors and well-being outcomes such as better health, reintegration into society and reaching full potential [50]. To achieve optimal adaptation and functioning of people with opioid dependence, WHO recommends the use of psychosocial interventions in addition to OMT, depending on the needs of patients [23]. It is also recommended to provide assistance with housing, work, education, and social security.

The view of what constitutes an effective opioid treatment is largely defined by specialists and the state or even society, with less weight given to the views of opioid-dependent individuals themselves [61]. In the process of treating and reducing opioid use, people may change their motivation and goals [62]. Even if the intended result is not achieved, this should not be considered a failure as treatment may still be beneficial [50]. Goals can range between abstinence and recovery, recovery with substitution treatment, or harm reduction through continued but controlled opioid use [63]. This is understandable, since a specific feature of opioid dependence is ambivalence, which is intensified by the presence of tolerance and physical withdrawal following drug use cessation [64]. Treatment success rates are not necessarily the same for patients and researchers or clinicians. For instance, for people with opioid dependence who have severe physical or mental multiple illnesses, active employment is unlikely to be an indicator of treatment success, but a disability pension may be more preferable and appropriate. By asking patients about their priorities and assessments of non-medical outcomes, such as life satisfaction and quality of life, clinical attention can be focused on areas that patients need during treatment, such as work, relationships or transportation, to name just a few. When treating addiction, the overall life satisfaction and preference for treatment are important aspects. People with opioid dependence are known to have strong opinions about the type of treatment they would like to receive [65], and this is likely to influence their treatment behavior such as opioid use,

adherence, and therefore increased overall life satisfaction. If patients are successful in obtaining these outcomes, they might feel more confident in their capacity to select the optimal treatment method in the future.

1.2.1 Satisfaction with life as a treatment goal

To improve the lives of people, research since the 1940s has focused primarily on dysfunctions and abnormalities in human functioning and thus on identifying negative aspects of life. Recently, however, more attention has been paid to improving overall health and wellness [66]. This shift deals with concepts like quality of life, well-being, life satisfaction, and happiness. Ed Diener, a positive psychology researcher, coined the term *"subjective well-being"* in 1984 and points out that the term *"happiness"* is often used as a synonym for it [67, 68]. Subjective well-being is defined as a broad category of phenomena that can be used to describe how people perceive their lives positively or negatively.

There are three main indicators of well-being: life satisfaction, positive affect and negative affect [68]. The last two indicators track people's emotional responses to their living conditions. Life satisfaction is a subjective cognitive assessment that people make about the quality of their lives in general or certain domains specifically, such as work, relationships with family and/or friends, personal development and health, by comparing their life circumstances by their own standards [69]. In other words, personal satisfaction with life is contingent upon the particular aspects that an individual places the highest value on at the present time, rather than being determined by external opinions. This is how life satisfaction will be referred to in the present study.

The terms “global quality of life” and “overall quality of life” are often used interchangeably when referring to life satisfaction. But the very concept of *"quality of life"* is related to the conditions of life, such as the quality or quantity of food, the state of health and the quality of housing or social interactions [70]. Compared to the quality of life, life satisfaction is more subjective and emotional. Although individuals may share many of the same life factors, such as health, social connections, leisure activities, and living conditions, they may allocate different levels of importance to each,

resulting in varying levels of life satisfaction. For instance, a disabled man who is rich and has a good family around him is probably happier than a poor healthy man with conflict-filled family relationships. This is not only about what is important to the person, but also what is considered important in society. Important aspects of life satisfaction are also the societies in which we live and the sense of belonging. This corresponds to Maslow's Hierarchy of Needs, or "Happiness Pyramid" as it is commonly called, which includes five levels of needs: physiological needs, safety, love and belonging, respect or esteem needs, and self-actualization [71].

Understanding the variables that influence life satisfaction can certainly lead to a deeper understanding of the broader terms of well-being and happiness [72]. In relation to drug addiction, this means a better understanding of how OMT patients experience treatment and how best to tailor that treatment to suit their satisfaction with specific life domains. For example, the life domains health and social support [73] may impact life satisfaction in diverse and unpredictable ways. Research shows that in terms of received social support, close family and networking relationships may be perceived as a source of stress, rather than one of support, as is often assumed initially [74]. As a result, stressful personal relationships can seriously impair functioning and health [75]. Moreover, some studies show that during stressful episodes, social support may have little effect on well-being and even increases negative mood [76, 77]. When an individual with OUD is undergoing treatment, their relatives may require support to modify their interactions and avoid repeating negative patterns that can be detrimental to both parties.

Using self-assessment of quality of life as an evaluation criterion can give a better understanding of life satisfaction [78, 79]. Various studies examined several predictors of life satisfaction. Generally, people are more satisfied with life, feel happier, and function better in life when they have a satisfying job, live in a safe society, and/or when they are socially engaged [67, 80]. However, these social and material effects are only a small part of what may explain the differences of overall life satisfaction [81]. The level of life satisfaction is also affected by internal factors, for example, personality

and temperament [82, 83]. However, the relationship between personality and overall life satisfaction appears to be complex, involving both direct and indirect pathways such as various life circumstances [82], demographics or cultural factors [84]. In addition, mental health may be an important predictor of life satisfaction, and studies show that the presence of serious mental health problems is usually associated with a decrease in life satisfaction [85]. There is also a reciprocal influence between overall life satisfaction and mental health problems [86]. People with low life satisfaction are at higher risk of suicide and fatal overdose [87, 88], while people with higher life satisfaction have a longer life expectancy, better disease tolerance and fewer mental illnesses [87, 89].

1.2.1.1 Comorbidity: substance use and other mental disorders

Individuals who have substance use disorder are considerably more prone than the overall population to experience mental health issues [90-92], and many of the patients who receive OMT suffer from mental disorders [93]. A recent systematic review, including more than 340 studies in a meta-analysis, found that depression (36%), anxiety (29%), attention deficit hyperactivity disorder (21%), post-traumatic stress disorder (18%), and personality disorders (34%) were especially common among people with OUD. Studies in Norway have shown that almost 70% of patients with substance use disorders had one or more personality disorders [90, 94] such as borderline, antisocial, and paranoid personality disorders, and nine out of ten patients had one or more mental disorders [95].

Substance use and mental comorbid disorders place a heavy load on a person's ability to manage both problems. Individuals who suffer from mental health issues frequently refrain from seeking professional therapy and attempt to self-treat, resulting in the development of addictions before they recognize the problem, leading to a harmful cycle [96, 97]. Others refuse to acknowledge their mental health problems, feel ashamed, or lack the motivation to seek help [96].

Concomitant opioid dependence and psychiatric distress also create additional vulnerability. For example, while OUD itself is associated with a risk of suicide 14 times greater than in the general population, then additional psychiatric diagnosis in

patients with opioid dependence increases their risk of suicidal thoughts, deterioration in physical health and reduced quality of life [98-100]. Research shows that OMT alone does not improve patients' mental health and well-being in the long term [101]. They suggest that the burden of comorbidities calls for additional interventions because mental illness and well-being can both precede and result from substance abuse. Patients themselves believe that in addition to enhancing their mental health and well-being, successful treatment requires them to be opioid-free, maintain positive connections, and be socially active [102].

One meta-analysis of RCTs compared mental health outcomes between different OMTs and those not currently receiving OMT and between the different opioids themselves [103]. Treatment with buprenorphine and methadone was linked with better mental health than those not receiving OMT. Mental health improved more with diacetylmorphine than with methadone, and depressive symptoms and mental health quality of life have improved more with buprenorphine compared to a waitlist or placebo. In addition, researchers have been concerned about the effect of naltrexone on anhedonia, depression, and reduced enjoyment [104-107]. However, patients treated with either oral naltrexone or XR-NTX over time experienced improvements in their levels of anxiety, depression, anhedonia, insomnia [104, 108], and depressive symptoms [109-111].

1.2.1.2 Life satisfaction in relation to opioid addiction

The overall life satisfaction of those who use substances is lower compared to the general population [112] and other patients diagnosed with chronic diseases [113]. However, the level of life satisfaction among individuals with OUD show improvement during opioid treatment [114-117]. Thus, the key element of enhancing the general quality of life and the recognized measure of treatment effectiveness may be minimizing the consumption of substances [79, 118, 119].

There is growing evidence that data on quality of life and overall life satisfaction provide useful information for comparing and evaluating the effectiveness of OMT programs [120-123]. While treatment may increase life expectancy, gauging symptoms

or other indicators of chronic disease status alone is insufficient in revealing a patient's current life situation. In Norway, a randomized, double-blind, placebo-controlled project was launched in 2002 to alleviate the problems and suffering of people with opioid dependence awaiting comprehensive methadone maintenance treatment [124]. The project also made it possible to study the efficacy of the new drug buprenorphine. The participants on buprenorphine increased their life satisfaction during the first three months. However, they emphasized that life is still not considered as good, and that it is difficult for them to continue treatment for a longer period without psychosocial support [124]. This is probably because opioid dependence has an impact on all areas of people's lives: physical, psychological, and interpersonal. To assess the effectiveness of treatment approaches, it is advisable to involve the patient in the evaluation of treatment success based on the attainment of their individual goals [102]. When patients visit OMT clinics, it would be beneficial if clinicians could actively discuss patients' lives and how content they are rather than focusing only on urine tests, drug use, or physical and mental health.

Life satisfaction can be regarded as a key outcome measure, as it is an important predictor of treatment success [78]. Collecting information on life satisfaction during OMT may be a valuable means of acknowledging how patients are equipped to facilitate improvements to their own treatment, and that improving well-being is not solely centered on decreasing substance use or increasing life expectancy. Indeed, while most cross-sectional studies show that substance use is associated with poor quality of life, qualitative studies suggest that the primary incentive for treatment is the motivation to improve quality of life, rather than the reduction in substance use itself [118, 125].

A recent qualitative study involving primary care physicians and OUD patients undergoing treatment suggested that outcomes other than abstinence should be considered, including relationships, mental health and well-being [102]. In addition, having regular contact with the patient and discussing treatment success together, as well as taking the patient's treatment preferences into consideration, may strengthen the relationship between patient and health care provider, build trust between them and, as a result, improve treatment outcomes [126].

1.2.2 Preference for treatment

Assessing patient preferences for OMT is included in practice guidelines for opioid treatment in several countries [127-129]. A systematic review of patient participation in treatment found that preference for treatment was an appropriate patient-oriented approach that requires further evaluation using different methods and study populations [130]. Considering the distinct treatment preferences in the early stages of recovery may help design interventions that are more appropriate for this group of patients, otherwise, patients may receive treatment that does not meet their needs and goals, resulting in reduced adherence or less effective outcomes.

Although there is no consensus on the definition of the term "patient preferences", there seems to be an agreement that patient preferences are individuals' statements about the desirability of a range of health experiences, treatment options, or health conditions [131]. Patient treatment preferences are one of the factors influencing healthcare decision-making [132].

There are three different approaches to making treatment decisions [132]. The first is the information method, which is based on the idea that patients should choose treatment after being informed by clinicians about treatment alternatives, potential risks, and benefits. The second is a more traditional approach, known as paternal or paternalistic suggesting that the clinician makes the final decision with minimal patient involvement. The third is the shared decision-making approach, which involves (i) information exchange, (ii) deliberating on options, and (iii) deciding and acting on the decision [132]. During this process, a continuing partnership is established. Often, clinicians first share information about available treatment options and possible outcomes, matching evidence-based data with the patient's problem and communicating information about potential benefits and side effects. In turn, patients share with the clinician their knowledge and experience, as well as their goals, wishes, and, preferably, their lifestyle and circumstances. Thus, treatment preferences encourage active mutual collaboration in shared decision-making between the patient

and health care provider to develop and manage an individualized comprehensive treatment plan [133, 134].

The approach to shared decision-making in clinical practice may be subject to some adjustments, move from shared decision model to parental, or to informational one, or have a hybrid model [135]. A number of factors can influence this move, such as participant might be reluctant to make a decision after the treatment information is presented, or conversely, patients might gain the confidence and knowledge required to make their own decision. In relation to OMT, clinicians have a special responsibility to facilitate patients to find the best treatment during shared decision-making [135].

The key takeaway message from a systematic review about patient preference and shared decision-making in the treatment of SUD was that patients should be involved in treatment decisions, just like patients with other illnesses [130]. The literature indicates that decisions to treat chronically ill patients most likely require an active role for the patient in the implementation of the decision, as well as opportunities for revision or reversal of decisions [133]. Furthermore, patients actively involved in health-related decision-making are more likely to adopt a healthy lifestyle and engage in health-promoting or health-maintaining behaviors [136]. Treatment preferences seems to be of importance for effect of psychological treatment, suggesting regular assessment of patients' preferences [137].

Patients with OUD choose their type of treatment for a variety of reasons and considerations, among them reduction in cravings, prevention of other withdrawal symptoms such as anxiety, insomnia, muscle pain, and prevention of relapse [138]. Each patient feels more in control of his or her treatment when they have freedom of choice and decision. To understand the impact on treatment preferences of OUD patients, the US survey showed that patients' preference for a particular treatment was predicted by their perceptions of the effectiveness, safety, and consistency of drug-free living [139]. With no experience with XR-NTX, 32% expressed an interest in it, 28% preferred buprenorphine and 22% would not take any medication. Thus, especially for buprenorphine and XR-NTX, beliefs, rather than structural barriers or previous experience, may have a large influence on patients' treatment preferences [139].

Despite the structural barriers (Fig. 1.2), most of the participants were confident that they would be able to start taking their preferred medications.

A meta-analysis regarding substance use treatments and mental health revealed that there were inconclusive findings on the impact of patients' preferences for different psychotherapeutic treatments, including pharmacotherapy, cognitive-behavioral therapy, and 12-step programs [140]. However, evidence indicates a statistically significant effect on improvement in a range of mental health outcomes, such as drug use, social adjustment, and panic disorders, when the patient preferences are accounted for [140]. The fact that patients were more likely to continue their preferred treatment can explain these results. This is also found in another study where patients were randomized to receive either medication or counseling [141]. In a brief pre-treatment survey, they were asked about their preferred type of treatment or whether they preferred to receive no treatment. The findings demonstrated that matching treatment preferences had a direct impact on attending psychotherapy, which in turn had a direct impact on depression outcomes.

Usually, preference for treatment is based on personal experience [142, 143], but in the absence of experience, another factor influences the choice – patients' belief in the effect of treatment [139]. There has been relatively little work on examining treatment preferences in people with OUD. In one study, Kayman and colleagues examined the attitudes toward methadone and the impact of such beliefs on treatment entry and outcome [144]. They found that treatment dropout within a year of methadone maintenance treatment enrollment was predicted by negative attitudes toward methadone in the beginning. Therefore, assessing patients' attitudes towards treatment, both at admission and possibly again when monitoring the patient's progress thereafter is of great benefit to the patient, the treatment institution, and society [144].

Research on preferences have mostly used a binary approach that is, preference for one treatment over another, and therefore impose certain limitations on the results. Treatment preference alone may not be sufficient to predict treatment adherence and outcomes. In the study by Raue et al., patients with major depression were asked to

rank their treatment preferences and rate the degree of their preference for receiving either psychotherapy or medication [145]. They were then randomized to receive treatments that matched or did not match their primary stated preferences. The results showed that the *degree* of preference for antidepressants or psychotherapy was a stronger predictor of treatment initiation and adherence than the matching preference *per se* [145]. Thus, it would be more significant and more relevant to assess how strongly individuals with OUD favor a particular treatment.

1.2.3 Relapse

According to the Cambridge dictionary, relapse means "to become ill or start behaving badly again, after making an improvement" [146]. There are considerable variations in definitions and assessments of relapse to the use of illegal opioids [147]. The term relapse in opioid addiction typically refers to "the recurrence of daily opioid use after a temporary period of abstinence from daily use" [148]. Relapse may also be defined as a return to prior drug use behavior during or after treatment, when a single use of a substance increases over time [149]. There is a risk of relapse and overdose after the abstinence-based treatment for opioid dependence [6, 150] or detoxification [151]. In fact, more than 50% of patients relapse after treatment [152]. Due to the loss of tolerance to opioids, the first few days after discharge from treatment or release from jail are the most crucial periods [7, 8].

Vulnerability to relapse is increased by various factors such as the previous frequency and severity of substance use, patterns of use, and psychiatric comorbidities. Some of these are stable or slowly changing factors such as lack of social support, inability to overcome difficulties, and low self-efficacy [153]. Other factors include cravings, triggers, and high-risk situations [154]. Opioid-dependent patients often have comorbid psychiatric and medical diseases that, if ignored, can provide substantial barriers to effective OMT outcomes [155]. Therefore, treatment for these conditions should be considered in a thorough relapse prevention strategy.

A 20-year cohort study identified factors that prevented relapse among patients addicted to heroin [156]. This includes mandatory supervision such as employment,

substitution maintenance therapy, new social and stable relationships, and membership in support groups such as Narcotics Anonymous. When studying relapse prevention in a randomized one-year trial, researchers focused on craving triggers and coping mechanisms [157]. Behavioral strategies include analysis of the relapse process, and role-playing games to develop skills to prevent situations that can provoke a relapse. Cognitive strategies include identifying situations and emotional states that trigger cravings and are associated with a high risk of relapse. As a result, OMT patients reported no excessive drug cravings and confirmed that relapse prevention sessions helped them to develop coping skills, in contrast to the placebo group. Thus, the combination of OMT and intensive psychosocial therapy has shown to be effective in the treatment of heroin addiction [157]. Medications generally affect the symptoms of substance use but have little effect on the long-term behavioral correlates of drug dependence [158]. Supportive counseling can help identify high-risk situations, develop coping skills and strategies, and acquire a common plan for dealing with relapse and building on the patient's strengths. Medication may be useful in strengthening a patient's ability to remain abstinent or provide an alternative to illicit drugs, but recovery from opioid addiction is a process where individual motivation and support from social services are key elements to help people lead healthier lives.

According to a 12-year cohort study of relapse and recovery after treatment, people often returned to daily opioid use, as a withdrawal-relapse cycle with numerous episodes [148]. However, as the length of abstinence increased, so did the level of resistance to relapse. Behavioral improvements such as a decrease in arrests and incarcerations, and an increase in employment have also been observed. Unfortunately, there did not seem to be a cutoff point for abstinence that would ensure a full recovery. Further research is required on the readiness to change among individuals with OUD as well as a systematic assessment of effective motivational factors, such as friends and social pressure [148].

1.3 Opioid addiction treatment modalities

1.3.1 Psychosocial interventions

The main treatment recommendations for people seeking help for OUD are based on pharmacological agonist therapy, in conjunction with psychosocial interventions [23]. If opioid abstinence is the desired treatment goal, this may be achieved during detoxification followed by relapse prevention. To improve abstinence, opioid-dependent patients may benefit from a range of psychosocial interventions such as contingency management, counseling, cognitive behavioral therapy and motivational interventions [159]. For example, contingency management rewards patients with vouchers or bonuses in response to a desired behavioral outcome, usually abstinence [160]. Whereas during motivational interviews with a counselor, people learn to find motivation to change their drug-related behavior [161]. The new mindfulness-based approach [162-164] includes interventions such as Mindfulness-Oriented Recovery Enhancement [165] and Mindfulness Training [166] that help reduce substance use and stress compared to treatment as usual. These interventions prepare people for the risk of relapse of an environmental nature (see Fig. 1.1) that they are likely to face after completing inpatient programs [162, 167, 168]. However, the results of abstinence-based treatment studies to date are inconsistent; overdose is a major problem in treatment and the risk of relapse is common [152, 169, 170].

People, who inject opioids, as well as those at high risk of overdose and relapse, may particularly benefit from combined pharmacological and psychosocial approaches [23, 171, 172]. Treatment planning requires individually tailored strategy that identifies the patient's specific physical and mental health needs, level of substance use, and life circumstances, as well as an assessing the effectiveness of previous therapy and the availability of treatments. For a holistic treatment to meet each of these needs, it is recommended that personal preferences and prior therapeutic experiences be taken into account [23].

1.3.2 Pharmacological interventions

Evidence-based pharmacological treatments for opioid dependence include a variety of medications (Fig. 1.5). Because of historical, economic, and legal factors, there are

significant disparities in the accessibility and provision of certain pharmacological treatments between nations [173].

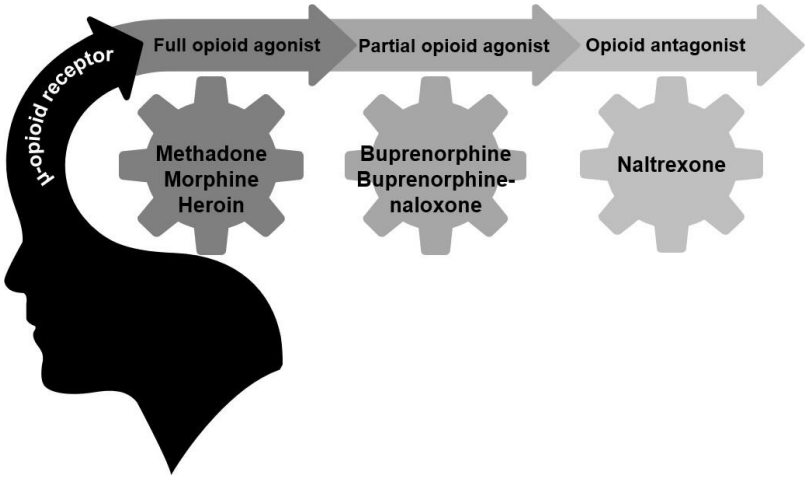

Figure 1.3 Medications for the treatment of opioid dependence, showing variation from a full opioid agonist to an opioid antagonist (figure is based on graphics created by SlideModel.com).

The two most common OMT medications worldwide are methadone (full opioid agonist) and buprenorphine (partial opioid agonist). Some countries also make use of other opioid agonists such as slow-release morphine and heroin, or opioid antagonists such as naltrexone.

1.3.2.1 Methadone maintenance treatment

Methadone maintenance treatment is recommended by WHO guidelines [23] and is the first choice for treating opioid dependence in most countries [174]. Numerous experimental and observational studies have demonstrated its efficacy since the 1960s [175-177], when methadone was first developed in the United States. A review of 11 randomized clinical trials by Mattick *et al* found methadone to be more effective than abstinence-based approaches in treatment retention and reducing heroin use [178]. Empirical studies have shown that taking methadone as prescribed reduces cravings for illicit opioids [179, 180], drug injection [181], criminal activity and mortality [182].

In addition, the physical and mental status of patients improve [183], as well as social productivity such as getting a job or enrolling in school [184].

Methadone is usually given daily as a mixture or tablet, and its effect is partly dose-dependent [185, 186], delaying the onset of withdrawal symptoms for approximately 24 hours. Although it is crucial to take into account individual variations in methadone dose requirements [187], the majority of patients tend to benefit from daily methadone doses of between 60-120 mg, which appear to be associated with enhanced treatment retention and decreased use of illicit opioids [188].

While methadone is effective and safe, there are a number of possible side effects of methadone treatment [189]. These may include increased sweating, decreased libido and constipation [190]. In addition, when combined with alcohol, depressants or sedatives, severe reactions may occur, including respiratory depression, loss of consciousness, coma and death [151, 191, 192]. Negative attitudes and stigmatization are also associated with methadone treatment [51, 193, 194].

1.3.2.2 Buprenorphine treatment

The other most commonly used OMT medication is buprenorphine. It was developed in the late 1970s and was incorporated into the WHO list of essential medications in 2005 [195]. Buprenorphine is mainly administered in the form of tablets or films that dissolve under the tongue, that is, sublingually.

Systematic reviews found that buprenorphine is effective in the long-term treatment of heroin dependence [196, 197]. In a Cochrane meta-analysis, compared with the placebo group, illicit opioid use was reduced and retention rate was increased in the buprenorphine group [197] Compared to methadone, both medication were equally effective in maintaining treatment and suppressing illicit opioid use, even though buprenorphine was found to have lower retention rates. However, adherence was enhanced with higher sublingual dosages [197], underlining the significance of the proper dose and also supporting the effectiveness of buprenorphine in long-term treatment.

However, sublingual buprenorphine itself is highly addictive, so it can be dissolved and then injected. Also, the combination of buprenorphine with alcohol or sedatives, such as benzodiazepines, may increase intoxication and cause overdose [198]. This has resulted in the development of a new formulation of buprenorphine in combination with naloxone, a medication used to block the effects of opioids. The buprenorphine-naloxone (later referred to as BP-NLX) combination is less attractive for diversion than ordinary buprenorphine and applies antagonist properties when injected.

Both buprenorphine and BP-NLX are effective in treatment adherence and in reducing illicit opioid use [199-201], withdrawal symptoms [202] and opioid craving [203]. In addition, combining buprenorphine treatment and psychosocial intervention in the form of weekly group counseling sessions improved the participants' health-related quality of life [204].

Sustained-release buprenorphine formulation is a novel long-acting form of the existing opioid pharmacotherapy of buprenorphine and was not approved in Norway at the time of starting this study [205]. Weekly and monthly depots are expected to be superior to traditional daily dosage formulations, thereby reducing the clinic visits and take-home doses, and hence improving treatment adherence. The potential for street diversion, unintended use, accidental poisoning, and other potential risks associated with sublingual tablets are eliminated because healthcare professionals administer the extended-release injection [206, 207]. However, a qualitative study showed that, on the one hand, participants viewed the depot buprenorphine as a discrete intervention, minimizing stigma and allowing freedom for other activities and the start of a "normal" life [208]. On the other hand, some people have been concerned that monthly or weekly administration of buprenorphine does not offer an opportunity to adjust the dose daily or stop treatment completely until the effect wears off, resulting in loss of control over their medication treatment. Although a recent naturalistic open-label RCT found that the group receiving injection formulation showed significant improvements in treatment efficacy, convenience, and patient satisfaction compared to daily buprenorphine [209].

1.3.2.3 Naltrexone treatment

To achieve long-term abstinence, a new approach was developed in the 1970s with substantial support from the US National Institute on Drug Abuse [210]. With its antagonistic property, naltrexone blocks the opioid euphoric effect and prevents relapse after detoxification. Also, naltrexone is not addictive, so discontinuing it will not lead to withdrawal [211] and risk of diversion [212]. Naltrexone is available in oral, implanted or injectable sustained release forms.

Oral naltrexone

The oral formulation was approved for the treatment of opioid dependence in 1984 [211, 213, 214], but poor treatment adherence limits the effectiveness of oral naltrexone. In the absence of contingency management interventions during oral naltrexone treatment, adherence problems reduce its effectiveness [215, 216] and therefore increase the risk of overdose [217, 218]. Motivated individuals, however, (such as those on probation or healthcare workers) tend to complete treatment [219-221]. Overall, oral naltrexone may be seen as an attractive option for those who prefer abstinence and a substitution-free treatment [139, 212, 222, 223] and is recommended by WHO in the absence of other treatment options [23].

Naltrexone implant

Extended-release formulations were developed in the 1990s to increase adherence and eliminate the need to make daily medication decisions [224-227]. The implant was studied extensively in Australia [228] and approved in Russia [229, 230]. The naltrexone implant is effective in reducing relapse to heroin use and opioid overdose compared to oral naltrexone [226, 231, 232]. Also, research has shown similar rates of substance overdoses in individuals receiving opioid maintenance treatment and naltrexone implants [233]. However, the low power, poor methodological quality and insufficient evidence for the safety and efficacy of research on the naltrexone implant have become barriers to its use [212, 234, 235]; for example, cases have been reported in which patients attempted to remove the implant themselves [64].

Intramuscular naltrexone

Since 2010, extended-release injectable naltrexone (XR-NTX) has been approved for the prevention of opioid relapse in three countries: USA, Russia and Ukraine. In the United States, there is a growing number of treatment programs offering intramuscular XR-NTX [236], and interest in XR-NTX is growing worldwide [237, 238]. For example, in the Netherlands, many patients treated with methadone or heroin-assisted treatment were willing to try XR-NTX to become abstinent from all opioid agonists [49]. In Norway, more than half of the 731 opioid users who completed the one-page questionnaire were interested in receiving opioid-blocking medication [239]. In addition, family members of young people with opioid dependence in the US were interested in XR-NTX as a promising treatment option [240]. However, a recent 2018 literature review of the therapeutic efficacy of XR-NTX, including 34 studies of varying design and quality [241], identified two problems. First, many people who intend to start XR-NTX do not do so, mainly because they cannot complete the detoxification. Second, most of those who start XR-NTX stop treatment prematurely, perhaps due to lack of motivation or unmet expectations.

XR-NTX induction differs from that with methadone and buprenorphine. Future XR-NTX patients after agonist withdrawal should remain opioid-free for several days to prevent severe withdrawal. To minimize these symptoms and improve naltrexone induction, various approaches have being tested, including sedation or anesthesia [242].

Sleep impairment, headaches, gastrointestinal discomfort and nausea have been frequently reported, especially during the induction phase [111, 243], and – less often – severe reactions at the injection site [224]. Among participants who successfully initiated XR-NTX, treatment outcomes were comparable to BP-NLX, as reported in one study that directly compared the efficacy of these medications [244]. Compared with oral naltrexone [245], placebo [54, 104, 246] or usual treatment [222], patients treated with XR-NTX reported higher retention rates, fewer relapses, reduced drug

cravings and fewer overdoses. XR-NTX is well tolerated and has few serious physiological side effects [222, 246-251].

Concerns have been raised that patients receiving naltrexone for a long period may become dysphoric or anhedonic to the extent that it could cause a reduction in life satisfaction, since naltrexone not only blocks illicit opioids but also some of the patient's endogenous opioids (e.g. 'endorphins') [235]. A number of naltrexone studies have focused on dysphoria and depression [105, 110] but have not identified these as possible side effects of naltrexone [104, 105, 110, 111, 229]. Some studies that used behavioral therapy have found improvements in depressive symptoms [105, 111] and reductions in anxiety and sleep impairment during naltrexone treatment [105, 110, 111, 251]. Clinical studies of XR-NTX have shown no increase or improvement in measures of depression or simple anhedonia in people with opioid dependence [110, 249, 252, 253]. An open-label study of opioid-dependent health professionals showed that long-term XR-NTX did not raise new safety concerns and found improved retention rates, reduced opioid craving and improved quality of life in mental health as well as re-entry into the workforce [247]. In a naturalistic study, patients with alcohol or opioid use problems treated with XR-NTX had superior outcomes on measures combining abstinence, self-help participation, employment and arrests compared with those treated with other medication-assisted therapies [254].

1.3.3 Opioid maintenance treatment in Norway

In Norway, the number of people receiving OMT is increasing every year and in 2020 it reached 8099 [255, 256] (Fig. 1.3).

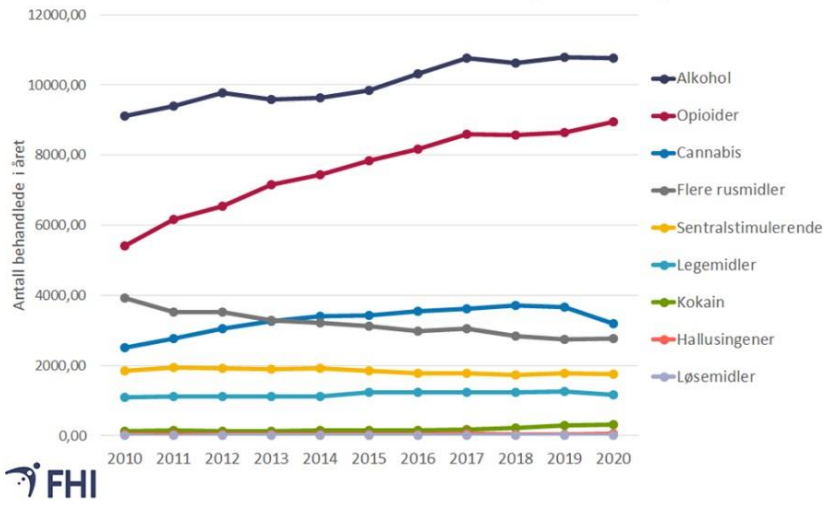

Figure 1.4 Number of people treated for substance abuse disorders in specialist health service from 2010–2020 on the most important diagnoses of substance abuse. Data from the Norwegian Patient Registry.

To tackle the HIV epidemic among injecting drug users, methadone was introduced through projects in the 1990s [127] and approved for treatment in 1998 [257]. Treatment is mostly outpatient, with medications provided free of charge at opioid treatment centers or local pharmacies. Since 2002, buprenorphine has been systematically used to treat opioid dependence in the Norwegian OMT program [127], and methadone treatment has gradually declined to cover only 35% of the total 8198 patients registered at the end of 2021 [255, 258, 259]. Since 2019, buprenorphine depot injections have been available for Norwegian patients. According to OMT guidelines, buprenorphine depot injection may be appropriate in several cases: if frequent controlled doses and visits are not needed due to work or other reasons; if frequent visits may be a risk of dropping out of treatment; if there is an increased risk of misuse by injection [260].

The Norwegian policy guidelines adopt a biopsychosocial approach involving collaboration between multidisciplinary specialized treatment of substance use dependence, the municipality, the patient's general practitioner and the patients themselves [127, 261]. Interdisciplinary outpatient OMT clinics combine

pharmaceutical and psychological treatments. Patients are directly observed for treatment and consultation. Based on individual evaluation, dosage at home is possible [259]. The Norwegian model of OMT provides psychosocial services to improve patients' health and well-being in order to realize their individual potential [262], and demonstrates stability and the ability to track people over time with minimal loss to follow-up [263].

However, the OMT system was subjected to some criticism such as stigmatization from people outside the OMT system and the OMT system itself; lack of knowledge and incompetence of medical staff; and lack of communication and relationship between the patient and the health care provider. In addition, patients' expectations for non-health outcomes, such as better housing and social relationships, are highlighted as a problem [264].

To integrate OMT into the health service and contribute to ensuring that patients in OMT receive a holistic treatment offer, the national OMT guidelines were updated in 2022 by the Directorate of Health [260]. The new OMT guidelines emphasize greater user influence, greater individual adaptation, and the use of different medical treatments. Buprenorphine and methadone are still considered the main recommended treatment options, but if they do not produce the expected results, long-acting morphine or levo-methadone should be considered. The goal of the OMT is to establish trust and dialogue between patient and caregivers, not a measure of control. There is no time limit for OMT and patients can be treated for life.

1.4 Knowledge gaps

The overall rationale for this study was to compare the effects of XR-NTX on opioid use, relapse and treatment adherence versus BP-NLX among people with opioid dependence about to complete their stay in a controlled environment.

Although the efficacy and safety of XR-NTX have been continuously studied for over 15 years, international and Norwegian health organizations recommend further investigations. Among questions not previously answered is whether the risk of first relapse might be a clinically useful outcome measure for evaluating the efficacy of XR-

NTX treatment. In addition, comparison of results between studies may provide insight into the clinical significance of the results.

To our knowledge, no study has examined the relationship between patient preference and treatment outcomes after induction to XR-NTX treatment compared to opioid agonist treatment. Comparison of any new treatment with recommended or standard treatment is often done as a routine part of later phase trials. The BP-NLX was recommended as the first choice in Norway, as in many other countries, and was therefore a natural comparison to the XR-NTX. At the time of our trial development, no other studies comparing XR-NTX with BP-NLX had been conducted in any clinical setting. The data generated by the study may be used to inform treatment decisions at both the clinical and policy levels.

Compared to research on other clinical populations, addiction research neglected the importance of overall life satisfaction as an outcome in clinical trials and increased research into its role in treatment is recommended [119]. When we measure the effect of treatment, we traditionally measure the reduction in drug use. It is important not only to consider drug use as a "hard" measure of the effect of treatment, but also to supplement it with indicators of improved overall life satisfaction. The fact that we are looking at both drug use/relapse and overall life satisfaction with it means that we are looking at addiction and recovery in a broader context, in a more holistic perspective.

In addition, there is limited knowledge about the relative effect compared to preferred treatment and the effects of respective treatment for a year or more. Previous XR-NTX studies have been conducted mainly in countries where any opioid maintenance medication is prohibited by law [265] and access to treatment is limited due to high medical costs [54, 212, 247]. Longer follow-up studies are needed to assess the clinical potential of XR-NTX in clinical settings where treatment is available free of charge [212, 223].

2. AIMS AND OBJECTIVES

The main aim of the study was to assess changes in both illicit opioid use and life satisfaction in adults with opioid dependence receiving treatment in an outpatient setting in Norway.

The specific objectives were:

1) To assess the risk of relapse to heroin and other illicit opioids (Paper I).
2) To compare to what extent pre-treatment preference influenced treatment adherence (Paper II).
3) To compare to what extent pre-treatment preference influenced illicit opioid use and risk of relapse to illicit opioids (Paper II).
4) To evaluate if overall life satisfaction improves or stabilizes (Paper III).
5) To assess trends and trajectories of life satisfaction among different sub-groups (Paper III).

Objectives were evaluated during the short-term period (i) among participants randomized to XR-NTX (380 mg/month) and BP-NLX (8-24 mg/day) in the 12-week RCT, and the long-term period (ii) among participants continuing XR-NTX and inducted on XR-NTX in the 36-week follow-up. The aims and objectives of this study were partly determined by the original study design [266].

3. MATERIALS AND METHODS

3.1 Study designs

The XR-NTX vs BP-NLX project conducted a multi-site open-label randomized controlled trial (RCT) for 12 weeks. This was led by the Norwegian Centre of Addiction Research in collaboration with addiction units at five hospitals linked to cities in Norway [197, 198]. Participants were randomized to treatment with monthly injections of XR-NTX or sublingual BP-NLX in a 1:1 ratio. The RCT was carried out between 1 November 2012 and 23 October 2015. The graphical timeline of the study is presented in Fig. 3.1.

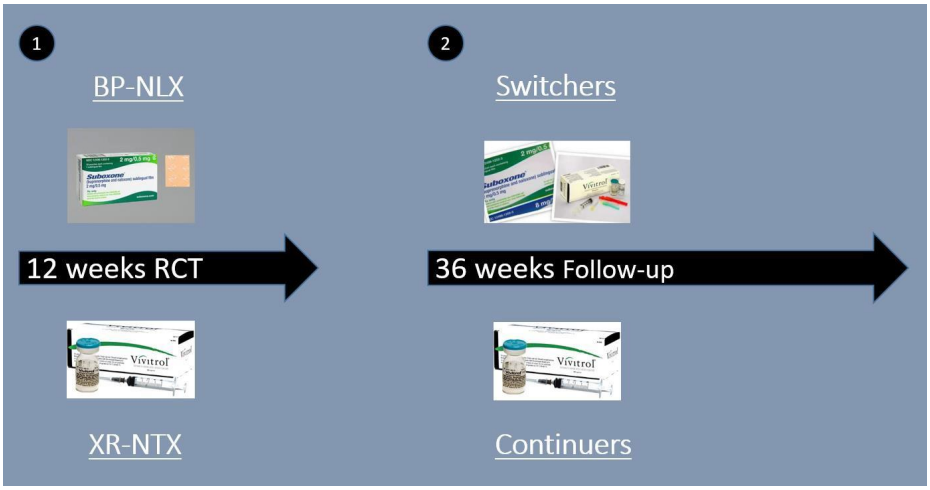

Figure 3.1 The timeline of the one-year study, including a 12-week randomized trial between extended-release naltrexone (XR-NTX) and buprenorphine-naloxone (BP-NLX) groups and a 36-week follow-up between continuers on and switchers to XR-NTX treatment.

All participants, including those who dropped out of the trial, were offered to continue treatment with the preferred study medication, XR-NTX or BP-NLX, for an additional 36-week follow-up period. The majority of participants chose the XR-NTX medication in the follow-up study, and only five participants chose BP-NLX. Due to this distribution of participants, the original follow-up study design of both groups was

changed to a cohort of people continuing or switching to XR-NTX. Two groups were used for the analysis: continuers, those who had used XR-NTX throughout the study, and switchers, participants who changed medication after the RCT period. The longitudinal prospective cohort study was completed on July 6, 2016.

3.2 Study procedures

Five hospitals, Akershus University Hospital, Haukeland University Hospital, Oslo University Hospital, Stavanger University Hospital and Vestfold Hospital Trust participated in the study. Trained research personnel at each site recruited eligible participants. They provided information about the study to people with opioid dependence and services working with them, such as OMT clinics, prisons, and detoxification units in the catchment area of each study hospital. Information was also distributed through the media, including newspapers and the internet. Enrolled participants were also expected to disseminate information about the study among their peers, thereby indirectly participating in the recruitment process [266].

Interested individuals contacted study personnel directly or through the OMT clinicians and social workers. Study personnel arranged appointments with potential participants and provided them with detailed information about the study. The study personnel also collaborated with OMT clinicians in planning and implementing start-up procedures and treatment visits.

3.3 Study sample calculation

The sample size was estimated in two scenarios. First, the superiority scenario assumed that out of the total 12 opioid-negative urine samples, the participants in the XR-NTX group would have a mean of 7 opioid-free samples (7/12 or 0.58) while participants in the BP-NLX group would display a mean of 4 opioid-free samples (4/12 or 0.33). Given a significance level of 95% ($p < 0.05$), a standard deviation of 3.0 in both groups, and power (beta) set to 90%, the estimated sufficient sample size would be $n = 17$ participants per treatment arm or a total of $n = 34$. The sample size calculations were

based on Norwegian patients treated with long-acting naltrexone in a 2009 study [248], and on the frequency of illicit opioid use during buprenorphine treatment in the Norwegian national OMT program [266]. The basis for calculating the sample size in our study was the results of the difference in illicit opioid use between these two samples.

Second, for the non-inferiority scenario, both groups were expected to retain 70% of their participants at the end of Week 12, allowing the power (beta) set to 90%, and a significance level at 95%. The margin was set at 20% and this gave minimum sample size n = 58 in each treatment arm, total n = 116. Based on calculations of the sample size and risk of discontinuation, a recruitment target was set to n = 90 in each group or N = 180 in total [266]. The recruitment in our study was in line with the non-inferiority scenario because this required the largest sample size.

3.4 Participant inclusion and exclusion criteria

To be included in the study, each patient had to meet all of the following criteria:

- Aged 18 to 60;
- Diagnosed with opioid dependence according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition);
- Women of childbearing age were required to consent to the use of contraceptives throughout the study period;
- Participating in the national OMT program through one of the study hospitals;
- Voluntarily seek treatment for opioid dependence in a treatment or criminal justice setting;
- Understand and follow the protocol, meet protocol visit schedules or visit requirements, and sign an informed consent document.

To ensure patient safety and minimize confounding factors, any of the following was considered an exclusion criterion from the study:

- Alcohol dependence;

- Severe somatic illnesses such as acute liver failure or clinically significant symptoms of progressive AIDS;
- Serious chronic or acute mental illness, such as psychosis or suicidal tendencies;
- Pregnant and/or currently breastfeeding women were not included in the study due to insufficient data on the effect of naltrexone on the fetus [267].

Participants with less severe somatic illness, including hepatitis C seropositive, and less severe mental illness, such as depression or anxiety disorders, were eligible.

3.5 Measurements

The data was collected using the paper-and-pencil method during the first year and a half of the study. The questionnaires for the survey were computerized since June 2014.

3.5.1 Pre-treatment preference

A one-page questionnaire on treatment preferences under the title *Questions about heroin blocking treatment* [239, 266] was developed and distributed to people with opioid dependence as part of the dissemination of information about the study. The introduction stated, *"Below are various statements about the use of heroin and other opioids and the possibility of treating it with naltrexone. Naltrexone is an opioid-blocking medication that can be given as a long-acting depot, without any potential for abuse or intoxication."* The two questions were adapted from an earlier study of naltrexone use in pregnant women [268]. In total, five questions tried to capture the participants' interest in a new treatment; see Table 3.1.

Table 3.1 Measurement instrument of preference for extended-release naltrexone treatment using 5-point Likert scale.

Questions about heroin blocking treatment					
How interested would you be in...	Not interested 0	Slightly interested 1	Some-what interested 2	Quite interested 3	Very interested 4
receiving medication to reduce the craving for most intoxicants					
receiving medication that blocks the effect of heroin (after detoxification)					
receiving an injection with a drug blocking the effect of heroin for four weeks					
receiving this type of treatment for one year					
participating in a research project that will offer such treatment in the near future					

To avoid skewed selection of participants reducing generalizability of the study, the questionnaire was handed out by members of the study team to individuals with opioid dependence at OMT sites, detoxification units, outpatient units, long-term treatment facilities and prisons. A professional translation agency was used to obtain an authorized translation of the questionnaire into English for publication purposes [239].

3.5.2 Screening procedures

Interested individuals were screened for psychiatric disorders using the MINI 6.0 (Mini-International Neuropsychiatric Interview) [269] by the study personnel. They were also examined for the presence of severe somatic diseases by the study physicians prior to inclusion. An anamnesis was obtained and clinical laboratory tests were performed: a biochemical blood test, hematology, screening for hepatitis and HIV and a pregnancy test.

In the RCT, weekly urine drug tests were collected to test for heroin, other opioids, benzodiazepine, cocaine, amphetamine and cannabis. The drug tests were analyzed by independent laboratories.

3.5.3 Patient-reported outcomes

At baseline and every four weeks, participants completed a number of self-report questionnaires [270, 271]. The European version of the Addiction Severity Index was used to collect patient-reported outcomes by the Timeline Follow-Back method [272, 273]. This questionnaire covered demographic information, employment, social support, treatment experience, legal status, psychological and physical problems, and use of substances.

The McGill Pain Questionnaire was used to assess Present Pain Intensity [274] and is considered accurate for measuring pain [275]. It has been adapted and translated into Norwegian [276]. The Present Pain Intensity scale consists of a vertical 6-point ordinal scale with reference points 0 = no pain and 5 = excruciating pain. During the interview, participants were asked to report the intensity of their pain over the past five days.

Hopkins Symptom Checklist-25 was used as the screening instrument to assess anxiety and depression symptoms [209]. The 25 items are scored on a 4-point scale from "not at all" (=1) to "extremely" (=4) and summed up to calculate a total score of distress. The items include 15 depression-related items and 10 anxiety-related items. The robust validity and reliability of the instrument has been confirmed in several versions and languages [277].

The self-reporting instrument TSWLS (Temporal Satisfaction with Life scale, present subscale items) was used to measure life satisfaction [278]. The scale was developed as an adjunct to the five-item global Satisfaction with Life Scale developed 36 years ago by Diener et al. [279] with high internal consistency. TSWLS includes 15 items that rate the past, present and future satisfaction with five statements in each period [278]. These scales are validated [278, 280-284] and have been widely utilized with general population samples and clinical studies [281-283, 285], as well as with a substance-dependent population [46, 286, 287]. The results of the McIntosh study [283] support both the inclusion of a temporal component in the life satisfaction construct and the TSWL scale as a valid measure of life satisfaction. The TSWLS *present* subscale items used are shown in Table 3.2.

Table 3.2 Measurement instrument of Temporal Satisfaction with Life using 7-point Likert scale.

TSWL scale 'present' items	Strongly Disagree 1	Disagree 2	Slightly Disagree 3	Neither nor 4	Slightly Agree 5	Agree 6	Strongly Agree 7
I would change nothing about my current life.							
I am satisfied with my current life.							
My current life is ideal for me.							
The current conditions of my life are excellent.							
I have the important things I want right now.							

The participants were instructed to indicate their disagreement or agreement with each item, using a seven-point Likert scale from "strongly disagree" to "strongly agree".

3.6 Interventions and start-up procedures

Inclusion and randomization procedures were usually completed at detoxification units. Initially, participants who were not abstinent from opioids had an individual opioid use tapering schedule. During this process, while not under the influence of any other illicit substances, participants were re-informed of the study requirements. After tapering from BP-NLX to a maximum of 4 mg/day and 0 mg/day for all other opioids, participants were randomized. This planned start-up procedure was seen as an important strategy to reduce dropout rates between randomization and study medication administration.

Non-study personnel performed computerized random allocation to treatment groups using a permuted block algorithm and not stratified for site or sex [288]. Permuted block algorithm was provided by the regional monitoring authority. Communication with the study personnel was by phone in an open-label manner. Participants randomized to BP-NLX were inducted on a flexible dose with a target dose of 16 mg/day and a range of 4:1 to 24:6 mg/day (Suboxone®). After stabilization on the individually required BP-NLX dose, they were discharged from the detoxification

departments. Further BP-NLX treatment was continued at OMT clinics in accordance with national guidelines [127].

If randomized to the XR-NTX group, participants completed detoxification and had to remain in a controlled environment for at least 72 hours from their last intake of any opioid agonist before the XR-NTX induction procedure. To confirm the absence of an opioid agonist, a test dose of naloxone (0.4 mg) was administered, after which the participants were observed for two hours. If necessary, a second naloxone dose was offered within 24 hours. The injection of 380 mg XR-NTX (Vivitrol®) was set into the gluteal muscle, alternating buttocks for each subsequent injection. To receive adequate pharmacological treatment for any withdrawal reactions after the first injection, participants were advised to stay in the hospital for 1-3 days.

To enter the follow-up study, participants underwent a start-up procedure similar to the one described above and switched from BP-NLX to XR-NTX. At the end of the follow-up period, participants randomized to the XR-NTX group received 13 injections. BP-NLX participants, including those who switched to XR-NTX and those who were re-enrolled in the study at 12 weeks, received 10 injections.

OMT staff followed up all study participants in a "treatment as usual" regimen following the national guidelines. Once a month, participants visited the research department for XR-NTX injections and/or a monthly interview. For those who were physically unable to travel to the study unit, the study nurse and researcher visited their home, prison, or hospital for XR-NTX injections and/or interviews. In addition, OMT clinicians could refer the patients on to other relevant treatment if the patients wanted/needed this.

3.7 Outcomes

Relapse was defined as any heroin or non-study opioid use in four consecutive weeks, or use of heroin or non-study opioid in seven consecutive days. *Dropout* was characterized as not attending the scheduled assessment within three days, terminating the study, and refusing to receive the study medicine. The *use of illicit opioids* was assessed as the number of days of heroin or non-study illicit opioid use.

In **Paper I,** the primary outcome variable was the *time to first* relapse to heroin or other illicit opioid use in the RCT. Time to first relapse was defined as the interval (in weeks) between treatment start and the first occurrence of a relapse using the Cox regression model.

The secondary outcome in the RCT was the *risk of any relapse* to heroin or other illicit opioid use, and the follow-up outcome variable was the r*isk of any relapse*. The risk of any relapse was measured by the number of relapses during the study periods to assess differences between the groups using an extended Cox regression model, adjusting for within-patient correlations occurring due to repeated measurements.

In **Paper II,** the outcome variables were adherence to treatment, use of illicit opioids, and risk of *first* relapse to illicit opioids.

In **Paper III,** the outcome variable was life satisfaction measured by the TSWLS present subscale items. An overview of the participant characteristics for each paper is presented in Table 3.3.

Table 3.3 Demographic characteristics, comorbidities and outcome variables, used in the published papers.

Variables	Paper I	Paper II	Paper III
Sociodemographic			
Age	x	x	x
Gender	x	x	x
Civil status			x
Common residential situation in the last 3 years			x
Leisure time spent alone or with family/friends			x
Substance use			
Heroin and other illicit opioids	x	x	x
Alcohol	x		
Cannabis	x		
Amphetamines	x		
Benzodiazepines	x		
Overdose events	x		
Injecting substances	x		x
Self-assessed problem drug use	x		
Psychosocial and physical characteristics			
Mental health	x	x	
Pain intensity		x	
Chronic illness that affects life		x	
Hepatitis B or C		x	
The number of years in prison		x	
Illegal activities for profit		x	
Money used on drugs	x		
Previous treatment	x	x	
Abstinent period after treatment		x	
Preference for treatment		x	
Treatment outcomes			
Adherence to treatment		x	
Days of illicit opioid use		x	x
Risk of first relapse to illicit opioids	x	x	
Time to first relapse to heroin and other illicit opioid use	x		
Life satisfaction			x

3.8 Data analyses

The collected data was entered into the Good Clinical Practice database and de-identified prior to quality control and further calculations. To protect any information that might reveal the group distribution, the analyses had to be censored. The analyses were performed separately for the 12-week trial period and the subsequent 36-week

follow-up. In the RCT, analyses were performed between participants randomized to XR-NTX or BP-NLX. In the follow-up, analyses were performed between the participants who continued XR-NTX treatment and switched from BP-NLX to XR-NTX. An independent study statistician performed most of the analyses. The first author has performed descriptive analyses in papers II and III.

In the descriptive analyses, baseline characteristics were described as means and standard deviations (SD) or frequencies and percentages. Results were presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI) and p-values, or as regression coefficients and standard errors, and illustrated graphically. The results with p-values below 0.05 were considered statistically significant in all analyses. The analyses were performed in STATA SE16, SPSS version 25 and SAS version 9.4. Table 3.4 presents an overview of the statistical methods used in the papers.

Table 3.4 Statistical methods used in the published papers.

Statistical analysis	Paper I	Paper II	Paper III
Frequency	x	x	x
Log-rank test	x		
Kaplan-Meier survival curves	x		
Cox (proportional hazards) regression model	x	x	
Extended Cox regression model	x		
Exploratory factor analysis		x	
Spearman's correlation coefficient		x	
Linear mixed model with fixed effects		x	
Linear mixed model with random effects			x
Growth mixture model			x
Logistic regression model			x

Paper I presents a comparison of retention in the treatment groups using a log-rank test. Kaplan-Meier survival curves have been plotted to present *time to first* relapse. The modified intention-to-treat analysis was used with the specific criteria: who received at least one dose of study medication and had at least one valid assessment after randomization.

In addition, comparative analyses on the *risk* of relapse to heroin and other illicit opioids between the groups were presented. Two types of analyses were performed as

participants may have multiple relapses, one, or none at all. The Cox regression model was estimated to compare the risk of the *first* relapse. The extended Cox regression model was estimated to assess risk of *any* relapse [289].

Paper II presents association analyses between the initial preference for treatment and the outcome variables: adherence to treatment, use of illicit opioids and risk of first relapse to illicit opioids. Five statements of preference for opioid antagonist treatment were used as the basis for the treatment preference variable. The statements were scored using a 0–4 Likert scale from not interested (0) to very interested (4) (Table 3.1). By using STATA SE16, the analysis procedure was as follows: First, in order to generate the preference variable, exploratory factor analysis was performed, resulting in one principal factor. Internal consistency for the five variables was measured in terms of item-total correlations and Cronbach's alpha. For each person, the total preference score was calculated as a weighted sum score with factor loadings as weights. Then, the scores were ranked in ascending order. After that participants with the highest scores of total 20 were placed in the group with the highest preference level (54%); those with the scores between 17 and 19 were placed in the group with the medium level (24%); those with the scores between 16 and less were placed in the group with the lowest level of preference (22%).

The Cox proportional hazard model was estimated to assess the relationship between the preference and (i) adherence rate as well as (ii) risk of the first relapse. The model contained preference as a categorical variable, a dummy for study arms (participants randomized to XR-NTX or BP-NLX), and the interaction between them. The model with interactions was explored further in post hoc analyses.

A linear mixed model with fixed effects for non-linear time (in weeks), preference, and the interactions between these two variables was estimated to assess the association between the preference for treatment and use of heroin or other non-study opioids. Random effects for time and individuals nested within the study site were included.

Paper III presents an association analysis of the TSWL changes between the treatment groups using a mixed model with random effects. A post hoc analysis was performed to assess the differences between groups at different time points.

In addition, three exploratory analyses were carried out. Linear mixed models with random effects were estimated to assess the association between TSWL and the covariates separately: (i) the use of illicit opioids, adjusted for age and gender; (ii) satisfaction with civil status, living arrangements and leisure time; and (iii) years of opioid use. The models included fixed effects for non-linear time (in weeks) and covariates, but no stratification by treatment group. Bayes Information Criterion was used to reduce the models for excessive interactions.

Furthermore, a growth mixture model was used as an exploratory approach for identifying potential homogeneous groups of participants following different life satisfaction trajectories, evaluating all participants in each study period [290]. The logistic regression model was estimated to assess the associations between group belonging and several covariates assessed at baseline (sex, age, opioid use, years of opioid use, treatment group and satisfactions with civil status, living arrangements and leisure time).

3.9 Author's role in the study

The author was responsible for the recruitment and follow-up of 40 participants at Haukeland University Hospital in Bergen, Norway. The author had several responsibilities: providing information about the study, scheduling meetings with those interested in participating in the study, recruiting participants and planning their attendances, scheduling admissions to detoxification units, conducting interviews, arranging meetings with OMT clinic personnel, recording all data, and updating the case report forms and the medical records. The author contributed with data collection, analysis, interpretation of results and editing of the papers, and is the first author of Paper II and Paper III.

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 hospitals: Akershus University Hospital, Haukeland University Hospital, Oslo University Hospital, Stavanger University Hospital and Vestfold Hospital Trust. The Norwegian Centre of Addiction Research sponsored the study and hosted the data management and regulatory center. The PhD position was funded by the Department of Addiction Medicine at Haukeland University Hospital in Bergen, Norway.

This was an investigator-initiated trial. The funding organizations did not participate in the design and conduct of the study, nor in the collection, analyses and interpretation of data. The co-authors contributed by preparing, reviewing and approving the manuscript, and deciding on the submission of the manuscript for publication. Under this agreement, Alkermes Inc. provided the XR-NTX (Vivitrol ®), as the medicine was not available for purchase in Europe. OMT clinics in the participating hospitals provided the BP-NLX, as for any patient enrolled in the OMT program in Norway.

3.11 Ethics

Participation in the study was voluntary, informed and safe. The study was conducted in accordance with the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, World Medical Association [291]. Participants could withdraw from the study at any time without any negative consequences and, if they wished, start methadone or buprenorphine treatment as part of the OMT.

Before the participants agreed or declined to participate, information about the purpose of the study, benefits and risks was provided orally and in writing, especially about the possible consequences and side effects of the study medications. Interested patients received detailed information in both outpatient and inpatient settings, as patient understanding was essential to obtain valid informed consent. In order not to harm the

patients, before being included in the study, the research personnel examined them for the presence of severe mental disorders and somatic diseases, and women were tested for pregnancy. By signing a consent form, participants agreed to the random allocation of study medications. Both the participant and one of the study personnel signed the informed consent, and a copy was given to the participant.

During the study, participants were informed of the sensitive nature of the survey questions and were assured that their responses would be kept confidential. If the participant was intoxicated or felt unwell, we postponed the registrations. In addition, psychosocial interventions and other services were offered to all OMT participants throughout the study period.

It was important for us that the participants knew that they were not just participants in the study, but also its main component. During the visits, study personnel explicitly told participants that their information and knowledge, especially when asked personal questions, was important to the research and improvement of OMT. Study researchers and research nurses also visited them at home, in the hospital or in prison when they could not come for interviews and XR-NTX.

Figure 3.2 Plastic card issued to participants. Scheduled injection dates were updated after each XR-NTX injection.

For emergency or acute pain management, information about taking XR-NTX was recorded in the participants' electronic medical records. Furthermore, the participants were given a wallet-sized plastic card (Fig. 3.2).

The card contained brief information about XR-NTX, the need to use other non-opioid medications if necessary, the telephone number of the doctor on duty in the department of narcology, the participant's name and the dates of their last and next injections.

The participants were not paid, but received reimbursement for travel expenses if necessary. They were also given lottery tickets of approximately USD2 / EUR1.7 each as an incentive to take urine drug tests during the RCT.

When participants did not come at the scheduled time, the study personnel tried at least three times to contact them by telephone. Participants were considered lost for further follow-up if they did not respond to our attempts to contact them. During this time, study personnel worked closely with OMT clinicians. Participants who dropped out of the study could no longer receive XR-NTX treatment. However, OMT clinicians continued to be responsible for their care as they were still enrolled in the program. Participants who discontinued treatment were reminded of the gradual decline of naltrexone in their blood levels and the increased risk of opioid overdose.

All personal information about the participants, including their names and national identification numbers, was stored with appropriate security measures. Due to the sensitive nature of the information contained in the registries, it was important to handle data with caution. Therefore, throughout the study, data was stored exclusively on research servers that were approved for this purpose. For consistency and quality across all study objectives, the research personnel were trained and certified in the Good Clinical Practice. They were also trained in the use of the European version of the Addiction Severity Index structured interview [272] and the Common Terminology Criteria for Adverse Events [292]. Reported Adverse Events and Serious Adverse Events were recorded on study forms using terminology criteria. Approved monitors from clinical research support departments at the hospital sites were involved in the design, implementation and completion of the study. During their annual visits,

monitors reviewed signed consent forms, case report forms, medical records and study facilities.

The site investigator, research personnel and OMT clinician jointly made decisions about participant eligibility, treatment planning, Adverse Events reporting, and possible study discontinuation. The guidelines of CONSORT and STROBE checklists were applied for data quality assurance and data analyses [293, 294].

To avoid ethical issues in research communication, we have presented the results of our research in an honest, reliable and trustworthy manner and have tried to make them as transparent as possible. We have submitted our papers to high-quality peer-reviewed journals as original articles. Respecting the opinions, ideas, and knowledge of other people who have contributed to our research, including our participants, we have given them appropriate credits in the acknowledgment section for their contributions. There were no conflicts of interest.

The study was registered and described online: ClinicalTrials.gov (# NCT01717963) [228]. A methodology paper was published in 2016 [266]. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) for Southeast Norway (#2011/1320), the Boards of Research Ethics at the participating hospitals, and the Norwegian Medicines Agency (EudraCT: 2011-002858-31). Eleven amendments were approved and implemented during the study. One important amendment was the design of the follow-up period. Other amendments related to the registration of research personnel and the prolonged part of the study. To confirm compliance with the requirements of Good Clinical Practice, the study was carried out following international quality standards provided by the International Council of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [295].

4. RESULTS

4.1 Study sample and participant characteristics

This section includes results in accordance with the objectives published in the three papers.

The CONSORT flowchart shows that n=232 people were assessed for eligibility (Fig. 4.1). Among eligible individuals, n=73 were excluded, of which n=67 before inclusion and n=6 before randomization. As a result, n=159 participants were allocated to RCT groups, n=80 participants were randomized to the XR-NTX group and n=79 to the BP-NLX group.

After 12 weeks in the RCT, all participants, including those who dropped out, were offered XR-NTX treatment for the next 36 weeks. A total of n=117 participants agreed to take part in the follow-up study period, of which n=56 continued with XR-NTX and n=61 who switched from BP-NLX to XR-NTX.

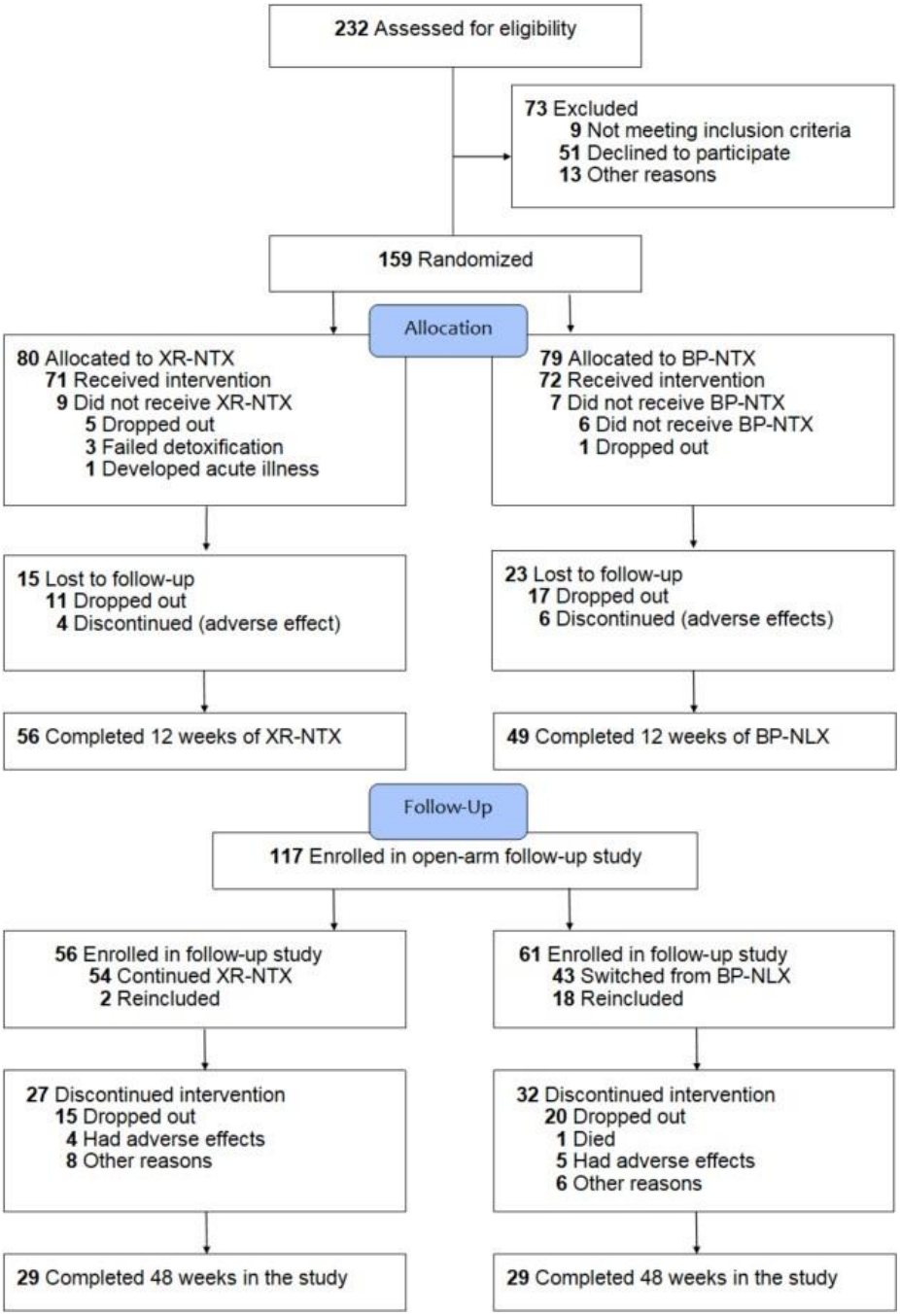

Figure 4.1 CONSORT Flowchart

The average age of the participants was 36.1 years [SD=8.5]; 73% were men. Of all participants, n=86 tested positive for hepatitis C and n=4 tested positive for HIV. The participants receiving XR-NTX and BP-NLX were similar according to years of substance use and other demographic and clinical characteristics, see Table 4.1.

Table 4.1 Demographic and baseline clinical characteristics of participants randomized to treatment with extended-release naltrexone (XR-NTX) or buprenorphine-naloxone (BP-NLX).

Lifetime characteristics	XR-NTX (n = 80)	BP-NLX (n = 79)
Age, mean (SD)	36.4 (8.8)	35.7 (8.5)
Sex, No. (%)		
Men	61 (76.3)	54 (68.4)
Women	19 (23.6)	25 (31.6)
Duration of substance use, mean (SD), years		
Heavy opioid use	8.9 (7.8)	9.6 (10.5)
Heroin	6.9 (5.8)	6.7 (5.2)
Other illicit opioids	2.4 (5.1)	3.2 (7.0)
Alcohol for intoxication	3.5 (4.8)	2.9 (4.1)
Amphetamines	6.7 (7.3)	6.3 (6.6)
Cannabis	9.0 (7.3)	10.2 (9.0)
Benzodiazepines	5.1 (6.0)	5.9 (8.7)
Cocaine	1.4 (3.1)	1.7 (2.8)
Baseline substances use, past 30 days, mean (SD)		
Heroin	7.6 (11.0)	12.0 (12.9)
Other illicit opioids	8.2 (11.1)	14.5 (13.2)
Amphetamines	3.4 (7.4)	5.4 (9.1)
Cannabis	8.2 (11.1)	10.2 (12.6)
Cocaine	0.2 (0.7)	1.3 (3.9)
Intravenous injection users, No. (%)	72 (90)	64 (81)
Hepatitis C seropositive, No. (%)	44 (55)	42 (53)
HIV positive No. (%)	2 (2.5)	2 (2.5)

4.2 Risk of and time to first relapse to heroin or other illicit opioids, Paper I

Analyses included n=143 participants randomized to XR-NTX (n=71) and BP-NLX (n=72). The mean *time* in the RCT for both groups was nearly the same: 10.8 weeks for the XR-NTX group and 10.6 weeks for the BP-NLX group. However, the *risk of first* relapse was significantly reduced in the XR-NTX group by 54% to heroin and 89% to other illicit opioids. Moreover, there was a reduction in the *risk of any* relapse

to heroin or other illicit opioids in the XR-NTX group, where participants had a total of 14 relapses to heroin and 11 relapses to other opioids. For comparison, the participants in the BP-NLX group had 95 relapses to heroin and 147 to other opioids. Thereby, the pooled risk of *first* or *any* relapse to any illicit opioids strongly favored XR-NTX (Fig. 4.2).

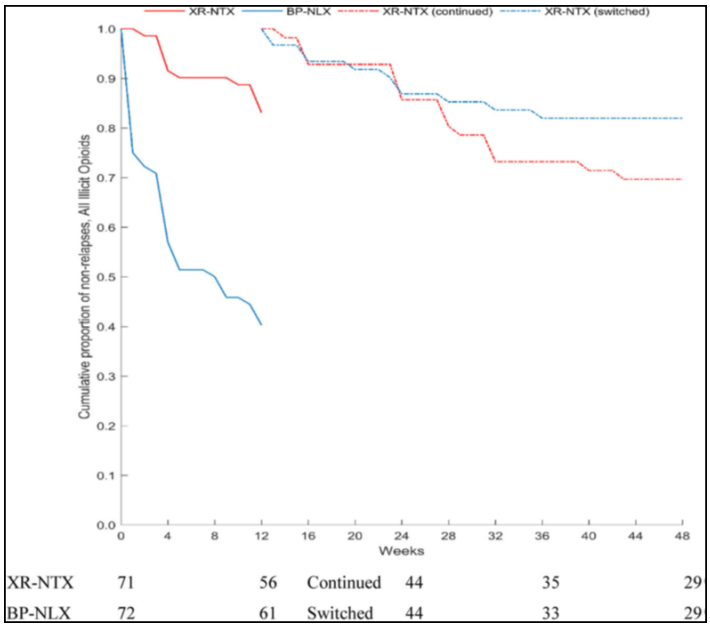

Figure 4.2 Kaplan-Meier curve presenting time to first relapse to all illicit opioids in XR-NTX and BP-NLX groups in the RCT and between continuing XR-NTX and switching from BP-NLX to XR-NTX in the follow-up period.

The mean *time* in the follow-up between 12 and 48 weeks was 37.5 (SE = 1.6) weeks for those who continued on XR-NTX and 37.1 (SE = 1.6) weeks for those who switched after RCT. There were no differences between the groups in the *time to first* relapse to heroin and other illicit opioids (Fig. 4.2). In addition, both groups had almost the same number of heroin relapses, 27 among those who switched and 29 among those who continued, and both groups had a consistently low risk of relapse. However, during the first month in the follow-up, the relapse rates to other illicit opioids were higher among switchers compared to continuers (HR 0.45, 95%CI 0.22-0.94; p = 0.034).

4.3 Preference for treatment, Paper II

Out of randomized n=159 participants, n=6 participants had missing data on preference. Therefore, in the analysis of the association between preference and *dropout* were included n=153 participants. Further, out of n=143 participants who took at least one dose of the study medication, n=4 participants lacked data on preference. As a result, in the analyses on the association between preference and the *use of illicit opioids* or *risk of first relapse* were included n=139 participants. In the follow-up period, n=117 participants were included or re-included; however, n=3 had missing data on preference. Thus, the regression analysis included n=114 participants.

The main motivation for receiving XR-NTX was the reduction in opioid cravings, reported by 84% of participants (Table 4.2). The group with the highest level of preference included 54% (n=82) of participants, the group with the medium level included 24% of the participants (n=34), and the group with the lowest level included 22% (n=37).

Table 4.2 The interest in extended-release naltrexone (XR-NTX) treatment before the study inclusion.

Baseline responses on the XR-NTX questionnaire, n (%)						
How interested are you now in ...	Not interested 0	Slightly interested 1	Somewhat interested 2	Quite interested 3	Very interested 4	Mean (SD)
receiving medication to reduce craving for most intoxicants	1 (0.6)	-	5 (3)	19 (12)	128 (84)	3.8 (0.7)
receiving medication that blocks the effect of heroin (after detoxification)	-	2 (1)	4 (3)	30 (20)	117 (76)	3.7 (0.6)
receiving an injection blocking the effect of heroin for 4 weeks	-	4 (3)	13 (8)	29 (19)	107 (70)	3.6 (0.8)
receiving this type of treatment for one year	1 (0.6)	1 (0.6)	12 (8)	18 (12)	121 (79)	3.7 (0.8)
participating in a project that will offer such treatment in the near future	1 (0.6)	1 (0.6)	10 (6)	27 (18)	114 (75)	3.7 (0.8)

In the RCT, the BP-NLX group for all preference levels had significantly higher rates of both the risk of first opioid relapse and the number of days of illicit opioid use, but not in terms of adherence (Fig. 4.3a). In the follow-up, adherence was twice as high among all participants with the highest preference compared to participants with the lowest preference (HR 2.2; 95%CI 1.2–4.0, p = 0.013). Opioid use was also significantly higher among the switchers with the lowest preference level compared to

those with medium (p = 0.003) or higher (p = 0.001) preference (Fig. 4.3b). No such association was found among the continuers.

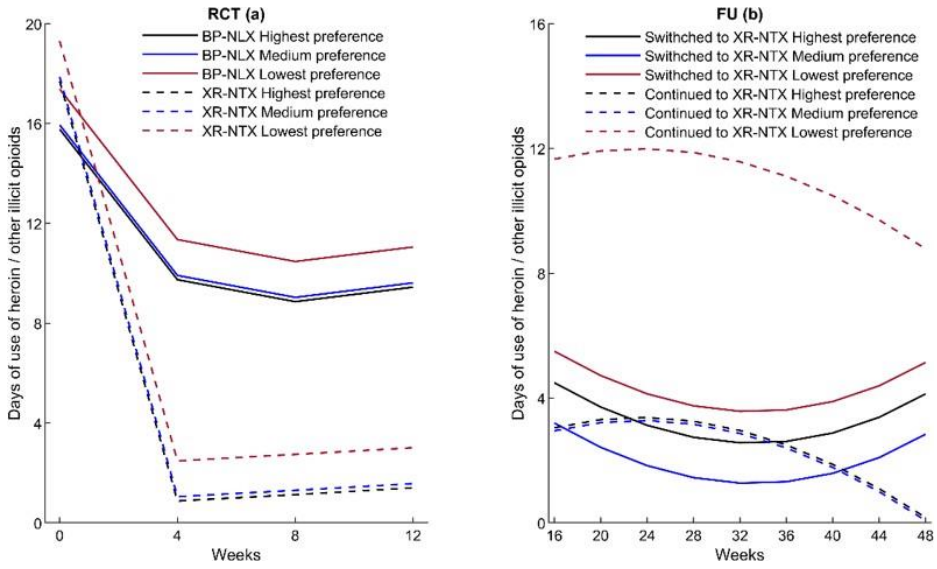

Figure 4.3 Use of heroin and other illicit opioids for different preference levels: (a) between the BP-NLX and XR-NTX groups in the 12-week RCT; (b) between switched to XR-NTX and continued on XR-NTX in the 36-week follow-up period.

Interestingly, among those who continued on XR-NTX, there was a significantly higher risk of the first relapse with lower (p = 0.002) and medium (p = 0.043) preference levels compared to participants with a higher level, shown by post hoc analyses. However, no such differences were found among the switchers.

4.4 Life satisfaction changes, Paper III

At baseline, the BP-NLX and XR-NTX groups showed similar TSWL distributions (mean [SD], 11.3 [7.5], and 11.0 [6.9], respectively). The presented results show the difference in the change in life satisfaction between groups in both periods of the study. In the RCT period, TSWL scores were significantly higher at Week 4 (p = 0.013) and Week 8 (p = 0.002) in the XR-NTX group compared to the BP-NLX group (Fig. 4.4A).

In the follow-up period, the group continuing with XR-NTX had higher TSWL scores compared to the switched group at Week 16 (p = 0.031) and Week 48 (p = 0.025), shown in Fig. 4.4B.

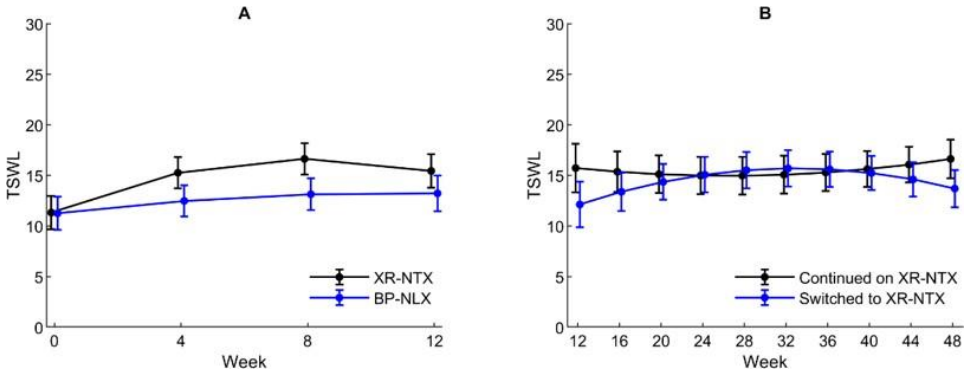

Figure 4.4 Life satisfaction changes (A) among participants randomized to XR-NTX and BP-NLX treatment and (B) among the continuers with XR-NTX and the switchers from BP-NLX to XR-NTX treatment in the follow-up period; results of mixed model.

When assessed for all participants in the RCT period, a significant trend was observed in TSWL depending on opioid use. Use of opioids over 20 days a month was associated with low TSWL scores at Week 4 and Week 8. However, at Week 12, life satisfaction was relatively the same regardless of opioid use (p = 0.562) in both groups.

When including data of all participants in the follow-up period, no significant trend in TSWL was found. However, more use of illicit opioids was associated, on average, with lower TSWL both before (p = 0.027) and after adjustment (p = 0.028) for age and sex. An increase in opioid use by one day was associated with a 0.12-point lower mean in TSWL score.

Trajectory analyses were conducted among all participants simultaneously in both study periods. Two distinct groups were identified with low and high life satisfaction trajectory without overlapping 95% confidence intervals at each study period. In the RCT, the group with low life satisfaction had three times more participants than the group with higher life satisfaction, n=116 and n=35, respectively. In the group with low life satisfaction, TSWL scores increased from Week 0 to Week 8 (p <0.001) but flattened out by Week 12 (Fig. 4.5C). In the group with high life satisfaction, the

increase in TSWL scores was less but still significant when compared between baseline, Week 0, and the end of the RCT, Week 12 (p = 0.011).

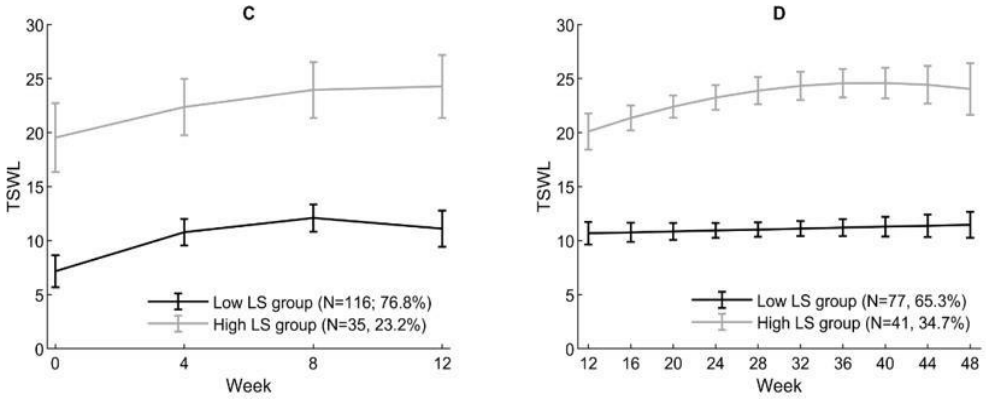

Figure 4.5 Life satisfaction trajectories in two groups of participants (C) in the RCT and (D) in the follow-up period using growth mixture model not stratified by treatment group.

In the follow-up, the group with low life satisfaction, n=77, showed stable and significantly lower TSWL scores compared to the group with high life satisfaction, n=41 (Fig. 4.5D). In contrast, the high life satisfaction group showed a non-linear increase in scores towards Week 28 and flattened out at Week 48, and their level of life satisfaction showed a significant increase between Week 16 and Week 48 (p = 0.003).

5. METHODOLOGICAL CONSIDERATIONS

The research presented in this dissertation and in the enclosed papers has some methodological limitations, and the results should be interpreted with these limitations and biases in mind.

5.1 Study designs

5.1.1 The randomized controlled trial, XR-NTX vs BP-NLX

A detailed protocol was prepared for the study describing the research work carried out during the course of the study and the analyses of the data. In terms of the chronic nature of opioid dependence, the 12-week RCT is short. However, in our study, the duration was considered appropriate for comparing the effectiveness of the study medications.

RCTs are reliable methods to establish the effectiveness of treatment [296-298], and differences found in study outcomes are more likely to be related to intervention rather than differences between randomized groups such as age and gender. Important factors in reducing the risk of bias and ensuring the best quality of RCTs include sequence generation, concealment of sequence allocation, blinding of participants and staff, and complete data on results according to the Cochrane Handbook [298, 299]. However, there are potential sources of bias that may affect validity [235], such as open-label design, treatment preference [300], placebo effects [301] and clinician-patient relationship [302, 303]. These and other possible biases in our study will be discussed below.

The RCT design was chosen for our study to compare the effect of the new injectable XR-NTX with first-line oral BP-NLX. It was possible to randomize opioid-dependent individuals, but it was impossible to blind the participant or investigator due to the nature of the RCT. Although the use of placebo blinding is beneficial to avoid bias [304], for ethical reasons, an available effective opioid substitution medicine such as BP-NLX should be used as an alternative to intervention [197, 305]. Moreover, even if participants were blinded, they could easily find out what treatment they received

while taking opioids. Besides, previous blinded placebo-controlled and cross-sectional studies of XR-NTX have already established the efficacy of this medication [54, 222, 229, 246]. Consequently, we concluded that masking and use of placebo were inappropriate, and the concealed research method seemed less important [306]. Therefore, this study was conducted as an open-label RCT that may increase generalizability.

Two factors most likely contributed to the generalizability of our results, the naturalistic clinical design and the heterogeneity of the participants. The naturalistic clinical setting was a strong advantage of our study as all participants had access to an opioid treatment program. The heterogeneous group of participants and the population of people with opioid dependence in Norway were not significantly different from each other on age, gender and psycho-social factors, as shown in our results.

5.1.2 The longitudinal prospective cohort study with XR-NTX

Longitudinal prospective design means that participants are followed over a long period and data is collected at different points to measure the frequency of one or more outcomes and influencing factors [296]. In our prospective study, we followed participants after they had completed the RCT and preferred to receive XR-NTX over 36 weeks.

According to the protocol, participants were offered to continue follow-up treatment with either XR-NTX or BP-NLX after a randomized period so that the comparative analyses could be performed between the two groups. If we could compare the XR-NTX cohort with BP-NLX as a control group, we could assess whether the results were associated with the effect of XR-NTX over a longer period. However, out of 122 participants, only five chose the BP-NLX, while 117 participants chose the XR-NTX. Because of this disproportionate distribution, this comparative analysis was not carried out as planned. The absence of a comparative control group in the follow-up part of the study is considered a methodological limitation.

However, comparative analyses were conducted in the follow-up study between participants who continued with XR-NTX and participants who were switched from BP-NLX to XR-NTX after the RCT period. To minimize the attrition bias we re-included participants who discontinued participation during the trial. Therefore, we consider the protocol is robust enough to provide clinically and scientifically relevant information [266].

Psychosocial treatment was not a required part of the study. However, if XR-NTX treatment had been accompanied by counseling, we would likely have had better results [307]. It was noticeable that those participants who received additional counseling within the framework of the OMT program or visited motivational organizations had better treatment adherence, though no systematic data was collected on this issue.

None of the treatment discontinuations during the follow-up was associated with tolerability issues; some participants who discontinued the study did not like the effect of XR-NTX, and others wanted to try without it. Of the 117 participants, 50% completed follow-up, with 29 participants in each group. The best way to deal with missing data to assess treatment effect in a longitudinal study is through well-designed and careful data collection [308]. Unlike RCTs, prospective longitudinal cohort studies are even more prone to bias, increasing the risk of internal validity [309]. Factors such as no control group, 50% dropout rates, and the potential for Type 1 and Type 2 errors can influence the results of a follow-up study. This is why it is important to interpret research results with caution.

5.2 Research quality and study strengths

5.2.1 External and internal validity

Validity refers to how well a study or a scientific test actually measures what it aims to do. Research validity is considered to have two aspects, external and internal (Fig. 5.1). External validity is related to whether the study raises an appropriate research question and how well the results can be generalized and applied in real-world settings [310, 311].

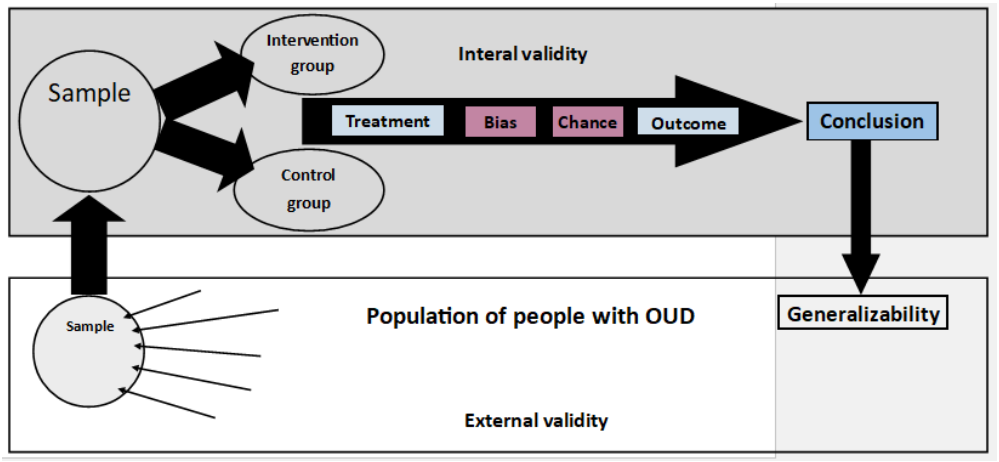

Figure 5.1 Internal and external validity in research. Adapted from: Fletcher, 1996.

The baseline characteristics of our study participants, such as substance use and addiction problems, were within the described range for those who received OMT in Norway [312, 313]. But the mean age of study participants was about eight years younger than those in the OMT program [314]. This age difference between OMT patients and study participants may be explained by the fact that at a younger age, people may be more interested in new treatments and medications, and may also be more adaptable and open to innovation [315].

Internal validity is the degree to which a study establishes a reasonable cause-and-effect relationship between treatment and outcome [316]. It also reflects the quality of the study and the ability to rule out alternative explanations for the results, i.e. free from bias. An RCT design in general have high internal validity. However, RCTs can also be affected by possible sources of bias. One such bias was the lack of treatment blinding.

It is necessary to be critical about which variables to use in the analyses, given the exploratory nature of our study and the number of variables collected. Type 1 error is the false rejection of the null hypothesis when the null hypothesis is true, and can be high if significant results were found by chance. The risk of making this error is

determined by the chosen level of significance, represented by α-alpha. The significance level in our study was set at α = 0.05 or 5%, which means that if the null hypothesis is true, the probability of obtaining results is 5% or less.

Type 2 error means that it is not possible to conclude the presence of an effect when it actually occurred, and actual differences between groups are not detected [317]. The Type 2 error, represented by β-beta, may occur if the sample size is not large enough, so the study will not have sufficient statistical power to detect an effect of a certain size. The chance that a study will be able to demonstrate a significant difference, if any, is known as study power. A power level of 80% or higher is generally considered acceptable. In our clinical study, the power was set at 90%.

Research bias or error that reduces representativeness and affects treatment outcomes may be associated with the design, implementation and analysis [318-320] and therefore cause misinterpretation of results. Some possible biases, such as selection bias, information bias and confounding factors, will be discussed below (Fig. 5.3).

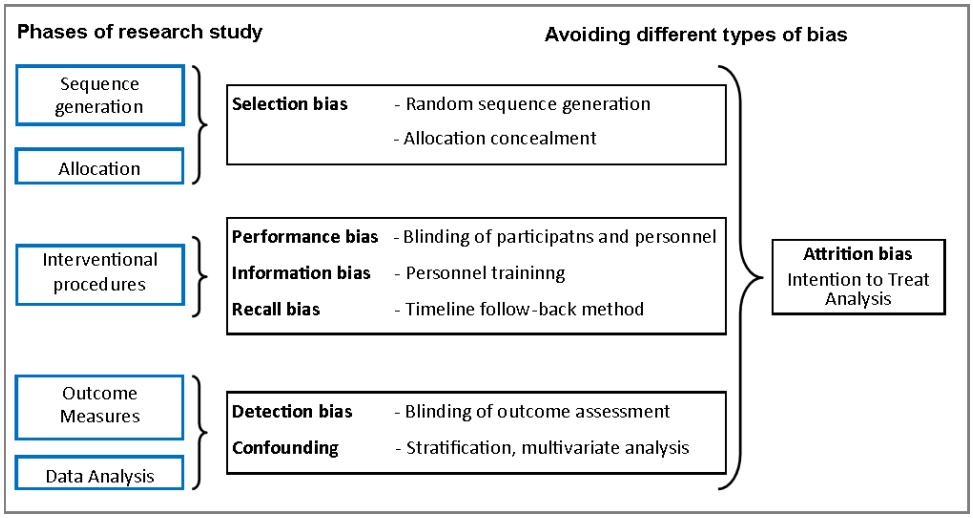

Figure 5.2 A common classification scheme for bias in the research process of the Cochrane 'Risk of bias tool'. Adapted from Meursinge Reynders, 2015.

5.2.2 Selection and sample bias

Selection bias applies to both the recruitment process and the inclusion criteria [321]. Recruited participants should meet the research objectives and represent the study

population; the distribution of participants will ensure similarity between comparison groups. The risk of selection bias in the recruitment process may be increased due to the multicenter design of the study [322, 323], as different centers may have different approaches to the recruitment process, e.g., due to study site location and access to patients. In addition, the attitude towards XR-NTX of OMT clinicians, who were the main source of recruitment, may have influenced the decision to present the study to patients or not. Some illicit opioid users may not have been informed about the new study, so they never had the opportunity to be included in it.

Differences between those who consent and those who do not consent may also influence the study results [324]. For example, a systematic review comparing participants and non-participants in observational studies found differences across all outcomes, including age, gender, income, education and health status [325]. Moreover, due to the experimental design of this study, people interested and motivated to receive a new type of medication agreed to randomization; others turned down the invitation because they had never heard of the treatment before and did not want to be 'guinea pigs'.

To minimize selection and recruitment biases in our study, we invited people with opioid dependence into our study through a variety of channels, including OMT clinics, detoxification units, prisons and the media. All people with opioid dependence receiving treatment under an OMT program were eligible to participate, with the exception of those who had other drugs and/or alcohol dependence and severe physical and/or psychological problems. The multicenter design includes five large urban drug treatment clinics in Norway, which increases generalizability.

Furthermore, allocation concealment, sequence generation, masking and complete data outcomes are factors representing a well-designed RCT study [303, 326]. Selection bias can arise from a selective enrollment of participants, when it is possible to foresee interventions that will lead to failure of allocation sequence concealment [321]. However, the allocation in our study was independent of clinicians and study personnel. At randomization, neither the investigator nor the participant influenced the

choice of intervention. Non-study personnel communicated with study personnel by telephone, performed sequence generation, computerized using the block-permuted logarithm, independently of participant gender and study site [327]. It can be assumed that the RCT design largely minimized selection bias for evaluating two alternative treatments, BP-NLX and XR-NTX, during the trial period.

A prospective design that minimizes recall and selection bias can be considered a strength of our study, but it may also include dropout or loss to follow-up [323]. To understand the impact of naltrexone on opioid dependence, previous research highlights the importance of adequate treatment retention [216, 328, 329]. A meta-analysis of the efficacy of naltrexone treatment also emphasizes the importance of maintaining the treatment retention, as this reduces treatment efficacy [216]. The sample size calculation in our study had sufficient power to detect differences between the two randomized groups [330]. Although we planned to recruit 180 participants, we believed that 159 randomized participants should be sufficient [317].

5.2.3 Performance bias

In the absence of blinding in our study, performance bias in the RCT could arise for two reasons. On the one hand, the researchers may have treated the study groups differently, influencing the conclusion that the effect was due to the intervention rather than the level of care or attention [326]. It is possible that due to almost daily visits to the clinic for medication, the BP-NLX group received more attention from the OMT staff in the form of advice or verbal support compared to the XR-NTX group, who only came once a month [212].

On the other hand, participants in different study groups could behave differently and change their answers because they knew which study group they belonged to [326]. Participants in the XR-NTX group may have deliberately avoided heroin use because they knew what study medication they received and were aware of its blocking effect. It was clear that XR-NTX was preferred over BP-NLX in our study. Among participants not randomized to the preferred treatment group, some may have been disappointed and possibly withdrew from the study prior to treatment [306, 331]. To minimize this risk of disappointment, we offered XR-NTX treatment to all randomized

participants after 12 weeks. It can be assumed that some participants who used BP-NLX before participating in the study did not mind being randomized to the BP-NLX group, knowing that after 12 weeks they would receive XR-NTX.

5.2.4 Information bias

During data collection, information bias may take place that affects the internal validity of the study [318]. If the information collected in a study is incorrect or the variables are misclassified, we call it an information error [323]. A large body of research data has been based on patient-reported outcomes [332]. The accuracy of such data is often of concern, as it can be influenced by participants who are under the influence of drugs or have cognitive problems, leading to recall bias. In addition, exaggeration and falsification of reported information can reduce the reliability and validity of the data. Boredom, fatigue and irritation can lead to information bias when a large number of the same questionnaires are filled out multiple times over the course of a study, as in our study when participants answered the same questions every four weeks [333]. This repetitive approach can be perceived as demotivating, causing careless answers, especially if the answers were given in exchange for the study medication rather than with the intention of providing accurate information.

In our study, various precautions were taken to minimize these risks [318, 332]. To reduce information bias, study personnel received appropriate training on the use of standardized questionnaires such as the European version of the Addiction Severity Index. To reduce recall bias, a timeline follow-back method was used [334]. Retrospective estimates of daily drug use four weeks prior to the interview date were obtained using a calendar format. This method can be used with little loss of accuracy to collect information on substance use [335]. To increase confidentiality and reduce participant anxiety about giving personal information that could lead to negative consequences, participants were informed that such information will be completely anonymous, kept separate from the medical records, and will not be shared with anyone outside the research.

Despite the training and coordination of study personnel and clinicians, other individual characteristics may have influenced the overall outcome. First, personnel could interpret the questions in different ways, which led to different ways of reporting the results. Secondly, the different professional and clinical backgrounds of the study personnel likely influenced their communication with the participants which, in turn, may have influenced the responses received. The stigmatizing attitude that people with OUD have experienced over the years may have led to defensive reactions, e.g. when personal and sensitive issues are raised during an interview. We believe that establishing a trusting relationship between the researchers and our participants helped them open up. Conversely, in cases where trust was not established or where participants did not meet with the same study personnel, they may not have been entirely truthful or even discontinue the study.

We can also suggest the presence of a social desirability bias, where participants respond in a socially favorable manner rather than giving honest answers, especially to sensitive questions [336, 337]. There may also be response bias, that is, a choice or a tendency to respond in a certain way [337]. Regardless of what was asked, how a person interprets a question can bias the answer, emphasizing the importance of questionnaire clarity [338]. Also, the lack of flexibility with fixed-choice questions can be a disadvantage and perhaps contribute to a lower validity. Asking participants to rate a statement limits their ability to express their thoughts and feelings [339]. Misunderstanding the questions may also reduce reliability or results. However, we used self-report questionnaires for a number of reasons. We were able to use them for a large group of people without spending much time and money [332, 340, 341]. We collected data on behaviors and personal issues that could not be measured otherwise, such as life satisfaction [342, 343]. In addition, self-report questionnaires allowed for the collection of a large amount of quantitative data on substance use, social problems, physical and mental health, and the results could be generalized [340, 341, 344].

5.2.5 Attrition bias

One problem with RCTs is non-adherence, that is, the number of randomized participants lost to follow-up. This leads to a decrease in the reliability and

generalizability of the study results [345-347]. Systematic differences between participants who discontinue the study and those who continue it may lead to attrition bias [298, 348, 349]. Reasons for discontinuation may vary, such as intolerable side effects or lack of motivation to participate [349]. In particular, withdrawal symptoms in our participants may have increased the dropout rate in the early phase of XR-NTX [246]. In addition, violations of the study protocol, such as randomization or patient compliance may serve as exclusion from the study, and should be reported as emphasized by Sweetman and Doig [350]. As can be seen from the present study, the distribution of missing data was approximately the same in the two randomized groups, nine in the XR-NTX group and seven in the BP-NLX group, and this may have reduced the attrition bias caused by missing data during 12 weeks of the RCT.

Miller and Wright highlight that, in some cases, systematic attrition bias may skew the results, leading to inaccuracies because it affects internal validity when there are differences between the experimental and control groups, and external validity when the final sample differs significantly from the original [351]. To avoid increasing bias, we had mandatory enrollment in the national opioid treatment program where participants could access additional support and counseling services during the study. In addition, any adverse events were recorded and considered not only during but also after the study, so the participants were not completely lost to follow-up.

The intent-to-treat analysis is recommended in RCTs as the best statistical method to avoid attrition bias associated with loss, misallocation or non-adherence [345, 347]. Therefore, all 159 randomized participants were included in this analysis, as well as those who discontinued the study [296]. A modified intention-to-treat analysis based on defined criteria was also used [345, 352]. Specific criteria were participants who attended at least one assessment survey and took at least one dose of study medication. In the end, out of 159 randomized participants, 143 met these criteria. This modified intention-to-treat sample was found to be the most appropriate for the analysis of time to first relapse. To reduce the risk of detection bias in the analysis, the dataset was de-identified, the allocation was masked, and most of the analyses were performed by an

independent statistician. Yet, there are other factors to consider, which will be discussed below.

5.2.6 Confounding and mediation

When two or more groups are compared in an observational study, there may be systematic differences between groups not because of actual exposure or intervention but because of a confounding factor. Confounding factors occur before exposure, such as medical history or demographic data, and influence both the dependent variable and independent variable [353]. The confounding factor may lead to an overestimation or underestimation of the treatment effect (Fig. 5.4).

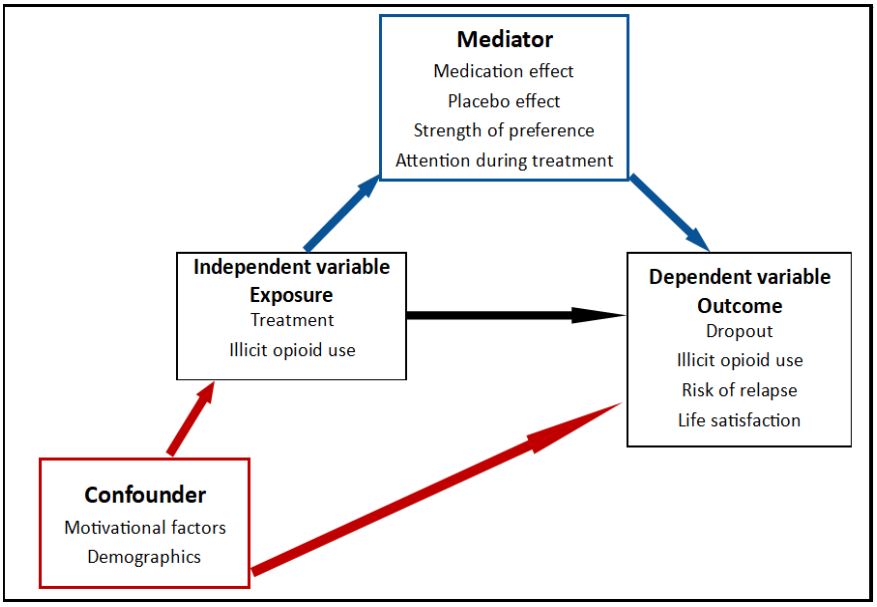

Figure 5.3 Mediators and confounders. Blue arrows indicating the causal pathway exposure→mediator→outcome. Red arrows pointing the directions of a confounder that influences both the exposure and the outcome. Adopted from Mascha et al., 2013.

Another bias in the study could be a mediator. Mediator factors differ from confounding factors in the direction of causality; they lie on a causal pathway between treatment and outcome. Thus, the mediating variable occurs after exposure; it is both caused by the exposure variable and is the cause of the outcome [354].

The relationship between outcome and treatment may be concealed or even false due to the presence of confounding factors [296]. To avoid misinterpretation, confounding factors must be considered in advance and reflected in the study design. The analysis should also examine the relationship between such factors and outcomes. During the study, appropriate methods can be used to reduce the influence of confounding factors [355]. To measure clinical parameters, we used a standardized follow-up every fourth week and used validated instruments such as the European version of the Addiction Severity Index. The XR-NTX and BP-NLX groups were considered similar in terms of sociodemographic characteristics and health status at baseline. We assume that these factors did not contribute to the differences in results between groups.

Gender and age are generally viewed as confounding factors in the analysis [356]. Data from a Norwegian survey indicates that the use of different substances varies by age and gender, with men using more opioids than women [357]. Women are also more likely to relapse than men [358]. The age of patients in OMT programs is increasing due to effective treatment and the oldest OMT population in Europe is in Norway [359]. In our study, the mean age of participants was lower compared to the mean age of OMT patients. To avoid bias and ensure balance, mixed model approaches were used and the analyses were adjusted for age and gender.

Participant preference for XR-NTX may confound the effect of the medication on illicit opioid use. We sought to collect a study sample that would be representative of the general population of people with opioid dependence. Despite this, we assume that many people were willing to participate in the study because the XR-NTX was new, easy to use (i.e. only once a month) and not available in Norway. This assumption is supported by the fact that only a few participants chose BP-NLX in the follow-up study. This confounder could be controlled if participants were asked about their preferred treatment in the RCT, or if participants were randomized into two sequences [306, 331]. In other countries, such as the United States, XR-NTX and BP-NLX are approved and available to opioid users. Structural barriers to treatment may limit access to opioid maintenance treatment in general, although it is likely that participants in the US

X:BOT study (Extended-Release Naltrexone vs Buprenorphine for Opioid Treatment) were equally interested in the two medications. Therefore, this confounding factor had less effect on their results than in our study [244].

There is no standardized or validated tool for determining treatment preferences for people with substance use dependence [130]. Therefore, the study used a self-made instrument that was not validated in the population of interest. The design and use of the survey instrument, as well as the subsequent interpretation of the results, can lead to survey errors. Such an error affects the reliability of the measurement and is called the measurement error. To minimize measurement errors, a complete set of carefully designed survey components should be developed. Hence, any conclusions drawn in our study cannot be formulated with complete certainty, since measurement errors are possible.

Two out of ten statements in our interest survey, was used in a previous study of potential interest in naltrexone treatment in 112 pregnant women in Norway [268]. The results showed a high interest in naltrexone treatment and in learning more about this treatment. The aim of our study was to compare the effect of pre-treatment preference on adherence, illicit opioid use and risk of relapse.

Before beginning our research, we surveyed people with OUD about their level of interest in discontinuing opioids in general and in undergoing opioid blockade in particular [239]. The main and only criterion for completing the survey was dependence on opioids. It was not necessary for all patients to be receiving treatment; some were in detoxification facilities, outpatient departments, OMT clinics, and jails during the assessment. Yet, the responses to all questions were slightly more positive from individuals who were not enrolled in OMT than from those who were enrolled [239].

The distribution of responses on a scale from "not interested" to "very interested" showed that only a few answered “slightly”, “somewhat” and “quite”. OMT medications are well known to people with opioid dependence, and this distribution of responses showed that people know which medication they prefer. Our survey results demonstrated that 56% would prefer OMT if they were given a choice of treatment

next week, while 44% chose an opioid blocking treatment [239]. We believe that pre-study interest in treatment can be seen as a preference for treatment during the recruitment phase and during the trial period because the same people who answered the questionnaire entered the study having already made a decision about their treatment preferences.

In our study, five statements of the survey reflected the level of interest in receiving XR-NTX for (i) reducing cravings, (ii) blocking the effect of heroin, (iii) receiving an injection every four weeks, (iv) receiving medication for one year and (v) participating in a study using this medication [239]. This survey suggested greater adherence with each statement, and interestingly, more respondents were positive and fewer were negative about broader, non-committal statements. Only a third of the respondents were very interested in participating in the research but over half of the respondents were very interested in the medication that blocked the effects of heroin for four weeks. Therefore, we tried to be precise in estimating the gradation of preference levels, using "higher" and "lower" rather than "high" or "low."

Participant motivation can be considered a confounder. Our participants were not only those in OMTs, but also those who were not receiving any treatment prior to the study and joined the OMT program only to be included in the study and receive XR-NTX. However, precise inclusion and exclusion criteria were developed to ensure that only eligible participants were recruited, and we suggest that the included participants were adequately representative. Therefore, in terms of gender, age and psychosocial characteristics, the participants in our study rather represented the average population with opioid dependence.

The placebo effect can be a confounder or a mediator. When participants were given information that XR-NTX reduced heroin cravings, their expectations may have influenced how they perceived and reported cravings. Another modifier could be the attention and relationship between study personnel and participants. Close attention from study personnel may have affected patient self-esteem, which in turn may have

led to self-efficacy as a potential moderator and, as a result, to changes in drug use and increased satisfaction with quality of life [360, 361].

5.3 Ethical considerations

It is challenging to conduct research among marginalized populations. Those with OUD are particularly vulnerable due to the complexity of opioid addiction. The trusting relationship between the patient and the clinician, or in this case, between the participant and the researcher, is one of the crucial components for the effectiveness of treatment [362]. To build a trustworthy relationship, research personnel interacted directly with potential participants from the very beginning of the study.

An ethical consideration in this study is the informed consent from people with an addiction. The general opinion is that people with substance use disorders are not capable of providing consent when they are under the influence of drug use or experiencing withdrawal symptoms at that time. From an ethical point of view, research consent should not be obtained from individuals who are vulnerable or susceptible to influence. Therefore, for a person to be capable of providing consent, they must be in their typical or sober state. Yet, voluntary involvement in research depends more on a person's traits than it does on their vulnerability in terms of belonging to a particular group [363]. In general, it is more ethical to consider patients with OMT to be mentally and functionally capable. To maximize the potential for consent, the individual must be given the opportunity to carefully consider their participation by not rushing them into signing but giving them extra time [363]. To allow time for a decision to be made, several meetings were held with each potential participant before signing the consent.

The potential risks associated with the course of treatment in the study and the consequences after participation such as overdose may be of ethical concern. Some provide statements such as “an addict once - an addict forever”, which in itself is stigmatizing and ethically problematic. This mindset implies that the participants are not individuals capable of taking responsibility for their actions, and because of the addiction complexity, they are likely to return to their previous addiction regime after

treatment. It is important to note that discontinuing XR-NTX treatment does not necessarily result in a return to drug use. Some participants had no inclination or intention of using heroin or other opioids again and instead viewed it as an opportunity to start a new life free of drugs. However, for others, there was a significant risk of opioid use and overdose. If participants reported using opioids, they were informed of a gradual decrease in the blocking effect by the end of the fourth week and a decrease in opioid tolerance.

Because XR-NTX was unfamiliar to the Norwegian OUD population, it was essential to draw the attention of those who were interested in XR-NTX to any potential side effects and risks. To avoid the risk of overdose, participants had to be enrolled in the OMT system, which entitled them to start another type of medication, e.g., methadone or buprenorphine, as soon as possible after ending XR-NTX. The process of switching was carefully planned together with OMT personnel at least one month prior to the time when tolerance was low and XR-NTX coverage was declining. All participants were given information about the risks of an overdose at all stages of the study, before, during, and after it.

The researchers' potential authoritarian position may also present an ethical dilemma. Researchers can influence participants with their knowledge, experience, points of view, and opinions [364]. For example, during an interview, participants may behave in a socially acceptable way if they think the interviewer expects "good feedback" from them. Also, they may view the researcher as having "power" over the medication, as the patient/participant must answer questions. Furthermore, research personnel may be seen as someone who can help the participant gain influence or support from social services, the OMT, or a therapist. To reduce this ethical issue, research personnel provided participants with information about the difference between research and treatment during the first consent conversation. On the other hand, research personnel play an important role in creating a sense of security and a supportive environment for participants. In case of experiencing stress during the study brought on by physical

symptoms or psychological discomfort, participants may require support from the research personnel in the form of counseling and empathy [365].

Substance use is a form of social deviance, and people who use substances often face a dilemma between the pleasure and pain they inflict on themselves, family, friends, and society. If a person with OUD does not seek treatment out of their own volition, but rather because of external pressure from sources such as their family or social services, the question arises as to whether the treatment can truly be considered a freely made choice. Considering that many of the study participants had never attended the OMT before, for them, participation in the study was perhaps more conscious and thoughtful, choosing XR-NTX instead of the well-known OMT.

Individuals with OUD could only receive XR-NTX during the study, and if they discontinued treatment, they could not be re-enrolled in the study. Yet, they were given the choice of whether to participate in the study or not, as well as to continue or discontinue their participation, depending on their preferences, satisfaction with the treatment, and other personal traits and life situations. For example, our pre-trial survey found that 56% of respondents were interested in OMT rather than XR-NTX [239]. In addition, we observed that during the trial, some participants chose to return to or switch to OMT instead of continuing to take XR-NTX while they were incarcerated or for other reasons.

6. DISCUSSION OF THE FINDINGS

"Opioid treatment saved my life, but ... this is not the life I want."
- Patient in the study

This is the first study comparing XR-NTX and BP-NLX for the treatment of opioid dependence. The study provided important information about the efficacy and safety of the injectable XR-NTX compared to the well-studied oral BP-NLX. The risk of first or any relapse to illicit opioid use was significantly reduced in the XR-NTX group compared to the BP-NLX group. Dropout rates, risk of first opioid relapse, and illicit opioid use were linked to treatment preference. Life satisfaction moderately increased in both randomized groups in favor of the XR-NTX group.

6.1 Relapse to illicit opioids

The low relapse rate to illicit opioids found in the XR-NTX group during the study is consistent with other XR-NTX treatment studies [249, 366]. Compared to those receiving treatment or a placebo, XR-NTX participants show greater retention in outpatient and inpatient settings and report less craving, use, and relapse to illicit opioids [244, 249, 250, 367]. However, there may be some difficulty in generalizing the results due to the very definition of relapse. Some studies characterize relapse as any opioid use [368, 369] while others are more flexible and measure it, for example, by the number of days or positive and absence of urine drug tests [54, 222]. Our results showed a modest superiority of XR-NTX over BP-NLX in terms of days of illicit opioid use, but a slightly modified definition is likely to result in a larger difference between groups. We would like to note that most of those who relapsed once completed treatment, and the low relapse rate of opioid use was maintained during the follow-up period among all participants.

Furthermore, participants who were asymptomatic or had low levels of anxiety or depression had virtually no relapses to opioids at 24 weeks and onwards. We, therefore,

question whether relapse rates can be used as a meaningful guide for clinicians in choosing opioid treatment for their patients. The term "relapse" can be seen as a derogatory label, implying that there are only two possible states during treatment: achievement or failure. Perhaps relapse should be considered as a signal for an adjustment in the treatment. Relapse may lead to an intervention that may include psychosocial support [370]. For example, there is a well-known bi-directional relationship between self-efficacy and relapse [371]. This association suggests a need for improved self-efficacy during relapse, which in turn correlates with longer intervals between relapses [372]. Clinicians will play an important role in implementing self-efficacy interventions, such as cognitive behavioral therapy, including relapse prevention and coping skills training [361].

Another aspect is that negative social support can play a role in relapse when, for example, peer pressure tries to persuade a person to use drugs. As a result, the effectiveness of treatment may be hindered if various forms of social support are not utilized [373, 374]. By involving patients in the workforce and educational system, it is essential to assist patients in acquiring new healthy behaviors and social functioning [375].

In addition, the differences in results between the XR-NTX and BP-NLX may be explained by differences in the administration and effects of the two medications. Unlike BP-NLX, XR-NTX takes longer to start up and has some obstacles. The initiation of XR-NTX is best performed in an inpatient setting with full detoxification and several opioid-free days, while BP-NLX can be easily initiated on an outpatient basis [124,136]. When the opioid withdrawal process may take up to 10 days or more, this experience can, for some, be a significant barrier to successfully initiating XR-NTX treatment [60, 241, 376]. If a patient who has discontinued XR-NTX treatment wishes to restart it, they will need to repeat the same detoxification process if opioid use has occurred. While if the BP-NLX patient has stopped the medication treatment, it can easily be restarted. Therefore, under normal clinical conditions, this procedure may create a retention problem with poorer outcomes for those treated with XR-NTX compared to BP-NLX.

Another form of buprenorphine, Buvidal, is a novel extended-release injectable solution approved for use in Norway after the completion of our study. It has almost the same structure as XR-NTX, with monthly or even weekly injections at doses of 8 mg, 16 mg, 24 mg, and 32 mg. If the study were conducted today, we would probably see two different options, which would clarify the reasons for participating in the study. Perhaps some people enrolled in the trial because XR-NTX was a new monthly option, not because they wanted to stop using opioids completely.

Buvidal depot may currently be an appealing choice for some people with OUD, as it may reduce the need for daily OMT medications. This is expected to be a favorable incentive for many patients to start treatment. Nonetheless, taking depot preparations does not imply that clinical follow-up is no longer necessary. On the contrary, many patients require and desire closer monitoring than is provided by the interval between medication administrations alone. According to the OMT Status Report, 15% of OMT patients used Buvidal in 2021, and for some, the pandemic has influenced medication preferences [259]. It is likely that the percentage of patients using Buvidal will continue to rise.

During the follow-up period, the risk of relapse to opioids may be explained by the fading of the treatment novelty effect. The novelty of the XR-NTX likely played a positive role during the trial period, but during the follow-up, when the novelty factor was no longer present, the participants in the continuing group, especially those who were initially skeptical of the XR-NTX, were at higher risk of relapse. A meta-regression of 61 hepatitis C treatment trials found that the same treatment was 12% more effective when it was labeled experimental than when it was labeled controlled [377].

During treatment with XR-NTX, patients lose tolerance and, as a result, those who try to overcome the blockade of opioid receptors increase the risk of overdose. This is especially important in the last week of treatment or after missing a scheduled XR-NTX injection. Morgan's study confirms that premature discontinuation of XR-NTX increases the risk of mortality compared to BP-NLX treatment [378]. In our study, there

were no cases of opioid overdoses in either short or long periods of treatment [379]. We believe that our participants were sufficiently motivated, and therefore it is necessary to identify those who strongly prefer XR-NTX and express an intention to continue treatment until goals are achieved in order to reduce the risk of overdose due to early XR-NTX discontinuation.

Another factor that can affect relapse may be motivation. A recent literature review by Jarvis et al. found that data on adherence and retention of XR-NTX treatment compared to BP-NLX treatment are limited and inconsistent [241]. So far, only two trials have been comparing BP-NLX with XR-NTX, one in Norway [330] and one in the USA [244]. Although the results show that both medications were equally effective after the successful initiation of treatment, we have to consider some factors when comparing the results of these two studies. First, these two countries have different healthcare systems. OMT, including psychosocial services in Norway, is government funded, while in the USA patients must find other ways of payment, have insurance, or apply for different federal and local programs, which then cover the charges [380]. Second, opioid treatment in Norway does not include XR-NTX, limiting the choice of medications. However, participants in the US X:BOT study likely intended to receive OMT for their dependence, and not for abstinence *per se* acquired through antagonists [244]. Our participants, we believe, entered the study primarily to receive an unavailable new treatment for craving reduction and opioid use, especially heroin [239]. The disproportional distribution of participants, who chose BP-NLX after the randomized part of the study, including only five people, supports this assumption. Another recent study on the treatment preference of people with OUD also confirms our findings [381]. In a study by Mannelli et al., 63% of participants were motivated to start XR-NTX treatment because they did not want to use opioids, while 26% were tired of taking pills every day [381]. Moreover, 78% of these participants did not even know there was an opioid-blocking treatment option when they initiated treatment with BP-NLX.

Due to the strain of complete detoxification and subsequent opioid abstinence in the days before initiating XR-NTX, there is a potential risk of relapse at this time. To enhance the impact of XR-NTX by minimizing withdrawal symptoms and the risk of

potential relapse, methods to improve retention rates are needed [382]. A double-blind, placebo-controlled, randomized study showed that – although low, ascending doses of oral naltrexone did not improve the rate of induction compared to placebo – the results support a short-term dose reduction of buprenorphine in combination with additional medications and counseling [382].

Throughout our study, several participants underwent inpatient detoxification during the induction period. Some individuals reported experiencing cravings and other withdrawal symptoms during the taper. Among them were those who could not tolerate it and left the study before receiving the first XR-NTX injection. Consistent with our observations, adverse effects were less common with the longer opioid-free period before the initial XR-NTX injection. Hence, we advised study participants to wait for a more extended period, exceeding the initial 72 hours, prior to taking the naloxone test dose. Some participants waited up to 7–10 days and fewer adverse events were reported. Others, although aware of the risks of withdrawal symptoms, decided against extending the waiting period due to cravings and concerns about dropping out. The detoxification process was an individually planned process.

The likelihood of successful initiation of XR-NTX treatment may increase, and the number of negative effects may decrease due to improved detoxification processes [383]. Difficulties with detoxification were emphasized as a major obstacle to the use of XR-NTX in the US X:BOT trial [244]. When using XR-NTX for individuals with OUD, it is advisable to implement an initial treatment plan based on recommendations that will yield the most effective induction on XR-NTX. In another study, the regimen included a 7-day incremental daily dose of oral naltrexone followed by a first injection of XR-NTX [384].

Moreover, we believe it is important to learn from patients themselves about the factors that facilitate and hinder long-term abstinence from opioids in order to optimize future XR-NTX treatment. A study on the relationship between hope for the future and time to relapse after detoxification found that higher levels of hope were strongly linked to reduced rates of relapse [385]. As a result, empowering those who are in recovery and

offering additional support during treatment may be a helpful method to lower relapse rates among patients in OMT [385].

6.2 Pre-treatment preference and its strength

In this study, the patient's initial preference for XR-NTX treatment may have influenced the high number of successful inductions. Participants randomized to the preferred XR-NTX treatment reported less opioid use and a lower risk of first relapse at all preference levels compared to the BP-NLX group during the 12-week study period. In addition to the blocking effect, the initial preference for XR-NTX may explain the increased use of illicit opioids among BP-NLX patients and suggest that patient inclusion in treatment decisions is an important factor for positive treatment outcomes [130, 138, 142]. The willingness to undergo induction therapy twice within four months indicates a very high motivation among the participants.

Furthermore, the current results are also consistent with previous studies suggesting that the strength of patient preference is associated with successful treatment initiation and treatment adherence [4], highlighting the potential clinical value of measuring preference levels. We found that participants with lower preferences had higher dropout rates during the follow-up period. A possible explanation for this could be the initial ambivalence towards the new treatment. The ambivalence may be due to either a lack of knowledge about XR-NTX and doubts about its effects, strong substance use habits as people have no previous experience with opioid-blocking medications, or hesitation to go through a detoxification process that many of them have experience in the past.

Opioid use was higher during the first weeks of XR-NTX treatment among participants with a lower preference level compared to participants with medium and higher levels in the switching group. The same pattern was shown in other XR-NTX studies where participants were tempted or wanted to test the blocking effect of the injection [138] [386, 387]. In a qualitative study by Velasquez et al., some XR-NTX participants admitted to using heroin after being released from jail, mainly wanting to confirm that the treatment blocked the euphoric effects of opioids [138]. Others had no strong

motivation or desire to abstain from opioids, relapsed immediately after release, and no longer sought treatment if previously treated. For some participants in our study, peer pressure may have been a negative factor leading to opioid use. Peer pressure may not only contribute to initial substance use during adolescence [388] (Fig 1.1), but may also influence older people in OMT, in this case putting pressure on them to test blocking effects.

In the group that continued XR-NTX treatment, participants with a lower and medium level of preference had a higher risk of first relapse compared with a higher level of preference. One reason for this may be that the participants had a period of improvement at the beginning of treatment, but after a while, people may not have been able to cope with some personal problems, such as chronic physical pain, emotional distress, or strong external opioid temptation [389]. They may have had other alternative courses of action, but perhaps they were trying to deal with problems the way they were used to: with opioids. Reassuringly, the XR-NTX and BP-NLX groups reported significant reductions in anxiety and depression, and insomnia [108], and no increase in chronic pain in the XR-NTX group [390]. This finding is consistent with the results of the X:BOT study, which assessed participants' pain status using the EuroQol, the instrument measuring the quality of life [391]. In particular, treatment with both XR-NTX and BP-NLX was associated with a reduction in pain from baseline, with a slight advantage for XR-NTX during the follow-up period [391].

In addition, a cross-sectional study among patients with chronic disease has shown that treatment-related characteristics such as route, complexity and frequency may play an important role in patient preference for diabetes treatment [392]. The same can be assumed among patients with chronic opioid dependence. Thus, a previous Norwegian study found that participants preferred oral methadone over naltrexone implants [331], perhaps for two reasons. First, because access to methadone was, at that time, limited in Norway, or secondly, the method of obtaining the medication in the form of an implant was not of interest. These issues, such as limited access and lack of interest in medications, could potentially impact the study's outcomes. However, they could also

play a crucial role in determining which treatment options are acceptable in a clinical setting.

Besides high motivation and preference for treatment, patients' baseline characteristics may influence the outcomes. First, the presence of high levels of physical pain and psychological problems was associated with a high risk of treatment discontinuation during short-term treatment. In addition, illicit activities for profit have been associated with frequent opioid use. The criminal environment may have influenced the use of opioids at the time when the participants received new, previously unknown treatment. In the follow-up, no such association was observed, which could be explained either by (i) no desire to "throw money down the drain" after confirming the blocking effect of XR-NTX [222], (ii) a change in priorities during treatment with XR-NTX, or (iii) exclusion from the criminal environment when making money from criminal activities turned out to be irrelevant. Psychiatric problems such as depression and anxiety were also associated with an increase in days of opioid use during short-term but not long-term treatment, supporting previous findings [108]. Finally, women used more illicit opioids than men during both short- and long-term treatment, which is consistent with previous studies highlighting gender differences and higher risk among women [393].

During our research, the patient advocacy group proLAR Nett conducted a survey among patients with OUD [65]. Over a thousand OMT patients responded to the questionnaire. For 40% of respondents, the reason for enrolling in OMT was the intention to start work or school, but the main goal was to improve the quality of life. While many people expressed satisfaction with OMT, they also reported dissatisfaction with their participation in the program, citing a lack of meaningful social interaction and a sense of belonging. As a result, the survey recommended that participants' perspectives be considered when tailoring OMT to meet the needs of each individual, particularly with regard to medication selection.

6.3 Life satisfaction changes

Although some people seek stress-reduction therapy with the primary objective of receiving the required medicine, others decide to seek treatment because they want to

improve their quality of life and change it for the better [118]. The change in life satisfaction during treatment showed a significant increase in favor of XR-NTX. This can be explained by the different treatment structures between XR-NTX and BP-NLX. Monitoring daily or near-daily consumption of BP-NLX may have had a negative impact on participants' overall life satisfaction. In particular, this reason may have affected those participants who joined the study to try XR-NTX, but were instead randomized to the BP-NLX group. Such participants may include those who have not previously received OMT due to a number of external and internal barriers (Fig. 1.2), as well as those who have not been satisfied with their opioid maintenance regimen. However, it is important to note that this may not be the case for every individual. A descriptive study conducted in Norway found that OMT patients expressed a desire for supervision in order to maintain their drug-free status and reported an enhancement in their quality of life despite having to comply with rules and regulations, such as adhering to a treatment regimen [394].

Another possible explanation for the difference in life satisfaction scores between the XR-NTX and BP-NLX groups could be the motivation for XR-NTX treatment. Our study included more than 40% of participants who were not previously enrolled in an opioid treatment program [55] despite the fact that methadone and buprenorphine are available and fully funded by the government [258]. Perhaps the time consumption, stigma, and the temptation to use illicit drugs were barriers to maintenance treatment [138, 264]. Our participants reported satisfaction with XR-NTX treatment and would highly recommend it to others [330]. Treatment satisfaction likely had a positive impact on the lives of the participants, however, we cannot say to what extent and how it positively impacted lives based on this variable alone.

In the follow-up period, we also found a significant difference between the groups in the life satisfaction changes in favor of the continuing group compared to the switching group. These changes in life satisfaction were associated with the use of illicit opioids, which is in line with previous findings; an observational study showed an association between higher life satisfaction and lower levels of opioid use among new OMT

patients during one year of treatment [115]. The Norwegian study by Hagen et al. [287] found that life satisfaction improved among those who quit substance use for one year compared to those who relapsed. We assume that the relationship between life satisfaction and opioid use might be related to the level of motivation to abstain from substance use and focus on the recovery process [118]. This is supported by other XR-NTX studies in which higher motivation for abstinence was observed among participants who used fewer illicit opioids during treatment [244, 248].

Because a population with opioid dependence is heterogeneous, our study also examined life satisfaction trajectories. Most of the participants belonged to the group with low life satisfaction. Although this group showed a slight increase in life satisfaction level in the randomized part of the study, it remained relatively stable and low in the follow-up. For some participants, one possible explanation for this outcome may be a failure to meet treatment expectations [395]. A recent qualitative study of XR-NTX in Norway highlighted unfulfilled expectations from XR-NTX treatment as the main reason for treatment discontinuation [396]. Their unfulfilled expectations included not only unexpected negative physical, emotional, and mental reactions, but also the lack of anticipated effects in particular; some participants experienced the opioid effects of buprenorphine [396].

Life satisfaction changes may be further explained by personality traits and genetics [397] and, therefore, by individual differences in coping strategies [398, 399] or lack thereof [398]. Forced abstinence from opioids for long periods during XR-NTX treatment may have acted as physiological and social stress for some people. Participants did not have the opportunity to manage stress with opioids as they could before [400]. People respond differently to the same life circumstances because of their cognitive schemas and beliefs [81, 401]. Previous research has emphasized the importance of identifying personal characteristics for individualized treatment and improved retention [402, 403]. Happy people are more resilient and better at coping with stress and trauma. The reason for the direction of course goes both ways, e.g., happier people are more likely to be more adherent to treatment, but successful treatment also makes people happy.

The fact that participants with low life satisfaction at baseline continued to have the same level of life satisfaction at follow-up is a troubling finding. Other studies have found an increase in overall life satisfaction during OMT [114, 115, 121, 404, 405]. For instance, during the first 12 months in OMT, patients showed an increase in quality of life [115]. An eight-month follow-up study showed that the quality of life among participants in the buprenorphine group steadily improved over time and reached a consistently high level, whereas for participants in the methadone group, an initial increase in quality of life was observed in the first month, which then remained stable [406]. An 18-month study by Wang et al. [407] found an improvement in quality of life during the first three months of methadone treatment, but a slower change thereafter. Evidence suggests that OMT is beneficial in improving global quality of life and health-related quality of life, particularly early in treatment, but may have drawbacks in the long term.

Although XR-NTX treatment provided relief for some participants, it was not enough for others. Factors such as the duration of substance use, comorbid mental disorders, education, source of income, social network, and living conditions, in addition to the type of treatment received, may influence a person's overall life satisfaction.

Social support from family and friends, along with a sense of community and enjoyment of social activities, may play an important role in achieving successful outcomes. Therefore, quality of life assessment may be a better approach to monitoring treatment progress and identifying potential risks for patients with substance use disorders rather than focusing on substance use [408].

A study of patients recently admitted to OMT found that distinct domains such as leisure, housing, and financial situation are positively associated with the overall quality of life [115]. Financial satisfaction, particularly, influenced the quality and satisfaction with life. However, other studies showed that OMT patients were dissatisfied with their financial quality of life even five years after treatment [409]. Perhaps this could be connected to a lack of social ties and relationships: as some OMT patients found themselves isolated and lonely [410, 411]. Impaired ability to trust

others is a common issue for OMT patients due to negative experiences and stigma, which can lead to avoidance of new relationships and social isolation, especially among those over 50 years of age [113]. On the other hand, network development is an essential aspect of OMT, as the abstinence network has been associated with significant improvements in overall quality of life and social quality of life during treatment [79].

In addition, limited financial resources contribute to the low financial satisfaction of OMT patients after six months of treatment [112]. Low satisfaction with the financial situation may be associated with spending money on substance use, debt, rent, or other bills [115, 412]. Some OMT patients receive social benefits, but this is just a minimum living wage that is limited to basic needs, i.e. household and food [115]. In addition, patients in OMT may experience housing instability or difficulties finding suitable accommodation, which can adversely impact their satisfaction with life. Participants in our study did not differ in income, living conditions, or education from the OMT population. Perhaps the only difference between participants in the study and those who chose not to participate was the motivation to try a new treatment, although highly motivated patients in a vulnerable position may overestimate the benefits and/or underestimate the risks of XR-NTX [396].

Patients with substance use disorders and comorbid mental disorders need meaningful activities and opportunities to be part of society [32, 413], which subsequently increases life satisfaction [414]. As already mentioned, there is a significant relationship between high satisfaction in leisure and high overall quality of life [115]. Engaging in leisure activities can provide patients in OMT with the opportunity to establish new social connections and form meaningful relationships. Our study showed that a significant proportion of participants (36%) spent their leisure time in isolation, and only a small fraction (9%) reported they were satisfied with their leisure activities. Surprisingly, those who reported feeling "indifferent" to their leisure time (40%) had higher levels of life satisfaction compared to those who were dissatisfied (51%). It can be assumed that the opportunity to give such an answer caused some participants to refrain from *yes* or *no*, or maybe, being in the process of recovery, they felt that "*indifferent*" was enough for them at that moment. In any case, having something meaningful in life contributes to living a fulfilling life, and avoiding substance use

[116, 415]. Having supportive family and friends can play a crucial role in enhancing well-being of OMT patients, as well as participation in social activities and finding a sense of belonging within a community can provide a renewed sense of purpose.

7. IMPLICATIONS

7.1 Clinical implications

For patients with stabilized opioid dependence and/or specific goals that include opioid cessation, XR-NTX might be an appropriate alternative to existing methadone and buprenorphine treatment options for several reasons. First, because XR-NTX is not addictive and has little to no interaction with other drugs, the risk of diversion is minimal and there is no need for regular monitoring, as is the case with buprenorphine and methadone [174]. In addition, it is easier for people to adhere to monthly XR-NTX injections than to daily or weekly clinic visits, especially for those who are difficult to contact and include in treatment and for those who are unable to attend clinics daily due to their work or school. XR-NTX may also be the preferred treatment option for individuals at high risk of relapse and overdose due to loss of tolerance [151, 378] after discontinuation of substitution therapy and release from prison [222, 379, 416, 417]. Its benefits may be of clinical relevance, indicating a need for treatment in people with opioid dependence.

Initiating XR-NTX treatment faces a significant challenge due to the induction period, which poses a higher relapse risk compared to BP-NLX. The most difficult aspect of detoxification is the period of opioid abstinence before the first XR-NTX injection. There is no single ideal detoxification method to prevent relapse and minimize withdrawal symptoms. It is likely that the most successful approach will depend on two factors that clinicians and patients should decide together: the level of distress experienced by the patient during detoxification and the length of this period [418]. A motivational factor such as the patient's initial preference for XR-NTX is needed to overcome this process. Our results corroborate previous studies, emphasizing that a higher level of patient preference is strongly associated with successful treatment initiation and treatment adherence [145]. Including individual preferences in shared decision-making can enhance adherence and outcomes [130, 419]. Patients who are uncertain about which treatment option to choose require adequate time to make an informed decision, as the initial phase of treatment is critical, and it may require

multiple attempts to overcome it. Some of the participants who were initially ambivalent completed the study period. As treatment experience and life circumstances may change, initial treatment preferences may not remain fixed, and hence it would be useful to measure patient preferences over the course of treatment.

Improved treatment adherence, setting realistic expectations for recovery, sharing useful information, and building meaningful relationships are all benefits of shared decision-making. A recent survey amongst Norwegian OMT patients [420] indicated issues that needed to be addressed to improve the OMT system: a need for active user involvement in planning their individualized treatment, and a need to improve trusting relationships with counselors and physicians. In addition, the importance of empowering patients, including comprehensive treatment, reducing stigmatization of OMT users, and including a wider choice of OMT medicines was enhanced. These factors influence OMT patients' lives and thereby their experiences of life satisfaction.

Yet, there are several potential disadvantages to this approach [421]. For example, shared decision-making in clinical practice may require additional time, which can lead to patients feeling that they do not have adequate time to ask questions during visits. Also, patients may view decision-making as a burden, as it can be challenging to make decisions while grappling with physical and mental distress. The approach may also face communication barriers, as patients may feel like they are speaking different languages than their clinicians and may worry about expressing their needs and being understood. Shared decision-making can lead to competition between people who want to "win" the decision. To overcome some of these barriers, it may be worth including user organizations in treatment planning [422].

Norway is among the countries with a higher level of happiness and quality of life in the general population [423]. However, some groups of people, such as people with substance use disorders, have a low quality of life. Many individuals with OUD who seek treatment want to improve their quality of life, employment status, and educational level. Each individual's level of happiness is likely to vary based on their

value preferences. To facilitate such change, OMT patients often require empowerment and support from various sources, including user organizations.

7.2 Research implications

Along with the efficacy and safety of XR-NTX, changes in life satisfaction, association with treatment preference, and relapse dynamics during XR-NTX treatment should be further investigated. Furthermore, measuring life satisfaction and inclusion of psychosocial interventions may contribute to even better outcomes in long-term XR-NTX treatment.

The study did not collect information on changes in treatment preferences over time, although participants had the opportunity to express any changes throughout the study. Moreover, it can be argued that participants had the chance to communicate their preferences during the 12-week period, as they could choose to continue using XR-NTX, switch to BP-NLX, or discontinue treatment. Additionally, the fact that participants completed the study could be indicative of their preference. However, further longitudinal studies are needed to measure preference over the course of XR-NTX treatment and its association with treatment adherence.

For individuals living with OUD, a trusting relationship with their clinicians is essential for shared decision-making. The advantage of shared decision-making is that during this mutual participation, the experience and autonomy of OUD patients is recognized. However, while the majority of patients value the fact that professionals consider their opinions when making decisions, not all patients would accept increased responsibility, and may leave the final decision for the clinician. Therefore, both parties should agree in advance on whether there is a need for shared decision-making and to what extent it should be used. We need to learn more about the present and preferred roles that patients would like to play in making decisions regarding their treatment.

We assessed preference for long-acting naltrexone and used sublingual buprenorphine-naloxone as the first choice of opioid treatment for comparison. At the time of the study, long-acting injectable buprenorphine was not accessible in Norway and was only approved after the trial was concluded. Therefore, we did not assess the preference for

the long-acting treatment *per se*. However, there is currently a growing interest in long-acting buprenorphine, and further research is needed to compare effectiveness and initial preference for long-acting medications such as XR-NTX and extended-release buprenorphine [376]. This will help to inform clinical guidelines and best practices for the use of XR-NTX treatment.

7.3 Policy implications

The OMT system has become more flexible in recent years, with more pharmacological options available [260]. The integration of new and effective treatments for opioid dependence (such as XR-NTX, in addition to existing ones) is a necessary implementation [424]. Our results indicate that XR-NTX is an attractive option for opioid users who are not enrolled in OMT for various reasons and are at risk of overdose. This finding is important because the availability of XR-NTX for opioid dependence may increase the overall number of patients. This may involve providing funding for the medication and training healthcare providers to administer it.

The approach of shared decision-making is recognized globally, yet, its implementation varies across nations. In some countries like the UK, it is incorporated into policies, while in others like Peru, it is an area of interest [425]. During the implementation of this approach, various obstacles may arise that can hinder the process, including a busy medical practice schedule, limited resources, and lack of financial support. Therefore, for many countries, there is still a notable gap between the intention and actual practice of shared decision-making. Policymakers should promote the use of shared decision-making between clinicians and OMT patients to guarantee that patients are well-informed about the benefits and risks of treatment, including XR-NTX.

Stigma associated with opioid use disorder and OMT discourages patients from seeking treatment and leads to inadequate access to care. More attentions needs to be paid to reducing stigma through the inclusion of public education campaigns, training health

professionals in stigma reduction techniques, and increased funding for the treatment of mental illness and substance use disorder treatment.

There are two different goals of drug policy: recovery, including improvement of quality and satisfaction of life, and harm reduction e.g., overdose, mental and physical health impairments. We believe that both aspects are important in policy development and both OMT and XR-NTX are treatment options that can be used to achieve these goals.

8. CONCLUSIONS

"I'm lucky to get the chance... My family was very proud when I told them that opioid use was over."
-Patient from the study

In this clinical study, we found that XR-NTX was an effective and safe treatment option and more effective than BP-NLX in preventing relapse to heroin and other illicit opioids. Participants randomized to the preferred treatment used illicit opioids less than those who did not. In long-term treatment with XR-NTX, a higher level of preference for opioid abstinence was associated with treatment adherence and opioid use. Ambivalence was not a barrier during the XR-NTX treatment, as the difference between higher and medium preference levels was quite modest. Monthly XR-NTX treatment was associated with higher life satisfaction compared to daily use of BP-NLX. We found a significant relationship between frequent opioid use and low or reduced level of life satisfaction. The group with low life satisfaction at baseline showed positive changes at the beginning of treatment, but remained low and unchanged during longer periods.

Based on our findings, healthcare professionals should recognize the benefits of considering each person's preferences as well as their strength in collaborative decision-making to optimize adherence and outcomes. The XR-NTX treatment should not be seen as a replacement for the long-studied and effective OMT, rather XR-NTX is a new alternative, especially for those who do not see OMT as a viable option. Having a number of agonist OMT approaches provides an opportunity to try an alternative in the presence of negative effects from one of the medicines. Better matching treatment-to-patient can increase the percentage of OUD patients in OMT and improve treatment adherence and life satisfaction.

Achieving a satisfying life and abstinence from opioid use are the primary goals for many opioid users, so a wider choice of medication alternatives would enable the course of treatment to be better adapted to the preferences and needs of the individuals

with OUD. For people interested in longer opioid abstinence and able to successfully undergo detoxification, XR-NTX may be offered as a first-line treatment. Our study placed a strong emphasis on specific but structurally different treatment outcomes: relapse to opioids, life satisfaction, and pre-treatment preferences. Life satisfaction and pre-treatment preferences were equally important to the evaluation of XR-NTX treatment as was assessing the hazards of opioid relapse. Our findings illustrated the importance of a holistic approach in treatment, which involves the physical, emotional, and mental health of the individual. With this approach, the treatment of opioid dependence can become more attractive.

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Errata

Page 5 Misspelling: “recommented” – corrected to “recommended”

Page 8 Misspelling: “disoders” – corrected to “disorders”

Page 9 Misspelling: “witth” – corrected to “with”

Page 34 Misspelling: “quidelines” – corrected to “guidelines”

Page 34 Misspelling: “clinitians” – corrected to “clinicians”

Page 65 Misspelling: “resondents” – corrected to “respondents”

Page 68 Misspelling: “re-inrolled” – corrected to “re-enrolled”

Page 71 Misspelling: “enjectable” – corrected to “injectable”

Page 79 Misspelling: “recentrly” – corrected to “recently”

Page 82 Misspelling: “detoxificationand” – corrected to “detoxification and”

Page 85 Misspelling: “inclucion” – corrected to “inclusion”

Page 87-88 Re-formulating: “individual opioid user” – corrected to “individuals with OUD”

Page 90 Reference 30 Misspelling: “Europeian” – corrected to “European”

Page 91 Reference 42 Misspelling: “Europian” – corrected to “European”

Page 100 Reference 184 Misspelling: “Gearing, F.R.J.A.J.o.P.H., Methadone maintenance treatment five years later—where are they now? 1974. 64(12_Suppl): p. 44-50.” – corrected to “Gearing, F.R., Methadone maintenance treatment. Five years later—where are they now? Am J Public Health. 1974. 64(12_Suppl): p. 44-50.”

Page 106 Reference 281 Misspelling: “Jounal” – corrected to “Journal”

Paper I

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

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

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INTRODUCTION

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

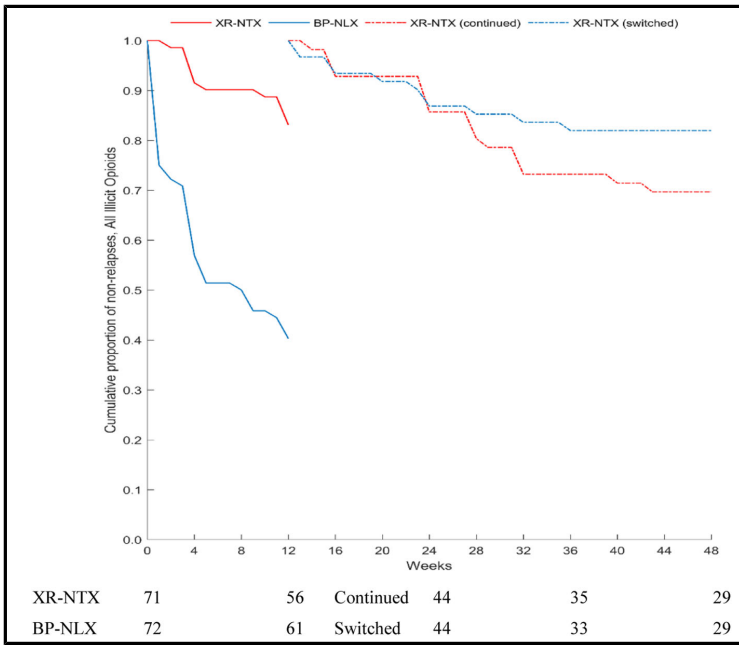

FIGURE 1. Kaplan-Meier curve presenting time to first relapse to all illicit opioids, including heroin in XR-NTX and BP-NLX groups. The first 12 weeks represent the trial period and weeks 12 to 48 represent the follow-up period, where those continuing XR-NTX are compared with those switching from BP-NLX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

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

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

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

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

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

MATERIALS AND METHODS

Methods

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

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

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

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

Participants and Setting

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

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

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

Statistical Analysis

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

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

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

RESULTS

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

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

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

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

DISCUSSION

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

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

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

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

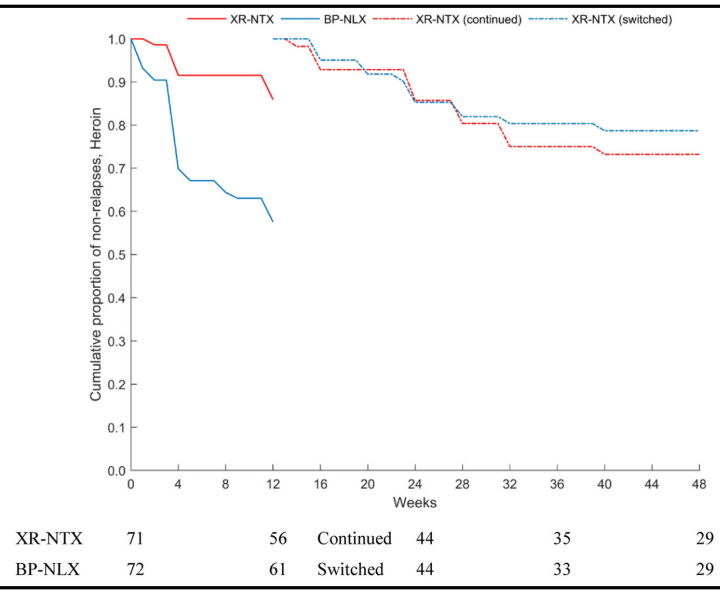

FIGURE 2. Kaplan-Meier curve presenting time to first relapse to heroin in XR-NTX and BP-NLX groups. The first 12 weeks represent the trial period and weeks 12 to 48 represent the follow-up period, where those continuing XR-NTX are compared with those switching from BP-NLX to XR-NTX. BP-NLX = buprenorphine-naloxone;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

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

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

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

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

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

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

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

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

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

Limitations

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

CONCLUSIONS

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

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Clinical Trial Registration

clinicaltrials.gov Identifier: NCT01717963.

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Paper III

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Life satisfaction among individuals with opioid use disorder receiving extended-release naltrexone: A 12-week randomized controlled trial and a 36-week follow-up

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ABSTRACT

Introduction: Life satisfaction (LS) in opioid-dependent individuals is lower than in the general population. This study aimed to explore changes in LS during short- and long-term treatment with extended-release naltrexone (XR-NTX).

Methods: This open-label 12-week clinical trial randomized 159 participants to either monthly XR-NTX or daily buprenorphine-naloxone (BP-NLX). In a subsequent 36-week follow-up study on XR-NTX, participants either continued or switched to XR-NTX. The study collected data on the Temporary Satisfaction with Life (TSWL) and illicit opioid use every fourth week. The research team assessed changes in TSWL by a linear mixed model and growth mixture model. The study assessed relationship between opioid use and TSWL by a linear mixed model.

Results: Change in LS differed significantly between the groups in both study periods. TSWL scores were significantly higher in the XR-NTX group at week 4 ($p = 0.013$) and week 8 ($p = 0.002$). In the follow-up period, the groups were significantly different only at week 16 ($p = 0.031$) and week 48 ($p = 0.025$), with the higher TSWL scores in the XR-NTX continued group. Increase in opioid use by one day was associated with a 0.12 point lower mean TSWL score. Both study periods identified groups with low and high LS levels. In the trial period, the TSWL scores exhibited a significant increase from baseline to week 12 in both groups, $p < 0.001$ and $p = 0.011$ in the low and high LS group, respectively. In the follow-up period, the TSWL scores exhibited a significant increase from week 16 to week 48 ($p = 0.003$) in the high LS group, while the low LS group showed persistently lower values throughout that period.

Conclusions: XR-NTX treatment given once monthly is associated with higher LS, as measured by TSWL, compared to daily use of BP-NLX. The majority of the participants had relatively low TSWL scores and did not report any change in TSWL during longer-term treatment. The study found a significant association between more frequent illicit opioid use and a low or decreased LS during follow-up.

1. Introduction

The American Society of Addiction Medicine recognizes opioid dependence as a chronic, recurrent disease (American Society of Addiction Medicine, 2011). Research has shown that opioid maintenance treatment (OMT) is the most effective intervention (Volkow & Blanco, 2020; WHO, 2009), because it reduces overdose mortality rates, illicit opioid use, and the risk of relapse (Andersson et al., 2019; Sordo

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et al., 2017; Zhang et al., 2003). Unlike OMT treatment, the opioid antagonist extended-release naltrexone (XR-NTX) blocks opioid receptors without the potential for abuse and diversion. Several studies have shown that XR-NTX is a promising treatment for opioid dependence, when compared to OMT (Alderks, 2017; Jarvis et al., 2018; Lee et al., 2018; Solli et al., 2018; Tanum et al., 2017).

OMT patients seek to abstain from illicit opioids, promote recovery, and improve quality of life (QoL). The field has increasingly used patient-reported outcome research to evaluate the QoL of OMT patients (Carlsen et al., 2019). While research has had an interest in how specific areas of life are important for enhancing well-being, research has also had an interest in how these specific elements may lead to a general sense of well-being. For well-being in general, research has used the term life satisfaction (LS). The most commonly used definition of LS is the degree to which people evaluate the overall quality of life based on the factors that matter most to them, that is, by comparing their life circumstances with the standard that is set by each person (Diener et al., 1985).

LS does not focus on any particular moment in time or specific areas of life, such as employment or health. Yet LS strongly influences health and well-being and a higher LS is associated with longer life expectancy, better disease tolerance, and fewer mental disorders (Diener & Chan, 2011; Koivumaa-Honkanen et al., 2001). Self-reported low LS is associated not only with poor health, but also with a higher risk of suicide, including drug-related deaths (Koivumaa-Honkanen et al., 2001; Oquendo & Volkow, 2018). Opioid-dependent individuals seeking treatment have a rather low LS compared to the general population (Luty & Arokiadass, 2008; Pavot & Diener, 2008, 2009).

Limited research exists on how OMT programs influence global LS (Krook et al., 2002; Laudet, 2011). For example, Laudet et al. (2009) found that higher overall LS was associated with an increased likelihood of prolonged abstinence among individuals with substance dependence. Another study by Krook et al. (2002) showed an increase in LS among participants inducted to buprenorphine compared to a control group during a three-month trial. However, participants emphasized that their lives were still not good, only somewhat better than before (Krook et al., 2002). While these studies often show similar results, we know less about the LS trajectories among individuals with OUD during treatment (Laudet et al., 2009). Therefore, we aimed to identify potential homogeneous groups of participants following distinct LS trajectories.

Earlier assessments of the main outcomes of our trial have shown that XT-NTX was non-inferior to buprenorphine-naloxone (BP-NLX) in terms of retention and abstinence from illicit opioids, and in secondary analyses it performed better than BP-NLX (Tanum et al., 2017). To our knowledge, no previous study has explored how treatment with XR-NTX influences LS compared to BP-NLX. Hence, this is the first study to assess LS among opioid-dependent individuals receiving XR-NTX treatment in a randomized open-label trial phase.

The main objective of this study was to assess changes in LS in the course of treatment. We hypothesized that treatment with short-term XR-NTX would be associated with increased LS among opioid-dependent individuals compared to treatment with BP-NLX, and with further increased LS during longer-term treatment with XR-NTX. In addition, we aimed to assess the association between LS and illicit opioid use; years of opioid use; and subjective measures of social relationships such as satisfaction with civil status, with living arrangements, and with leisure time.

2. Methods

2.1. Design

An open-label controlled 12-week clinical trial, with either monthly intramuscular injection of XR-NTX or daily sublingual BP-NLX, performed randomization using a permuted block algorithm. A subsequent 36-week open-label follow-up study included participants who continued on XR-NTX and participants who switched from BP-NLX to XR-NTX (Fig. 1). A more detailed description of the study design is available in Kunoe et al. (2016) and Tanum et al. (2017). The study took place at 5 research hospitals in south east and western Norway between November 2012 and July 2016.

Study staff obtained informed consent from eligible participants. The Regional Committee for Medical and Health Research Ethics, South-Eastern Norway, the Norwegian Medicines Agency, and the boards of research ethics at the participating hospitals in 2011 approved the study (#2011/1320).

2.2. Measures

2.2.1. Life satisfaction "present" item

At baseline and every 4 weeks during randomization and follow-up, the study assessed participants for global LS using the Temporal Satisfaction with Life Scale (TSWLS) "present" items (Pavot et al., 1998), based on the Satisfaction with Life Scale (SWLS) (Diener et al., 1985). Research has demonstrated the original SWLS to have a strong internal consistency and a moderate temporal stability with Cronbach's alpha of 0.87, a 2-month test-retest reliability of 0.82 (Diener et al., 1985), and an acceptable convergent validity (Pavot & Diener, 2008). The short 5-item instrument has a 7-point Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree).

2.2.2. Covariates

The study used the European version of the Addiction Severity Index (EuropASI) every 4 weeks to register the number of days of heroin and other illicit opioid use (Kokkevi & Hargers, 1995), using the time-line follow-back method. In addition, study staff performed weekly urine drug tests in the randomized controlled trial. The study collected the number of years of opioid use at inclusion.

The study measured social relationships with three questions from the EuropASI. The questions were: "Are you satisfied with your civil status?"; "Are you satisfied with your living arrangements?"; and "Are you satisfied with spending your leisure time like this?" The questions had three possible responses: no (0), indifferent (1), and yes (2).

2.3. Procedures

Men or women aged 18 to 60 years with physical dependence on opioids according to the DSM-IV criteria were eligible to participate in the study. Alcohol dependence, pregnancy or breastfeeding, and serious mental (based on MINI 6.0) or somatic illness that could interfere with study participation were exclusion criteria. Women of childbearing potential had to use contraceptive methods.

After screening for psychiatric disorders and serious somatic diseases, eligible participants were referred to the in-patient detoxification before they were randomly allocated to either 380 mg XR-NTX every 4th week (Vivitrol®) or daily sublingual BP-NLX, 4:1–24:6 mg/day, with a target dose of 16 mg/day (Suboxone®). BP-NLX was administered during daily or near daily visits at the local OMT clinic, resulting in often more than 20 visits every month. XR-NTX was administered every 28 days at the study sites. Both groups had scheduled follow-up visits with data collection every 4 weeks. The study requested that all participants attend regular OMT program counseling.

After the completion of the 12-week trial, all participants, including those who had dropped out, could choose one of the two study medications. Only five participants chose BP-NLX, and no participant switched from XR-NTX to BP-NLX. Due to this distribution of participants in the follow-up period, the research team changed the original trial design to a cohort design, splitting the participants into one group that continued on XR-NTX from the randomized phase and another group that switched from BP-NLX to XR-NTX on entering follow-up. Participants on BP-NLX underwent detoxification and were in a controlled environment for a minimum of 72 h before entering the

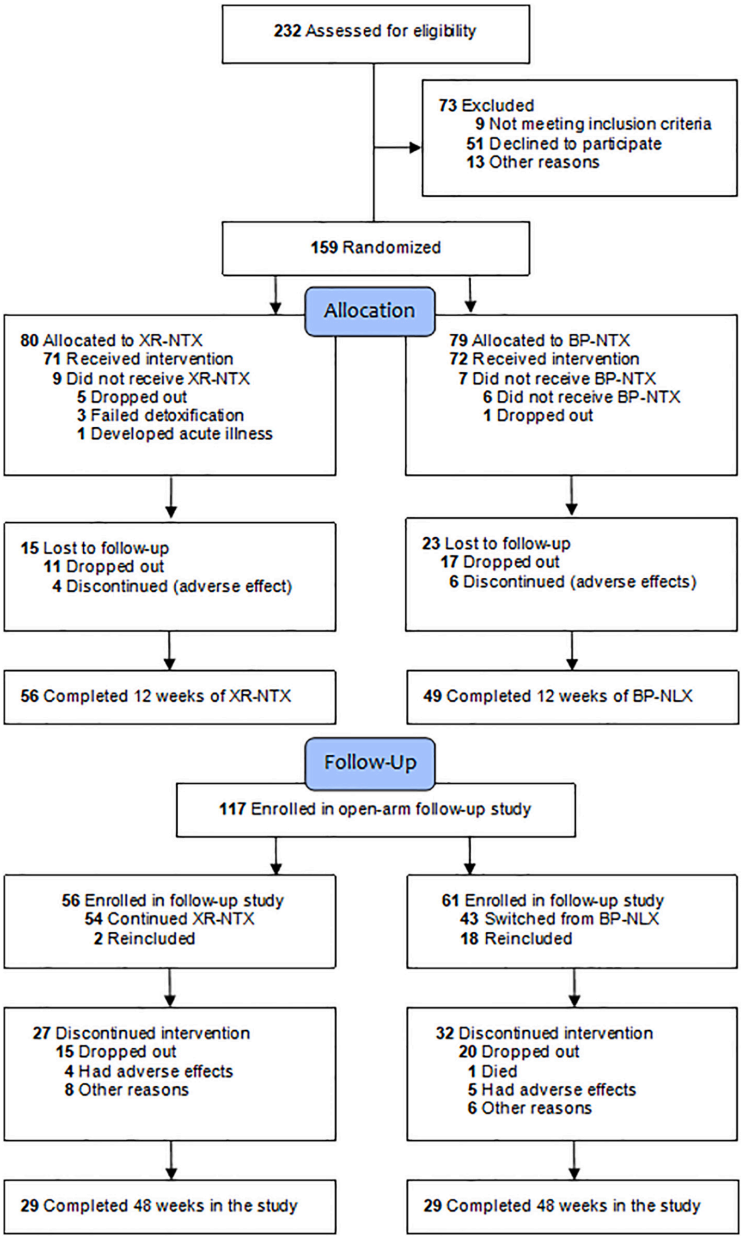

Fig. 1. CONSORT flowchart.

follow-up study. Participants did not receive any monetary payments for taking part in the study.

2.4. Statistical analyses

The study team estimated a mixed model with random effects for participants and fixed effects for non-linear time (in weeks), group, and the interaction between time and group to assess the differences between the groups in the TSWL trend. The study performed the analyses separately for the randomized period between the XR-NTX and BP-NLX groups and the follow-up period between continuers and switchers. Research staff performed post hoc analyses to assess the between-group differences at different time points.

The study team estimated three linear mixed models with random effects for participants to assess the association between simultaneously measured TSWL and the use of opioids, adjusted for age and gender;

between simultaneously measured TSWL and satisfaction with civil status, satisfaction with living arrangements, and satisfaction with leisure time; and between TSWL and years of opioid use measured at baseline. The models included fixed effects for non-linear time (in weeks) and covariates, but the study did not include stratification by treatment group. We included interactions between time and the covariates. The study used Bayes Information Criterion (BIC), where the smaller value means a better model, to reduce the models for excessive interactions.

As an exploratory approach, the research team estimated a growth mixture model (Nagin & Nagin, 2005) with the attempt to identify potential homogeneous groups of participants following distinct LS trajectories separately in the randomization and follow-up phases of the study. In this analysis, the study assessed all participants simultaneously, i.e. not stratified by treatment group. The approach is designed to identify groups of participants based on individual profiles by using a combination of several statistical criteria. The study used the following criteria: BIC, which assesses model fit by balancing between model complexity and goodness of fit; average within-group probabilities representing classification accuracy of at least 0.80; reasonable group sizes; and non-overlapping 95% confidence intervals (CIs) for trajectories in identified groups. The logistic regression model assessed the associations between group belonging and several covariates assessed at baseline (treatment group; sex; age; use of opioids; years of opioid use; and satisfaction with civil status, living arrangements, and leisure time).

The study presents results as regression coefficients, standard errors (SE), p-values, and illustrated graphically. We considered results with p-values below 0.05 statistically significant. The research team performed analyses using STATA SE16, SPSS v25, and SAS v9.4.

3. Results

3.1. Participants characteristics

The study randomized a total of 159 participants to either XR-NTX (n = 80) or BP-NLX (n = 79). In the follow-up study, 56 participants continued with XR-NTX and 61 switched to XR-NTX (shown in Fig. 1). Detailed demographic and clinical characteristics for each group are previously published in Tanum et al. (2017) and Latif et al. (2019). Men accounted for 73% of all participants. The average age of individuals was 36.1 years [SD = 8.5]. Prior to the study, 79% were never married; 40% lived alone, 20% had no stable living accommodation, lived with friends, in institutions or in prisons; 40% spent their leisure time with friends and family without drug problems (i.e., stable in OMT), and 36% spent their leisure time alone (see Table 1). At baseline, the XR-NTX and BP-NLX groups displayed similar TSWL distributions (mean [SD], 11.0 [6.9] and 11.3 [7.5], respectively).

3.2. Life satisfaction in study groups

In the trial period, the interactions between time and study group in the mixed model were significant, implying that the groups differed concerning trends in TSWL, presented in Table 2A. The trend in the BP-NLX group was flatter than in the XR-NTX group (see Fig. 2A). According to post hoc analyses, the groups were significantly different at week 4 ($p = 0.013$) and week 8 ($p = 0.002$), but not at week 0 or week 12.

At the beginning of the follow-up period, the group continuing on XR-NTX showed a higher TSWL score than the group switching from BP-NLX to XR-NTX (15.4 [7.7] and 13.1 [6.7], respectively). The interactions in the mixed model were significant, implying that the groups differed with respect to the trend in TSWL (see Table 2A). The trend in the group continuing on XR-NTX was flatter than in the group that switched (Fig. 2B). Even though the tendencies in both groups were statistically different, according to post hoc analyses, the groups were significantly different only at week 16 ($p = 0.031$) and week 48 ($p = 0.025$), with the higher TSWL scores in the continuing group.

Table 1
Baseline demographic and clinical characteristics of participants (n = 159).

Characteristics	Frequencies or mean (SD)
Sex, n (%)[a]	
Men	115 (73)
Women	44 (27)
Age, mean (SD), years[a]	36.1 (8.5)
Civil status, n (%)	
Never married	123 (79)
Married	8 (5)
Other (divorced, separated, widowed)	25 (16)
Satisfaction with civil status, n (%)	
No	42 (27)
Indifferent	100 (65)
Yes	11 (7)
Common living situation past 3 years, n (%)	
Alone	61 (40)
With partner only	27 (18)
With family	33 (22)
No stable living situation	31 (20)
Satisfaction with living arrangements, n (%)	
No	58 (40)
Indifferent	73 (51)
Yes	13 (9)
Leisure time mostly spent, n (%)	
Alone	42 (36)
With family/friends *without* drugs problem	47 (40)
With family/friends *with* drugs problem	28 (24)
Satisfaction with leisure time, n (%)	
No	60 (51)
Indifferent	47 (40)
Yes	10 (9)
Years of illicit opioid use, mean (SD)[a]	7.6 (6.4)
Years of injecting substance use, mean (SD)[a]	10.1 (9.0)
Life satisfaction 'present' item, mean (SD)	11.1 (7.2)

[a] Demographic and clinical characteristics for each group are published in Tanum et al., 2017 and Latif et al., 2019.

3.3. Life satisfaction and covariates

In the trial period, a significant trend occurred in TSWL when assessed for all participants, but this trend differed with varying levels of reported *use of opioids* (see Table 2B and Fig. 3). For those not using opioids at all or using only a few days a month, the TSWL scores were stable through the RCT, with a small increase from baseline to week 12. For those using opioids frequently (20 or more days a month), more use of opioids was associated with lower TSWL scores, particularly at weeks 4 and 8. The differences in TSWL scores were significant for varying use of opioids at week 0 ($p = 0.019$), week 4 ($p = 0.001$), and week 8 ($p = 0.026$). However, at week 12 the LS level was more or less the same independently of the use of opioids ($p = 0.562$). In the follow-up period, no significant trend occurred in TSWL when including all participants. More use of opioids was associated with, on average, lower TSWL both before ($p = 0.027$) and after adjustment ($p = 0.028$) for age and sex. An increase in the use of opioids by one day was associated with a TSWL reduction of, on average, 0.12 points.

Associations between LS and satisfaction with civil status, satisfaction with leisure time, satisfaction with living arrangements, and years of opioid use are presented in Table 2C. In the RCT period, those rating their satisfaction with leisure time as "indifferent" had significantly higher LS than those who were not satisfied ($p < 0.001$). Satisfaction with civil status, satisfaction with living arrangements, and years of opioid use were not associated with TSWL. In the follow-up period, those rating their satisfaction with living arrangements and with leisure time as "indifferent" had significantly higher TSWL than those who were not satisfied ($p = 0.003$ and $p < 0.001$, respectively). The study found no association between TSWL and satisfaction with civil status and years of opioid use in the follow-up period.

Table 2
Linear mixed model assessing the differences between (A) the extended-release naltrexone (XR-NTX) and buprenorphine-naloxone (BP-NLX) groups in Temporary Satisfaction with Life (TSWL) trend during the randomized trial and between continuers and switchers in the follow-up period (BP-NLX group was a reference in the trial. Switch group was a reference in the follow-up); (B) TSWL and the use of opioids, adjusted for age and gender; (C) TSWL and satisfaction with civil status, satisfaction with living arrangements, and satisfaction with leisure time; and between TSWL and years of opioid. Growth mixture model assessing groups among study participants in TSWL in (D) the trial and (E) the follow-up period. Two groups of participants were identified in each study period, the low LS and high LS.

Parameter	Trial period		Follow-up	
	Regression coefficient (SE)	p-Value	Regression coefficient (SE)	p-Value
(A) Study groups				
Intercept	11.26 (0.84)	**<0.001**	6.76 (2.47)	**0.006**
Week	0.38 (0.25)	0.125	0.55 (0.16)	**0.001**
Week × Week	−0.02 (0.02)	0.373	−0.008 (0.003)	**0.001**
Group (BP-NLX – ref.)*	0.07 (1.19)	0.951	10.75 (3.58)	**0.003**
Week × Group	0.93 (0.35)	**0.008**	−0.74 (0.23)	**0.002**
Week × Week × Group	−0.06 (0.03)	**0.028**	0.01 (0.004)	**0.001**
(B) Use of illicit opioids				
Intercept	11.96 (2.63)	**<0.001**	12.01 (3.60)	**0.001**
Week	0.79 (0.22)	**<0.001**	0.18 (0.12)	0.122
Week × Week	−0.05 (0.02)	**0.004**	−0.002 (0.002)	0.181
Use of opioids	−0.09 (0.04)	**0.020**	−0.12 (0.06)	0.028
Week × Use of opioids	−0.07 (0.03)	**0.009**		
Week × Week × Use of opioids	0.006 (0.002)	**0.011**		
Age	−0.003 (0.06)	0.961	−0.002 (0.07)	0.981
Sex	0.35 (1.09)	0.749	0.20 (1.45)	0.889
(C) Covariates				
Satisfaction with civil status			0	
No – ref.	0		0.90 (0.71)	
Indifferent	0.23 (0.90)	0.795	0.12 (0.99)	0.207
Yes	−0.82 (1.36)	0.543		0.902
Satisfaction with living arrangements			0	
No – ref.	0		1.75 (0.60)	
Indifferent	1.40 (0.80)	0.083	1.09 (0.98)	**0.003**
Yes	0.65 (1.22)	0.596		0.268
Satisfaction with leisure time			0	
No – ref.	0		2.47 (0.60)	
Indifferent	4.11 (0.79)	**<0.001**	1.20 (0.91)	**<0.001**
Yes	1.88 (1.25)	0.132	−0.17 (0.11)	0.189
Years of opioid use	−0.08 (0.08)	0.318		0.125

(D) Trajectories, trial period	Low LS (N = 116, 76.8%)		High LS (N = 35, 23.2%)	
Intercept	7.16 (0.76)	**<0.001**	19.53 (1.62)	**<0.001**
Linear	1.19 (0.28)	**<0.001**	0.86 (0.53)	**0.104**
Quadratic	−0.07 (0.02)	**0.002**	−0.04 (0.04)	0.345
Average group probability		0.96		0.86

(E) Trajectories, follow-up	Low LS (N = 77, 65.3%)		High LS (N = 41, 34.7%)	
Intercept	10.53 (0.94)	**<0.001**	9.14 (4.32)	**0.035**
Linear	0.02 (0.03)	0.571	0.89 (0.30)	**0.003**
Quadratic			−0.01 (0.005)	**0.009**
Average group probability		0.97		0.92

Bold type helps highlight important results in a large table, making it more readable.

3.4. Life satisfaction trajectories

A growth mixture model identified two distinct groups of participants with similar TSWL profiles in the randomization phase of the study and two groups in the follow-up phase, called the low LS and high LS groups (see Table 2D and E). In both cases, the average group probabilities were high and well above the pre-specified level, and 95% CIs were not overlapping.

In the randomized phase of the study, the low LS group, constituting the majority of participants (n = 116), had a significantly lower TSWL score at baseline than the high LS group (n = 35) (non-overlapping 95% CIs), as Table 2D shows. The low LS group showed a significant non-linear development with a slight increase toward week 8, which flattened out toward week 12 (see Fig. 2C). In the low LS group, a significant increase occurred in TSWL scores from week 0 to 12 ($p < 0.001$). In the high LS group, the increase in scores was nearly linear and weaker but still significant from week 0 to 12 ($p = 0.011$).

According to the multiple logistic regression model, odds for belonging to the high LS group were significantly lower among those using more opioids at baseline (OR 0.95 (0.90; 1.00), $p = 0.047$). Moreover, the odds of belonging to the high LS group were significantly higher among those who rated their satisfaction with leisure time as "indifferent" compared to those who answered "not satisfied" (OR 12.88 (3.18; 52.23), $p < 0.001$). The study identified no other significant associations (numbers not shown).

In the follow-up period, the low LS group also constituted the majority of the participants (n = 77); see Table 2E. The low LS group showed stable and significantly lower TSWL scores at week 16 and throughout the follow-up compared to the high LS group (n = 41). The high LS group showed a non-linear increase in scores toward week 28 but flattened out toward week 48, as Fig. 2D shows. An increase in TSWL scores was significant from week 16 to week 48 ($p = 0.003$). In the multiple logistic regression model, the only covariate associated with the group belonging in the follow-up period was satisfaction with leisure time. Odds of belonging to the high LS group were significantly higher among those who answered "indifferent" compared to those who answered "not satisfied" (OR 3.47 (1.18; 10.18), $p = 0.023$).

4. Discussion

To our knowledge, this is the first study assessing changes in LS in the course of short-term XR-NTX treatment compared to BP-NLX among opioid-dependent individuals, and further LS changes during longer-term treatment with XR-NTX using the TSWL scale.

We found a moderate increase in TSWL scores in both randomized treatment groups, with a significant difference between the groups at weeks 4 and 8 in favor of the XR-NTX group. As shown for the main outcomes of our trial, XR-NTX was non-inferior and actually performed better than BP-NLX (Tanum et al., 2017), thus the difference in LS trends favoring XR-NTX may not be surprising.

Possible explanations for the difference in LS between the treatment groups may be the treatment structure and motivation for treatment with XR-NTX. The observed daily or near daily dosing of BP-NLX may have had a negative impact on participants' LS, especially among participants who joined the study to obtain XR-NTX treatment but were randomized to BP-NLX. Patients may perceive the daily supervised dosing at OMT outpatient clinics or pharmacies as an act of mistrust and suspicion. In a previous qualitative study of OMT, patients reported a better life with OMT despite having to comply with rules and regulations such as observing dose intake (Granerud & Toft, 2015).

Although OMT is widely available and fully funded by the government in Norway (Riksheim et al., 2014), most participants were highly interested in receiving the prolonged-release opioid antagonist naltrexone. In fact, the study attracted more than 40% of participants who were not in the OMT program (Solli et al., 2019). Our previous study found that participants who received XR-NTX were satisfied with

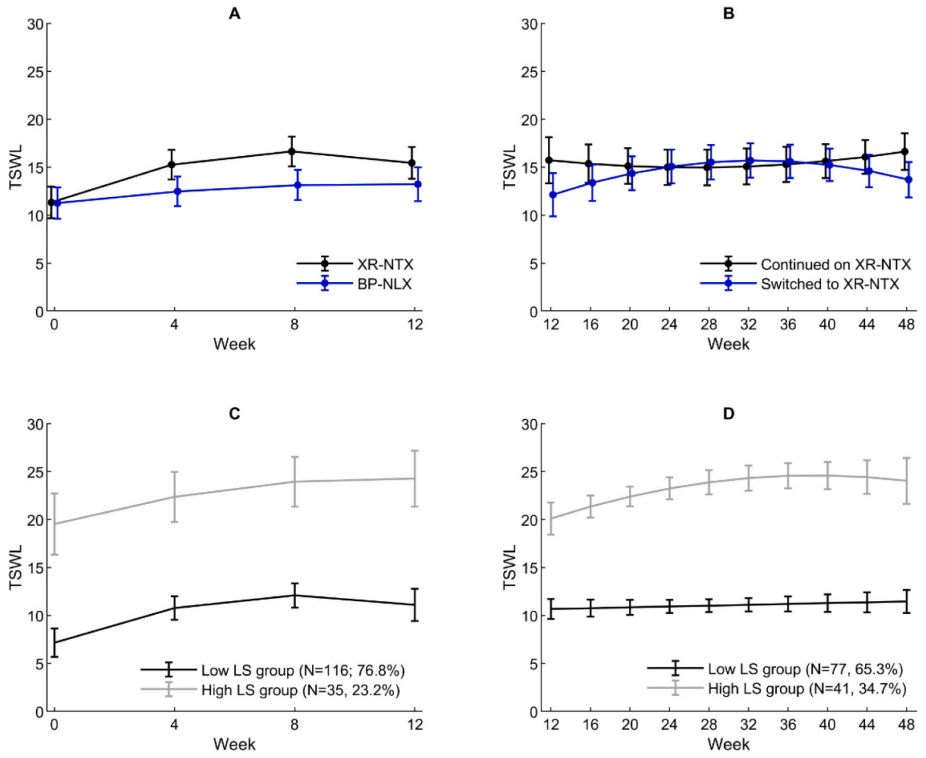

Fig. 2. Changes in life satisfaction among study participants in the randomized trial (from weeks 0 to 12) and follow-up period (from weeks 16 to 48) measured by the TSWL, 'present' item questionnaire. (A) TSWL scores among participants randomized to XR-NTX and BP-NLX treatment and (B) In the follow-up period, the TSWL scores among the group continuing with XR-NTX and the group switched from BP-NLX to XR-NTX treatment; results of mixed model. Trajectories of life satisfaction in two groups of participants identified by growth mixture model not stratified by treatment group (C) in the trial and (D) in the follow-up period.

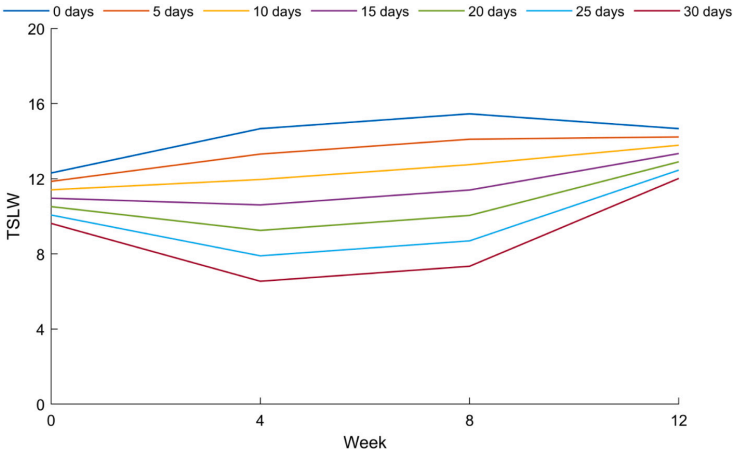

Fig. 3. A trend in Temporary Satisfaction with Life (TSWL) by use of illicit opioids when assessing for all participants together every four weeks using EropASI questionnaire in the randomized study. The different colors indicate the number of days of opioid use.

it and were willing to recommend XR-NTX to others (Tanum et al., 2017). This finding may indicate that not all opioid dependent people are satisfied with the present structure of OMT, probably because it can be time-consuming, stigmatizing, and tempting to use illicit drugs (Steiro et al., 2020; Velasquez et al., 2019; Yarborough et al., 2016).

In the follow-up period, no significant trend occurred in LS scores when the study assessed all participants together, but in a stratified analysis, we found a significant difference between the groups. The group that continued XR-NTX treatment showed higher LS at the beginning and the end of the follow-up period and had a flatter trend throughout the entire follow-up compared to the group that switched to XR-NTX. The changes in LS among our study participants appeared to be closely associated with a high use of illicit opioids, and continued abstinence from opioids seemed important to maintain higher LS. A recent study of first-time OMT patients reported the same trend, where higher LS was related to lower opioid use over the course of one year of treatment (Carlsen et al., 2020). Likewise, the study by Hagen et al. (2017) found a link between LS and opioid use, with absentees reporting higher LS compared to the relapse group. The relationship between LS and opioid use may be explained, in part, by the motivation to focus on the recovery process and thereby abstain from substance use (Laudet et al., 2009). Previous XR-NTX studies have suggested that participants' higher motivation for abstinence might be related to reduction in opioid use (Kunoe et al., 2009; Lee et al., 2018; Tanum et al., 2017).

LS among adults with opioid dependence is heterogeneous. In this study, LS followed two different trajectories identified by the growth mixture model: a high and a low level. Most of the participants belonged to the group with the low LS level. The low LS group showed a slight improvement in the randomized part of the study and, surprisingly, remained relatively stable and low during the follow-up part of the study. That those participants did not show any change in LS during long-term treatment is worrisome. Even though the majority were initially highly interested in XR-NTX treatment, for a number of reasons they seemed to be disappointed with their life situation, expressing it in unchanged LS. These participants may have had higher expectations for the treatment than were met during the study (Muthulingam et al., 2019).

For some individuals, long-acting naltrexone treatment may have acted as a physiological and social stressor due to forced abstinence from opioids and, thus, eliminating the option to address stress by using opioids (Inagaki et al., 2019). Therefore, the LS changes may be further explained by individual differences in coping strategies (Hyman et al., 2007; Kornør & Nordvik, 2007) or even having a low desire to cope with increased stress at all (Hyman et al., 2009), depending on the personality traits. Variation in personality traits and individual genetics may be related to how participants expressed their well-being and LS (Røysamb et al., 2018).

4.1. Limitations

Our findings should be interpreted with caution. The study findings can only be generalized to opioid-dependent individuals with high motivation for opioid abstinence. Our participants were probably more motivated for treatment with XR-NTX compared to most individuals being offered such treatment in a clinical setting. Further, they did not suffer from any serious mental or physical illness or alcoholism. The number of participants was also too limited to provide any therapeutic conclusions. In our study, participants reported indifference toward satisfaction with living arrangements and leisure time, which was associated with their LS. This finding should be interpreted with caution, since participants did not elaborate on their answers but only indicated being indifferent toward their social circumstances.

5. Conclusions

XR-NTX treatment given once a month is associated with higher LS, as measured by TSWL, compared to daily use of BP-NLX. The majority of participants had relatively low TSWL scores throughout the study and did not report any change in TSWL during longer-term treatment. The study found a significant relationship between more frequent use of illicit opioids and a low or decreased LS during the follow-up phase of the study.

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CRediT authorship contribution statement

Zhanna Gaulen: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft; Writing - review & editing
Jūratė Šaltytė Benth: Formal analysis, Methodology, Visualization, Writing - review & editing
Lars Thore Fadnes: Conceptualization, Formal analysis, Methodology, Supervision, Writing - review & editing
Ida Halvorsen Brenna: Writing - review & editing
Lars Tanum: Conceptualization, Data curation, Investigation, Methodology, Project administration, Funding acquisition and resources, Supervision, Writing - original draft; Writing - review & editing.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

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