Long-Term Effectiveness, Psychiatric Distress, and Chronic Pain in Opioid-Dependent Individuals Receiving Treatment with Extended-Release Naltrexone

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ABSTRACT

Background:

Opioid dependence is a chronic disease and leads to high costs for the individual user, their families, and society as a whole. Opioid-dependent individuals fulfilling the criteria for substance use disorder (SUD) have an increased prevalence of lifetime psychiatric disorders compared with the general population, often in combination with insomnia. Both anxiety and depression have a negative impact on the course and treatment outcomes in opioid use disorder. Agonist treatment with methadone or buprenorphine has been linked to positive effects on co-existing anxiety and depressive symptoms, but the data have not been consistent with regards to the type of substance used, frequency of intake, or poly drug-use. Insomnia is often unrecognized and untreated in opioid-dependent individuals, and is frequently related to increased risk of psychiatric morbidity. It has been estimated that between 10% and 15% of individuals with chronic sleep disturbances have underlying substance use problems, most frequently opioid abuse. In addition to illicit substances, opioids are frequently prescribed in medical practice in most western societies. Opioid prescriptions for chronic pain have increased in recent years due to increased awareness of chronic pain as a potentially disabling condition. Treatment is the most important factor in preventing harmful effects of opioid use. Opioid maintenance treatment (OMT) with opioid agonists such as methadone, buprenorphine, or buprenorphine-naloxone (BP-NLX), may contribute to a reduction in the use of illegal substances and to improvements in the health and social conditions of opioid users. However, opioid maintenance treatment is not a feasible treatment for those who want to achieve abstinence, or for other reasons prefer substitution-free treatment. Long-acting naltrexone has been proposed as an alternative to opioid maintenance treatment. Naltrexone inhibits the action of heroin and other opioid agonists through a competitive blocking of the opioid mu and kappa receptors. As opposed to opioid agonists, naltrexone lacks any abuse potential or risk of diversion and gives opioid users a prolonged period of abstinence from opioids with a high level of protection from relapse. No previous study has compared the effectiveness of extended-release naltrexone (XR-NTX) with buprenorphine-naloxone (BP-NLX) on the maintenance of opioid abstinence, or investigated how XR-NTX treatment influences comorbid symptoms of anxiety, depression, insomnia, and chronic pain among opioid-dependent individuals. Further, there is a lack of studies of longer-term treatment outcomes with XR-NTX in clinical settings where OMT is available at no cost.

Study aims:

- 1- To assess the effectiveness, safety and feasibility of longer term treatment with XR-NTX in 117 opioid dependent individuals continuing on XR-NTX or inducted on XR-NTX in a nine month follow-up study after a 12-week RCT.
- 2- To assess the change in psychiatric distress reported as symptoms of anxiety, depression, and insomnia in 159 opioid-dependent individuals who were randomized to short-term treatment with either XR-NTX or BP-NLX in a 12-week RCT, and in 117 participants continuing on XR-NTX or inducted on XR-NTX in a nine month follow-up study.
- 3- To assess any change in mild to moderate chronic pain in 143 opioid dependent individuals who received short-term treatment with either XR-NTX or BP-NLX in a 12-week RCT, and in 117 participants continuing on XR-NTX or inducted on XR-NTX in a nine month follow-up study.

Materials and methods:

In this multi-site clinical trial, n= 232 participants were assessed for eligibility and n=165 were included in the study. A total of n=159 were randomized (1:1) to 12 weeks of treatment (ITT study sample) with either XR-NTX (n=80) or BP-NLX (n=79).

The reasons for exclusion included refusal to participate (n=51), not meeting inclusion criteria (n=9), failed detoxification (n=6), and other reasons (n=7). Following the randomized part of the study, participants were given the opportunity to receive XR-NTX or BP-NLX based on their personal preference in a prospective 36-week follow-up study. Of the n=159 participants randomized to treatment, n=143 took at least one dose of study medication and met for at least one assessment (MITT study sample), and n=105 completed the 12-week study.

Most participants in the follow-up study (n=117 of 122) preferred XR-NTX. Among the XR-NTX participants in the randomized part of the study, n=54, continued on XR-NTX in the follow-up study. Some, n= 43, switched to XR-NTX from BP-NLX, and n=20 were re-included after having dropped out from the randomized part of the study. A total of 58 participants completed the follow-up study.

The five participants continuing on BP-NLX in the follow-up study were excluded from further analyses.

All XR-NTX participants in the follow-up study received their medication as an intramuscular injection every fourth week. Assessments of the use of opioids and other substances, cravings for heroin, use of other substances, addiction-related problems, treatment satisfaction and

recommendation, adverse events, and comorbid symptoms like psychiatric distress, sleep problems, and chronic pain were performed at every visit.

Results:

The ITT study sample consisted of n=159 participants while the MITT study sample included n=143 participants; n=117 study participants continued in the follow-up part of the study. In the follow-up part of the study, there was no significant difference in treatment retention or use of heroin and other illicit opioids between participants continuing on XR-NTX and participants inducted on XR-NTX. Participants that switched to XR-NTX reported significantly more heavy alcohol use and more days at work at the end of the study period than those continuing with XR-NTX. Significantly more heroin cravings were reported among participants switching to XR-NTX than participants continuing on XR-NTX treatment, but reduction in heroin craving was only significant to week 16 among switchers. A higher treatment satisfaction was reported among those who continued with XR-NTX. No differences in heroin cravings and treatment satisfaction were found between completers and non-completers. Adverse effects were most frequently reported during the induction phase of the XR-NTX treatment. No opioid overdoses were reported. No serious adverse events, including no overdose fatalities, were reported among the participants during the first three months following their completion of the study.

In the randomized part of the study, both treatment groups reported a significant improvement in anxiety and depression scores as measured by Hopkin Symptoms Checklist (HSCL-25). The insomnia severity index (ISI) showed similar improvement in both treatment groups from baseline to Week 4 and Week 8, but not to Week 12. Insomnia scores were positively associated with anxiety and depression scores in both treatment groups. Anxiety and depression scores were positively associated with the use of illicit substances, such as benzodiazepines, amphetamine, other opiates, and cannabis in both treatment groups. In contrast, heroin use was positively associated with depression scores only. There were no significant gender differences between the randomized treatment groups.

In the follow-up treatment period, there was a further significant improvement in anxiety, depression, and insomnia scores throughout the study period. There were no significant differences in anxiety, depression, or insomnia scores between participants continuing with XR-NTX and participants switching to XR-NTX in the follow-up part of the study.

In the randomized part of the study based on the MITT study sample, we found that individuals with opioid dependencies reported no significant differences in pain measured by Norwegian Short-Form McGill Pain Questionnaire (MSF-MPQ) after terminating their use of illicit or

prescribed opioids and starting treatment with either XR-NTX or BP-LNX. Moreover, in the follow-up part of the study, no increases in pain were reported among participants who switched from daily BP-NLX to XR-NTX treatment. We also found that women experienced more affective pain symptoms than men.

Discussion and conclusions:

In the follow-up part of the study, there were no differences in treatment retention or in the use of opioids and other illicit substances between participants continuing with XR-NTX and participants switching to XR-NTX. Though BP-NLX is available in Norway at no cost in the national OMT program, XR-NTX was only available for study participants. It is likely that study participation was motivated to a great extent by the possibility of obtaining XR-NTX. Due to the effectiveness and safety shown in this longer-term clinical treatment trial, XR-NTX should be made available as a treatment option for opioid-dependent individuals in Norway. Opioid-dependent individuals with comorbid symptoms of anxiety, depression, or insomnia showed a similar improvement on XR-NTX and BP-NLX in the randomized part of the study. Since treatment with XR-NTX and BP-NLX showed equal improvements in anxiety, depression, and insomnia as assessed by the HCL-25, such symptoms should not preclude the choice to leave opioid agonist treatment and be inducted to treatment with XR-NTX. Switching from opioid abuse or daily opioid agonist treatment to XR-NTX did not induce pain or aggravate mild to moderate chronic pain in the participants, either in the randomized part or the follow-up part of the study. This finding raises the question of whether individuals dependent on opioids and reporting mild to moderate chronic pain experience any analgesic effects from opioid treatments.

NORWEGIAN SUMMARY

Bakgrunn:

Opiatavhengighet er en kronisk sykdom og fører til høye kostnader for den enkelte bruker, deres familier og samfunnet. Personer med opiatavhengighet som oppfyller kriteriene for rusmiddelforstyrrelser (SUD), har en økt livtidsforekomst av psykiatriske lidelser i forhold til befolkningen generelt, og hyppig problemer med søvnløshet. Angst og depresjon har en negativ innvirkning på forløp og behandlingsresultater hos pasienter med opiat-avhengighetslidelser. Agonist behandling med metadon eller buprenorfin har vist positiv effekt på samtidig eksisterende angst og depressive symptomer. Likevel har ikke dataene vært konsistente med hensyn til hvilken type stoff som brukes, hyppighet av inntak eller hvorvidt det foreligger blandingsmisbruk. Søvnforstyrrelser er ofte ikke registrert, og ubehandlet hos opiat-avhengige personer. Risikoen for psykiatrisk morbiditet øker på grunn av søvnforstyrrelser og det er anslått at 10-15 prosent av individer med kronisk søvnforstyrrelse har et underliggende rusmisbruksproblem. I tillegg er opiater en av de mest foreskrevne medisinene for å behandle smerte. Bruk av forskrevne opiater for kroniske smerter har økt de siste årene, på grunn av økt bevissthet om kronisk smerte som en potensiell invalidiserende tilstand. Behandling er den viktigste faktoren for å hindre skadelige virkninger av opiatbruk. Legemiddelassistert rehabilitering (LAR) med opiat-agonister: metadon, buprenorfine eller buprenorfine-naloksone (BP-NLX), kan redusere bruk av illegale rusmidler og til bedre helse- og sosiale forhold hos opiat-avhengige. LAR er imidlertid ikke et aktuelt behandlingsalternativ for alle, spesielt ikke for de som foretrekker en substitusjonsfri behandling. Langtidsvirkende naltrekson gitt som intramuskulær injeksjon hver 4. uke (XR-NTX) er et lovende behandlingsalternativ for opiat-avhengighet. Naltrekson er en opiat-antagonist som beskytter mot overdose og blokkerer for ruseffekt av opiater som heroin. Naltrekson er ikke vanedannende, har få alvorlige bivirkninger og få interaksjoner med andre medikamenter. Det har ikke tidligere vært utført studier som sammenligner XR-NTX med BP-NLX, det anbefalte substitusjonsmedikament for legemiddelassistert rehabilitering i Norge. Det er også mangel på langtidsstudier hvor man sammenligner XR-NTX med BP-NLX på symptomer av angst, depresjon, søvnløshet og kroniske smerter.

Studieformål:

- 1- Å vurdere om XR-NTX kan være et effektivt og trygt behandlingsalternativ for opiatavhengige i en klinisk setting i Norge over en 36 ukers periode.
- 2- Å vurdere endringer i komorbide symptomer på angst, depresjon og søvnløshet hos opiat-avhengige som fikk behandling med enten XR-NTX eller BP-NLX i en 12 ukers

periode, og hos opiat-avhengige som valgte å fortsette med XR-NTX i ytterligere 36 uker.

- 3- Å vurdere endringer i kroniske smerter hos opiat-avhengige som fikk behandling med enten XR-NTX eller BP-NLX i en 12 ukers periode, og hos opiat-avhengige som valgte å fortsette med XR-NTX i ytterligere 36 uker.

Materialer og metoder:

I en klinisk multisenter studie ble data samlet inn for n=165 opiat-avhengige pasienter. Blant disse ble n=159 randomisert til å motta enten XR-NTX eller BP-NLX (1: 1) i en 12-ukers periode. Etter denne 12 ukers perioden, fikk alle deltakerne mulighet til å fortsette i studien i en ytterligere 36 uker periode. I denne 36 ukers perioden kunne de fritt velge mellom XR-NTX eller BP-NLX. Det var n=117 som valgte å motta XR-NTX og var gjenstand for undersøkelse i oppfølgingsstudien. Deltakerne fikk intramuskulære injeksjoner med XR-NTX hver 4. uke i studieperioden. Under studieoppfølgingene ble det innhentet data vedrørende bruk av opiater og andre illegale rusmidler, suget etter heroin, andre rusrelaterte problemer, behandlingstilfredshet, hvorvidt behandlingen vil bli anbefalt til andre, rapporterte bivirkninger, endringer i angst, depresjon, søvnproblemer og kroniske smerter.

Resultater:

Totalt var det n=159 pasienter som ble randomisert i den kliniske fasen av studien (ITT studiepopulasjon). MITT studiepopulasjonen besto av n=143 deltakere, og n=117 studiedeltakere fortsatte i oppfølgingsdelen av studien.

Det ble ikke funnet signifikante forskjeller mellom grupper som fortsatte med XR-NTX behandlingen og de som ble indusert på XR-NTX vedrørende retensjon i behandlingen, misbruk av heroin og andre illegale rusmidler i oppfølgingsdelen av studien. Signifikante forskjeller ble funnet mellom gruppene vedrørende alkoholmisbruk og totalt antall arbeidsdager, hvor de som hadde blitt indusert på XR-NTX hadde mer misbruk av alkohol og flere arbeidsdager mot slutten av studien. Høyere heroin-sug ble rapportert blant de som var blitt indusert på XR-NTX mens de som fortsatte med XR-NTX viste høyere behandlingstilfredshet. Det ble ikke funnet signifikante forskjeller vedrørende behandlingstilfredshet og heroin-sug mellom de som fullførte og de som ikke fullførte studien.

De fleste rapporterte bivirkninger var relatert til første dose med langtidsvirkende naltrexon. Ingen opiat-overdose ble rapportert. Det ble ikke rapportert om alvorlige bivirkninger eller dødsfall på grunn av overdose i løpet av de første tre månedene etter at studien var ferdig.

I den randomiserte kliniske perioden, meldte deltakere i begge gruppene signifikant forbedring i angst-, depresjon- og insomnia-skår (bortsett fra uke 12 i insomnia-skår). Insomnia-skår hadde positive assosiasjoner med angst- og depresjonsskår i begge behandlingsgruppene. Begge behandlingsgruppene viste positive assosiasjoner mellom angst og depresjonsskår og bruk av benzodiazepiner, amfetamin, andre opiater og cannabis. Depresjonsskår og heroinbruk var positivt assosiert. Det ble ikke funnet signifikante kjønnsforskjeller mellom behandlingsgruppene. I oppfølgingsperioden var det ytterligere forbedringer i angst-, depresjon- og insomnia-skår.

I den randomiserte kliniske fasen av studien, var det ingen forskjeller i rapportering av kroniske smerter blant opiatavhengige etter at de hadde sluttet med illegale eller forskrevne opiater og hadde startet behandling med enten XR-NTX eller BP-NLX. Videre i oppfølgingsfasen, ble det ikke rapportert noen økning i kroniske smerter blant de som ble indusert på XR-NTX behandling. Langtidsvirkende naltrexon behandling hadde ingen effekt på reduksjon av smerter intensitet over tid. Kvinner viste å være mer plaget av affektive smerter enn menn.

Diskusjon og konklusjoner:

Det var ingen signifikante forskjeller angående retensjon i behandling, bruk av opiater og andre illegale rusmidler mellom deltakerne som fortsatte med XR-NTX og de som ble indusert på XR-NTX i oppfølgingsperioden. Siden BP-NLX er tilgjengelig i Norge uten kostnad i et legemiddelassistert rehabiliteringsprogram (LAR), var XR-NTX bare tilgjengelig for studiedeltakere. Det er stor sannsynlighet for at deltakerne var motivert av muligheten til å skaffe seg XR-NTX. På grunn av effektiviteten og sikkerheten som er vist i denne kliniske studien i oppfølgingsperioden, bør XR-NTX betraktes som en av de behandlingsoalternativene som er tilgjengelige for opiatavhengige i Norge.

Opiat-avhengige med komorbide symptomer av angst, depresjon og insomnia viste tilsvarende forbedring på behandling med XR-NTX og BP-NLX i den randomiserte fasen av studien.

Derfor er vi av den oppfatning at komorbide symptomer av angst, depresjon eller insomnia ikke bør hindre bytte fra opioid-agonist behandling til XR-NTX blant opiatavhengige.

Ingen økning eller tilbakefall av kroniske smerter ble rapportert blant deltakerne som hadde sluttet med forskrevne eller illegale opiater og ble indusert på XR-NTX behandling, verken i randomiserte fasen eller oppfølgingsperioden. Våre resultater setter spørsmåltegn ved tidligere påstander om at opiater har smertestillende virkning på kroniske smerter hos opiatavhengige.

LIST OF PAPERS

I

Solli, K.K., Latif, Z. E., Opheim, A., Krajci, P., Sharma-Haase, K., Benth, J.S., Tanum, L., Kunøe, N. (2018). Effectiveness, safety, and feasibility of extended-release naltrexone for opioid dependence: a 9-month follow-up to a 3-month randomized trial. *Addiction*. doi:10.1111/add.14278.

II

Latif, Z. E., Benth, J.S., Solli, K.K., Opheim, A., Kunøe, N., Krajci, P., Sharma-Haase, K., Tanum, L (2018). Anxiety, Depression and Insomnia in Opioid-dependent Individuals Randomized to Treatment with Either Long-acting Naltrexone or Buprenorphine-Naloxone: A 3 Months Randomized Clinical Trial and A Subsequent 9 Months Follow-up Study. (*JAMA Psychiatry* December 2018)

III

Latif, Z. E., Solli, K.K., Opheim, A., Kunøe, N., Benth, J.S., Krajci, P., Sharma-Haase, K., Tanum, L (2018). No Increased pain among opioid-dependent individuals treated with extended-release naltrexone or buprenorphine-naloxone: A 3-month randomized study and a 9-month open treatment follow-up study. (Accepted for publication in *American Journal On Addictions*).

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

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

2. Sharma Haase K, Kunoe N, Opheim A, Gaulen Z, Nja AM, Latif ZE, Solli KK, Tanum L. (2016) *Interest in Extended Release Naltrexone among Opioid Users*. *European Addiction Research*. 2016;22(6):301-5 [3].

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

4. Arild Opheim¹, Zhanna Gaulen, Kristin Klemmetsby Solli, Zill-e-Huma Latif, Lars Thore Fadnes¹, Jurate Saltyte-Benth, Nikolaj Kunøe² and Lars Tanum. *Time to relapse to illicit opioid use among patients randomized to treatment with extended-release naltrexone or*

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ABBREVIATIONS

AE – Adverse events

AUD – Alcohol use disorders

BP-NLX – Buprenorphine-naloxone

BZD - Benzodiazepine

CI – Confidence interval

CRF – Case report form

CNCP – Chronic non-cancer pain

CSA – Central sleep apnea

CTCAE – Common Terminology Criteria for Adverse Events

Europ-ASI – The European version of the Addiction Severity Index

GCP – Good clinical practice

GP – Medical doctor, general practitioner

HSCL-25 – Hopkins Symptom Checklist-25

ISI – Insomnia Severity Index

IMF – Illicitly manufactured Fentanyl

ITT – Intention-To-Treat

LAR – Legemiddelassistert rehabilitering

LDN – Low-dose naltrexone

MAT – Medication Assisted Treatment

MITT – Modified intention-to-treat

MMT - Methadone maintenance treatment

MOS – Medical Outcome Study

NS-MPQ – Norwegian short-form of Mc-Gill Pain Questionnaire

NPS – New psychoactive substances

NTX- HCL Naltrexone hydrochloride

OMT – Opioid maintenance treatment

ODI – Opioid Dependent Individual

PN – Patient Navigation

PPI – Present pain intensity

RCT – Randomized clinical trial

REM – Rapid Eye Movement

SSS – Supplemental Sleep Scale

SAE – Serious adverse events

SD – Standard deviation

SUD – Substance-use disorder

TAU – Treatment as Usual

UDT – Urine drug test

VAS – Visual analogue scale

WHO – World health organization

XR-NTX – Extended-release naltrexone

PREFACE

Becoming a health research worker was a choice that I made wholeheartedly after my specialization in psychiatry. Working with patients suffering from severe psychiatric illnesses and with comorbid drug problems made me realize how important it was to find new ways, new treatments, and new approaches to helping them with their drug problems. With currently available treatments, patients got better, but it did not take long before they started using drugs again after discharge and had relapses of their psychiatric illnesses. This project introduced a new medicine, a new approach, and a new way of thinking to the opioid-dependent individuals who participated.

Both substance use disorders and mood and anxiety disorders are widespread in general population, and are associated with substantial societal and personal costs. Several clinical studies have reported that substance use disorders and symptoms of anxiety and depression have strong associations when considered on a lifetime basis. However, the nature of current or recent co-occurrence of substance disorders and mood or anxiety disorders remains largely unexamined and poorly understood (1, 2). Sleep disturbance is a prevalent symptom in a wide range of psychiatric disorders and almost 10%-15% of those with chronic sleep disturbances have underlying substance use problems. Opioid users commonly have comorbid conditions that are associated with sleep (3). There has been an increase in the use and misuse of prescribed opioids in the last years. Even though opioids are considered effective and are commonly prescribed for chronic non-cancer pain (CNCP), the evidence for the effectiveness of long-term opioid use in reducing pain is variable (4).

Being part of this project gave me the chance to make a contribution to this field of research. Every single smile on the faces of our study participants has been my greatest reward, and I sincerely hope that our project can help as many as possible to achieve a better life.

1. INTRODUCTION

1.1. Opioid Dependence

Opioid dependence is usually described as a group of cognitive, behavioral, and physiological features (5). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), an opioid use disorder diagnosis can be used if a problematic pattern of opioid use leads to clinically significant impairment, as manifested by at least two of the following criteria, occurring within a 12-month period: withdrawal, increased tolerance, craving, use of larger amounts/for longer periods, repeated attempts to quit or control use, amount of time spent obtaining/using/recovering, physical/ psychological problems related to use, social and interpersonal problems related to use, use in the physically unsafe situations, failure to fulfil obligations at work/school/home, and activities given up due to use (6).

Opioid dependence is a global health problem and leads to tremendous economical, personal, and public health issues (7). The economic burden on society includes the healthcare costs such as treatment, healthcare, and prevention services which are directly related to opioid use as well as impacts on the social welfare system and criminal justice services (8-10).

Unemployment, absenteeism, and premature mortality are the other issues related to opioid dependence (11).

Approximately 275 million individuals (15-64 years) worldwide used illicit drugs, at least once during 2016 (12). Of these, around 31 million people suffered from drug use disorders. Opioids were considered to be the most harmful drugs causing 76 % of deaths involving drug use disorders (12). Opioids are the most commonly used drugs of abuse in Asia, Europe, and most of Oceania, and it is estimated that global consumption of the opioid class of substances is increasing (12). A study reported that among the five most commonly used opioids, fentanyl and hydrocodone were the most used opioids in Asia, Europe, America and Oceania in 2015, while oxycodone was the second most used opioid (13).

In Norway, the estimated number of high-risk opioid users is between 6,200 and 10,300 (14). This number does not include patients that are stable in opioid maintenance treatment.

The opioid market is getting more diverse, as it includes both substances that are controlled internationally (heroin) and prescription drugs that are either produced as counterfeit medicines or redirected from legal market (15).

Due to the involvement of stimulants and synthetics, the current drug situation in Europe has become more complex (16). According to the European Monitoring Center for Drugs and Drug Addiction report published in 2015, more than 450 new psychoactive substances

(including 31 new synthetic cathinones and 30 new synthetic cannabinoid receptor agonist on the top), were being monitored in 2014 (16, 17).

Even though the understanding behind the development of opioid-dependence is still limited, there is an increasing agreement on the complex and multifactorial etiology of opioid use disorders (18). Genetic factors, environmental factors, neurobiological factors, comorbid physical and psychiatric conditions are among the contributing causes (18-20).

The most commonly used opioids (morphine, heroin, hydro-morphine, methadone, and pethidine) produce analgesia, mood changes, respiratory depression, psychomotoric retardation, slurred speech, and cause impaired concentration and memory (21, 22)

Secondary somatic consequences and complications of opioids administered intravenously include hepatitis B, hepatitis C, HIV, septicemia, endocarditis, pneumonia, lung abscesses, thrombophlebitis, and rhabdomyolysis (23). Non-medical opioid-use causes psychological and social impairment (24).

In addition to somatic comorbidity associated with intravenous drug use, illicit opioid use leads to high rates of psychiatric comorbidity, particularly depression and post-traumatic stress disorder (25, 26). Individuals with opioid dependencies have an increased risk of mortality compared to general population (27), to those with other drug-use disorders (28) and to people with severe mental illness (27, 29).

Fatal overdoses are most frequent opioid overdoses which has been devastating communities throughout USA for decades (30). Overdose deaths from opioids increased by 200% in USA between 2000 and 2014 (31). During this 14 years period there was a significant increase in the overall drug overdose deaths between 2013 and 2014 which was primarily due to an increase in opioid overdoses (31). According to the United Nations Office on Drugs and Crime report 2018, there was a 21% increase in overdose deaths from 2015 to 2016 and this was mainly due to the pharmaceutical opioids (illicitly manufactured fentanyl (IMF) and fentanyl analogues) (12, 32).

In United States, 63,632 persons died of a drug-overdose in 2016 (12) and among these deaths 66.4% involved an opioid, either prescription opioids (morphine, oxycodone), illicit opioids (e.g., heroin, illicitly manufactured fentanyl (IMF)) or both (32). There was a 27.9% rate increase in opioid overdose deaths from 2015 to 2016, mainly due to the involvement of the synthetic opioids (IMF, fentanyl analogues) (32, 33). Overdose deaths involving all opioids and synthetic opioids increased from 2016 to 2017, however deaths involving prescription opioids and heroin remained stable (34, 35).

In Europe, heroin is the most frequently used illicit opioid, but synthetic opioids like methadone, buprenorphine and fentanyl are also misused (36). In this population, the prevalence of high-risk opioid use in adults (15-64 years) is estimated at 0.4%, which equals 1.3 million high-risk opioid users in 2016. In Europe, opioids are present in 87% of deaths caused by overdoses (36).

Benzodiazepines (BZDs) and alcohol are often found in combination with opioids in the overdose deaths (22, 37). Overdose risk increases after being abstinent from opioids for a period of time, as an opioid relapse is not well tolerated by the body due to a loss of opioid tolerance (38-40). For this reason, the first few weeks, some studies suggest first four weeks (41), after dropping out from treatment, discharge from inpatient units, or after release from prison are the most vulnerable for opioid-dependent individuals (42, 43). This increase in overdose deaths can occur due to an increase in opioid tolerance level (44), psychological factors and co-existing use of respiratory depressant drugs (39, 45, 46).

However a Scandinavian study found similar concentrations of morphine in the blood of both tolerant and abstinent subjects and did not find abstinence as a decisive factor in heroin overdose deaths (47). It was proposed that factors such as concomitant intake of other drugs may be more important for such deaths. Many years of high-risk behavior and an unhealthy lifestyle also contribute to increased mortality among this population (23).

1.1.1. Anxiety and Depressive Symptoms and Opioid Dependence

Opioid-dependent individuals fulfilling the criteria for a substance use disorder (SUD) show an increased prevalence of lifetime psychiatric disorders compared to general population (48-51). Grant et al. reported that 20% of the US general population with a current SUD had at least one current independent mood disorder and at least one current independent anxiety disorder (1). Epidemiological studies also report a lifetime history of substance use disorders among 24% to 43% of individuals with anxiety disorders (52, 53).

Depression is a serious medical illness and is often seen in individuals with substance abuse and dependence as compared to general population (44-54% versus 16%) (50, 54).

Depression may be an independent disorder, or it may be related to the psychosocial stress associated with addictive behavior (55). It may also be a result of drug use and drug withdrawal effects (50, 56).

Opioid maintenance programs (buprenorphine, methadone) are an effective treatment for opioid-dependent individuals (57). Depression, however, is still prevalent in populations undergoing maintenance treatment and has a negative impact on treatment outcomes (56, 58,

59). Anxiety disorders are also prevalent in opioid maintenance treatment patients (60). The causes of anxiety disorders in this population are not fully understood, but substance abuse and drug withdrawal most likely play an important role (61). Individuals, who are already prone to anxiety, develop anxiety disorders when exposed to traumatic events in life (62-64). Depression and anxiety, often in combination with insomnia, are the most common psychiatric comorbidities among opioid-dependent individuals (65-67). Anxiety disorders may be solitary or coexist with depression (68) and can either facilitate the development of addiction or develop over the course of ongoing addiction (69, 70). The early onset of anxiety disorders during childhood or adolescence increases an individual's susceptibility to developing opioid dependence later in life (71, 72).

Major depression is often associated with other psychiatric co-morbidities, especially anxiety disorders (73, 74). Studies have discussed if depression causes drug abuse or one develops depression over the course of drug abuse (75, 76). Based upon the observed relationship between anxiety and depression, anxiety may also increase the risk of depression development in opioid dependent individuals (1, 74).

Both anxiety and depression negatively contribute to the course and treatment outcome in opioid use disorder (2, 77). Agonist treatment with methadone or buprenorphine or residential treatments have shown positive effects on coexisting anxiety and depressive symptoms. However, the data have been inconsistent (2, 77, 78), for the type of substance used, frequency of intake, or poly-drug use (79-83).

Individuals in methadone maintenance treatment (MMT) are the most thoroughly investigated group of opiate addicts. Strain et al. (84) interviewed 66 MMT patients and found a lifetime prevalence of major depression in 20%, dysthymia in 3%, and panic disorder in 2%. For patients with opioid dependencies and a lifetime history of major depression, the probability of using sedatives was 1.8 times higher and the probability of using cannabis was 1.9 times higher than in other patients. Van Limbeek et al. (85) examined 203 MMT patients and found an additional mental disorder (axis I) according to DSM-III-R in 57% of the cases, mainly major depression, phobic disorders, dysthymia, alcohol dependence, and antisocial personality disorder. Darke et al. (86) studied 222 MMT patients and found high depression and anxiety scores among the study participants.

Opioid-dependent patients who suffer from depression often remain less abstinent and have more problems related to housing or other psychosocial issues (2, 87-89). Clinical studies have suggested that approximately 50% of opioid-dependent individuals report depression

during their lifetime, whereas one-third have a depressed mood at the time of admission to addiction treatment (90).

John Marsden et al. (91) reported higher levels of psychiatric symptom among individuals at admission to specialist addiction treatment programs, and high suicidal ideation particularly among women. Another study (92) reported that substance abuse patients with significant psychopathology at admission, received greater amount and range of treatment services and also showed better long-term improvement than those with lower psychopathology score at admission.

Individuals in methadone maintenance treatment (MMT) programs with a history of opioid abuse or addiction show higher prevalence of anxiety symptoms (60, 63). A study conducted among individuals in MMT program reported that around 41.7 % of study participants experienced anxiety symptoms of varying severity (93). Benzodiazepine (BZD) use has documented positive effects in the treatment of anxiety disorders (94, 95), but is also associated with increased risk of overdose deaths and poor retention in treatment programs (96, 97). Opioid maintenance treatment patients have reported the use of BZDs to relieve anxiety symptoms (98). However, benzodiazepines use has also been reported to increase subjective and physiological opioid effects (99) and to achieve the reinforcing effects of BZDs themselves (100).

Buprenorphine maintenance shows comparable efficacy to methadone maintenance treatment (MMT) (101) and may have advantages, including taking buprenorphine dose on alternate days (102), a greater safety profile, and a milder withdrawal syndrome (103). Another possible advantage of buprenorphine is that it has an antidepressant effect (104). A study compared the effect of buprenorphine maintenance treatment (BMT) with MMT on depressive symptoms in heroin users (105). However, the study reported improvement in depressive symptoms in all study participants, with no difference between the treatment groups.

Another study (106) conducted among the United States civilian, non-institutional population (N=43,093) using the Alcohol Use Disorders and Associated Disabilities Interview Schedule DSM-IV version (AUDADIS IV) reported a positive and significant association between particular mood and anxiety disorders and particular drug use disorders. The study showed higher association between mood and substance use disorders than between mood and anxiety disorders.

1.1.2 Insomnia and Opioid Dependence

Insomnia as defined by the Diagnostic and statistical Manual of Mental Disorders V (DSM-V) is a complaint of dissatisfaction with sleep quantity or quality that is associated with difficulty initiating and/or maintaining sleep (6).

Insomnia, which is frequently seen in the general population, is considered a disorder when it occurs frequently (at least 3 nights per week), persists (for at least 3 months) and causes clinically significant distress in important areas of functioning (107). The prevalence of insomnia varies widely from 5% to 50% in epidemiological studies depending upon the surveyed population (108).

Insomnia represents an increased risk of health care problems, functional deterioration (109) and high morbidity (110-112). Since insomnia in the general population often remains unrecognized and untreated, it is important to identify insomnia to intervene early and to reduce morbidity (113). Individuals with opioid dependencies experience sleep distress at different stages: intoxication, withdrawal, long-term use, early recovery and in maintenance treatment (114, 115).

Psychiatric disorders are usually associated with insomnia and are estimated to be present in almost 40% of all insomnia patients (116, 117). Epidemiologic surveys of the general adult population have reported the presence of primary psychiatric disorders in at least one third of individuals with significant insomnia or hypersomnia complaints (116, 118). Depression is the most common among these psychiatric disorders (119). Sleep problems associated with illicit substance use is reported by several studies (120). Even though opioids have sedative effect, they disturb sleep by increasing wakefulness and decreasing total sleep time, slow wave sleep and rapid eye movement (REM) sleep (121). Prolonged substance use may induce persistent changes in sleep-wake systems (122), but it is also possible that sleep abnormalities may be related to a biologic predisposition to substance abuse (67, 123).

Sleep disturbances in the MMT population are often multifactorial in etiology (114).

Psychiatric illness, chronic pain, and benzodiazepine abuse are all associated with sleep disturbances and insomnia in this population (2, 63, 124). Stein et al. (3), reported an increased prevalence (84%) of sleep disorders in MMT patients, but these rates were found to be more reflective of the sleep problems in individuals with alcohol dependence (125)

Evidence regarding direct effect of opioids on sleep efficiency and quality is both inconsistent and inconclusive (126-128). Significant central sleep apnea (CSA) and hypoxemia on buprenorphine/naloxone treatment was reported by a cross-sectional observational study (129), while another case report indicated successful reversal of CSA when inducted on this

treatment (130). However, it is still uncertain whether the sleep quality gets better or worse with buprenorphine (130-132).

A prospective naturalistic study (133) evaluated opioid-dependent individuals' reports on their sleep while receiving buprenorphine in medication-assisted treatment (MAT). Sleep Scale from Medical Outcomes Study (MOS-Sleep), and a five-item supplemental sleep scale (SSS) were instruments used in the study. Almost 50% of study participants reported sleep improvement after initiating buprenorphine/naloxone treatment and strongly believed that their use of buprenorphine/naloxone was responsible for their improved sleep.

Chronic opioid use (more than six months) is hypothesized to cause disturbed sleep as well as excessive daytime sleepiness (128). In addition, it makes individuals vulnerable to the development of central sleep apnea, ataxic breathing, or both. These respiratory patterns are rare in patients without opioid use (134).

A clinical review examined the effect of short and long-term opioid use on sleep architecture and respiration during sleep (127). It was reported that the relationship between chronic opioid use and the development of central sleep apnea (CSA) is complex (127), however, methadone blood concentration can be used to predict CSA in stable MMT patients (135). It was further added that the pathogenesis of CSA in this patient group is related to a variable interaction of abnormalities in central controller function and central and peripheral receptor sensitivity (135, 136).

1.1.3 Relationship Between Symptoms of Anxiety, Depression, and Insomnia

Sleep disturbances are part of the primary diagnostic criteria and an associated feature for many psychiatric illnesses (116, 117). There is a complex interplay between symptoms of anxiety, depression, and insomnia (111, 137). Several factors are responsible for a strong relationship between sleep abnormalities and psychiatric disease (67). A number of psychiatric disorders have been associated with structural and biochemical abnormalities in the neural systems that might also be involved in sleep regulation (138). Among these, depressive and anxiety disorders are most frequently related to insomnia (139, 140). Medications used to treat psychiatric disorders may have a negative influence on sleep, including insomnia aggravation, initiation of primary sleep disorders, or both (138, 141, 142). As patients with sleep apnea usually present with symptoms of substance abuse, there may be an increased association between primary sleep disorders, psychiatric illnesses and substance abuse (143, 144).

1.1.4 Chronic Pain and Opioid Dependence

According to the International Association for the Study of Pain (IASP, 1986), chronic pain is defined as “pain that lasts past the normal time of healing,” which is three months or more (145). Chronic pain is also called chronic non-cancer pain (CNCP) in clinical medicine. The reported incidence of chronic pain has increased significantly in the western world during the last 50 years (146). Eighty million Americans suffer from chronic pain, which affects their lives in many different ways and utilizes enormous amount of resources (147).

A review of pain conditions in primary care patients by the World Health Organization showed that 22% of individuals diagnosed with pain conditions reported to experience pain that lasted more than six months (146). Over decades, opioids have been considered as the most beneficial and potent drugs to treat pain (148, 149), but concerns regarding addiction might have contributed to the under-treatment of chronic pain disorders (150-152). The use of opioids for CNCP remains controversial (148, 149, 153). Controversies usually surround the type of conditions needed to be treated, treatment safety and effectiveness in selected group of patients, and the clinical goals of the treatment (154, 155).

Opioids are one of the most commonly prescribed medications in pain treatment (156, 157). Their use, and simultaneously, misuse, has increased in the recent years (158). A recent survey indicated that up to 8 million Americans use opioids for chronic pain (159).

A possible explanation for this significant increase in the use and misuse of prescription opioids seems to be their easy availability and misconceptions about their capability to cause addiction (160). The misconception that opioids administered orally do not carry any major risk for dependence and addiction may explain, at least in part, this development in prescription patterns (160, 161). In addition, the potential risk of overdose with high potency oral opioids has, until now, been somewhat underestimated (162).

There is also an ongoing controversy about the insufficient evidence supporting opioids' long-term adequacy and effectiveness in treating chronic pain (147). Additional concerns have been raised regarding opioids side effects, induction of tolerance and addictive properties, which presents medical challenges in individuals who suffer from chronic pain (158, 163, 164). Studies report that opioid-use over longer periods of time, increases the risk of developing substance use disorders (165).

In the US, liberal opioid prescription practices have caused severe public health problems (161, 166). Since 1990, prescription of opioids for non-medical use has increased over threefold to nearly epidemic proportions (167, 168), with a 400% increase in hospital admissions related to opioids from 1998 to 2008 (165, 169). A significant increase in

prescribed opioid use has also been reported in countries, like Australia and New Zealand (170, 171).

It is not easy to determine the prevalence of substance-use disorders among chronic pain patients (172). However, the prevalence of chronic pain in individuals with opioid use disorders is reported to be significantly higher than in general population (173, 174).

A systematic review from 1992, reported a prevalence ranging from 3.2% (175) to a high of 16% (163) for the possibility of addiction in chronic pain patients (176). Other reports provide addiction rates from 2.8% (177) to 50% (178), dependent on the criteria chosen by researcher to define addiction (177, 179, 180).

Persons with a history of drug use, need safe and effective pain treatment as inadequate treatment or lack of treatment may result in the use of other illicit drugs (181), prescription opioid or benzodiazepine misuse, psychiatric distress, and functional impairment (182-184). In addition, pain complaints are more problematic in opioid-dependent individuals due to increased pain sensitivity than other addicted populations (174, 185).

1.1.5 Buprenorphine for Chronic Pain

Buprenorphine (partial opioid mu agonist) use is well established in the treatment of pain (186, 187). Sublingual buprenorphine is FDA approved only for the treatment of opioid addiction (opioid detoxification and maintenance), however it can be used to treat both addiction and pain in high-risk patients (188).

Two clinical reports have described the use of sublingual buprenorphine (subutex/suboxone) in chronic pain treatment, one illustrating its use in chronic non-cancer pain (CNCP) patients with failed or low treatment effect of other opioid analgesics (189) and the other illustrating the response of the patients with both acute and chronic pain and addiction problems (190). The results from both reports showed that buprenorphine provides successful pain relief, is well tolerated and improves mood and functioning.

Buprenorphine in patch form is approved only for analgesia (191). The transdermal patch is used to treat chronic pain in patients who need around the clock opioid treatment (187, 192, 193). A post-marketing surveillance study (194) and other studies have reported the efficacy and positive tolerability of buprenorphine transdermal patches in cancer and non-cancer pain (195).

The Center for Disease Control and Prevention (CDC) Guidelines 2016, recommend a strict monitoring and evaluation of opioid medications when used in CNCP treatment (196). A

number of recent studies have reported the safety, efficacy and tolerability of buprenorphine treatment in CNCP patients (197-199).

1.2. PHARMACOLOGICAL TREATMENT OF OPIOID DEPENDENCE

There are two general treatment paths available for opioid dependence: opioid maintenance treatment (200, 201) or detoxification and abstinence from opioids (202-205).

Opioid agonists, partial opioid agonists, opioid antagonists, and alpha-2-adrenergic agonists are the available pharmacotherapies for opioid addiction and are intended toward either detoxification or long-term agonist maintenance (202, 206, 207). Opioid maintenance treatment (OMT) is extensively used for treating opioid dependence (20) and is currently the recommended treatment option due to its better outcomes relative to detoxification (5, 208, 209). Detoxification protocols have limited long-term efficacy, and patient discomfort is a significant problem (210). The effectiveness of buprenorphine as compared to methadone remains controversial and may be most suitable for patients in need of agonist treatment in low doses (205, 211). However office-based treatment with buprenorphine has gained support in recent years (212).

Improved retention and sustained abstinence have been reported by the studies on sustained-release naltrexone formulations (207, 213-215).

1.2.1. Opioid Maintenance Treatment

Opioid maintenance treatment (OMT) has been proven to be effective with proper prescription and monitoring (216). It also provides safety, cost-effectiveness and reduces overdose risk (217). The chronic and relapsing nature of opioid dependence, makes OMT a life-long treatment (218, 219). It reduces negative health and psychosocial outcomes associated with opioid use and at the same time meets the physiological need of opioid dependent individuals for opioids (200, 220).

Even in the presence of many different medication assisted therapies (MAT) available for OMT, these medications are underused (216). According to the National Survey on Drug Use and Health conducted by the Substance Abuse and Mental Health Services Administration (SAMSHA), it was estimated that in the USA, less than 1 million out of 2.5 million American opioid users received medication assisted therapies in 2012 (221).

Opioid dependent individuals, who want to improve their life situation but are unable to discontinue opioids, may benefit from OMT. Studies on OMT programs have shown improvement in physical and mental health (222), work ability, interpersonal relations, social

well-being, while reducing the risk of infectious diseases and criminal activity in individuals with opioid dependencies (223, 224)

A reduction in overdose mortality is also shown in patients receiving OMT (38, 41). However studies have reported that mortality risk during and after OMT differs by the type of drug and varies with time (38, 39, 225). Methadone in high doses at induction taken with other illicit substances carries a higher overdose risk than buprenorphine (38, 225). In contrast, buprenorphine has been reported to be more effective than methadone in reducing overdose mortality (226-228).

Opioid maintenance treatment (OMT) implies treatment with either opioid agonist (methadone) (229), partial opioid agonist (buprenorphine) (230) or partial agonist in combination with antagonist (buprenorphine-naloxone) (231).

Methadone maintenance treatment occurs in almost three phases: induction, early stabilization and late stabilization phase (232). The recommended daily dose is 80 to 100 mg (233-235). The effectiveness of this treatment is well acknowledged and the World Health Organization has this drug listed as “essential medicine” (236).

Due to the pharmacological properties buprenorphine (BUP) and the buprenorphine-naloxone combination (BP-NLX) has in recent years been chosen as the first line medications to treat opioid dependence in a number of countries (5, 201, 237). Maintenance treatment with buprenorphine consists of a sublingual or buccal combination of buprenorphine and naloxone (opioid antagonist), usually in 4-1 ratio across the two drugs (206, 238). The treatment occurs in two phases: induction and stabilization phase (206, 220) and most patients are stabilized on doses ranging from 16 to 24 mg (206).

Even though substitution maintenance treatments are effective, it is recommended that this should be combined with psychosocial interventions to achieve better outcomes (239).

OMT medications carry a risk of diversion and misuse (239) due to the agonist properties. In some countries, clinical guidelines with recommendations have been made in an attempt to address these problems, like taking medicines under supervision, crushing the tablets (240, 241), prescribing products with lower misuse potential, using BNX (buprenorphine-naloxone) film or dilution forms of medicine rather than tablets (239, 242). However many OMT participants find it difficult to cope with these restrictions as it affects both their social and work life. Continuous physical dependence and side effects in the form of drowsiness, gastrointestinal problems, sexual dysfunctions, weight problems, are among the few disadvantages related to OMT medicines (243).

OMT is generally considered to be an important measure in harm reduction (244, 245) but non-adherence and drop-outs from OMT, increases the morbidity and overdose risk in this population (41, 246, 247).

Better retention in OMT is related with better outcomes; but there is a great variation in OMT retention rates. A systematic review found retention rates between 37%-91% at 12-month follow-ups (248). Even though studies claim that the extent of treatment accessibility and provision will influence the drug-related mortality substantially (244), high rates of overdose deaths were reported in a Danish study despite liberal OMT access (37).

The Norwegian OMT program is evaluated annually in a “national status survey”(249). In Norway, almost 50% to 60% of opioid users are enrolled in OMT and the treatment is free of cost (250). According to the OMT National Status Rapport 2016, 30% of OMT population was women and the mean age among the patients was 44.3years (251). The rapport further added that 41% of OMT patients reported no use of illicit drugs in the last 30 days, 18% reported some episodes and 26% reported regular use (251). 10% of OMT population use illicit opioids, 32% use cannabis, 39% use benzodiazepines, 15% use amphetamines, and 10% reported heavy alcohol use (251). According to the annual report from the Norwegian National OMT program, approximately 94% of patients remained in treatment (251), which is a high number compared to OMT programs in other western countries (248).

Buprenorphine-naloxone (BP-NLX) is the recommended treatment option in Norway, due to the safety profile and the injection-deterring potential of its naloxone component (250). The national mean prescribed dose for buprenorphine was 16mg/day, and for buprenorphine-naloxone 14mg/day in 2015 (250). A study investigating changes in treatment practices within Norwegian opioid maintenance program reported a shift from methadone to buprenorphine as a substitution medicine from 2002 to 2011(252). Although abuse rates with buprenorphine are relatively lower compared with full mu agonists, increased access and availability might lead to an increase in its abuse and diversion (253-255).

1.2.2. NALTREXONE

Naltrexone was synthesized in 1963 (256), and is identical both in structure and function to opioid antagonist naloxone (257). Naltrexone has a better oral bioavailability and a longer biologic half-life than naloxone (257). Naltrexone has been suggested as a third option in maintaining opioid abstinence (258, 259), in addition to OMT and follow-up treatment of drug-free patients after detoxification.

1.2.2.1 Oral Naltrexone

Naltrexone is a long-acting opioid antagonist with a high affinity to the mu and kappa opioid receptors. Increased tolerance or dependence has not been observed in the use of naltrexone (260). Oral naltrexone HCl was approved by FDA in 1984 for the treatment of opioid addiction and alcohol use disorders (AUDs) since 1994 (261). The recommended daily dosage for opioid addiction is 50.0–100.0 mg daily (262), and its use is legalized in a number of countries to prevent alcohol and opioid dependence relapse (263, 264).

Oral naltrexone has a rapid onset of action reaching peak plasma concentration within one hour, is almost totally absorbed in the gastrointestinal tract (GIT), and is metabolized by the liver (265). Initial fears that naltrexone would cause hepatotoxicity appear unwarranted (266, 267). However, an evaluation of the liver functions before starting the naltrexone treatment and avoid prescribing naltrexone given elevated liver function tests (3-5 times higher than normal) is still a common practice (207).

Studies report that the main problem with oral naltrexone is poor retention rates, low compliance and a high dropout rates, especially in the first weeks of the treatment (268-270). A Cochrane review reported that oral naltrexone either alone or in combination with psychotherapy was not superior as compared to placebo or non-pharmacological treatments in terms of treatment retention, use of illicit substances, or adverse events (270).

Individuals who prefer abstinence and an agonist-free treatment can be good candidates for naltrexone treatment (207). The World Health Organization's (WHO) guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (5) recommend treatment with oral naltrexone only to individuals with either no access to or interest in OMT.

1.2.2.2. Naltrexone Implants

Naltrexone implants have been approved for use in the USA and Russia. In the USA, naltrexone implants are approved for use in alcohol dependence. Only Russia has approved a naltrexone implant for the treatment of opioid dependence (271, 272). In Australia, naltrexone implants have been widely used in clinical practice but they are not approved by the Australian authorities (273).

Naltrexone implants may exert a therapeutic effect for up to six months (274). A high treatment retention rate, reduction in the use of heroin and amphetamine, and an improvement in the clinical condition for poly-drug use patients have been reported in studies with naltrexone implants (274-276). Irritation, inflammation, and infection at the implant site have

been reported as side effects (277). Attempts to remove the implant have also been reported among opioid-dependent individuals (278).

Norwegian studies have examined the use of naltrexone implants in opioid-dependent individuals and reported that the use of naltrexone implants secured a prolonged period of naltrexone protection (274, 275, 277). They further reported that the implants were mostly well tolerated, but that tissue reactions to repeat implants could be a problem. A RCT with 56 abstinence-motivated patients who had completed inpatient treatment for opioid dependence, reported reductions in opioid use in patients with naltrexone implants as compared to those who just received their usual aftercare (275). Another clinical trial compared the effects of naltrexone implants with MMT (279) and reported a reduction in the use of heroin and illicit benzodiazepines and in criminal activity after prison release in both treatment groups.

A systematic review and meta-analysis (271) assessed the safety and efficacy of naltrexone implants in opioid dependence treatment. Naltrexone implants were compared with placebo implants, oral naltrexone, treatment as usual and opioid substitution treatment. The results showed (271) no differences in induction to treatment and non-opioid use, but better treatment retention and low opioid-use was some shown in patients with naltrexone implants. There were no differences regarding overdoses and other side effects between all treatment modalities.

The WHO guideline from 2009 concluded that the current evidence of naltrexone implants was inadequate to support any recommendations for opioid-dependent individuals (5).

Studies on naltrexone implants have also been criticized for low power, poor methodological quality, and insufficient evidence of safety and efficacy rates (269, 271).

1.2.2.3. Injectable Extended-Release Naltrexone

Naltrexone in implant or injectable form has shown promising results in maintaining abstinence from opioids and acceptable retention rates in studies with durations of up to six months (273, 275, 280-282). Extended-release naltrexone (XR-NTX) intramuscular injections are administered every fourth week and have been found to be effective both in laboratory and clinical settings (258, 259, 280, 283). They are approved both in the USA and in Russia as a treatment option for alcohol and opioid dependence disorders (280, 284, 285). Extended-release formulations of naltrexone are considered well tolerated with few serious side effects (213, 258, 286, 287). The short-term efficacy, feasibility and tolerability of XR-NTX have been proved by several studies (40, 213, 214, 280, 281, 287).

The approval of XR-NTX in the USA was mainly based upon a RCT from Russia that showed promising results regarding retention in treatment and reductions in the use of illicit opioids (288). However, the Russian trial has been questioned as it compared XR-NTX with a placebo, which is ethically controversial as long as there is a well-recommended treatment option such as OMT available (289). As OMT is not approved in Russia, the results from the study may be less generalizable to western countries where OMT is extensively utilized (269). Two recently published RCTs from Norway and the United States (X:BOT study) compared the effectiveness of XR-NTX to buprenorphine–naloxone (BP-NLX) (258, 259). The Norwegian study reported that XR-NTX was as effective as BP-NLX in maintaining short term abstinence from the heroin and other illicit drugs (258). The US study found BP-NLX to be superior to XR-NTX in intention-to-treat (ITT) population, mainly due to detoxification failure or failure of XR-NTX induction (259). Among the participants successfully inducted on their randomized treatment, the US study found similar rates of retention in treatment and effectiveness and similar safety profiles in both groups.

1.2.2.4. Tolerability and Safety Aspects of Extended-Release Naltrexone

Long-acting naltrexone has a favorable safety profile with few severe adverse effects (213, 287, 290). Headaches, sleep disturbances, nausea, and gastrointestinal discomfort are the common side effects of this treatment, especially in the induction phase (219, 291). Severe injection site reactions are infrequently reported (284). The Food and Drug Administration (FDA) approved the use and safety of long-acting naltrexone for opioid dependence based on data from both the Russian and the US studies (213, 272, 292). However, the FDA has later been criticized for this decision due to the lack of data regarding post-treatment opioid overdoses or adverse events (289).

A Cochrane review (263) published a report about the effectiveness, safety, and adverse effects related to the use of long-acting naltrexone for the treatment of opioid dependence. After a thorough search of all relevant databases, 76 references were obtained in full text and a total of 17 primary references were included in the report. The report concluded with that the evidence was inadequate to determine the effectiveness of long-acting naltrexone in the opioid dependence treatment. A systematic review and meta-analysis underscored the need for better designed research to establish the safety and efficacy of naltrexone implants (271). However, a one-year follow-up Russian study (283) showed promising results with XR-NTX in terms of safety and effectiveness. A recently published two-year long open-label American study (293) among health care professionals administering XR-NTX showed that the safety

profile of XR-NTX was consistent with the randomized clinical trials conducted earlier (280, 287). The study showed no new safety concerns, high treatment satisfaction, adequate retention rates, and improved mental health quality. In this study, 55% of the n=38 participants received 12 monthly injections of XR-NTX, and 36.8% received all 24 injections (293). However, both of the studies (283, 293) had some limitations regarding generalizability due to the selection of participants.

It is important to inform patients about the increased overdose risk in case of opioid relapse when discontinuing extended-release naltrexone treatment (294). However, a recent study reported that there was no significant difference in rates of fatal and non-fatal opioid overdoses between individuals treated with methadone, buprenorphine, or naltrexone implants (295). A long-term follow-up study of community-based patients, treated with XR-NTX did not report an increase in overdose risk among opioid users (296).

Lack of withdrawal symptoms when discontinuing XR-NTX treatment makes it easier to drop out of naltrexone treatment, compared to OMT (37, 213, 278, 297). There is a further risk of early termination of naltrexone treatment due to the lack of opioid cravings, which can give the false feeling of being cured from opioid dependence (296).

1.2.2.5. Retention and Duration of Treatment with Extended-Release Naltrexone

The majority of studies on extended-release naltrexone (214, 215, 259) were conducted for a relatively short period of time, mostly between 1-6 months. However, a Russian study followed the study participants over a longer period of time and showed promising results with XR-NTX in terms of safety and effectiveness (283).

A RCT investigated the use of injectable extended-release naltrexone in 60 individuals with heroin dependence (213). Study participants went through an inpatient detoxification and then received oral naltrexone for three consecutive days. They were then randomized to receive either placebo or depot naltrexone in 192 mg, or 384 mg doses. The study reported (213) that treatment retention was superior for the two naltrexone conditions, relative to the placebo. In addition, participants receiving high doses of naltrexone remained longest in the treatment. Another study (207) examining different treatment options, including injectable XR-NTX for opioid dependence, reported improved retention with XR-NTX.

However, studies have also reported that improvements achieved during a relatively short period of treatment with XR-NTX declined after treatment discontinuation (26, 214, 296).

Achieving better retention in XR-NTX treatment is important but challenging. Complete detoxification from opioids before receiving naltrexone treatment can be demanding for many

opioid users. Combining psychosocial interventions with pharmacological detoxification treatments have shown better treatment retention rates, improved completion of treatment programs and reduced substance abuse in agonist maintenance treatments (298, 299). The effects of psychosocial interventions both at detoxification phase and after starting treatment with XR-NTX can be interesting to know (278, 298).

Encouraging results have been shown by studies investigating the effect of employment based reinforcement on adherence to XR-NTX in opioid users (300-302). Contingency management has been also been discussed to improve retention rates in opioid users (303), but there have been controversies around this approach. Among other approaches, patient navigation (PN) has also been developed to improve effects of naltrexone treatment (304).

An American study involving criminal justice offenders reported low opioid relapse rates with XR-NTX, but these prevention effects started declining after treatment discontinuation (214). Patient motivation and the use of other substances while receiving XR-NTX treatment are factors that should be taken into account when deciding the duration of XR-NTX treatment. Studies have shown positive results among individuals especially motivated to receive this treatment (281, 305).

Regarding duration of treatment with XR-NTX, there is still no available recommendation (296). In the absence of recommendations or guidelines for the duration of XR-NTX treatment, current treatments must be adapted individually and having in mind the chronic relapsing nature of opioid dependence.

1.2.2.6. Symptoms of Anxiety and Depression and Naltrexone Treatment

Anxiety symptoms can appear either before or after induction to naltrexone treatment. It has been suggested that these symptoms appear either as a part of withdrawal symptoms, as a part of the detoxification process, or as a part of fear of starting a new treatment (306, 307).

Increased anxiety and sleep problems observed on naltrexone induction have shown a decline after patients stabilize on treatment (307-309).

Depression and dysphoria have been reported as adverse events associated with naltrexone treatment (307). One of the early reports (310) showing association of depressive symptoms with naltrexone treatment emerged from a study of volunteers with no history of opiate use or misuse. Study reported that a single dose of 50 mg naltrexone led to a range of unpleasant symptoms including dysphoria in NTX patients as compared to placebo group (310). A study involving a cohort of naltrexone-treated opioid addicts (311) reported that patients receiving treatment with naltrexone tablets exhibited higher rates of overdose and suicide. During a 12-

month study period, four out of 81 subjects on naltrexone treatment died by overdose. There were three accidental overdoses, one intentional overdose, and nine non-fatal overdoses. However, the study (311) also reported that depressive symptoms improved among subjects on naltrexone and there was no indication of greater depression or dysphoria among study subjects who overdosed.

Previous studies have reported depressive symptoms after naltrexone use (310, 312). Rea and colleagues (313) compared standard doses of NTX (50 mg daily) with low (0.5 mg) and ultra-low (0.05 mg) doses of NTX and reported a modest reduction in depressive symptoms regardless of dose. These findings were in contrast to the findings from previous studies that reported depressive symptoms after naltrexone use (310, 312).

A review investigated the association between naltrexone treatment and dysphoria symptoms but could not find any direct positive association (309). Studies have reported symptoms of nausea, fatigue, sleepiness, restlessness, loss of energy, gastrointestinal-disturbances and dysphoria with oral naltrexone (310, 312, 314). A 12-week RCT comparing the effect of naltrexone to disulfiram and a placebo in alcohol dependent individuals with co-morbid psychiatric disorders, reported that naltrexone was associated with improvement in depressive symptoms (315).

A randomized controlled open-label trial (307) comparing the effects of oral naltrexone with MMT in opioid dependent individuals reported lesser depressive symptoms in participants with better adherence to naltrexone treatment as compared to those who were non-adherent. The study further reported no increase in depressive symptoms in NTX group but reported worsening in anxiety symptoms in both groups. It was (307) proposed a bidirectional relationship between poor treatment adherence and depressive symptoms.

A relatively small exploratory study by Mysels and colleagues (291) reported improvement in depression symptoms in individuals receiving treatment with a long-acting depot naltrexone, with no increase in anxiety symptoms. Another RCT of naltrexone in alcohol dependent individuals described an improvement in depressive symptoms over time in both NTX and placebo group, but reported elevated depression scores in NTX group as compared to placebo group at study completion (316).

Even though depression has been reported as possible side effect of naltrexone use (310, 314), many recent studies have not supported this claim (308, 317). On the contrary, studies have reported a decrease in depression symptoms due to the possible treatment satisfaction experienced by opioid-users in the remission phase (308, 309, 317, 318).

Krupitsky and colleagues (308, 317) did not find any increase in symptoms of anxiety, depression or anhedonia in participants receiving treatment with either oral naltrexone or naltrexone implant.

It is recommended that opioid dependent individuals when entering naltrexone treatment should be diagnosed for depression at baseline and followed during treatment (291).

Antidepressants or behavioral treatment should be considered if depression does not improve (291).

1.2.2.8. Insomnia and Naltrexone Treatment

Sleep disturbances and insomnia are common consequences of the use of and withdrawal from substances of abuse (127). Emerging research now highlights the importance of a complex bi-directional relationship between sleep disorders and substance use (319, 320).

Regarding insomnia and opioid antagonist treatment, the literature is rather scarce. It seems difficult to find studies where participants were recruited to monitor the effect of opioid antagonist treatments on insomnia or sleep problems. However, insomnia has been addressed indirectly in a few studies that were conducted to investigate effects of opioid antagonist treatments on psychiatric distress such as depressive symptoms (291). A recent survey of meta-analyses (Cochrane Database of Systemic Reviews) reported an increase in sleep disturbances among alcohol dependent individuals receiving treatment with opioid antagonists (naltrexone) (321).

Mysels et al. (291) reported a transient worsening of insomnia among study participants receiving extended-release naltrexone, but this study was conducted to investigate the opioid antagonist treatment effects on depression.

1.2.2.9. Chronic Pain and Naltrexone Treatment

Chronic non-cancer pain (CNCP) is associated with nervous system inflammation due to tissue damage, abnormal immune system reactivity or nerve injury (322). Studies have proposed that chronic pain mainly arises from a state of neuro-inflammation that can be maintained by dynamic interplay between the hypothalamic-pituitary-adrenal axis, stress and neuro-immune functions (323). Thus long-standing pain might be maintained by peripheral and central nerve inflammation or degenerative process (322, 323).

Naltrexone, significantly blocks the activity at mu- and kappa opioid receptors and to a lesser degree the delta-opioid receptors at normal doses (324). Naltrexone exerts its effects through two distinct receptor mechanisms. While naltrexone exerts its antagonist effect on mu-opioid

and other opioid receptors, it has at the same time an antagonist effect on non-opioid receptors (325, 326).

Naltrexone is not generally considered an adequate treatment for opioid dependent individuals with chronic pain mainly due to concerns that blocking opioid receptors could worsen pain symptoms or trigger recurrent acute or chronic pain conditions (327).

A study with two groups of participants, one with chronic pain and other without any chronic pain, all study participants were treated with low-dose oral naltrexone. None of the study participants reported any increase in pain threshold or tolerance (262). Low-dose naltrexone (LDN) treatment reduces pain in a number of chronic pain conditions and is thought to involve inflammatory processes (262). In this context naltrexone may exert anti-inflammatory effects via a pathway that does not involve its opioid antagonist activity (328).

Compton et al.(329) previously reported that opioid dependent individuals experienced improved pain tolerance upon receiving NTX treatment. Welsch et al. (330) performed a systematic review of 10 RCTs on pain treatment efficacy. It was reported that opioid agonist and antagonist treatments are equally effective in reducing chronic pain in opioid dependent individuals however, antagonist treatments showed few advantages over agonist treatments. Moreover, their data did not support the common notion that CNCP requires opioid treatment (196).

Studies have reported that ultralow-dose opioid antagonist in combination other opiates provide better and long-term analgesia (331, 332). Cruciani et al. (331) reported greater reductions in pain intensity in non-opioid-using populations with combinations of an opioid with low-dose naltrexone as compared to opioids alone. A multicenter clinical trial (332)also reported significant and better pain control when using combinations of opioid agonist with ultralow-dose naltrexone. However a prospective double-blind RCT reported an increase in opioid requirements and pain intensity in patients receiving a combination of low-dose antagonist and opioid agonist (333).

It should be noted that there was a difference in opioid antagonist doses in the studies reporting pain reduction as compared to studies reporting an increase in pain when using a combination of an opioid agonist with opioid antagonist (332, 333).

1.3. Knowledge Gaps

Both the WHO and Norwegian guidelines for the Pharmacological Treatment of Opioid Dependence express the need for more studies on the effectiveness of sustained-release formulations of naltrexone (5, 334). Despite the number of studies published recently on the

efficacy and safety of XR-NTX, there are still aspects of this treatment option that need to be explored. It would be of clinical interest if future research could try to solve questions regarding whether patients will continue with prolonged treatment by XR-NTX and whether improvements shown during XR-NTX treatment will last after the treatment stops (278).

A recently published RCT (335) comparing effectiveness of XR-NTX with treatment as usual (TAU) reported similar opioid relapse rates in individuals with recent alcohol intoxication (before randomization) receiving treatment with XR-NTX and those in TAU group. The study proposed that heavy drinking might have lowered the effectiveness of XR-NTX. Further studies can also try to answer if there are particular groups of individuals who would benefit more from XR-NTX treatment than others (297).

Recently published clinical trials have documented the long-term effectiveness and safety of XR-NTX treatment that was previously questioned (258, 259).

There is no current evidence-based recommendation regarding the ideal duration of XR-NTX treatment, and we still do not know how this treatment will affect opioid use over the long term (336). There are also some serious concerns regarding increased overdose risks after naltrexone discontinuation (269, 311). It is important that future research explore these aspects of XR-NTX treatment.

Studies have reported high dropout rates with XR-NTX treatment (337). It has been suggested that family involvement in monitoring the treatment or the availability of a strong concurrent psychosocial intervention provide better adherence, and can at least partially solve dropout problems (89, 337-339). These unmet challenges regarding naltrexone treatment give us directions for future research.

Studies have discussed depression and dysphoria as common side effects of naltrexone treatment (307, 310, 312). Future research should be targeted at identifying subgroups of individuals who are at increased risk of developing symptoms of anxiety and depression and to recognize which treatment options and interventions will be effective for these individuals (307).

Opinions have been inconsistent regarding the effect naltrexone treatment on anxiety symptoms. While a few studies describe no worsening in anxiety symptoms (291), other studies report an increase in such symptoms (307-309). Even though studies have suggested that this worsening possibly happens due to the anxiety symptoms related to the detoxification process and a natural fear of starting a new treatment (307), we are still left with the question of whether there are some subgroups of individuals that are more prone to developing these

symptoms. Further research is needed to determine subgroups of individuals who are either prone or not to develop anxiety symptoms while receiving treatment with XR-NTX.

As mentioned earlier, it is difficult to find literature investigating insomnia or sleep problems in opioid-dependent individuals receiving treatment with naltrexone. This underscores the need for further research to investigate how short-term or long-term naltrexone treatment affects sleep patterns among opioid-dependent individuals with or without other psychiatric disorders.

Studies assessing changes in pain experienced by individuals receiving treatment with XR-NTX have not been able to find an increase in pain thresholds or pain tolerance (262).

Reductions in pain intensity with low-dose naltrexone (LDN) have been reported among non-opioid-using individuals (332), but clinical data supporting its use are very preliminary. It would be useful to examine the effects of LDN administered alone or concomitantly with opioid analgesics, both on a short-term and long-term basis. Naltrexone has not been considered an adequate treatment for opiate-dependent individuals with chronic pain for fear of pain aggravation or pain relapse (327). This explains the need for clinical trials investigating the effects of naltrexone on chronic pain among opioid-dependent individuals (329). More research is needed before this treatment approach can be widely recommended. Previous research on XR-NTX has been conducted mainly in countries where OMT has a limited availability due to structural barriers, for example in Russia (272), where OMT medication is illegal, or in populations where access is limited because health care costs have to be paid by the patient or by health insurance (269, 280, 293). To evaluate the clinical potential of XR-NTX in a clinical setting where OMT is available at no cost, studies with longer follow-ups are needed (269, 336).

In our study, we tried to fill a few of these knowledge gaps by answering some of the unanswered questions from the previous literature.

2. Study Aims

The primary aims of this thesis are:

1. To assess the effectiveness, safety and feasibility of longer term treatment with XR-NTX in 117 opioid dependent individuals continuing on XR-NTX or inducted on XR-NTX in a nine month follow-up study after a 12-week RCT.
2. To assess the change in psychiatric distress reported as symptoms of anxiety, depression, and insomnia in 159 opioid-dependent individuals who were randomized to short-term treatment with either XR-NTX or BP-NLX in a 12-week RCT, and in 117 participants continuing on XR-NTX or inducted on XR-NTX in a nine month follow-up study.
3. To assess any change in mild to moderate chronic pain in 143 opioid-dependent individuals who received short-term treatment with either XR-NTX or BP-NLX in a 12-week RCT, and in 117 participants continuing on XR-NTX or inducted on XR-NTX in a nine month follow-up study.

The secondary aims of the present study are as follows:

- 1- To investigate retention in treatment, treatment satisfaction, and recommendations to others among participants in a nine-month follow-up, comparing participants continuing on XR-NTX and participants inducted on XR-NTX (Paper I).
- 2- To investigate heroin cravings among participants in a nine-month follow-up, comparing participants continuing on XR-NTX and participants inducted on XR-NTX (Paper I).
- 3- To investigate the use of other substances and addiction-related problems among participants in a nine-month follow-up, comparing participants continuing on XR-NTX and participants inducted on XR-NTX (Paper I).
- 4- To assess the tolerability and safety aspects of XR-NTX among participants in a nine-month follow-up, comparing participants continuing on XR-NTX and participants inducted on XR-NTX (Paper I).
- 5- To investigate if there are any gender differences in affective pain, sensory pain, or pain intensity using the NSF-MPQ among study participants A) randomized to treatment with XR-NTX or BP-NLX in a three-month RCT, and B) participating in a nine-month follow-up study comparing participants continuing on XR-NTX with participants switching over to XR-NTX from BP-NLX (Paper III).

- 6- To investigate if there were any differences in demographic characters like age, hepatitis-C, heroin use by injection, and total years of heroin use among opioid dependent individuals with mild to moderate chronic pain A) randomized to treatment with XR-NTX or BP-NLX in a three-month RCT, and B) participating in a nine-month follow-up study comparing participants continuing on XR-NTX with participants switching over to XR-NTX from BP-NLX (Paper III).

3. MATERIALS AND METHODS

3.1. Study Design

The Norwegian Centre of Addiction Research (SERAF) conducted a multi-site open-label randomized clinical trial (RCT) in collaboration with five urban hospitals in Norway (340). The participants were randomly assigned to receive either XR-NTX or buprenorphine-naloxone (BP-NLX) on a 1:1 ratio for a 12-week period. The RCT period lasted from November 1, 2012 to October 23, 2015. After the first 12 weeks, all randomized participants were offered to option to continue treatment with either XR-NTX or BP-NLX, chosen according to their own preference, for an additional 36-week study period. A very small number of participants selected BP-NLX in this follow-up, and due to this disproportional distribution, only participants who chose XR-NTX were included in the data analyses. The last patient completed participation in the follow-up study in July 6, 2016.

Paper I

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

Paper II

Paper II presents changes in current comorbid symptoms of anxiety, depression, and insomnia among opioid-dependent individuals in a 12-week RCT and a 36-week follow-up study. In the RCT period, comparisons were made between participants randomized to either XR-NTX or BP-NLX, and in the follow-up period, between participants who continued with XR-NTX and those who were inducted on XR-NTX. Depression and anxiety symptoms were measured using the Hopkins Symptoms Checklist-25 (HSCL-25) and insomnia was measured using Insomnia Severity Index (ISI).

Paper III

Paper III presents changes in mild to moderate chronic pain in opioid-dependent individuals in both a 12-week RCT and a 36-week follow-up study. Comparisons were done between participants randomized to either XR-NTX or BP-NLX in the RCT period, and in the follow-up period between participants who continued with XR-NTX and those who were inducted on XR-NTX. Chronic pain was measured using the Norwegian short form of the McGill Pain Questionnaire (NSF-McGill).

3.2. Study Procedures

The study was registered at ClinicalTrials.gov (# NCT01717963): October 28, 2012 (341), and performed according to the protocol version #3C, 12 June 2012. The study protocol is briefly summed up in a previous methodology article from our research group (340) and in the registration at ClinicalTrials.gov. The study was approved by the Regional Ethical Committee for Research in Southeast Norway (#2011/1320), by the Boards of Research Ethics at the participating hospitals, and by the Norwegian Medicines Agency (EudraCT: 2011-002858-31). In addition to the original protocol, 11 amendments were approved and implemented during the study period, the last amendment being made in November 2016. The study was conducted according to the international quality standards provided by the International Council of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to confirm compliance with Good Clinical Practice (GCP).

The calculation of sample size was partially based on results from previous research on sustained release naltrexone in Norway (275) and partially on the annual reports from the OMT cohort in Norway (340). The findings of opioid use among these two samples were the basis of the calculated sample size. The power was set to 90% and the significance level to 5%. Further, it was assumed that both randomized groups would retain 70% of their participants at the end of Week 12. A minimum sample size was estimated for two scenarios. For the non-inferiority scenario, 20% was set as the margin, and this yielded a minimum sample size of $n=58$ in each treatment arm: $n=116$ in total. The superiority scenario assumed XR-NTX participants to have a mean of seven opioid negative samples out of the total 12 (7/12 or 0.58) samples, while participants receiving BP-NLX would display a mean of four opioid negative samples (4/12 or 0.33). Assuming a standard deviation of 3.0 in both groups and a significance level of 5%, the estimated sample size would be $n=17$ patients per medication arm, or $n=34$ total as sufficient to show a significant difference between the arms with a power of 90%.

The original recruitment target was a total of $n=180$ participants (340). Allocation to either XR-NTX or BP-NLX was conducted by non-study personnel, using a block permuted algorithm independent of site and gender and communicated by phone to study personnel in an open label manner.

To ensure consistency and quality of all the tasks that were performed during the study, the study personnel were trained in the different approaches and routines. The training included a GCP course and training and certification in the structured interview of the European version of the Addiction Severity Index (EuropASI) (342). The study personnel were also trained in

the use of Common Terminology Criteria for Adverse Events (CTCAE), and adverse events were coded according to these criteria. The different sites coordinated their procedures, including the registration of case report form (CRF). The study was monitored by approved monitors from the Departments of Clinical Research Support at the participating hospital sites. The monitors took part in the design, implementation, and completion of the study. Once a year they visited the study sites, focusing on verifying patient consent, verifying CRFs and medical records, and verifying the study facilities. The decisions about eligibility of the participants were made jointly by the site investigator, the study personnel, and a clinician from the OMT clinic. They were also responsible for reporting adverse events (AE) and made decisions regarding treatment planning and possible study discontinuations for the participants. To ensure the quality of the reported data and the performed analyses, the guidelines of CONSORT, STROBE, and other recommended relevant checklists were applied (343, 344).

3.3. Participants

Individuals with opioid use disorders and clinicians were informed about the study via the Internet, newspapers, study personnel at the OMT clinics, detoxification units, and other services in the catchment area of the study hospitals. The OMT clinicians and study personnel provided information to the patients and arranged a meeting for inclusion in the study. We assumed that opioid users who were given information about the study actively participated in spreading the information among their peer networks and in the community of opioid users, thus participating indirectly in the recruitment process (340).

Individuals with opioid use disorders (DSM-IV) between 18 and 60 years of age were considered eligible for participation. Eligible participants were interviewed and underwent extensive screening. Criteria for exclusion were other drug or alcohol dependence and serious somatic or psychiatric psychotic illness that, according to hospital records and our clinical judgment, interfered with study participation. Females of childbearing age could not be pregnant or lactating and had to agree to use contraceptive methods. Study personnel screened patients for psychiatric disorders using the M.I.N.I. Interview 6.0 (345) and a physician examined patients for serious somatic diseases. Individuals with severe pain disorders or suffering from severe pain were not encouraged to participate in the study.

Those considered eligible for inclusion had to be registered in the national OMT program via one of the study hospitals. This offered them psychosocial help and referrals to other services if needed during the study period and also guaranteed substitution medication without any

delay in case of study discontinuation. Study consultants and OMT clinicians cooperated in all study-related events. Participants who dropped out of the RCT were offered re-inclusion in the follow-up study after Week 12.

In Paper I, n=117 chose treatment with XR-NTX in the follow-up study. These participants were the subjects of the investigation. The few participants choosing buprenorphine-naloxone in the follow-up study (n=5) were excluded from analysis due to statistical reasons.

In Paper II, n=159 intention-to-treat participants were the subjects of the investigation.

In Paper III, n=143 modified intention-to-treat patients were the subjects of the investigation.

3.4. Screening Procedures and Measurements

All eligible participants underwent a medical examination. A medical history was obtained and clinical lab tests (blood chemistry, hematology, hepatitis- and HIV-screening, vital signs, and pregnancy tests for women) were taken before inclusion. At the baseline interviews and during the first one and a half years of the study period, data were collected manually with paper and pencil. From the summer of 2014, the interviews and questionnaires were mainly computerized.

MINI 6.0 interviews (345) screened participants for acute or chronic suicidality and psychotic disorders. The Europ-ASI interview was used to gather information about demographic data, physical and mental health, education and work, drug use (measured by age at onset, usage, current use, and duration of use), treatment experiences, and criminal behavior (342). Data were collected using a timeline follow-back method (346). In addition, the participants completed several self-reporting questionnaires collecting patient-reported outcomes (PROs): a visual analogue scale (VAS) 1-10 assessed cravings for heroin, treatment satisfaction, and recommendations to others; the Hopkins Symptom Checklist (347-350) assessed depression and anxiety symptoms; the Temporal Satisfaction With Life scale (351) assessed present satisfaction with life; the McGill Pain Questionnaire (352-354) assessed current experiences of pain; the Insomnia Severity Index (355) assessed quality of sleep; and the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES-8D) (356) assessed motivation for abstinence. The Europ-ASI and the self-reporting questionnaires were completed every fourth week at each follow-up visit throughout the entire study period. Urine drug tests (UDT) were collected every week during the RCT period. Study independent laboratory units analyzed the UDTs.

Adverse effects of study medication and serious adverse events (SAE) were reported by the participants to study personnel every fourth week at the follow-up visits. The Common Terminology Criteria for Adverse Events (CTCAE) was used to classify adverse events.

3.4.1. Hopkins Symptoms Checklist-25 (HSCL-25)

The Hopkins Symptom Checklist-25 (HSCL-25) was originally a 90-item questionnaire with a number of later minimized versions (347, 357, 358). It was constructed as a self-reporting rating scale to be used for the assessment of changes in anxiety and depressive symptoms over the course of clinical treatment of psychotherapy patients (359, 360). It was later validated as a screening instrument in a number of versions and languages and has shown a robust validity and reliability (361-364).

The HSCL-25 version (365) took 10 elements from the HSCL-58 anxiety set (being suddenly scared for no reason, feeling fearful, faintness, dizziness or weakness, nervousness or shakiness inside, heart pounding or racing, trembling, feeling tense or keyed up, headaches, spells of terror or panic, feeling restless, not being able to sit still) and 13 elements from the depression set (feeling low in energy, slowed down, blaming oneself for things, crying easily, loss of sexual interest or pleasure, feeling lonely, feeling hopeless about the future, feeling blue, thoughts of ending one's life, feeling trapped or caught, worrying too much about things, feeling no interest in things, feeling everything is an effort, feeling of worthlessness). It also includes two additional somatic symptoms (poor appetite, difficulty in falling asleep or staying sleep) (365). The 25 questions are graded from "not at all" (=1) to "extremely" (=4). A mean score is computed if 20 or more of the 25 elements are answered, with a clinical cut-off score of 1,75 (366, 367).

The HSCL-25 has been widely utilized in different clinical studies (361, 365, 366) with general population samples (349, 368), and its validity has been well established across the framework of two or more cultures with immigrants and refugee populations (369-371).

3.4.2. Insomnia Severity Index (ISI)

The Insomnia Severity Index (ISI) is a brief questionnaire that was developed to assist in the clinical evaluation of patients with insomnia complaints and to measure outcomes in treatment research (355). It is a seven element self-report questionnaire meant to assess insomnia over the last four weeks. It is widely used to assess treatment response on sleep and has robust psychometric properties.

The ISI measures the severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, daytime functioning affected by sleep difficulties, sleep problems apparent to others, and anguish caused by sleep difficulties. Scoring is done on a five point rating scale where 0 = no problem and 4= very severe problem, and the total score ranges from 0 to 28. Score results are interpreted as follows: score of 0-7 indicate an absence of insomnia, 8-14 indicate sub-threshold insomnia, 15-21 indicate moderate insomnia, and 22-28 indicate severe insomnia. The ISI is available in a patient (self-administered) version, a significant other version (usually a spouse), and a clinician version (113).

3.4.3. The Mc-Gill Pain Questionnaire (MPQ)

This questionnaire was developed by Melzack and Torgerson in 1971 (352, 353), and defines specific pain characters and qualities.

The MPQ is regarded as an accurate, dependable, persistent, helpful, and beneficial questionnaire to measure pain (353). It covers the sensory, affective, and evaluative aspects of subjective pain experiences and has the ability to differentiate between different pain disorders (372). The MPQ has been adapted and translated to many different languages (373, 374), including Norwegian (375).

The Norwegian short form of the MPQ is frequently used in clinical practice and in studies for self-reported pain (352, 354, 376, 377). Its accuracy, dependability, reliability, and validity have been confirmed a number of times (354, 377). The questionnaire consists of three different components: pain descriptors, a present pain intensity (PPI) scale, and a visual analogue scale (VAS) (354, 378). The 15 pain descriptors include a sensory subscale, which comprises 11 pain-related words, and an affective subscale, which comprises 4 pain-related words. Descriptors are rated as 0=none, 1= mild, 2= moderate, or 3= severe. The PPI scale is comprised of a vertical 6-point ordinal scale, with anchors of 0=no pain and 5=excruciating pain. The VAS covers the average pain intensity on a 100-mm horizontal line, with anchors of 0 = no pain and 100 = worst possible pain. Participants in our study were instructed to report pain intensity over the last five days at each assessment.

3.5. Interventions and Start-Up Procedures

Before randomization, the participant, if not abstinent from opioids, had an individually adapted tapering schedule to a maximum of 4 mg/day of buprenorphine. The inclusion and randomization procedures were typically completed at a detoxification unit. This ensured that the participants, not being under the influence of any illicit substances, could repeatedly

receive information about the study procedures before entering the study. These procedures were also important to reduce the risk of dropout between randomization and induction on study medication.

If randomized to BP-NLX, the participant was inducted on a flexible dose of BP-NLX. The target dose was 16 mg/day, with a range of 4 mg/day to 24 mg/day (340). Upon reaching a stable therapeutic dose of BP-NLX, the participant was discharged from the detoxification unit. The further prescription and administration of BP-NLX were conducted by the OMT clinics according to the national OMT guidelines.

As induction on XR-NTX may induce withdrawal symptoms, the participants who were randomized to XR-NTX were tapered off any opioids and completed a minimum 72-hour period without any opioids. Before XR-NTX was administered, a same-day urine drug test had to be negative for opioids, and the participant was given an intramuscular test dose of 0.4 mg naloxone as an opioid antagonist challenge. If the participant did not respond with any acute withdrawal symptoms within two hours after the naloxone injection, an intramuscular injection of 380 mg Vivitrol ® was administered. The injection was set into the gluteal muscle. The participants were advised to remain in the detox ward for a couple of days after the first injection so they could get adequate pharmacological treatment for any late onset withdrawal reactions to the XR-NTX injection. The participants who were induced on XR-NTX in the follow-up study after Week 12 went through a similar start-up regimen as that described above.

Participants who were randomized to XR-NTX and also completed the follow-up study received a total of 13 XR-NTX injections and thus were blocked against opioids for a one-year period. Participants randomized to BP-NLX and who switched to XR-NTX after Week 12 and participants who were re-included after Week 12 received a total of 10 injections, and were blocked against opioids for nine months if they completed the study.

3.6. Outcomes

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

on XR-NTX in the 36-week follow-up part of the study, and between completers and non-completers.

Paper II: The outcome variables of this 48-week long prospective study were to assess the changes in psychiatric distress reported as symptoms of anxiety, depression, and insomnia in opioid-dependent individuals randomized to a 12-week treatment with either XR-NTX or BP-NLX followed by a 36-week follow-up period with either drug (the participant's choice). The Hopkin Symptoms Checklist-25 (HSCL-25) and the Insomnia Severity Index (ISI) were used to measure symptoms of anxiety, depression, and insomnia among study participants. In the RCT period, these outcomes were compared between participants randomized to receive treatment with either XR-NTX or BP-NLX. In the 36-week follow-up period, outcomes were compared between participants continuing on XR-NTX and those inducted on XR-NTX treatment after Week 12. Changes in symptoms of depression, anxiety, and insomnia were also assessed within four treatment groups over the entire study period. As exploratory analyses, associations between anxiety/depression and use of illicit substances, gender differences, and insomnia were assessed.

Paper III: The outcome variables of this 48-week prospective study were to assess changes in mild to moderate chronic pain in opioid-dependent individuals randomized to a 12-week treatment with either XR-NTX or BP-NLX, followed by a 36-week follow-up with either drug (the participant's choice) for a period of 36 weeks. In the RCT period, chronic pain symptoms were compared between participants randomized to receive treatment with XR-NTX and to participants randomized to receive treatment with BP-NLX. In the 36-week follow-up period, chronic pain symptoms were compared between participants continuing on XR-NTX and those inducted on XR-NTX treatment after Week 12. Changes in mild to moderate chronic pain were also assessed within both treatment groups over the entire study period.

3.7. Data Analyses

The collected data were entered into a GCP-compliant database and de-identified before quality control and further computing. A study independent statistician conducted most of the analyses presented in papers I, II, and III. The data were de-identified and the analyses were censored for any information that could disclose the group allocation. The author has performed the descriptive analyses in papers II and III and any supplementary analysis in the thesis.

In Paper I, statistical analyses were based on 117 participants who received at least one injection of XR-NTX during weeks 12-48. The study compared the outcomes between participants continuing XR-NTX treatment ($n = 54$) and the participants inducted on XR-NTX ($n = 63$) and between completers and non-completers. Data were described using means and confidence intervals (CI) or frequencies and percentages. Kaplan–Meier survival curves were presented and log-rank tests were performed to assess differences in retention in treatment. Differences between groups regarding changes throughout 9-months period in substance use, addiction-related outcomes, and treatment satisfaction were assessed using linear mixed models with random effects for time and participants nested within sites. Fixed effects for time up to third-order handling of non-linear patterns were included together with treatment groups and interactions between the group and time. The results were presented as observed means with a 95% CI, mean differences with a 95% CI and p -values derived from linear mixed models. Differences in the number and type of adverse events between the participants who continued on XR-NTX and those inducted on XR-NTX in the follow-up study were assessed using Fisher’s exact test. Analyses were performed using SPSS version 24 and SAS version 9.4.

In Paper II, the main analyses assessed the differences between the XR-NTX group and the BP-NLX group in trend in three outcome measures – the anxiety, depression, and insomnia scores – by estimating a linear mixed model with fixed effects for the group, non-linear time, and the interaction between group and time for each measure.

Three exploratory analyses were carried out. Associations between anxiety/depression scores and substance abuse (heroin, other opiates, benzodiazepines/sedatives, amphetamine, and cannabis) were assessed for all participants together and using linear mixed models with fixed effects for non-linear time and substance use. Next, the main analysis stratified by gender was repeated including additional fixed effects for gender and three-way interactions between group, gender, and time, as well as all lower-order interactions in the linear mixed model. Associations between insomnia scores and anxiety/depression were examined using the same linear mixed models as in the main analysis with additional fixed effects for anxiety/depression scores and three-way interactions between time, group, and score, as well as all lower-order interactions. All linear mixed models included random intercepts for participants and additional fixed effects for the period (RCT or follow-up), followed by interactions between the time period and relevant variables. The cluster effect on site level was negligible and not included into the models. Linear mixed models were estimated on the ITT sample.

In Paper III, data were described as means and standard deviations (SD) or frequencies and percentages. To assess whether the trends in the NSF-MPQ components (PPI, VAS, and Sensory and Affective pain scores) were different between the XR-NTX group and the BP-NLX group, we estimated a linear mixed model, one for each variable, with random intercepts for participants. The site effect was negligible; thus the models were not adjusted for site. Models included fixed effects for non-linear time, treatment group, and the interaction between time and treatment group.

To identify potential distinct groups of participants having similar profiles of NSF-MPQ components, we estimated group-based trajectory models. We used Akaike's Information Criterion, where a smaller value indicates a better model, to identify groups of patients. We also used other criteria to identify groups, including a reasonable sample size for identified group, non-overlapping 95% confidence intervals (CIs) for each trajectory that represented a group of participants, and average within-group probabilities of 0.80 or higher. Identified groups were compared with respect to a number of parameters by estimating bivariate nominal regression models. The results were presented as odds ratios with corresponding 95% CIs. The methods applied handle unbalanced data sets by including all available observations, also from drop-outs.

In all papers, a significant interaction would imply that there was a difference between the two treatment groups in the way that the outcome variables developed. Further, all the statistical analyses were performed using SPSS v25, STATA v14, and SAS v9.4. Results with p-values below 0.05 were considered statistically significant, and all tests were two-tailed.

3.8. The Author's Role in the Study

As a research fellow, the author was mainly responsible for recruiting and following up with study participants at Akershus University Hospital. This included making appointments with potential study participants and their consultants at the treatment clinics, providing detailed study information to participants and other relevant individuals, and being available on the study telephone during work hours and in periods outside working hours. The author made appointments at OMT clinics for detoxification and medicine start times, and scheduled meetings with OMT personnel after patients decided to take part in the study. The author also had responsibility for XR-NTX administration, monthly interviews, data collection, and updating CRF and medical records. In addition, author made a small contribution to the registration of the data. The author contributed to writing Paper I and is the first author for papers II and III.

3.9. Ethics

The study was conducted in accordance with the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, World Medical Association (379). Opioid users who expressed interest in the study were given detailed information. In particular, they were informed about the possible effects and side effects of the study medications.

Information was provided both verbally and in writing, and participants were given a copy of their written informed consents according to the Helsinki declaration. By signing the consent documents, they agreed to participate in the RCT and were also given an option to participate in the follow-up part of the study. Participants were able to withdraw from the study at any time and could commence opioid agonist medication on the day of study discontinuation if medically feasible. As all participants were enrolled in the OMT program; those who discontinued the study or were lost to follow-up could be followed up with at the OMT clinics for clinical care and treatment.

The participants were provided a wallet-sized card that contained brief information about XR-NTX and noted the date of their last administrated injection. Information about XR-NTX and the study participation was registered in the participants' electronic medical records at the hospitals, in case of emergency or need of acute pain treatment. The participants were not paid or compensated for taking part in the study, with the exception of reimbursement of travel expenses. They did receive lottery tickets as incentives for providing the UDTs (approximate value of \$2 USD each).

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

3.10. Role of the Funding Source

The study was funded by unrestricted grants from the Norwegian Research Council's Clinical Research Program in 2011, the Norwegian Centre of Addiction Research (SERAF) at the University of Oslo, the Western Norway Regional Health Authority, and the participating study hospitals: Akershus University Hospital, Haukeland University Hospital, Oslo University Hospital, and Vestfold Hospital Trust. The sponsor of the study was SERAF, which also hosted the regulatory and data management center.

The funding organizations had no role in the design and conduct of the study, and they did not participate in the collection, management, analysis, or interpretation of the data. The authors were responsible for preparation, review, and approval of the manuscript and the decision to submit the manuscript for publication. This was an investigator-initiated trial (IIT). As XR-NTX is not available for purchase in Europe, XR-NTX (Vivitrol ®) was provided unrestricted by the manufacturer Alkermes Inc. in accordance with an IIT agreement [2]. BP-NLX was provided by the OMT clinics at the participating hospitals, as it is for other opioid users included in OMT programs in Norway.

4. RESULTS

4.1. The Study Sample

The intention-to-treat population (ITT) was used in Paper II and the modified intention-to-treat population (MITT) was used in Paper III, according to the needs of each paper. In Paper I, we present results from the nine-month open label follow-up study.

4.1.1. Intention-To-Treat (ITT) Population

The ITT population included all participants who were enrolled in the study and randomized for treatment with a study medication.

Among the 232 participants assessed for eligibility, 165 were included in the study and 159 (27.4% women) were randomized to treatment with XR-NTX (n=80) or BP-NLX (n=79). A total of n=73 participants were excluded from participation. The reasons for exclusion included refusal to participate (n=51; 69.9%), not meeting inclusion criteria (n=9; 12.3%), failed detoxification (n=6; 8.2%), and other reasons (n=7; 9.6%).

4.1.2. Modified Intention-To-Treat Population (MITT)

The MITT population was a subset of the ITT population consisting of randomized participants that took at least one dose of study medication and attended at least one assessment.

Among n=159 randomized for treatment with XR-NTX or BP-NLX XR-NTX (113 males, 46 females), n=143 took at least one dose of study medication and attended at least one assessment, and were therefore included in the MITT population.

4.1.3. Nine-Month Follow-Up Study

After 12 weeks, n=105 had completed the randomized part of the study. Of the n=143 participants in the MITT sample, n=117 (81.8%) chose XR-NTX treatment in the follow up study, n=54 continued on XR-NTX, n=43 changed from BP-NLX to XR-NTX, and n=20 were re-included in the follow-up part and inducted on XR-NTX after having previously dropped out of the RCT part of the study. Among the n=117 participants on XR-NTX, n=89 were men and n=28 were women. Another n=5 participants (3.5%) chose BP-NLX in the follow-up part but were excluded from analyses for statistical reasons. At Week 16, n=8 participants dropped out leaving n=109 participants in the study. A total of n=58 participants completed the follow-up study (n=10 women, n=48 men).

Figure 1: CONSORT FLOW CHART

*additional 5 patients continued with the BP-NLX treatment but were not included in the analysis.

4.2. Participant Characteristics

Table 1. Lifetime and Baseline Clinical Characteristics of participants Randomized into treatment groups

Lifetime Characteristic	Extended-Release Naltrexone (n=80)	Buprenorphine-Naloxone (n=79)
Age, mean (SD), y	36.4 (8.8)	35.7 (8.5)
Sex, No. (%)		
Male	61 (76.3)	54 (68.4)
Female	19 (23.6)	25 (31.6)
White, No. (%)	72 (90.0)	70 (88.6)
Injecting (intravenous) users, No. (%)	72 (90)	64 (81)
HIV positive, NO. (%)	2 (2.5)	2 (2.5)
Hepatitis C Seropositive, No. (%)	44 (55.0)	42 (53.2)
Years of substance use, Mean (SD)		
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)
Cannabis	9.0 (7.3)	10.2 (9.0)
Amphetamines	6.7 (7.3)	6.3 (6.6)
Cocain	1.4 (3.1)	1.7 (2.8)
Benzodiazepines	5.1 (6.0)	5.9 (8.7)
Alcohol for intoxication	3.5 (4.8)	2.9 (4.1)

*Extended-release naltrexone (XR-NTX), Buprenorphine-naloxone (BP-NLX)

4.3. Paper I

4.3.1. Retention in Treatment

After nine months in the follow-up study, n=58 participants (49.6%) had attended all scheduled visits and received all XR-NTX injections as prescribed (figure 2). This included n=28 (51.9%) who continued XR-NTX from the RCT and n=30 (47.6%) who were inducted on XR-NTX after the RCT. There were no differences in retention between groups regarding the mean (95% CI) number of weeks in treatment. The mean number of weeks in participants continuing with XR-NTX was 25.6 (22.3–29.0), versus 25.4 (22.4– 28.4) in those inducted on XR-NTX. Non-completers (n=59) expressed different reasons for discontinuing the study: 35 (59.3%) were lost to follow-up, 14 (23.7%) wanted to manage without any further medication or disliked the effect of XR-NTX, n=7 (11.9%) reported adverse events (see below), n=2 (3.4%) reported serious adverse events, and n=1 (1.7%) died in an accident.

Figure 2.

Retention in treatment for the 117 participants who received extended-release naltrexone (XR-NTX) in the follow-up study. Kaplan-Meier survival curves for 54 participants continuing on XR-NTX in this follow-up study and the 63 participants inducted on XR-NTX.

4.3.2. Use of Opioids

No significant differences were found in heroin or other illicit opioid use between participants continuing on XR-NTX and those inducted on XR-NTX. The reduction in the use of heroin from Week 12 to Week 36, and for other illicit opioids, to Week 24, was significant among those continuing on XR-NTX. The reduction in the use of heroin and other illicit opioids was significant to Week 48 and Week 36 respectively in those inducted on XR-NTX. Abstinence from all opioids was reported by 53.7% (29 of 54) of participants continuing with XR-NTX and 44.4% (28 of 63) of participants inducted on XR-NTX.

We found no significant differences in heroin use between completers and non-completers, with completers reporting significant reductions in heroin use to Week 32 and non-completers to Week 24. However, non-completers had a significantly higher use of other opioids

($p=0.018$) than completers up to week 16. Moreover, reduction in the use of other illicit opioids was significant to week 16 among completers and to week 40 among non-completers.

4.3.3. Other Outcome Measures

There were significant differences in heavy alcohol use ($p=0.045$) and days of work attended ($p=0.016$) between those continuing with XR-NTX and those inducted on XR-NTX. Those inducted on XR-NTX after Week 12 reported more heavy alcohol use but more days at work at the end of the study period. A significant reduction in money spent on drugs up to Week 32 was reported in both groups. Those inducted on XR-NTX reported significantly more heroin cravings ($p=0.009$) as compared to participants inducted on XR-NTX but reduction in heroin craving was only significant to Week 16 among those inducted on XR-NTX. Participants continuing XR-NTX treatment reported higher treatment satisfaction ($p<0.001$), which was increasing to week 24 in both groups.

No significant differences in heroin cravings or treatment satisfaction were found between completers and non-completers (figure 3).

Figure 3. Number of days of use of Heroin, Other Opioids, Craving scores and Treatment satisfaction.

Estimated mean number of days of use of (a) heroin, (b) other opioids, (c) mean craving scores, and (d) mean treatment satisfaction. (a,b) mean number of days with use of heroin (a) and other opioids (b) last 4 weeks; (c,d) visual analogue scales were used to assess craving (c) (0-10 with 0 indicating none and 10 indicating very strong) and treatment satisfaction (d) (0-10 with 0 indicating very low and 10 indicating very high). *significant difference between completers and non-completers, $p < 0.05$; ** significant differences between completers and non-completers, $p < 0.01$; *** significant differences between completers and non-completers, $p < 0.00$; \$significant differences between continuing extended release naltrexone (XR-NTX) and induced on extended-release naltrexone, $p < 0.05$; \$\$ significant differences between continuing XR-NTX and induced on XR-NTX, $p < 0.01$; \$\$\$significant differences between continuing XR-NTX and induced on XR-NTX, $p < 0.001$.

4.3.4. Safety and Tolerability of Extended-Release Naltrexone

A total of $n=62$ (53%) participants reported at least one non-serious adverse event: $n=37$ of those induced on XR-NTX and $n=25$ of participants continuing with XR-NTX ($p=0.198$). A

total of n=37 participants reported between 2 and 15 different adverse effects, most frequently withdrawal-like symptoms, reported by the participants who were inducted on XR-NTX in the follow-up period. Other adverse effects were infections, non-serious injuries, and various pain conditions. Injection site problems and initial withdrawal-like symptoms were considered to be related to XR-NTX. Seven participants discontinued treatment due to adverse events, including withdrawal-like symptoms (two participants), psychological reactions (two participants), need for opioid agonist pain treatment (one participant), seizures (one participant), and insomnia (one participant). Five participants reported a serious adverse event requiring hospitalization: two infections, one planned surgery, and two serious injection-site reactions requiring surgery. All participants recovered completely and continued XR-NTX treatment except those with injection-site reactions, who were told to terminate the study by the principle investigator. One participant died of internal injuries after an accident. No opioid overdoses were reported. No serious adverse events or overdoses were reported among the participants during the first three months following their completion of the study.

4.4. Paper II

4.4.1. Twelve-Week Randomized Clinical Trial (RCT)

There were no overall differences between the XR-NTX and BP-NLX groups regarding trends in anxiety and depression scores, but insomnia scores were significantly lower in the XR-NTX group (table 2). The difference would remain significant after adjustments for multiple testing. The estimated effect sizes were small and the 95% confidence intervals (CI) were relatively narrow: -0.14 (-0.47; 0.19) for anxiety scores, -0.12 (-0.45; 0.21) for depression and -0.32 (-0.65; 0.02) for insomnia. Interaction term further explored showed that both groups reported a significant reduction in anxiety and depression scores from baseline to Week 4, Week 8, and Week 12. The insomnia score improved significantly in both groups from baseline to Week 4 and Week 8, but not to Week 12.

Since there were no differences between the treatment groups shown, the associations between the anxiety/depression scores and illicit substance abuse were assessed for all participants together. Higher anxiety scores were related to the use of most illicit substances but not to the use of heroin. For one day extra use of other opiates, amphetamine, benzodiazepine, or cannabis, the anxiety score increased significantly by on average 0.17 ($p=.002$), 0.08 ($p=.013$), 0.10 ($p<.001$), and 0.05 ($p=.019$), respectively. The depression scores were significantly higher by on average 0.14, 0.27, 0.17, 0.20, and 0.15 respectively, for one extra day use of heroin ($p<.001$), other opiates ($p=.003$), benzodiazepines ($p<.001$),

amphetamine ($p=.001$), and cannabis ($p=.001$). When adjusted for substance use, the trend in anxiety and depression scores remained unchanged.

The study was not able to show any overall gender differences in the trends for anxiety, depression, and insomnia scores between the two treatment groups. Exploring interactions showed that in the BP-NLX group, women reported significantly higher anxiety, depression, and insomnia scores than men at all time points. No significant gender differences were observed in the XR-NTX group.

An increase in the anxiety and depression scores were significantly associated with on average 0.56 and 0.38 higher insomnia score, respectively ($p<.001$), but with no difference between treatment groups identified.

We found only weak correlations between cravings for opioids and anxiety, depression, or insomnia scores.

Among completers, there were no significant differences between the treatment groups regarding anxiety and depression scores, but the overall insomnia scores were lower in the XR-NTX group ($p=0.015$). Participants who continued with XR-NTX treatment experienced better sleep. The scores were moderately to highly intercorrelated: anxiety and depression 0.73, anxiety and insomnia 0.58, and depression and insomnia 0.56.

4.4.2. Thirty-Six-Week Follow-Up Period

No overall differences in anxiety, depression, and insomnia scores were detected between participants continuing with XR-NTX from the RCT and participants switching from BP-NLX to XR-NTX after Week 12 (table 2). The estimated effect sizes were 0.04 (-0.34; 0.42) for anxiety, -0.04 (-0.42; 0.33) for depression, and 0.04 (-0.33; 0.42) for insomnia scores.

Exploring the interaction term showed a significant reduction in anxiety scores between weeks 16 and 20 in both groups. For depression, the reduction in scores was significant between weeks 16 and 20, and for insomnia, between weeks 16 and 24 in both groups.

When assessing all participants as one treatment group, one day extra use of heroin, benzodiazepines, amphetamine, and cannabis, respectively, was significantly associated with on average 0.11 ($p=.013$), 0.13 ($p<.001$), 0.16 ($p<.001$), and 0.06 ($p=.004$) higher anxiety scores and on average 0.25 ($p=.001$), 0.25 ($p<.001$), 0.30 ($p<.001$), and 0.13 ($p<.001$) higher depression scores. We found no association between the use of other opioids and depression or anxiety scores.

An increase in anxiety and depression scores was significantly associated with higher insomnia scores (on average 0.65 and 0.43 respectively) in the follow-up period ($p < .001$), with no differences detected between the treatment groups.

Analyses did not show any overall gender differences in trends for anxiety, depression and insomnia scores between the two groups of participants. Exploring the associations further, we found that among switchers to XR-NTX, women exhibited significantly higher anxiety scores than men over the entire follow-up period, while differences in depression scores were only significantly higher only up to Week 24. No significant differences were found in insomnia scores at any time.

Table 2: Descriptive statistics for Anxiety, Depression and Insomnia score (total) by treatment group and time

Week	BP-NLX	XR-NTX	Total Anxiety Score, Mean (SD)		Total depression Score, Mean (SD)		Total Insomnia score Mean (SD)	
	(N)	(N)	BP-NLX	XR-NTX	BP-NLX	XR-NTX	BP-NLX	XR-NTX
0	79	80	18.2 (6.7)	19.0 (6.9)	31.6 (10.3)	30.6 (10.2)	12.9 (8.0)	13.4 (8.2)
4	71	69	16.4 (5.4)	18.2 (6.8)	27.5 (9.5)	28.7 (10.1)	13.4 (7.8)	12.3 (7.3)
8	57	56	16.8 (6.8)	16.3 (5.7)	27.7 (8.9)	25.5 (9.7)	11.3 (7.5)	9.8 (7.6)
12	49	56	16.3 (5.4)	16.1 (5.6)	28.4 (8.5)	26.0 (9.3)	12.8 (7.4)	9.2 (7.3)
			Switch Group	Maintenance Group	Switch Group	Maintenance Group	Switch Group	Maintenance Group
12	61	56	18.2 (6.6)	16.1 (5.7)	30.5 (9.6)	25.9 (9.4)	13.7 (7.8)	9.1 (7.5)
16	59	50	18.1 (7.4)	15.3 (5.0)	28.3 (10.0)	25.9 (9.0)	13.2 (8.7)	9.2 (7.2)
20	50	45	16.6 (7.1)	15.3 (5.4)	26.1 (9.8)	24.7 (9.9)	11.8 (8.4)	7.9 (7.1)
24	44	44	16.0 (6.9)	15.6 (6.0)	25.0 (9.7)	24.8 (8.6)	9.4 (7.6)	7.1 (6.5)
28	41	38	15.8 (7.2)	14.4 (5.1)	26.0 (11.1)	23.9 (9.2)	10.4 (8.3)	7.6 (7.0)
32	37	33	15.5 (7.4)	15.2 (5.9)	25.1 (10.4)	24.5 (9.2)	8.7 (7.6)	7.4 (7.4)
36	33	35	16.7 (7.1)	16.1 (6.0)	27.8 (10.8)	26.2 (10.3)	11.0 (8.3)	9.1 (7.9)
40	31	30	15.5 (6.5)	13.3 (4.3)	26.2 (10.7)	22.8 (7.1)	9.5 (8.5)	7.5 (7.0)
44	28	32	15.5 (7.1)	14.1 (4.7)	26.6 (9.6)	23.0 (7.8)	10.6 (9.1)	8.0 (7.4)
48	29	29	16.2 (7.8)	13.7 (5.6)	25.6 (10.7)	21.5 (6.4)	9.6 (8.0)	6.6 (6.1)

Abbreviations: extended-release naltrexone (XR-NTX), combined buprenorphine-naloxone (BP-NLX)

4.5. Paper III

4.5.1. Twelve-Week Randomized Clinical Trial (RCT)

Since the baseline assessment was performed just prior to or during the detoxification phase, we chose Week 4 as the first assessment in our analyses. At Week 4, n=81 participants reported chronic pain and 55 participants reported no pain (7 assessments were missing). There were no significant differences in assessed pain between the treatment groups from Week 4 to Week 12. In both treatment groups, there was a slight increase in the number of participants reporting no pain from Week 4 to Week 12 on the PPI and VAS scales. Among participants with a present pain condition that had lasted for more than three months prior to the study, the mean PPI, VAS, sensory, and affective pain scores showed statistically non-significant improvements in both treatment groups from weeks 4 to 12 (Figure 4).

There were no significant differences in opioid or other illicit substance use, including cannabis, between participants reporting pain and those reporting no pain.

4.5.2. Thirty-Six-Week Follow-Up Study

Week 12 was considered to be the baseline for the 36-week follow-up study. In this part of the study most participants chose XR-NTX (117 out of 122). Since only five participants chose BP-NLX, the difference in-group size prevented further comparisons between the treatment groups during the follow-up period. We therefore divided the XR-NTX participants into two groups: participants that continued with XR-NTX from the RCT phase of the study (maintenance group), and participants switching from daily BP-NLX treatment to XR-NTX after Week 12 or being re-included in the follow-up phase after having dropped out of the RCT phase (switch group). The mean PPI and VAS scales showed non-significant improvements in pain scores over time in both the XR-NTX maintenance and switch groups. The maximum reduction in pain scores on the PPI and VAS scales was observed at Week 32 for the maintenance group and at weeks 32 and 36 respectively for the switch group. The maximum reduction in pain scores was followed by a statistically non-significant incline until Week 48 in both groups (Table 3, Figure4).

Both groups showed statistically non-significant improvement in mean sensory pain scores and mean affective pain scores from Week 16 to Week 48 (Figure 4). The PPI and VAS scores were highly inter-correlated from Week 4 to Week 48, with correlation coefficients ranging from 0.46 to 0.90. We found no significant differences between the treatment groups in affective or sensory pain scores.

Table 3. Descriptive statistics of the Present Pain Intensity, Visual Analog Scale, Affective Pain and Sensory Pain among study participants in the randomized and the follow-up period of the study.

Week	XR-NTX				BP-NLX			
	PPI		VAS		PPI		VAS	
	Total	% No Pain	Total	% No Pain	Total	% No Pain	Total	% No Pain
4	63	41.3	64	37.5	73	39.7	72	40.3
8	63	39.7	68	35.3	72	43.0	67	41.8
12	49	57.1	49	51.0	56	44.6	56	41.0
	XR-NTX (Maintenance Group)				XR-NTX (Switch Group)			
16	52	50	52	48.1	62	40.3	62	40.3
20	53	50.9	51	47.1	59	47.5	61	45.9
24	56	46.4	52	46.2	57	45.6	60	43.3
28	53	43.4	52	38.5	61	44.3	60	45.0
32	53	54.7	51	43.2	59	50.8	61	50.8
36	57	47.4	56	42.9	56	53.6	56	48.2
40	53	52.8	54	48.1	58	50.0	57	45.6
44	58	51.7	53	45.3	56	50.0	57	47.4
48	56	53.6	55	45.4	56	50.0	56	44.6
	Affective pain		Sensory pain		Affective pain		Sensory pain	
	Total	% No Pain	Total	% No Pain	Total	% No Pain	Total	% No Pain
4	64	46.8	65	36.9	73	42.5	72	37.5
8	64	57.7	69	43.5	71	49.3	66	42.4
12	49	46.9	49	44.9	56	48.2	56	39.3
	XR-NTX (Maintenance Group)				XR-NTX (Switch Group)			
16	52	51.9	52	44.3	62	38.7	62	32.3
20	53	52.8	51	45.1	59	50.8	61	44.3
24	56	35.7	52	55.7	58	29.3	60	46.7
28	54	51.8	53	41.5	61	40.9	60	46.7
32	54	55.6	52	38.5	59	52.5	61	47.5
36	57	52.6	56	41.1	56	57.2	56	50.0
40	54	55.6	53	52.8	57	52.6	58	51.7
44	56	66.1	54	46.3	57	52.6	58	50.0
48	56	62.5	54	51.8	56	60.7	57	43.8

*PPI (present pain intensity), VAS (visual analogue scale), AP (affective pain), SP (sensory pain), XR-NTX maintenance group (participants who continued with the XR-NTX after week 12), XR-NTX switch group (participants who switched from BP-NLX to XR-NTX treatment after week 12).

*Missing values PPI and VAS respectively (week 4= 7, week 8= 8, week 16 = 3, week 20 = 5, week 24= 4 and 5, week 28 = 3 and 5, week 32 = 5, week 36 = 4 and 5, week = 40 = 6, week 44 = 3 and 7, week 48 = 5 and 6).

Figure 4. Changes in the pain score among study participants both in the randomization period and follow-up period of the study

Changes in the pain score measured by 4 components of McGill pain questionnaire, A: Present Pain Intensity (PPI), B: Visual Analogue Scale (VAS) C: Affective Pain Score (AP), D: Sensory Pain Score (SP) among participants randomized to XR-NTX (black line) or BP-NLX (red line) treatment from week 4 to week 12 and between participants continuing on XR-NTX (red line) and participants switching from BP-NLX to XR-NTX (black line) from week 16 to week 48 in the follow-up period.

4.5.3. Trajectories of Reported Pain

Because the treatment groups showed no significant differences regarding overall trends in reported pain components (XR-NTX versus BP-NLX and XR-NTX continuers versus XR-NTX switchers), we pooled all participants into one group and performed a group-based trajectory modeling (figure 5).

We identified three distinct trajectories in the PPI scores (Figure 5a). The first group reported low PPI scores (average 0.2) at Week 4 (low PPI group). This group showed a small but significant improvement in PPI scores throughout the entire study period. The second group reported moderate pain scores (average 1.5) at Week 4 (low-moderate PPI) and showed a significant improvement at Week 48 (score 1.0). A third group showed somewhat higher

moderate pain scores (average 2.0) at Week 4 (high-moderate PPI), with no significant change through Week 48. Participants that were negative for hepatitis C were more likely to exhibit a low PPI than a high to moderate PPI ($p=0.048$).

We further identified three trajectories in VAS pain scores (Figure 5b). These groups were significantly different at Week 4 and showed no significant changes throughout the study period. One group experienced no pain at Week 4 and continued to remain pain-free. Another group experienced mild pain (VAS pain score of 2.0) at Week 4 and reported a slight decrease in pain throughout the study. The third group experienced moderate pain (VAS pain score of 5.2) at Week 4 and reported a non-significant reduction towards the end of the study period. None of the considered demographic characteristics differed between these groups.

For affective pain scores, we identified two trajectories (Figure 5c). One group showed a mean affective pain score of 1.2 (mild) at Week 4. The other group showed a mean affective pain score of 4.3 (moderate) that declined insignificantly towards the end of study period.

Women were more likely to experience high affective pain than men ($p=0.01$).

For sensory pain scores, we also identified two trajectories (Figure 5d). One group showed a mean sensory pain score of 3.2 (mild) at Week 4 that declined significantly towards the end of the study. The other group displayed a mean sensory pain score of 10.5 (moderate) at Week 4 with no significant improvement over time. None of the considered demographic characteristics differed between the groups.

Figure 5. Trajectories of pain components of the McGill pain questionnaire among all study participants pooled as one group from week 4 to week 48

The trajectories of different components of the McGill Pain Questionnaire from week 4 to week 48. All participants were pooled as one group and were further divided on basis of their pain levels. In Present Pain Intensity (PPI) (A) and Visual Analogue Scale (VAS) (B), three groups of participants were made, while in Affective Pain (AP) (C) and Sensory Pain (SP) (D), two groups of participants were made. Each line represents the changes with time in pain score in one particular group.

5. Methodological Considerations

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

5.1. Study Designs

Two types of study design were used in this study:

- a randomized clinical trial (XR-NTX vs. BP-NLX) and
- a longitudinal prospective cohort study.

5.1.1. The Randomized Clinical Trial (XR-NTX vs. BP-NLX)

Randomized clinical trials (RCTs) are considered to present the best evidence on treatment effectiveness and health care interventions (380). Their key elements are (380):

- The comparison of the group receiving the treatment (or intervention) under evaluation with a control group receiving either best practice, or an inactive intervention.
- Use of randomization scheme to ensure that no systematic differences, in either known or unknown prognostic factors, arise during allocation between the groups. This should ensure that the estimated treatment effects are not biased by confounding factors.
- Allocation concealment: successful implementation of a randomized scheme depends on making sure that those responsible for recruitment or allocating participants to the trial have no prior knowledge about which intervention they will receive. This is called allocation concealment.
- Where possible, a double blind design in which neither participants nor study personnel know what treatment has been received until the `code is broken` after the end of the trial. This is achieved by using a placebo, a preparation indistinguishable in all respects to that given to the treatment group, except for lacking the active component. If a double blind design is not possible the outcome assessment should be done by an investigator blind to the treatment received.
- An intention to treat analysis in which the treatment and the control groups are analyzed with respect to their random allocation, regardless of what happened subsequently.

We chose a RCT design for our study because we wanted to see the effect of a new medicine XR-NTX in opioid-dependent individuals living in Norway, and to compare this to BP-NLX.

In our study the randomization of participants to study treatments was conducted by non-study personnel using a computerized block permuted algorithm independent of site and gender, as clearly defined and written in the study protocol. This reduced the risk of selection bias as it occurred independently of both gender and site (340).

A total of 232 individuals were assessed for eligibility, of whom 165 were included in the study and 159 were randomized to treatment with XR-NTX (n = 80) or BP-NLX (n = 79). In the RCT period, the BP-NLX participants had a regular contact with their counselors at the OMT clinics. The doses of BP-NLX were received on a daily basis at the OMT clinics or dedicated pharmacies. Participants who dropped out of treatment with XR-NTX were offered treatment with an opioid agonist and further follow-up by OMT clinics.

At week 12, 105 participants had completed the randomized part of the study. Most participants (117 of 122) preferred XR-NTX when entering the follow-up study after week 12. Only 5 participants chose BP-NLX in the follow-up part. As OMT was available for all study participants, we assume that motivation to participate in this study was to receive XR-NTX. Participants' disappointment after being allocated to BP-NLX could have affected their adherence in the RCT. We tried to minimize this risk of disappointment by offering them XR-NTX after Week 12. We assume that these factors and the follow-up from the OMT clinics in addition to the study visits influence the adherence to treatment positively in both groups, and this can perhaps explain the higher retention in treatment than reported in most other trials with XR-NTX (381). It is also important to mention that no participant left the study due to being randomized to the unwanted treatment group.

There are different types of deviations from a true ITT analysis that are suggested as Modified Intention-To-treat (MITT) strategy in different studies (382). These studies have used different criteria or descriptions of these deviations to define MITT population (383-385).

In our study we defined MITT population as a subset of the ITT population consisting of randomized participants who took at least one dose of the study medication and attended at least one assessment. Among n=159 randomized for treatment with XR-NTX or BP-NLX, n=143 fulfilled the criteria to be included in MITT population.

Although ITT analyses are considered as the preferred option, a meta-analysis comparing ITT and MITT in n=72 RCTs found comparable estimates of treatment effects, and the conclusion was that MITT analyses did not bias trial results compared to ITT (386). In the present study the MITT sample was considered most relevant in the analysis of adverse events and in the assessment of chronic mild to moderate pain.

Study population is defined in the study protocol and the data sets that are acquired from this already defined study population are used for statistical analysis in RCTs (380). The primary population for analysis is the intention-to-treat (ITT) population and this is the preferred analysis of any RCT (380). An ITT analysis avoids the possibility of any bias associated with any loss, mis-allocation or non-adherence of participants (380). The strategy to analyze ITT data is conservative, that is, the treatment effect tends to be underestimated irrespective of whether the primary endpoint represents an improvement or deterioration (387, 388).

We assume the number of participants in our study was adequate to provide an acceptable statistical power. When analyzing our data the data sets were de-identified and allocation was masked, which reduced the risk of detection bias in the analyses. Precise inclusion and exclusion criteria were elaborated to recruit only eligible participants.

The two study groups of participants were considered homogeneous with regard to demographic characteristics, disease state and ethnicity. We do not expect that any differences in outcome between the treatment groups were influenced by such factors. We standardized the follow-up routines (control every fourth week) and used standard methods and instruments to measure the clinical parameters (NSF-MPQ, ISI, SCL-25, EUROP-ASI, VAS). Blinding reduces the risk of bias and increase the reliability of RCTs (389). Performing an open-label study without masking could potentially influence the clinical effects differently in the two groups. This may include performance bias, detection bias and bias in the analyses despite masking of the treatment groups in our analyses files. However, we chose not to blind or mask the treatment or use placebo. The rational for this was mainly ethical considerations and practical hurdles. We feared that study participants would try to de-mask the treatment by intake of opioids, and that they would quickly recognize their respective treatment due to their long experience with opioid use. In addition there is an increased risk of opioid overdose after a full detoxification, a danger that we tried to avoid in our study.

Through comprehensive previous research, including blinded placebo-controlled studies, the difference between placebo and XR-NTX has been established (213, 214, 288, 390). Together with the fact that the use of placebo in previous naltrexone studies has been criticized (289), we decided to not use placebo in our study. We also assumed that an open-label study may increase XR-NTX clinical generalizability. BP-NLX as a substitution medicine has also been tested against placebo and is considered both effective, ethically acceptable and so far the best possible treatment option for opioid dependence (218, 391).

Poor compliance is a big issue when recruiting patients with substance use disorders (215) and also a great challenge in RCTs (392). We assumed that both non-compliance and

withdrawal symptoms in the initial phase of XR-NTX treatment might have increased the dropout rate particularly among study participants in the XR-NTX group (213). However in our study, attrition rates among the participants who dropped out from the two treatment groups between randomization and the first medication dose were almost equal. We therefore believe that this may have influenced the results to a lesser degree compared to a situation where the attrition was skewed due to major attrition in one of the randomized groups. The RCT period in our study lasted for only 12 weeks. This is a short duration of a study when reflecting on the chronic nature of the opioid dependence. However, we found this period appropriate for comparing short term effectiveness between these two treatment groups. Since there is no definition of an adequate treatment period for XR-NTX, we considered short term treatment effectiveness as a start. Our follow-up study showed a longer term effectiveness of XR-NTX but unfortunately this did not work out as a comparison study with BP-NLX.

5.1.2. The Longitudinal Prospective Cohort Study

In a longitudinal study individuals are followed over time to measure the incidence and natural history of the disease (380). More commonly it is a prospective design and because of this, longitudinal studies have often been called prospective studies (380). A prospective cohort study is a longitudinal cohort study in which a group of individuals is followed over time and the incidence of one or more outcomes is recorded, together with exposure to one or more factors (380).

In our prospective study, we did not follow any cohort but a selected group of opioid users who had completed a RCT study and who continued to receive XR-NTX during a 36-week follow-up period with recorded study variables and outcomes as the study progressed.

Our study participants were not rewarded or paid to participate in the study. The same time study personnel at each site had the responsibility to follow-up patients from their study site, securing inter-personal continuity during the follow-up. The information that we gathered from the participants provided us with a greater understanding of the effectiveness, safety, and feasibility of XR-NTX.

A longitudinal study is vulnerable to drop-out and missing data, thus appropriate analysis methods are required to handle the missing data and to estimate treatment effects for those who dropped out (393).

In our study a total of 105 participants completed the randomization part of the study and after re-inclusion 117 participants entered the follow-up study. However, only a total of 58

participants, 29 participants in each group completed the study, reflecting a substantial drop-out in the follow-up period. Attrition bias in the RCT may also have impact on the following cohort study. We assume that by re-including participants (17 participants) who dropped out of the RCT, we minimized attrition bias in the follow-up cohort study.

In the follow-up period, according to protocol, participants could choose between XR-NTX and BP-NLX. Most of the study participants (117 of 122) preferred XR-NT when entering the follow-up study after week-12. This disproportion in distribution made it impossible for us to perform a comparative analysis as planned. The lack of a comparative control group in the follow-up period is considered a limitation to this study. Our data were based on XR-NTX participants only, that is, those who continued with XR-NTX and those who switched from BP-NLX to XR-NTX.

However this disproportion in distribution in the follow-up period given us a better understanding of possible future clinical settings, if XR-NTX was made available as a standard treatment options to all the opioid users in Norway.

5.2. Common Biases Related to the Study Designs

Bias can be defined as any systematic error in the design, conduct, or analysis of a study (394). Selection bias and information bias are the two most common sources of biases in the medical and health research fields (394). Bias usually affects the research outcomes and their validity (394).

It is important to be aware of type 1 and type 2 errors (395). Type 1 errors can appear randomly in the presence of too many variables while type 2 errors are errors where one fails to detect an effect or result that is actually present.

5.2.1. Sample and Selection Bias

Cochrane in its risk of bias tools defines selection bias as the result of “systematic differences between baseline characteristics of the groups that are compared” (396, 397).

Selection bias usually occurs during identification of the study population, in the recruitment process and due to the drop-outs (398). Different factors affecting the participation in the study can also be the source of selection bias (399). Prospective studies especially RCTs are less vulnerable to selection bias (398) but drop-outs (loss to follow-up) is a selection bias that may affect these studies (399).

Previous naltrexone studies have underlined the importance of an adequate retention in treatment to understand how naltrexone exerts its effects on opioid dependence (303, 400,

401). A meta-analysis regarding efficacy of naltrexone maintenance treatment also underscored the importance of treatment retention as it moderates the treatment efficacy (402).

In our study, the sample size was calculated to have enough power to detect differences between the two randomized groups (258). Our target was to recruit n=180 participants. We believe that the number of opioid users who participated in the study was sufficient enough to avoid Type 2 error, which appears in cases of small sample size (395, 403).

As we have suggested earlier, many opioid-users joined the study to get XR-NTX as this is not an available treatment option in Norway. According to the participants' age, gender and psychosocial characteristics, our study population seems to correspond to and represent an average sample of opioid users. However, we selected mainly abstinence-motivated individuals, which probably is not representative for the cohort of opioid dependent individuals in Norway. Since we recruited participants from the OMT programs and participants receiving no treatment, we believe that we have adequate representativeness within this sample, especially regarding OMT affiliation.

Selection bias could also have occurred due to clinicians' opinions about NTX or through different approaches used by the clinicians at different study sites. Clinicians in OMT recruited the majority of participants from different study sites. We believe that their negative and positive experiences with XR-NTX might have influenced their motivation to inform and recruit opioid-dependent individuals at different study sites. It is also possible that many opioid users were never given information about the study.

5.2.2. Information Bias

Information bias usually occurs during the process of data collection and affects the internal validity of a study(394). If information collected in a study is not correct or if variables are misclassified we refer to this as information bias (399).

A large amount of data in the study was based on information gathered from the patients and different instruments, like HSCL-25, ISI, and NSF-MPQ, used in the study. The information bias related to different instruments is described in detail in the next section.

Information bias was reduced at least in part by using standardized questionnaires and procedure manuals and by extensive staff training (394, 404). In our study, we tried to reduce this bias by providing the proper training to the study personnel involved this work, and used the timeline follow-back method to reduce recall-bias. Both for confidentiality purposes and to avoid any trust issues with the study participants, we decided to keep the research data

separate from the participants' medical records. Not all information that participants shared with the study personnel was made available to their respective clinicians.

Despite a few limitations related to the participants reported outcomes, they can provide the useful information, especially when conditions (clarity of the items, extensive staff training, longer/descriptive questions, clear instructions, standardization of assessment settings and procedures etc) are designed to maximize response accuracy (404).

However, in a multi-center study that involves several clinicians and study personnel there will always be a potential of error variance. We assume that our study personnel's professional background, long work experience with this particular group, standardized methods of communicating and reporting data, and finally their own experience with previous NTX studies might have influenced the recruitment and treatment process.

According to our observations, a trustful relationship between participants and study personnel helped our study participants to answer the questions that were both personal and challenging.

5.2.3. Attrition Bias

According to the Dictionary of Epidemiology, attrition is reduction in the number of participants in a study as it progresses (during follow-up of a cohort study or RCT) due to withdrawal, dropouts, or protocol deviations (405). The Cochrane Risk of Bias Tool defines attrition bias as the result of "systematic differences between groups in withdrawals from a study" (396, 397).

Attrition bias can affect interventional and observational studies (406) and is a well-known problem in studies of illicit substance users (248). It may lead to a large amount of missing data and thus reduce the validity and generalizability of study results (386).

It is recommended to use ITT samples to reduce attrition bias in RCTs (407), but the results can be still affected if there is a large disproportion in attrition between the two randomized groups.

In our study the distribution of the missing data was about equal in the two randomized groups and we assume that this reduced the attrition bias caused by missing data in the randomized period of the study. A total of n=117 participants entered in the follow-up study period, but only 58 participants completed the entire study period. Among non-completers (n=59) in the follow-up period, 35 were lost to follow-up, 14 wanted to manage without any further medication or did not like the effect of XR-NTX, seven reported adverse events, two reported serious adverse events and one died in an accident not related to the medication.

It is general presumption that the non-completers often are participants not satisfied with treatment and therefor least likely to adhere to the treatment (408). We did not find any differences in treatment satisfaction among completers and non-completers in our follow-up study, which indicates that dropping out before study completion most probably was due to other factors.

It is important to choose statistical analysis methods that can handle missing data (409). In our study we used linear mix model approach that is considered a suitable approach to handle the missing data and appropriate for assessing longitudinal data.

5.2.4. Confounding Factors

Confounding variables either correlate positively or negatively with both the dependent and independent variable (410). It is important to check carefully whether the exposure-outcome affiliation has been influenced by factors (confounding factors) that are not similar between the exposure groups and which also affect the outcome, before one can acknowledge that difference in outcome between the exposure groups is due to the exposure itself (380, 411).

Confounding bias can occur due to the failure to detect and control these factors (380).

A characteristic must meet two criteria before it can be considered a confounder in a particular study. First different distribution of characteristic between two groups and second its relation to the outcome regarding prognosis or vulnerability (412).

Confounding factors may mask an actual association or falsely demonstrate an association between treatment and outcomes (380). Using appropriate methods that adjust for the effect of confounding variables can reduce this effect (411). Confounding factors must be measured and reported while designing the study. During analyses, the association between such factors and the outcomes must be explored.

In RCTs, it is expected that all known and unknown confounders are equally distributed between the groups being compared (413). However, cohort studies are vulnerable to unknown confounders (412).

We aimed at collecting study sample that was representative of the general population of opioid-users in Norway. However, many participants joined the study because of their intention to receive XR-NTX. This is supported by the fact that it was only a small proportion of the study participants who chose BP-NLX in the follow-up study as compared to those who chose XR-NTX.

Other motivational factors to join the study reported by the study participants were adverse events of opioid agonist treatments, practical difficulties in getting OMT medicine daily, and

regular urine sample controls. We assume that participants' treatment preferences, above mentioned motivation factors, and disappointment over not being randomized to the preferred medication might have confounded the study results (414).

The American X:BOT study also compared the effects of XR-NTX with BP-NLX, but such confounding factors were probably reduced or only partially present as both medications are legally available in the USA (259).

Craving scores and severity and duration of opioid dependence are reported as potential confounders in XR-NTX studies (415). In our study we found higher craving score among those who were inducted on treatment after week-12 compared to those continuing on XR-NTX treatment. Our data indicated that craving ceased over time on XR-NTX treatment. We therefore expect higher craving scores in participants newly inducted on XR-NTX compared to those continuing on XR-NTX. Also the level of craving before induction on XR-NTX might have influenced these scores during the first weeks of treatment.

Age and gender are often considered as confounding factors (412, 416). Mean age among our study population was lower than average OMT population. Assuming that this may have an impact on the results of the analyses, we chose mixed model approaches and in addition the analyses were adjusted for age and gender.

5.3. Internal and External Validity

RCTs are among the most reliable methods to establish treatment effects and must be internally valid (417). To ascertain internal validity of RCTs, it is important to reduce every possible bias while designing and performing them (417, 418). Internal validity is the degree to which a study determines the cause-and-effect relationship between the treatment and the observed outcome (419).

External validity and generalizability means that the research findings are relevant to a describable group of patients in a certain clinical setting (417). Patient preference (420), placebo effects (421) and doctor-patient relationship (422) can affect the response to and/or adherence with the treatment in a RCT. Though difficult but not impossible as one can try to reduce the effect of these factors by using blinding, placebo control and excluding the patients with strong treatment preferences (417).

A randomized clinical trial is considered to have high internal validity (423), however there are possible sources of bias that can affect the validity of a RCT (424-426).

We did not use blinding in our study. Previous blinded placebo-controlled studies in clinical and laboratory settings are considered to provide sufficient evidence to prove XR-NTX

efficacy (285). The use of placebo and/or masking of medications were not considered ethically correct, due to an increased overdose risk in newly detoxified opioid dependent individuals (258). We considered most patients were capable of de-masking or recognizing their respective treatments quickly given their long experience with opioid use. Since we wanted to perform the study in a naturalistic setting, attempts to de-mask the treatment could easily turn into disturbing elements interfering with the true-effectiveness assessment (258). A longitudinal cohort study is exposed to bias to a greater extent than a RCT, and this may lower the internal validity (427). Absence of control group, 50% attrition rate, and the possibility of Type 1 and 2 errors are among factors that may bias the results from our follow-up study. That's why it is important to interpret the study results with caution and the study may advantageously be repeated to strengthen the reliability of the results.

External validity of a study can be affected by the sample size (power) and whether the study sample is representing the population being studied (417). In the RCT part of our study, the sample size was considered to have sufficient power to provide reliable results. The external validity in our study is considered acceptable due to the naturalistic, clinical setting (258). It is likely that our study results can be generalized to other high-income countries with equivalent health care systems and regulatory frameworks with regards to OMT as in Norway (428).

5.4. Rating Scales

In this section, the author will discuss in detail the methodological considerations or limitations related to different instruments used in the study.

5.4.1. Hopkins Symptoms Checklist-25 (HSCL-25)

The HSCL-25 has been used in the Nordic countries for the screening of anxiety and depressive symptoms (349, 361, 362) and is considered suitable both for the young population above 18 years and the adult population. It has been used to quantify the extent of symptoms among psychiatric outpatients and treatment effects among inpatients (429, 430).

An adequate validity and reliability of this instrument have been reported when measuring psychiatric symptoms and when distinguishing between normal and neurotic individuals (349, 364, 431, 432). The neurotic patients showed higher levels of symptom distress. HSCL-25 has been translated in different languages (433) and several versions of this instrument, ranging from 25 to 90 items, have been used to screen for psychotic, paranoid, and anxiety symptoms in outpatient facilities (432).

A study done by Veiljola et al. (368) illustrated the peculiarity of HSCL-25 as a screening instrument. For any present DSM-III-R axis-I psychiatric disorders, HSCL-25 showed 48% sensitivity and 87% specificity. It showed 100% sensitivity for cases with comorbid psychiatric disorders. The study reported that HSCL-25 can be used for the screening of psychiatric disorders. Another study (434) used HSCL-25 to determine the prevalence of mental illness among primary health care patients. This instrument disclosed mental illness in one-fourth of the sample, while only two-fifths of the sample was determined to have mental illness by family physicians. A study done by Frojdth et al. (435), underscored that any depressive illness can be discovered by HSCL-25 and suggested its use in general practice and for studies regarding depression screening among the elderly.

The primary focus in our study was to assess symptoms of psychiatric distress that patients would express in term of anxiety and depressive symptoms during the treatment rather than changes in anxiety and depressive disorders as diagnostic entities. In addition, our hypothesis was that extended-release naltrexone (XR-NTX) may unmask symptoms of unspecific psychiatric distress being concealed by the daily intake of opioids. The HCL-25 describes symptoms of anxiety and depression, but is not a diagnostic tool. Our data cannot describe any prevalence of ongoing anxiety or depressive disorders, but merely describes symptoms of distress perceived and reported in terms of anxiety and depressive symptoms. Another possible weakness with such a questionnaire is that there will be variations in participants understanding of the questions, their introspective ability to provide an accurate response to a question, and their understanding of the rating scales. Even though these questionnaires were used under the supervision of study personnel, the assessment of changes in symptoms over time could have been compromised at many points due to these factors.

5.4.2. Insomnia Severity Index (ISI)

In the present study, we used the patient version of the ISI (113). The ISI is a reliable and valid instrument used to quantify perceived insomnia severity in young (18 years and above) and old patients and in patients with primary and secondary insomnia (355). The instrument has shown adequate psychometric properties (436), internal consistency, and concurrent and content validity (113, 437, 438). These properties were documented by measuring significant correlations with an equivalent clinicians' version and with a sleep diary (437) and polysomnographic measures (355, 438). A principal component analysis investigated the impact, severity, and satisfaction of this instrument and verified the validity of its contents

(438). The ISI has been found useful and provides relevant information in both clinical and research settings (113, 439) and across the cultures (440, 441).

The ISI is brief, easy to administer, easy to score (437), and its content partly correlates to the diagnostic criteria of insomnia (6). It measures nature of sleep difficulties, insomnia severity and determines the clinical significance of subjective complaints of insomnia (437). It helps the clinicians to decide when an insomnia complaint reaches the diagnostic threshold, and is also used to evaluate treatment outcomes both in clinical practice and in research (355).

Previous studies (355) have suggested the need for validation of ISI against a structured diagnostic interview for insomnia. . As our study did not measure insomnia as a diagnostic entity, and rather only as a symptom, we think this recommendation does not directly apply to our study. The ISI has four items that are related to sleep and three items that are related to waking and it has been suggested to add few more items to increase its diagnostic specificity (355). We did not experience any difficulties in using this instrument.

5.4.3. Norwegian Short Form-McGill Pain Questionnaire (NSF-MPQ)

The NSF-MPQ (376) is frequently used for self-reported pain (442) and has high reliability and validity (377). The McGill Pain Questionnaire (MPQ) was developed to capture pain as a multidimensional phenomenon, recognizing the shortcomings of simple pain intensity scales (353). It has been translated into different languages and inspired the development of adapted pain assessment tools, taking differences in languages and culture into consideration (443, 444). The MPQ provides the clinician and researcher with valuable information about the patient's perception, reaction, and cognition of their pain state when choosing adequate treatment modalities and assessing the effect of interventions (352, 445).

A study reported adequate test-retest reliability and responsiveness of this instrument (445) however, it was also mentioned that the measurement properties differed between different groups of pain patients.

The NSF-MPQ is easy to apply, understand, and explain and is recommended for use in physiotherapy (376). It is useful in measuring the patterns of pain characters and in approaching the right diagnosis due to its differentiating ability (352, 446, 447). Studies have reported adequate accuracy and dependability of the NSF-MPQ (354, 377, 448).

However, reports have pointed out that when individuals did not experience any particular pain, they chose not to score that pain descriptor at all, even though they were instructed to score zero (377). For this reason, it has been recommended to the clinicians and researchers to instruct individuals strictly in order to get accurate data. In our study we provided our study

personnel proper and extensive training in the use of different questionnaires and rating scales in order to collect as accurate as possible study data.

Questions have been raised about the NSF-MPQ's discriminative ability in discriminant analysis. It differentiates between two broad categories of pain which are sensory and affective pain, but it is possible that the finer distinctions in the pain qualities experienced by the patients that contain necessary information to distinguish between patient groups cannot be detected by this instrument (376).

Another concern related to self-reporting of prior pain levels is the memory of pain (449). A number of studies have reported that present pain intensity influence the memory of the prior pain intensity (449, 450) and that chronic pain patients may overestimate their initial pain reports after a rehabilitation program (451, 452). Since our study participants had follow-up visits every 4th week, there is a possibility for that they might have reported the pain intensity they were experiencing the day they visited their study counselor and not what they had experienced in the last 2 weeks.

5.5. Concerns Related to Self-Reporting Questionnaires

In this section, I will discuss some general advantages and disadvantages of using self-reporting questionnaires.

Advantages of self-reporting questionnaires:

Self-reporting questionnaires can be used in a large group of people without using much time, effort or money (404, 453, 454). They make it possible to collect large amounts of quantitative data, study findings can be generalized particularly when randomly collected sample and are mostly used as screening instruments in epidemiological studies (453-455). Furthermore, it is believed that the information provided by the participants in self-reported questionnaires is more correct as they are much closer to the issues in question than other individuals (456, 457).

Disadvantages of self-reporting questionnaires:

The validity and reliability of the questionnaires can be affected by many factors. The possibility of getting invalid answers is the biggest disadvantage as participants may not answer correctly, particularly on sensitive questions (458, 459). This is called social desirability bias, in which the participants may answer in a socially favorable way rather than an accurate way. Response bias is another problem in using these questionnaires and is defined as an individual's choice or trend to respond in a certain way irrespective of the question asked (459).

Different participants interpreting same question in a different way can also bias the response which marks the importance of the clarity of items in a questionnaire (460).

Another disadvantage can be the lack of flexibility, especially with fixed-choice questions. Asking the participants to rate a statement gives them limited ability to express themselves and their feelings (461).

Different biases related to questionnaires used in our study and how we tried to minimize these biases is discussed under the relevant sections.

5.6. Study Strengths

This is the first study comparing XR-NTX with BP-NLX, and thus it provides valuable information regarding the effectiveness and safety of XR-NTX compared to the well-documented effects of BP-NLX. A recently published American X:BOT study with a sample size of n=570 presented results that were comparable to our study results (259). We assume that corresponding results from this study and other studies might strengthen the validity of our study.

Our study was conducted under a naturalistic clinical setting, and all of the participants had access to opioid maintenance treatment (OMT). Opioid-dependent individuals who volunteered to participate in the study were motivated to receive XR-NTX treatment. Further, the heterogeneous group of our study participants did not differ much from the general population of opioid-dependent individuals in Norway. We consider that the naturalistic clinical setting of the present study and the heterogeneity of its participants make it easier to generalize the study findings.

The mandatory enrolment in OMT implied that the participants could obtain substitution medication in case they decided to discontinue the study. This also ensured that the participants had access to ancillary services after the study discontinuation. This gave us the advantage that participants who discontinued the study were not completely lost to follow-up and that any adverse events that occurred after study discontinuation were reported and taken care of.

None of the dropouts occurred due to tolerability problems. Participants who discontinued the study were either motivated to go without medications or did not like the effect of XR-NTX. This study is the first study of XR-NTX treatment of opioid users in Norway and in Western Europe. Although the medication is approved in Russia and in the USA, there are many societal and policy aspects that differ between these countries and Western Europe, which may have affected the treatment outcomes. The clinical setting of the RCT, where the

participant characteristics to a great extent correspond with the national OMT population in Norway, is also considered beneficial compared to a RCT conducted among criminal justice offenders or in countries where OMT is illegal (259, 280).

5.7. Ethical Considerations

All participants gave written informed consent before study inclusion (379). Opioid-dependent individuals who showed interest in the study were provided detailed information about the study process and treatment options. Study participation was based on free will and participants had the option of leaving the study at any point of time.

Opioid-dependent individuals are often regarded as unstable and vulnerable due to their substance use. Establishing a positive patient-clinician relationship with this study population is not easy, but is of utmost importance to their success in treatment (462). Our study personnel were trained and instructed to be polite and service-oriented, and some of them had work experience with this patient group. Participants came to the study locations to receive study medicine and sit for follow-up interviews every fourth week. This helped study personnel to build trusting and stable relationships with the study participants.

All study participants were required to accept enrolment in local OMT program to ensure adequate follow-up and rapid access to opioid replacement treatment in case of study discontinuation. Participants were informed of the increased risk of overdose after discontinuing XR-NTX.

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

6. Discussion of Results:

6.1. Participant Characteristics

XR-NTX is an unknown treatment option in Norway, and observing other opioid users having positive treatment outcomes may have had an impact on the recruitment process (463).

Recruitment became easier when participants contributed to spreading information about XR-NTX due to their positive experiences.

The data showed that substance use and addiction-related problems among the present study sample did not differ much from the general population of opioid-dependent individuals in Norway enrolled in OMT (251). The characteristics of our study sample were in compliance with findings presented in other naltrexone studies with clinical samples of opioid-dependent individuals (259, 277).

Unlike Russia and the USA, where legal framework and financial and insurance restrictions may prevent opioid-dependent individuals' access to OMT, all our study participants had free access to OMT. We assume that study participation was motivated by the unavailability of XR-NTX outside our study, and the disproportional distribution of participants who chose BP-NLX treatment supports this suggestion. An earlier Norwegian survey has suggested that opioid-dependent individuals would be interested in receiving XR-NTX if it was available to them, and our study findings confirms this (464). The naturalistic setting of our study may give us a realistic insight into how XR-NTX may attract opioid-dependent individuals in a clinical setting in countries with similar drug policies and regulations as in Norway.

We assume that the main goal for the participants was abstinence from opioids. It is also likely that all of them wanted to achieve better control of their use of other substances. XR-NTX seems to match the goals and needs of those who prefer abstinence from opioids.

Complete abstinence from drugs is not necessary for engagement, and the patient's engagement in treatment is important for them to succeed. However, improvements are difficult to measure and outcomes other than abstinence are seldom regarded as successful.

The number of prescribed opioids users has increased rapidly around the world in recent years (165). Compared to heroin users, users of prescribed opioids may be marginalized to a lesser extent (465). As we discriminated between heroin and other opioids and found decreased use of both types of substances, we suggest that our findings may be relevant for both heroin users and for those who are addicted to other opioids, such as prescribed opioids.

Symptoms of anxiety, depression, and insomnia in substance users or opioid-dependent individuals are not uncommon. Opinions have not been consistent regarding the use of

antagonist treatment in patients with such symptoms. In our study, both treatment groups showed equal improvement in symptoms of anxiety, depression, and insomnia, which means that the presence of these symptoms should not be a hindrance to starting treatment with XR-NTX in opioid-dependent individuals.

Individuals with severe chronic pain were not encouraged to participate in the study due to fear of aggravation of their chronic pain. However, individuals with mild to moderate chronic pain were included in the study. Since we did not find any difference in pain improvement or pain aggravation in the two treatment groups in the RCT period of the study, we suggest that BP-NLX treatment is not superior to XR-NTX treatment in treating abstinence-motivated opioid-dependent individuals with mild to moderate chronic pain.

6.2. Paper I

6.2.1. Retention in Treatment

We found no differences in retention in treatment between participants continuing on XR-NTX and participants inducted on XR-NTX after Week 12. While XR-NTX has a limited distribution in a few countries, BP-NLX is widely offered in OMT programs in many countries, making the comparisons between our study and other studies not necessarily equivalent (466). Retention rates usually decrease over time in clinical treatment studies. We had a retention rate of 49.6% in our study. Two other studies had retention rates of 55% (293) and 62.3% (283) respectively after one year of XR-NTX treatment. We assume that these differences may due to different study designs, OMT medication availability, and inclusion criteria. Our study design did not include any mandatory supplementary intervention such as psychosocial treatments or mutual support groups, and we suggest that implementing such interventions could improve retention in XR-NTX treatment.

6.2.2. Heroin Cravings and Opioid Use

All participants showed a substantial reduction in the use of opioids and reported a reduced craving for heroin. Significantly, more heroin cravings were seen in those inducted on XR-NTX and non-completers, but reductions in heroin cravings were only significant to Week 16 among those inducted on XR-NTX treatment. There was no significant difference in craving scores between completers and non-completers at any time. This is in line with a number of previous XR-NTX studies (218, 269) that have also reported reduced cravings for heroin (213, 283, 293). A number of participants inducted on XR-NTX did use heroin or other

opioids during the first four weeks of treatment, but did not use later them in the study. It is likely that some of these episodes of opioid use can be attributed to the opioid blockade testing phenomenon (467).

6.2.3. Use of Other Substances and Addiction-Related Problems

The study participants showed a reduction in illicit substance use and improvements in addiction-related problems. These findings are consistent with findings in previous XR-NTX studies showing improvements in alcohol use, illicit drug use, and addiction-related problems (259, 280, 283, 293). Participants inducted on XR-NTX had a significantly more frequent alcohol use at the end of the study period. The numbers, however, were very low: 0.6 days with heavy alcohol use compared to 0.3 days over the last four weeks among those inducted on XR-NTX.

The study cohort displayed many addiction-related problems at study inclusion, and few were employed.

6.2.4 Treatment Satisfaction and Further Recommendations

Participants who were inducted on XR-NTX were less satisfied with XR-NTX in the first weeks compared to those who continued with XR-NTX. This corresponded with the participants' expression that a certain adaption period was necessary before they were fully satisfied with the XR-NTX treatment. Treatment satisfaction among completers was higher than among non-completers, but both groups recommended XR-NTX treatment to other opioid-dependent individuals, a finding consistent with another study report on XR-NTX treatment (296).

6.2.5 XR-NTX Tolerability and Safety

The majority of adverse events were withdrawal related and reported primarily in the XR-NTX inducted group after the first injection. Only a few adverse events were reported among those continuing on XR-NTX. These findings are consistent with previous study reports (259, 284, 293). Except for the two participants who experienced serious injection-site reactions requiring surgery, none of the other serious events were assessed as likely related to XR-NTX. The two participants with injection site reactions were asked by the principal investigator to discontinue the study.

We administered the first XR-NTX injection after a minimum of 72 hours of complete abstinence from any opioids, even though other studies have recommended a longer period of

opioid abstinence (283, 293). Many participants requested not to wait more than 72 hours due to heroin cravings and fear of dropping out of the study before the first injection. We assume that improving the detoxification procedures may decrease the number of adverse effects and increase the likelihood of a successful start on XR-NTX (468). In the US X:BOT study, participants' abilities to successfully complete detoxification were emphasized as the most important barrier to the induction of XR-NTX (259).

No opioid overdoses were reported in our study. These results are similar to another XR-NTX trial (214) which did not report any overdose deaths in 153 participants treated with XR-NTX over 18 months in contrast to seven among treatment-as-usual controls. After a period of abstinence from opioids, such as dropping out of residential treatment or discontinuation of XR-NTX, the risk of overdose increases due to the loss of tolerance of opioids (42, 246). Information about these risk factors and an adequate follow-up by clinicians after discharge or treatment discontinuation is very important. Study personnel cooperated closely with the clinicians.

6.3. Paper II

To our knowledge, no previous study has compared the effects of XR-NTX injections with daily BP-NLX treatment on comorbid symptoms of anxiety, depression, and insomnia assessed by HSCL-25 and the ISI inventory. We hope that our findings can contribute to a better understanding of possible treatment alternatives for opioid-dependent individuals with comorbid symptoms of anxiety, depression, and insomnia.

6.3.1. Changes in Symptoms of Anxiety, Depression, and Insomnia

In the RCT period, we found no significant differences in mean anxiety and depression scores between the XR-NTX and the BP-NLX group, but the mean insomnia scores were significantly lower in the XR-NTX group. Within both treatment groups, there was a significant improvement in anxiety, depression, and insomnia symptoms. In the follow-up period, no significant differences in mean anxiety, depression, and insomnia scores were found between participants continuing with XR-NTX and participants inducted on XR-NTX after Week 12. A significant reduction in mean anxiety, depression, and insomnia scores was seen in both treatment groups. Among completers in the RCT period of the study, we did not find any significant differences between the treatment groups regarding mean anxiety and depression scores, but there was a numerical non-significant small overall difference in mean insomnia scores.

Our hypothesis was that treatment with XR-NTX might unmask the symptoms of anxiety, depression, and insomnia. However, abstinence from opioids induced by XR-NTX did not unmask such symptoms. In contrast, we observed an equal improvement in reported symptoms in both treatment groups. Previous papers have discussed anhedonia, depression, and reduced pleasure after induction of either XR-NTX or oral naltrexone in subjects with and without SUDs (308, 469-471). However our findings are consistent with a study by Krupitsky et al. that reported gradual improvements in anxiety, depression, anhedonia, and insomnia over time in participants treated with either oral naltrexone or the XR-NTX implant (308). Studies by Zaaier et al., (472) and Mysels et al., also reported significant improvements in depressive symptoms on NTX treatment. Mysels et al.(291) reported additional improvements in anxiety symptoms, but a transient worsening of late insomnia. A study by Dean et al. showed improvement in depressive symptoms only, and a worsening of anxiety symptoms with oral naltrexone (307). Common to these studies showing a worsening of anxiety symptoms on NTX treatment is that the worsening is reported either prior to the start of NTX treatment or around and immediately after the detoxification phase. One can question if these reports actually reflect symptoms from NTX treatment or merely reflect outcomes caused by ongoing withdrawal symptoms.

6.3.2. Association Between Symptoms of Anxiety, Depression, and Insomnia

Higher anxiety and depression scores were significantly associated with higher insomnia scores in the XR-NTX group and BP-NLX group in the RCT period of the study. They were also seen among those who were inducted on XR-NTX and those who continued with XR-NTX in the follow-up period of the study. In the follow-up period, insomnia scores improved in both treatment groups during the first weeks of treatment. However, the reduction in insomnia scores was only significant for participants with high anxiety and depression scores. There is assumed to be a complex interplay between sleep disturbances, anxiety and depressive symptoms, and the use of illicit substances. Sleep problems are regarded as a risk factor, consequence, and complication of both depression and opioid dependence. A number of studies have reported that opioid agonists have positive psychotropic effects on mood, sedation, and anxiety, and that buprenorphine and buprenorphine-naloxone are useful in treating symptoms of depression and anxiety in opioid-dependent individuals (133, 473, 474). A study reported reductions in depressive symptoms following methadone treatment (471). Studies have suggested that depression and insomnia may share a common etiology or may simply co-exist (3), and that depression and anxiety disorders independently affect sleep

among illicit substance users (108, 116). We assume that the improvements in anxiety and depressive symptoms and possibly reductions in substance abuse may have led to the reported improvement in insomnia (475).

6.3.3. Association Between Substance Use and Symptoms of Anxiety and Depression

Since there were no differences between the treatment groups shown, the associations between the anxiety/depression scores and illicit substance abuse were assessed for all participants together in both study periods.

Among opioid-dependent individuals, anxiety and depressive symptoms are influenced by the use of illegal substances (476). A 10-year prospective study of patients on OMT (78) found that high and stable scores of anxiety and depression corresponded strongly with substantial difficulties in reducing the abuse of benzodiazepines and cannabis. This is in line with our finding of a higher use of illicit substances in participants reporting more symptoms of anxiety and depression. While no improvement was noticed in the above-mentioned study at any point of time, our results showed improvements in anxiety, depression, and insomnia only few weeks after the beginning of either study medicine. Furthermore, there was a reduction in the use of opioids and other illicit substances in both treatment groups. This is in accordance with a study by Comer et al. reporting a reduction in illicit opioid use among participants treated with XR-NTX compared with placebo injections (213), general treatment aftercare (477), or oral naltrexone treatment (273). However, it is difficult to know if the observed improvements in symptoms of anxiety, depression, and insomnia were merely a reflection of the reduced use of illicit substances or a positive pharmacological effect of the XR-NTX treatment per se.

6.3.4. Gender Differences in Symptoms of Anxiety, Depression, and Insomnia

There were no significant overall gender differences in anxiety, depression, and insomnia scores between the two treatment groups, either in the RCT or in the follow-up period of the study. In the RCT period, women in the BP-NLX group reported significantly higher anxiety, depression, and insomnia than men at all time points; meanwhile, no significant gender differences were observed within the XR-NTX group. In the follow-up period, women exhibited significantly higher mean anxiety scores than men in the switch group over the entire study period, while differences in mean depression scores were significantly higher in women only up to Week 24. No significant gender differences were found in mean insomnia scores.

This is in line with other studies reporting a higher incidence of any mood disorder or anxiety in female opioid users (2) and an unequal distribution of anxiety and depressive symptoms between male and female substance users (478). Compton et al. (478) reported similar results with higher rates of anxiety and any mood disorders among female substance users than male substance users. Brooner et al. (2) did not find any gender differences in psychiatric comorbidity rates, but underscored that female substance users had higher rates of mood disorders. We have no sufficient explanation of why we did not see this pattern of gender distribution in the XR-NTX group.

6.3.5. Association Between Symptoms of Anxiety, Depression, Insomnia, and Opioid Cravings

Symptoms of depression, anxiety, anhedonia, and craving are common among opioid-dependent individuals. We found only non-significant correlations between cravings for opioids and symptoms of anxiety, depression, or insomnia in the RCT period of the study. Positive correlations between cravings and depression symptoms have also been reported by another study (479). High correlations between cravings and anxiety and between withdrawal-induced cravings and anxiety have been reported in literature (480).

6.4. Paper III

To our knowledge, no previous study has compared the effects of XR-NTX and BP-NLX on chronic mild to moderate pain among individuals with opioid dependencies.

6.4.1. Changes in Chronic Pain

At the study start, none of the study participants with chronic pain experienced any aggravation of pain when entering XR-NTX treatment. Moreover, our findings suggested that opioids have limited analgesic efficacy on chronic pain in opioid-dependent individuals. A study by Compton et al. reported that pain tolerance improved among opioid-dependent individuals during NTX treatment, a finding consistent with our results (329). A systematic review by Welsch et al. (330) of 10 randomized controlled trials on the efficacy of pain treatment reported no significant difference in pain-reducing efficacy between opioid and non-opioid analgesic drugs. In addition, their data did not support the concept that chronic non-cancer pain (CNCP) required opioid treatment (330). Another study also proposed that opioid agonist and antagonist treatments were equally effective in reducing chronic pain among opioid-dependent individuals, with antagonist treatments showing few advantages

over agonist treatments (196). Nevertheless, different mechanisms are involved in analgesic effects induced by opioid antagonists and opioid agonists (481).

6.4.2. Mechanisms Involved in Chronic Pain

Chronic pain has been associated with neuro-inflammation based on findings of nerve tissue damage, abnormal reactivity in the immune system, and nerve injury (322). This state may be maintained by a dynamic interplay between the hypothalamic-pituitary-adrenal (HPA) axis, stress, and neuro-immune functions (323). Since opioid receptors do not seem to play a major role in this particular pain mechanism, it is assumed that long-standing pain might be maintained by peripheral and central nerve inflammatory or degenerative processes (322, 323). Low-dose naltrexone (LDN) has been reported to reduce pain in a number of chronic pain conditions involving inflammatory processes; in this context, naltrexone is thought to exert anti-inflammatory effects via a non-opioid antagonist pathway (328). Further chronic administration of naltrexone is also associated with sustained elevations in beta-endorphin levels in opioid-dependent individuals (482).

Prolonged opioid exposure is reported to cause changes at both receptor and cellular levels in the neuronal system, which might increase pain sensitivity and modulate pain perception among opioid-dependent individuals (162). As a result, these individuals are at risk of experiencing increased pain, new types of pain, pain relapses, and pronounced pain in response to an acute injury. In chronic pain states, opioid agonists inhibit the endogenous production of both opiate peptides and mu-opioid receptors, which leads to the development of hyperalgesia, tolerance, and addiction (483).

In our study, participants treated with BP-NLX did not report any increases in pain. One potential explanation for this finding could be that the participants could not distinguish between abstinence symptoms, increased pain sensitivity, and cravings related to substance-use. Alternatively, the participants might have already developed lowered tolerance and increased sensitivity to pain due to prolonged opioid use before they were included in the study, and therefore did not report any increases in pain.

We assume that the potential anti-inflammatory effects of XR-NTX and an increase in beta-endorphin levels might explain, at least in part, the minor reductions and lack of aggravation of mild to moderate chronic pain observed in the study participants.

6.4.3. Association Between Chronic Pain and Use of Illicit Substances

Persistent chronic pain has been reported in individuals with opioid dependencies or prolonged periods of opioid use (154). An increase in the prevalence of prescribed and non-prescribed opioid use in long-standing pain conditions has been reported by other studies (165, 167). Our study participants reported a reduction in the use of illicit substances. Further, we did not find any difference in the use of cannabis among participants experiencing chronic pain and those reporting no pain. The slight decrease in pain intensity reported by XR-NTX participants cannot be explained by an increased use of cannabis (258). In contrast to our study findings, previous studies have reported an increased use of cannabis in individuals with long-term pain, with or without opioid dependence (484, 485).

6.4.4. Chronic Pain and Psychiatric Comorbidities

A thorough search of previous relevant literature displays a strong association between chronic pain and symptoms of anxiety, depression, and illicit substance use (486-488). Previous studies also found a stronger association between any anxiety disorder and chronic pain than between chronic pain and depression. One can assume that the reported improvements in anxiety and depressive symptoms in our study participants might have contributed to a perceived improvement in mild to moderate chronic pain (486).

6.4.5. Chronic Pain and Gender Differences

Our study results showed that women experienced greater affective pain than men according to the McGill Pain Questionnaire. A study published in 2007 (489) reported a higher prevalence of almost all pain conditions in women (38.4%) compared to men (27.1%) in the general population, and a number of studies have shown that women experience greater pain than men (490, 491). The current literature supports the fact that negative cognitions and emotions, especially those relating to catastrophizing, affect women more than men (492-494). Our results support these observed psychological gender differences in pain perception. We postulate that the slightly improved or unchanged intensity of mild to moderate chronic pain in the XR-NTX participants might be due to a number of factors. The reduced use of illicit substances and changes in lifestyle might have contributed to opioid receptor up-regulation, increased beta-endorphin levels, and potentially, a reduction in chronic nervous system inflammation. Moreover, chronic inflammatory pain conditions can cause an up-regulation of delta opioid-receptor expression (495), which is not substantially blocked by XR-NTX (322).

Our results challenge the perceived notion that an opioid antagonist (XR-NTX) would most likely aggravate long-standing pain in opioid-dependent individuals. Our findings also question whether opioids can provide an adequate analgesic efficacy in opioid-dependent individuals that experience chronic mild to moderate pain.

None of our study participants left the study prematurely due to pain issues. Participants who terminated the study prematurely and those who completed the study did not differ in pain severity, characteristics, or patterns.

7. STUDY IMPLICATIONS

7.1. Clinical Implications

Based on our study findings, XR-NTX is considered to be a valuable supplement to existing treatment modalities and can represent an alternative treatment for abstinence-motivated opioid-dependent individuals. As XR-NTX is not an addictive drug and has few interactions with other drugs, the risk of diversion is low and there is no need for a monitoring regime (20). Monthly injections make it easier for patients to participate in daily activities and maintain attendance at work or school. Our clinical impression in this study is that many women wanted to start XR-NTX because of this benefit. It is easier to adhere to injections of XR-NTX once every fourth week, especially for individuals who are hard to reach and difficult to include in other treatment options.

High relapse and overdose risks after discontinuing substitution medication is common among many drug users (247). We suggest that XR-NTX could be a preferred treatment option in a transition phase to those who want to cease substitution medication and a promising treatment alternative to opioid users who prefer a substitution-free treatment. Since treatment with XR-NTX was as effective as BP-NLX in reducing symptoms of anxiety, depression, and insomnia, such symptoms should not preclude the choice of leaving opioid agonist treatment and being inducted to treatment with XR-NTX. This is regarded as an important clinical implication among patients for whom the presence of these symptoms made clinicians hesitant to encourage them to start treatment with XR-NTX.

Persistent chronic pain has been reported in individuals who have either developed opioid dependencies or used opioids for prolonged periods (496). Because XR-NTX is an opioid antagonist, the treatment has not been considered adequate for opioid-dependent individuals suffering from chronic pain. Since we did not find any worsening in mild to moderate chronic pain, but rather a non-significant decrease in chronic pain, our findings suggest that XR-NTX treatment may be used also by opioid-dependent individuals with chronic pain symptoms.

7.2. Research Implications

A key question regarding the use of XR-NTX in a naturalistic setting is the recommended duration of XR-NTX treatment. Very few studies have investigated the effectiveness of XR-NTX over more than one year. Further, we have no knowledge of the of XR-NTX treatment duration that can be safe and provide stability to opioid-dependent individuals once the XR-NTX treatment is completed. It is also uncertain whether the improvements that were

achieved during the XR-NTX treatment will continue after the completion of the treatment or not. Keeping in mind the relapsing nature of opioid dependence (468), it is of utmost importance to explore these questions.

We hypothesize that perhaps those opioid-dependent individuals who have successfully recovered through opioid maintenance treatment might need XR-NTX for a shorter period, while those who continued illicit substance use both before and during XR-NTX treatment might need lifelong treatment with XR-NTX. However, this is merely an assumption, and no study to date has tried to investigate this. It would be useful to know more about these two alternatives regarding naltrexone treatment. After having completed the follow-up period, participants (completers) were offered the option to continue their treatment with XR-NTX for a longer, unspecified period. We hope that the data from this “prolonged study” will provide important information about how much time in XR-NTX treatment is necessary for long-term abstinence from opioids.

Study participants who were enrolled in OMT prior to study inclusion were using either methadone or buprenorphine (with or without naloxone) when entering the study. Some of them also used heroin or other illicit opioids. Participants not enrolled in OMT prior to the study inclusion mainly used heroin, but a minority abused mostly prescribed opioids. We did not examine whether there were any differences in retention in treatment regarding which opioid participants used prior to inclusion. In future studies, it may be interesting to investigate if the abuse of different kinds of opioids influences the outcome of XR-NTX treatment (290).

The HSCL-25 scale used in our study only describes and measures reported symptoms of anxiety and depression, and cannot predict any prevalence of ongoing anxiety or depressive disorders on a diagnostic level. Further research is needed to measure the prevalence of any ongoing anxiety and depressive disorders among opioid-dependent individuals inducted to XR-NTX treatment using more specific assessment tools for anxiety and depressive disorders. We did not encourage individuals with severe chronic pain to participate in the study. Consequently, our findings may not be generalizable to opioid-dependent individuals with severe chronic pain. Future studies should explore how opioid-dependent individuals with more severe chronic pain would tolerate XR-NTX treatment.

7.3. Policy Implications

XR-NTX should be an available treatment option for opioid-dependent individuals. Barriers to utilization of XR-NTX may be expressed in other ways in Norway and in other Western

European countries compared to USA, in regard to the differences in health policy and the funding of the healthcare system. It is important to try to integrate this novel treatment into existing treatment modalities in Europe and to identify possible barriers to the utilization of XR-NTX in clinical practice (290).

8. CONCLUSIONS

We found XR-NTX to be an effective and safe treatment option. The study participants were considered representative of opioid-dependent individuals in Norway. Meeting treatment preferences is important for treatment satisfaction and treatment adherence. A differentiated selection of available treatment modalities increases the likelihood of recruiting and keeping opioid users in treatment. Therefore XR-NTX could be a useful supplement to the existing selection.

We found no significant difference in treatment completion, abstinence rates, or adverse events among participants who continued with XR-NTX verses those who were inducted on XR-NTX in the follow-up study. The majority of the reported adverse effects were associated with symptoms of withdrawal from opioids and the initial injection of XR-NTX. All participants reporting a SAE recovered completely. Two participants were asked to discontinue their XR-NTX treatment due to injection site inflammation.

The treatment satisfaction with XR-NTX was high, and both completers and non-completers recommended XR-NTX to other opioid users. Since treatment with XR-NTX and BP-NLX showed equal improvements in anxiety, depression, and insomnia assessed by the HCL-25, such symptoms should not preclude the choice to leave opioid agonist treatment and be inducted to treatment with XR-NTX. There was a close relationship between higher HCL-25 scores and more frequent use of illicit substances.

Agonist treatment with BP-LNX was not superior to XR-NTX treatment in reducing chronic mild to moderate pain in abstinence-motivated individuals with opioid dependencies. Study participants that successfully switched from opioid agonist treatment to XR-NTX treatment did not experience any increases in pain.

REFERENCES:

1. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of general psychiatry*. 2004;61(8):807-16.
2. Brooner RK, King VL, Kidorf M, Schmidt CW, Bigelow GE. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Archives of General psychiatry*. 1997;54(1):71-80.
3. Stein MD, Herman DS, Bishop S, Lessor JA, Weinstock M, Anthony J, et al. Sleep disturbances among methadone maintained patients. *Journal of Substance Abuse Treatment*. 2004;26(3):175-80.
4. Manchikanti L, Benyamin R, Datta S, Vallejo R, Smith H. Opioids in chronic noncancer pain. *Expert review of neurotherapeutics*. 2010;10(5):775-89.
5. World Health Organization. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. 2009, World Health Organization (WHO). : World Health Organization; 2009.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®), American Psychiatric Publication, 2013. 2013.
7. McLellan A-T, Lewis DC, O'Brien CP, Kleber PHD. Drug dependence, a chronic medical illness. *The Science of Mental Health: Addiction*. 2001;5:29.
8. Clark N, Gospodarevskaya E, Harris A, Ritter A. Estimating the Cost of Heroin Use in Victoria. Report to the Premier's Drug Prevention Council Melbourne: Department of Human Services 2003 Available online at URL: http://www.druginfo.adf.org.au/hidden_articles/estimating_the_cost_of_heroin_1.html39. 2003.
9. Xie X, Single E, Robson L, Paul J. The economic costs of illicit drug use in Ontario, 1992. *Health Economics*. 1998;7(1):81-5.
10. Ruetsch C. Empirical view of opioid dependence. *Journal of Managed Care Pharmacy*. 2010;16(1):9-13.
11. Gomes T, Mamdani MM, Dhalla IA, Cornish S, Paterson JM, Juurlink DN. The burden of premature opioid-related mortality. *Addiction*. 2014;109(9):1482-8.
12. United Nations Office on Drugs and Crime. WORLD DRUG REPORT 2018 - United Nations Office on Drugs and Crime. 2018.
13. Erthal J, Berterame S, Clare P, Mattick RP. Hot Topic: Global Trends in the Use of Opioid Analgesics. *Current Addiction Reports*. 2019:1-8.
14. Norwegian Institute for Alcohol and Drug Research. The Drug Situation in Norway (Annual Report to EMCDDA), O. Hordvin, Editor. 2015, Norwegian Institute for Alcohol and Drug Research: Oslo. 2014.
15. Tyndale RF, Sellers EM. Opioids: The Painful Public Health Reality. *Clinical Pharmacology & Therapeutics*. 2018;103(6):924-35.
16. Mounteney J, Griffiths P, Sedefov R, Noor A, Vicente J, Simon R. The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. *Addiction*. 2016;111(1):34-48.
17. EMCDDA. European Drug Report—Trends and Developments 2015. European Monitoring Centre for Drugs and Drug Addiction Lisbon; 2015.
18. Sharma B, Bruner, A., Barnett, G., Fishman, M. Opioid use disorders. *Child and Adolescent Psychiatric Clinics*,. 2016;25(3):473-87.
19. Kreek MJ, Bart G, Lilly C, Laforge KS, Nielsen DA. Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. *Pharmacological reviews*. 2005;57(1):1-26.
20. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *Journal of addictive diseases*. 2012;31(3):207-25.

21. Wise RA. Opiate reward: sites and substrates. *Neuroscience & Biobehavioral Reviews*. 1989;13(2-3):129-33.
22. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug and alcohol dependence*. 2012;125(1-2):8-18.
23. Ronan MV, Herzig SJ. Hospitalizations related to opioid abuse/dependence and associated serious infections increased sharply, 2002–12. *Health Affairs*. 2016;35(5):832-7.
24. Samaan Z, MacKillop J, Dennis B, Bawor M. *Opioid Use Disorder*: Routledge; 2017. 124-49 p.
25. Hser Y-i, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Archives of general psychiatry*. 2001;58(5):503-8.
26. Ngo HT, Tait RJ, Hulse GK. Hospital psychiatric comorbidity and its role in heroin dependence treatment outcomes using naltrexone implant or methadone maintenance. *Journal of Psychopharmacology*. 2011;25(6):774-82.
27. Bogdanowicz KM, Stewart R, Broadbent M, Hatch SL, Hotopf M, Strang J, et al. Double trouble: Psychiatric comorbidity and opioid addiction—All-cause and cause-specific mortality. *Drug and alcohol dependence*. 2015;148:85-92.
28. Hayes RD, Chang C-K, Fernandes A, Broadbent M, Lee W, Hotopf M, et al. Associations between substance use disorder sub-groups, life expectancy and all-cause mortality in a large British specialist mental healthcare service. *Drug and alcohol dependence*. 2011;118(1):56-61.
29. Dickey B, Dembling B, Azeni H, Normand S-LL. Externally caused deaths for adults with substance use and mental disorders. *The journal of behavioral health services & research*. 2004;31(1):75-85.
30. Aizen R, Marcu G, Misra A, Sieber G, Schwartz DG, Roth A, et al., editors. Designing an emergency response community for opioid overdoses in Philadelphia. *Extended Abstracts of the 2018 CHI Conference on Human Factors in Computing Systems*; 2018: ACM.
31. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000–2014. *American Journal of Transplantation*. 2016;16(4):1323-7.
32. Seth P, Scholl L, Rudd RA, Bacon S. Overdose deaths involving opioids, cocaine, and psychostimulants—United States, 2015–2016. *Morbidity and Mortality Weekly Report*. 2018;67(12):349.
33. Seth P, Rudd RA, Noonan RK, Haegerich TM. Quantifying the epidemic of prescription opioid overdose deaths. *American Public Health Association*; 2018.
34. Gladden RM. Fentanyl law enforcement submissions and increases in synthetic opioid—involved overdose deaths—27 states, 2013–2014. *MMWR Morbidity and mortality weekly report*. 2016;65.
35. O'Donnell JK, Gladden RM, Seth P. Trends in deaths involving heroin and synthetic opioids excluding methadone, and law enforcement drug product reports, by census region—United States, 2006–2015. *MMWR Morbidity and mortality weekly report*. 2017;66(34):897.
36. European Monitoring Centre for Drugs and Drug Addiction. *EMCDDA, European Drug Report; Trends and Development*, 2018. 2018.
37. Tjagvad C, Skurtveit S, Linnet K, Andersen LV, Christoffersen DJ, Clausen T. Methadone-related overdose deaths in a liberal opioid maintenance treatment programme. *European addiction research*. 2016;22(5):249-58.
38. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug and alcohol dependence*. 2009;105(1-2):9-15.
39. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *Bmj*. 2010;341:c5475.
40. Cousins G, Teljeur C, Motterlini N, McCowan C, Dimitrov BD, Fahey T. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: a cohort study. *Journal of substance abuse treatment*. 2011;41(3):252-60.

41. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *bmj*. 2017;357:j1550.
42. Bukten A, Stavseth MR, Skurtveit S, Tverdal A, Strang J, Clausen T. High risk of overdose death following release from prison: variations in mortality during a 15-year observation period. *Addiction*. 2017;112(8):1432-9.
43. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*. 2011;106(1):32-51.
44. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone. *Clinical pharmacokinetics*. 2002;41(14):1153-93.
45. McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. *Bmj*. 2009;338:b2225.
46. Bell J, Trinh L, Butler B, Randall D, Rubin G. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. *Addiction*. 2009;104(7):1193-200.
47. Druid H, Strandberg JJ, Alkass K, Nyström I, Kugelberg FC, Kronstrand R. Evaluation of the role of abstinence in heroin overdose deaths using segmental hair analysis. *Forensic science international*. 2007;168(2-3):223-6.
48. Landheim AS, Bakken K, Vaglum P. Gender differences in the prevalence of symptom disorders and personality disorders among poly-substance abusers and pure alcoholics - Substance abusers treated in two counties in Norway. *European Addiction Research*. 2003;9(1):8-17.
49. Hintz T, Mann K. Comorbidity in alcohol use disorders: focus on mood, anxiety and personality. *Dual Diagnosis The Evolving Conceptual Framework*. 2005;172:65-91.
50. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. *Jama*. 1990;264(19):2511-8.
51. Strain EC. Assessment and treatment of comorbid psychiatric disorders in opioid-dependent patients. *The Clinical journal of pain*. 2002;18(4):S14-S27.
52. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of general psychiatry*. 1995;52(12):1048-60.
53. Wittchen H-U, Zhao S, Kessler RC, Eaton WW. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Archives of general psychiatry*. 1994;51(5):355-64.
54. Kranzler HR, Gelernter J, O'malley S, Hernandez-Avila CA, Kaufman D. Association of alcohol or other drug dependence with alleles of the μ opioid receptor gene (OPRM1). *Alcoholism: Clinical and Experimental Research*. 1998;22(6):1359-62.
55. Mahoney III JJ, Thompson-Lake DG, Cooper K, Verrico CD, Newton TF, De La Garza R. A comparison of impulsivity, depressive symptoms, lifetime stress and sensation seeking in healthy controls versus participants with cocaine or methamphetamine use disorders. *Journal of psychopharmacology*. 2015;29(1):50-6.
56. Pani PP, Vacca R, Trogu E, Amato L, Davoli M. Pharmacological treatment for depression during opioid agonist treatment for opioid dependence. *Cochrane Database of Systematic Reviews*. 2010(9).
57. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008;2(2).
58. Brienza RS, Stein MD, Chen M-H, Gogineni A, Sobota M, Maksad J, et al. Depression among needle exchange program and methadone maintenance clients. *Journal of substance abuse treatment*. 2000;18(4):331-7.
59. Teesson M, Havard A, Fairbairn S, Ross J, Lynskey M, Darke S. Depression among entrants to treatment for heroin dependence in the Australian Treatment Outcome Study (ATOS): prevalence, correlates and treatment seeking. *Drug and alcohol dependence*. 2005;78(3):309-15.

60. Milby JB, Sims MK, Khuder S, Schumacher JE, Huggins N, McLellan AT, et al. Psychiatric comorbidity: prevalence in methadone maintenance treatment. *The American journal of drug and alcohol abuse*. 1996;22(1):95-107.
61. Martins SS, Fenton MC, Keyes KM, Blanco C, Zhu H, Storr CL. Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. *Psychological medicine*. 2012;42(6):1261-72.
62. Bystritsky A, Khalsa SS, Cameron ME, Schiffman J. Current diagnosis and treatment of anxiety disorders. *Pharmacy and Therapeutics*. 2013;38(1):30.
63. Callaly T, Trauer T, Munro L, Whelan G. Prevalence of psychiatric disorder in a methadone maintenance population. *Australian & New Zealand Journal of Psychiatry*. 2001;35(5):601-5.
64. Bremner J. Functional neuroanatomical correlates of traumatic stress revisited 7 years later, this time with data. *Psychopharmacology bulletin*. 2003;37(2):6-25.
65. Schuckit MA. Comorbidity between substance use disorders and psychiatric conditions. *Addiction*. 2006;101:76-88.
66. Roncero C, Barral C, Rodríguez-Cintas L, Pérez-Pazos J, Martínez-Luna N, Casas M, et al. Psychiatric comorbidities in opioid-dependent patients undergoing a replacement therapy programme in Spain: The PROTEUS study. *Psychiatry Research*. 2016;243:174-81.
67. Benca RM. Sleep in psychiatric disorders. *Neurologic clinics*. 1996;14(4):739-64.
68. Judd L, Kessler R, Paulus M, Zeller P, Wittchen HU, Kunovac J. Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). *Acta Psychiatrica Scandinavica*. 1998;98:6-11.
69. Zimmermann P, Wittchen H-U, Höfler M, Pfister H, Kessler RC, Lieb R. Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychological medicine*. 2003;33(7):1211-22.
70. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clinical psychology review*. 2000;20(2):149-71.
71. Douglas KR, Chan G, Gelernter J, Arias AJ, Anton RF, Weiss RD, et al. Adverse childhood events as risk factors for substance dependence: partial mediation by mood and anxiety disorders. *Addictive behaviors*. 2010;35(1):7-13.
72. Burke Jr JD, Burke KC, Rae DS. Increased rates of drug abuse and dependence after onset of mood or anxiety disorders in adolescence. *Psychiatric Services*. 1994;45(5):451-5.
73. Zimmerman M, Chelminski I, McDermut W. Major depressive disorder and axis I diagnostic comorbidity. *The Journal of clinical psychiatry*. 2002.
74. Fava M, Rankin MA, Wright EC, Alpert JE, Nierenberg AA, Pava J, et al. Anxiety disorders in major depression. *Comprehensive psychiatry*. 2000;41(2):97-102.
75. Lynskey MT. The comorbidity of alcohol dependence and affective disorders: treatment implications. *Drug and alcohol dependence*. 1998;52(3):201-9.
76. Abraham HD, Fava M. Order of onset of substance abuse and depression in a sample of depressed outpatients. *Comprehensive Psychiatry*. 1999;40(1):44-50.
77. Rounsaville BJ, Weissman MM, Crits-Christoph K, Wilber C, Kleber H. Diagnosis and symptoms of depression in opiate addicts: Course and relationship to treatment outcome. *Archives of General Psychiatry*. 1982;39(2):151-6.
78. Ravndal E, Lauritzen G. Rusmisbruk, angst og depresjon etter 10 år: En prospektiv undersøkelse av stoffmisbrukere med og uten LAR-behandling. *Nordic Studies on Alcohol and Drugs*. 2015;32(5):495-508.
79. Verthein U, Degkwitz P, Haasen C, Krausz M. Significance of comorbidity for the long-term course of opiate dependence. *European addiction research*. 2005;11(1):15-21.
80. Tómasson K, Vaglum P. The 2-year course following detoxification treatment of substance abuse: the possible influence of psychiatric comorbidity. *European archives of psychiatry and clinical neuroscience*. 1997;247(6):320-7.

81. Öjehagen A, Schaar I. Förbättringsprocessen hos personer med svår psykisk störning och missbruksproblem: en långtidsuppföljning av Socialstyrelsens försöksverksamheter i samband med psykiatrireformen. (The process of recovery among severely mentally ill substance abusers: a long-term follow-up of a multicentre study in connection with the psychiatric care reform initiated by the Department of Social Affairs). Stockholm: Department of Social Affairs. 2004.
82. Schaar I, Öjehagen A. Severely mentally ill substance abusers: an 18-month follow-up study. *Social psychiatry and psychiatric epidemiology*. 2001;36(2):70-8.
83. Nishimoto RH, La Faune YG. The course of depressive symptoms over time for women who completed drug treatment. *Journal of substance abuse treatment*. 1997;14(2):123-31.
84. Strain EC, Stitzer ML, Bigelow GE. Early treatment time course of depressive symptoms in opiate addicts. *The Journal of nervous and mental disease*. 1991;179(4):215-21.
85. Limbeek Jv, Wouters L, Kaplan CD, Geerlings PJ, Alem Vv. Prevalence of psychopathology in drug-addicted Dutch. *Journal of substance abuse treatment*. 1992;9(1):43-52.
86. Darke S, Swift W, Hall W. Prevalence, severity and correlates of psychological morbidity among methadone maintenance clients. *Addiction*. 1994;89(2):211-7.
87. Rounsaville BJ, Kosten TR, Weissman MM, Kleber HD. Prognostic significance of psychopathology in treated opiate addicts: a 2.5-year follow-up study. *Archives of general psychiatry*. 1986;43(8):739-45.
88. Stein MD, Anderson BJ, Thurmond P, Bailey GL. Comparing the life concerns of prescription opioid and heroin users. *Journal of substance abuse treatment*. 2015;48(1):43-8.
89. Nunes EV, Sullivan MA, Levin FR. Treatment of depression in patients with opiate dependence. *Biological psychiatry*. 2004;56(10):793-802.
90. Rounsaville BJ, Weissman MM, Kleber H, Wilber C. Heterogeneity of psychiatric diagnosis in treated opiate addicts. *Archives of General Psychiatry*. 1982;39(2):161-6.
91. Marsden J, Gossop M, Stewart D, Rolfe A, Farrell M. Psychiatric symptoms among clients seeking treatment for drug dependence: Intake data from the National Treatment Outcome Research Study. *The British Journal of Psychiatry*. 2000;176(3):285-9.
92. Alterman AI, McLellan AT, Shifman RB. Do substance abuse patients with more psychopathology receive more treatment? *Journal of Nervous and Mental Disease*. 1993.
93. Koirala NR, Dev SV, Ojha SP, Pathak N. Prevalence of anxiety symptoms among the clients maintained in methadone maintenance treatment programme at Tribhuvan University Teaching Hospital. *Journal of Nobel Medical College*. 2011;1(1):15-9.
94. Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *Journal of clinical psychopharmacology*. 2005;25(2):141-50.
95. Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JR, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*. 2005;19(6):567-96.
96. Chan GM, Stajic M, Marker EK, Hoffman RS, Nelson LS. Testing positive for methadone and either a tricyclic antidepressant or a benzodiazepine is associated with an accidental overdose death: analysis of medical examiner data. *Academic emergency medicine*. 2006;13(5):543-7.
97. Shah N, Lathrop SL, Landen MG. Unintentional methadone-related overdose death in New Mexico (USA) and implications for surveillance, 1998–2002. *Addiction*. 2005;100(2):176-88.
98. Gelkopf M, Bleich A, Hayward R, Bodner G, Adelson M. Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: a 1 year prospective study in an Israeli clinic. *Drug and alcohol dependence*. 1999;55(1-2):63-8.
99. Preston KL, Griffiths R, Stitzer ML, Bigelow GE, Liebson IA. Diazepam and methadone interactions in methadone maintenance. *Clinical Pharmacology & Therapeutics*. 1984;36(4):534-41.
100. Griffiths RR, Weerts EM. Benzodiazepine self-administration in humans and laboratory animals—implications for problems of long-term use and abuse. *Psychopharmacology*. 1997;134(1):1-37.

101. Mattick RP, Ali R, White JM, O'brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction*. 2003;98(4):441-52.
102. Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clinical Pharmacology & Therapeutics*. 1999;66(3):306-14.
103. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clinical Pharmacology & Therapeutics*. 1994;55(5):569-80.
104. Nyhuis PW, Gastpar M, Scherbaum N. Opiate treatment in depression refractory to antidepressants and electroconvulsive therapy. *Journal of clinical psychopharmacology*. 2008;28(5):593-5.
105. Dean AJ, Bell J, Christie MJ, Mattick RP. Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. *European psychiatry : the journal of the Association of European Psychiatrists*. 2004;19(8):510-3.
106. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry*. 2006;67(2):247-57.
107. Fleming JA. *Insomnia: Epidemiology, Subtypes, and Relationship to Psychiatric Disorders*. *Sleep Disorders in Psychiatric Patients*: Springer; 2018. p. 99-107.
108. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep medicine reviews*. 2002;6(2):97-111.
109. Daley M, Morin CM, LeBlanc M, Grégoire J-P, Savard J. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. *Sleep*. 2009;32(1):55-64.
110. Weissman MM, Greenwald S, Niño-Murcia G, Dement WC. The morbidity of insomnia uncomplicated by psychiatric disorders. *General hospital psychiatry*. 1997;19(4):245-50.
111. Sivertsen B, Salo P, Mykletun A, Hysing M, Pallesen S, Krokstad S, et al. The bidirectional association between depression and insomnia: the HUNT study. *Psychosomatic Medicine*. 2012;74(7):758-65.
112. Fava M, McCall WV, Krystal A, Wessel T, Rubens R, Caron J, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biological psychiatry*. 2006;59(11):1052-60.
113. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601-8.
114. Peles E, Schreiber S, Adelson M. Variables associated with perceived sleep disorders in methadone maintenance treatment (MMT) patients. *Drug and alcohol dependence*. 2006;82(2):103-10.
115. Garcia AN, Salloum IM. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: a focused review. *The American journal on addictions*. 2015;24(7):590-8.
116. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *Jama*. 1989;262(11):1479-84.
117. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2007;3(5 Suppl):S7.
118. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment: prevalence and correlates. *Archives of general psychiatry*. 1985;42(3):225-32.
119. McCall WV. A psychiatric perspective on insomnia. *The Journal of clinical psychiatry*. 2001.
120. Colvonen PJ, Ellison J, Haller M, Norman SB. Examining insomnia and PTSD over time in veterans in residential treatment for substance use disorders and PTSD. *Behavioral sleep medicine*. 2018:1-12.
121. Kay DC, Pickworth WB, Neider G. Morphine-like insomnia from heroin in nondependent human addicts. *British journal of clinical pharmacology*. 1981;11(2):159-69.

122. Teichtahl H, Prodromidis A, Miller B, Cherry G, Kronborg I. Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction*. 2001;96(3):395-403.
123. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. *Archives of general psychiatry*. 1992;49(8):651-68.
124. Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A. Treatment of benzodiazepine dependence in methadone maintenance treatment patients: a comparison of two therapeutic modalities and the role of psychiatric comorbidity. *Australian & New Zealand Journal of Psychiatry*. 2003;37(4):458-63.
125. Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF. Insomnia, self-medication, and relapse to alcoholism. *American Journal of Psychiatry*. 2001;158(3):399-404.
126. Cheattle MD, Webster LR. Opioid therapy and sleep disorders: risks and mitigation strategies. *Pain Medicine*. 2015;16(suppl_1):S22-S6.
127. Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. *Sleep medicine reviews*. 2007;11(1):35-46.
128. Moore P, Dimsdale J. Opioids, sleep, and cancer-related fatigue. *Medical hypotheses*. 2002;58(1):77-82.
129. Farney RJ, McDonald AM, Boyle KM, Snow GL, Nuttall R, Coudreaut MF, et al. Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone. *European Respiratory Journal*. 2013;42(2):394-403.
130. Wang D, Lintzeris N, Leung S, Haber PS, Yee BJ, Grunstein RR. Reversal of central sleep apnoea with change from methadone to buprenorphine-naloxone: a case report. *European Respiratory Journal*. 2015;46(4):1202-5.
131. Dunn KE, Saulsgiver KA, Miller ME, Nuzzo PA, Sigmon SC. Characterizing opioid withdrawal during double-blind buprenorphine detoxification. *Drug and alcohol dependence*. 2015;151:47-55.
132. DeVido J, Connery H, Hill KP. Sleep-disordered breathing in patients with opioid use disorders in long-term maintenance on buprenorphine-naloxone: A case series. *Journal of opioid management*. 2015;11(4):363.
133. Zheng W, Wakim R, Geary R, Lander L, Wen S, Xiao M, et al. Self-reported sleep improvement in buprenorphine MAT (medication assisted treatment) population. *Austin journal of drug abuse and addiction*. 2016;3(1).
134. Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *Journal of Clinical Sleep Medicine*. 2007;3(05):455-61.
135. Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunningham D, et al. Central sleep apnea in stable methadone maintenance treatment patients. *Chest*. 2005;128(3):1348-56.
136. Teichtahl H, Wang D, Cunningham D, Quinnell T, Tran H, Kronborg I, et al. Ventilatory responses to hypoxia and hypercapnia in stable methadone maintenance treatment patients. *Chest*. 2005;128(3):1339-47.
137. Manber R, Edinger JD, Gress JL, Pedro-Salcedo MGS, Kuo TF, Kalista T. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep*. 2008;31(4):489-95.
138. Benson KL. Sleep in schizophrenia: pathology and treatment. *Sleep medicine clinics*. 2015;10(1):49-55.
139. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu H-G, et al. Cross-national epidemiology of major depression and bipolar disorder. *Jama*. 1996;276(4):293-9.
140. Ohayon MM, Shapiro CM, Kennedy SH. Differentiating DSM-IV anxiety and depressive disorders in the general population: comorbidity and treatment consequences. *The Canadian Journal of Psychiatry*. 2000;45(2):166-72.
141. Kupfer DJ, Spiker DG, Coble PA, Neil JF, Ulrich R, Shaw DH. Sleep and treatment prediction in endogenous depression. *The American journal of psychiatry*. 1981.

142. Ohayon MM, Caulet M, Arbus L, Billard M, Coquerel A, Guieu J-D, et al. Are prescribed medications effective in the treatment of insomnia complaints? *Journal of psychosomatic research*. 1999;47(4):359-68.
143. Reynolds CF, Kupfer D, McEachran A, Taska L, Sewitch D, Coble P. Depressive psychopathology in male sleep apneics. *The Journal of clinical psychiatry*. 1984.
144. Buysse DJ, Reynolds III CF, Kupfer DJ, Thorpy MJ, Bixler E, Manfredi R, et al. Clinical diagnoses in 216 insomnia patients using the International Classification of Sleep Disorders (ICSD), DSM-IV and ICD-10 categories: a report from the APA/NIMH DSM-IV Field Trial. *Sleep*. 1994;17(7):630-7.
145. Merskey HE. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. *Pain*. 1986.
146. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *Jama*. 1998;280(2):147-51.
147. Solanki DR, Koyyalagunta D, Shah RV, Silverman S, Manchikanti L. Monitoring opioid adherence in chronic pain patients: Assessment of risk of substance misuse. *Pain Physician*. 2011;14(2):E119-E31.
148. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol*. 2008;16(5):405-16.
149. McQuay H. Opioids in pain management. *The Lancet*. 1999;353(9171):2229-32.
150. Portenoy RK, Lesage P. Management of cancer pain. *The lancet*. 1999;353(9165):1695-700.
151. Schnoll SH, Weaver MF. Addiction and pain. *American Journal on Addictions*. 2003;12(2):S27-S35.
152. Jamison RN, Kerry Anne Sheehan B, Elizabeth Scanlan N, Ross EL. Beliefs and attitudes about opioid prescribing and chronic pain management: survey of primary care providers. *Journal of opioid management*. 2014;10(6):375-82.
153. Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain physician*. 2008;11(2 Suppl):S5-S62.
154. Ballantyne JC, LaForge SK. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-55.
155. Streltzer J, Johansen L. Prescription drug dependence and evolving beliefs about chronic pain management. *American Journal of Psychiatry*. 2006;163(4):594-8.
156. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. *New England Journal of Medicine*. 2015;372(3):241-8.
157. Institute of Medicine. Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington DC; 2011. Relieving Pain in America. National Academies Press Washington, DC; 2011.
158. Solis K. Ethical, legal, and professional challenges posed by "controlled medication seekers" to healthcare providers, part 2. *American Journal of Clinical Medicine*. 2010;7(2):86-92.
159. Reuben DB, Alvanzo AA, Ashikaga T, Bogat GA, Callahan CM, Ruffing V, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. *Annals of internal medicine*. 2015;162(4):295-300.
160. Jamison RN, Serrallier J, Michna E. Assessment and treatment of abuse risk in opioid prescribing for chronic pain. *Pain research and treatment*. 2011;2011.
161. Kuehn BM. Prescription drug abuse rises globally. *Jama*. 2007;297(12):1306-.
162. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med*. 2008;9(4):444-59.
163. Turner JA, Calsyn DA, Fordyce WE, Ready LB. Drug utilization patterns in chronic pain patients. *Pain*. 1982;12(4):357-63.

164. Ready LB, Sarkis E, Turner JA. Self-reported vs. actual use of medications in chronic pain patients. *Pain*. 1982;12(3):285-94.
165. Ling W, Mooney L, Hillhouse M. Prescription opioid abuse, pain and addiction: clinical issues and implications. *Drug and alcohol review*. 2011;30(3):300-5.
166. Han B, Compton WM, Jones CM, Cai R. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *Jama*. 2015;314(14):1468-78.
167. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *Jama*. 2008;300(22):2613-20.
168. Substance Abuse and Mental Health Services Administration. Office of Applied Studies. Results from 2007 National Survey on drug use and health. National Findings. 2008. . Substance Abuse and Mental Health Services Administration Rockville, MD; 2008.
169. Substance Abuse Mental Health Services Administration. Treatment Episode Data Set (TEDS). 2009. Substance Abuse and Mental Health Services Administration, Office of Applied Services, Based on administrative data reported by States to TEDS through July 1, 2010. 2010.
170. Fischer B, Rehm J. Illicit opioid use and treatment for opioid dependence: Challenges for Canada and beyond. SAGE Publications Sage CA: Los Angeles, CA; 2006.
171. The Royal Australasian College of Physicians. Prescription Opioid Policy: Improving Management of Chronic Non-malignant Pain and Prevention of Problems Associated with Prescription Opioid Use.: Royal Australasian College of Physicians; 2007.
172. Ballantyne JC. Assessing the prevalence of opioid misuse, abuse, and addiction in chronic pain. *Pain*. 2015;156(4):567-8.
173. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *Jama*. 2003;289(18):2370-8.
174. Compton P, Charuvastra VC, Kintaudi K, Ling W. Pain responses in methadone-maintained opioid abusers. *Journal of pain and symptom management*. 2000;20(4):237-45.
175. Benedikt RA, Kolb LC. Preliminary findings on chronic pain and posttraumatic stress disorder. *The American journal of psychiatry*. 1986.
176. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *The Clinical journal of pain*. 1992;8(2):77-85.
177. Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Medicine*. 2003;4(4):340-51.
178. Saper J, Lake Ar, Hamel R, Lutz T, Branca B, Sims D, et al. Daily scheduled opioids for intractable head pain: long-term observations of a treatment program. *Neurology*. 2004;62(10):1687-94.
179. Passik SD, Kirsh KL, Whitcomb L, Portenoy RK, Katz NP, Kleinman L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clinical therapeutics*. 2004;26(4):552-61.
180. Manchikanti L, Pampati V, Damron K, Beyer C, Barnhill R, Fellows B. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *The Journal of the Kentucky Medical Association*. 2003;101(11):511.
181. Portenoy RK, Ugarte C, Fuller I, Haas G. Population-based survey of pain in the United States: differences among white, African American, and Hispanic subjects. *The Journal of Pain*. 2004;5(6):317-28.
182. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *The lancet*. 1999;354(9186):1248-52.
183. Gureje O, Simon GE, Von Korff M. A cross-national study of the course of persistent pain in primary care. *Pain*. 2001;92(1-2):195-200.
184. Scimeca MM, Savage SR, Portenoy R, Lowinson J. Treatment of pain in methadone-maintained patients. *Mount Sinai Journal of Medicine*. 2000;67(5-6):412-22.

185. Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. *Pain*. 2001;90(1-2):91-6.
186. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. *Journal of pain and symptom management*. 2005;29(3):297-326.
187. Fishman MA, Kim PS. Buprenorphine for chronic pain: a systemic review. *Current pain and headache reports*. 2018;22(12):83.
188. Chow RM, Issa M. Buprenorphine. *Pain Medicine: Springer*; 2017. p. 159-60.
189. Malinoff HL, Barkin RL, Wilson G. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. *American journal of therapeutics*. 2005;12(5):379-84.
190. Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management. *The Clinical journal of pain*. 2008;24(2):93-7.
191. Purdue Pharma LP. Purdue Pharma LP. Butrans prescribing Information, 2014; (5). . 2014.
192. Budd K. Buprenorphine and the transdermal system: the ideal match in pain management. *International journal of clinical practice Supplement*. 2003(133):9-14; discussion 23-4.
193. Steiner D, Munera C, Hale M, Ripa S, Landau C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study. *The Journal of Pain*. 2011;12(11):1163-73.
194. Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13 179 patients. *Current medical research and opinion*. 2005;21(8):1147-56.
195. Kornfeld H, Reetz H. Transdermal buprenorphine, opioid rotation to sublingual buprenorphine, and the avoidance of precipitated withdrawal: a review of the literature and demonstration in three chronic pain patients treated with butrans. *American journal of therapeutics*. 2015;22(3):199-205.
196. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Jama*. 2016;315(15):1624-45.
197. Rauck RL, Potts J, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-naïve patients with moderate to severe chronic low back pain. *Postgraduate medicine*. 2016;128(1):1-11.
198. Wallace L, Kadakia A. Buprenorphine transdermal system utilization. *Postgraduate medicine*. 2017;129(1):81-6.
199. Yarlus A, Miller K, Wen W, Lynch SY, Ripa SR, Pergolizzi JV, et al. Buprenorphine Transdermal System Improves Sleep Quality and Reduces Sleep Disturbance in Patients with Moderate-to-Severe Chronic Low Back Pain: Results from Two Randomized Controlled Trials. *Pain Practice*. 2016;16(3):345-58.
200. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane Library*. 2009.
201. Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, et al. Treatment of patients with substance use disorders, American Psychiatric Association. *American Journal of Psychiatry*. 2006;163(8 Suppl):5-82.
202. Lobmaier P, Gossop M, Waal H, Bramness J. The pharmacological treatment of opioid addiction—a clinical perspective. *European journal of clinical pharmacology*. 2010;66(6):537-45.
203. Gowing L, Farrell M, Ali R, White JM. Alpha 2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews*. 2016(5).
204. Amato L, Davoli M, Ferri MM, Ali R. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews*. 2003(2).
205. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews*. 2009(3).
206. Soyka M. New developments in the management of opioid dependence: focus on sublingual buprenorphine–naloxone. *Substance abuse and rehabilitation*. 2015;6:1.
207. Stotts AL, Dodrill CL, Kosten TR. Opioid dependence treatment: options in pharmacotherapy. *Expert opinion on pharmacotherapy*. 2009;10(11):1727-40.

208. Davoli M, Amato L, Clark N, Farrell M, Hickman M, Hill S, et al. The role of Cochrane reviews in informing international guidelines: a case study of using the Grading of Recommendations, Assessment, Development and Evaluation system to develop World Health Organization guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. *Addiction*. 2015;110(6):891-8.
209. Dua T, Barbui C, Patel AA, Tablante EC, Thornicroft G, Saxena S. Discussion of the updated WHO recommendations for mental, neurological, and substance use disorders. *The Lancet Psychiatry*. 2016;3(11):1008-12.
210. O'Connor PG. Methods of detoxification and their role in treating patients with opioid dependence. *Jama*. 2005;294(8):961-3.
211. Cameron D, Allen D, Galway K. A pilot study of the effectiveness of buprenorphine and methadone as detoxification agents when choice is given to the consumer. *Journal of Substance Use*. 2001;6(2):101-9.
212. Suzuki J, Ellison TV, Connery HS, Surber C, Renner JA. Training in buprenorphine and office-based opioid treatment: a survey of psychiatry residency training programs. *Academic Psychiatry*. 2016;40(3):498-502.
213. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Archives of general psychiatry*. 2006;63(2):210-8.
214. Lee JD, Friedmann PD, Kinlock TW, Nunes EV, Boney TY, Hoskinson RA, Jr., et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *The New England journal of medicine*. 2016;374(13):1232-42.
215. Coviello DM, Cornish JW, Lynch KG, Boney TY, Clark CA, Lee JD, et al. A multisite pilot study of extended-release injectable naltrexone treatment for previously opioid-dependent parolees and probationers. *Substance Abuse*. 2012;33(1):48-59.
216. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. *New England Journal of Medicine*. 2014;370(22):2063-6.
217. Schwartz RP, Gryczynski J, O'grady KE, Sharfstein JM, Warren G, Olsen Y, et al. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995–2009. *American journal of public health*. 2013;103(5):917-22.
218. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane database of systematic reviews*. 2014(2).
219. Ayanga D, Shorter D, Kosten TR. Update on pharmacotherapy for treatment of opioid use disorder. *Expert opinion on pharmacotherapy*. 2016;17(17):2307-18.
220. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*. 2014;109(1):79-87.
221. Substance Abuse and Mental Health Services administration. National survey on drug use and health: conducted by Substance abuse and Mental health Services Administration (SAMSHA). . 2014.
222. Lawrinson P, Ali R, Buavirat A, Chiamwongpaet S, Dvoryak S, Habrat B, et al. Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. *Addiction*. 2008;103(9):1484-92.
223. Hubbard RL, Craddock SG, Anderson J. Overview of 5-year followup outcomes in the drug abuse treatment outcome studies (DATOS). *Journal of substance abuse treatment*. 2003;25(3):125-34.
224. Gossop M. The National Treatment Outcomes Research Study (NTORS) and its influence on addiction treatment policy in the United Kingdom. *Addiction*. 2015;110:50-3.
225. Kimber J, Larney S, Hickman M, Randall D, Degenhardt L. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. *The Lancet Psychiatry*. 2015;2(10):901-8.

226. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. *Jama*. 2001;285(1):45-.
227. Soyka M, Apelt SM, Lieb M, Wittchen H-U. One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy: a nationally representative cohort study in 2694 patients. *Journal of clinical psychopharmacology*. 2006;26(6):657-60.
228. Pirnay S, Borron S, Giudicelli C, Tourneau J, Baud F, Ricordel I. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. *Addiction*. 2004;99(8):978-88.
229. Martin WR, Jasinski DR, Haertzen CA, Kay DC, Jones B, Mansky PA, et al. Methadone—a reevaluation. *Archives of General Psychiatry*. 1973;28(2):286-95.
230. Lewis J. Buprenorphine. *Drug and alcohol dependence*. 1985;14(3-4):363-72.
231. Orman JS, Keating GM. Buprenorphine/naloxone. *Drugs*. 2009;69(5):577-607.
232. College of Physicians and Surgeons of Ontario. Methadone Program. (2011). Methadone maintenance treatment program standards and clinical guidelines. College of Physicians and Surgeons of Ontario.: College of Physicians and Surgeons of Ontario; 2011.
233. Pollack HA, D'annunzio T. Dosage patterns in methadone treatment: results from a national survey, 1988–2005. *Health services research*. 2008;43(6):2143-63.
234. D'Aunno T, Pollack HA, Frimpong JA, Wuchiet D. Evidence-based treatment for opioid disorders: a 23-year national study of methadone dose levels. *Journal of substance abuse treatment*. 2014;47(4):245-50.
235. College of Physicians and Surgeons of Ontario. Methadone maintenance treatment program standards and clinical guidelines; College of Physicians and Surgeons, Ontario; 2011. : College of Physicians and Surgeons of Ontario; 2011.
236. Leece P, Cavacuiti C, Macdonald EM, Gomes T, Kahan M, Srivastava A, et al. Predictors of opioid-related death during methadone therapy. *Journal of substance abuse treatment*. 2015;57:30-5.
237. Lingford-Hughes AR, Welch S, Peters L, Nutt D. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. *Journal of Psychopharmacology*. 2012;26(7):899-952.
238. Lintzeris N, Leung S, Dunlop A, Larance B, White N, Rivas G, et al. A randomised controlled trial of sublingual buprenorphine–naloxone film versus tablets in the management of opioid dependence. *Drug and alcohol dependence*. 2013;131(1-2):119-26.
239. Wright N, D'agnone O, Krajci P, Littlewood R, Alho H, Reimer J, et al. Addressing misuse and diversion of opioid substitution medication: guidance based on systematic evidence review and real-world experience. *Journal of Public Health*. 2016;38(3):e368-e74.
240. Ajayi T. Drug Misuse and Dependence: UK Guidelines on Clinical Management-Department of Health (England) and the devolved administrations, Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive, 2007, 128 pp. *Psychiatric Bulletin*. 2008;32(9):360-.
241. Lintzeris N, Clark N, Winstock A, Dunlop A, Muhleisen P, Gowing L, et al. National clinical guidelines and procedures for the use of buprenorphine in the treatment of opioid dependence. Canberra: Commonwealth of Australia. 2006.
242. Gowing L, Ali R, Dunlop A, Farrell M, Lintzeris N. National guidelines for medication-assisted treatment of opioid dependence. Commonwealth of Australia, Canberra. 2014:38-9.
243. Hooman Khademi M, Farin Kamangar M, Paul Brennan M, Reza Malekzadeh M. Opioid therapy and its side effects: a review. *Archives of Iranian medicine*. 2016;19(12):870.
244. Darke S, Degenhardt L, Mattick R. Mortality amongst illicit drug users: epidemiology, causes and intervention: Cambridge University Press; 2006.
245. Brugal M, Domingo-Salvany A, Puig R, Barrio G, Garcia de Olalla P, De La Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction*. 2005;100(7):981-9.

246. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. *Drug and alcohol dependence*. 2008;94(1-3):151-7.
247. Magura S, Rosenblum A. Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. *The Mount Sinai Journal of Medicine, New York*. 2001;68(1):62-74.
248. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. *Journal of addictive diseases*. 2016;35(1):22-35.
249. Waal H, Bussesund K, Clausen T, Håseth A, Lillevold PH. The Annual OMT Status Survey for 2012 (In Norwegian only: LAR som det vil bli fremover?), 2013. . Norwegian Senter for Addiction Research. , 2013 Contract No.: 2013.
250. Waal H, Busserud K, Clausen T, Skeie I, Lillevold P. The Annual OMT Status Survey for 2015 (in Norwegian Only: Statusrapport 2015 - Mot grensene for vekst og nytte). 2016, Norwegian Senter for Addiction Research. . Norwegian Senter for Addiction Research 2016.
251. Waal B, Clausen S. The Annual OMT status Survey for 2016 (in Norwegian only: Statusrapport 2016-Er kvalitetsforbedring nå viktigere enn kapasitetsutvikling?). 2017, Norwegian Senter for Addiction Research. . Norwegian Senter for Addiction Research. , 2017.
252. Riksheim M, Gossop M, Clausen T. From methadone to buprenorphine: changes during a 10 year period within a national opioid maintenance treatment programme. *Journal of substance abuse treatment*. 2014;46(3):291-4.
253. Clark RE, Baxter JD. Responses of state Medicaid programs to buprenorphine diversion: doing more harm than good? *JAMA internal medicine*. 2013;173(17):1571-2.
254. Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. *Journal of addiction medicine*. 2014;8(5):315.
255. Lofwall MR, Havens JR. Inability to access buprenorphine treatment as a risk factor for using diverted buprenorphine. *Drug and alcohol dependence*. 2012;126(3):379-83.
256. Resnick RB, Volavka J, Freedman AM, Thomas M. Studies of EN-1639A (naltrexone): a new narcotic antagonist. *American Journal of Psychiatry*. 1974;131(6):646-50.
257. Verebey K, Mule S. Naltrexone pharmacology, pharmacokinetics, and metabolism: current status. *The American journal of drug and alcohol abuse*. 1975;2(3-4):357-63.
258. Tanum L, Solli KK, Benth JŠ, Opheim A, Sharma-Haase K, Krajci P, et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. *JAMA psychiatry*. 2017;74(12):1197-205.
259. Lee JD, Nunes Jr EV, Novo P, Bachrach K, Bailey GL, Bhatt S, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X: BOT): a multicentre, open-label, randomised controlled trial. *The Lancet*. 2017.
260. Roozen HG, de Waart R, van den Brink W. Efficacy and tolerability of naltrexone in the treatment of alcohol dependence: oral versus injectable delivery. *European addiction research*. 2007;13(4):201-6.
261. Anton RF. Naltrexone for the management of alcohol dependence. *New England Journal of Medicine*. 2008;359(7):715-21.
262. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clinical rheumatology*. 2014;33(4):451-9.
263. Lobmaier P, Kornor H, Kunoe N, Bjørndal A. Sustained-release naltrexone for opioid dependence. *The Cochrane Library*. 2008.
264. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Archives of general psychiatry*. 1992;49(11):876-80.
265. Gonzalez JP, Brogden RN. Naltrexone. *Drugs*. 1988;35(3):192-213.
266. Brewer C, Wong VS. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. *Addiction biology*. 2004;9(1):81-7.
267. Yen M-H, Ko H-C, Tang F-I, Lu R-B, Hong J-S. Study of hepatotoxicity of naltrexone in the treatment of alcoholism. *Alcohol*. 2006;38(2):117-20.

268. Degenhardt L, Larney S, Kimber J, Farrell M, Hall W. Excess mortality among opioid-using patients treated with oral naltrexone in Australia. *Drug and alcohol review*. 2015;34(1):90-6.
269. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harvard review of psychiatry*. 2015;23(2):63-75.
270. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database of Systematic Reviews*. 2011(4).
271. Larney S, Gowing L, Mattick RP, Farrell M, Hall W, Degenhardt L. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. *Drug and alcohol review*. 2014;33(2):115-28.
272. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Current psychiatry reports*. 2010;12(5):448-53.
273. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. *Arch Gen Psychiatry*. 2009;66(10):1108-15.
274. Waal H, Frogopsahl G, Olsen L, Christophersen AS, Mørland J. Naltrexone implants—duration, tolerability and clinical usefulness. *European addiction research*. 2006;12(3):138-44.
275. Kunøe N, Lobmaier P, Vederhus JK, Hjerkin B, Hegstad S, Gossop M, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. *The British Journal of Psychiatry*. 2009;194(6):541-6.
276. Tiihonen J, Krupitsky E, Verbitskaya E, Blokhina E, Mamontova O, Föhr J, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. *American Journal of Psychiatry*. 2012;169(5):531-6.
277. Waal H, Christophersen A, Frogopsahl G, Olsen L, Mørland J. Naltrexone implants—a pilot project. *Journal for The Norwegian Doctors Association; Journal for The Practical medicine (In Norwegian only; Tidsskrift for den Norske lægeforening; tidsskrift for praktisk medicin)*. 2003;123(12):1660-1.
278. Woody GE. Antagonist models for treating persons with substance use disorders. *Current psychiatry reports*. 2014;16(10):489.
279. Lobmaier PP, Kunøe N, Gossop M, Katevoll T, Waal H. Naltrexone implants compared to methadone: outcomes six months after prison release. *European addiction research*. 2010;16(3):139-45.
280. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence. *The Lancet*. 2011;378(9792):665.
281. Crits-Christoph P, Markell HM, Gibbons MB, Gallop R, Lundy C, Stringer M, et al. A Naturalistic Evaluation of Extended-Release Naltrexone in Clinical Practice in Missouri. *J Subst Abuse Treat*. 2016;70:50-7.
282. Sullivan MA, Vosburg SK, Comer SD. Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. *Psychopharmacology*. 2006;189(1):37-46.
283. Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. *Addiction*. 2013;108(9):1628-37.
284. Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. *Annals of the New York Academy of Sciences*. 2011;1216(1):144-66.
285. Bigelow GE, Preston KL, Schmittner J, Dong Q, Gastfriend DR. Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: Dose—effects and time-course. *Drug and alcohol dependence*. 2012;123(1-3):57-65.
286. Kunøe N, Lobmaier P, Ngo H, Hulse G. Injectable and implantable sustained release naltrexone in the treatment of opioid addiction. *British journal of clinical pharmacology*. 2014;77(2):264-71.

287. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *Jama*. 2005;293(13):1617-25.
288. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *The Lancet*. 2011;377(9776):1506-13.
289. Wolfe D, Carrieri MP, Dasgupta N, Wodak A, Newman R, Bruce RD. Concerns about injectable naltrexone for opioid dependence. *The Lancet*. 2011;377(9776):1468-70.
290. Korthuis PT, Lum PJ, Vergara-Rodriguez P, Ahamad K, Wood E, Kunkel LE, et al. Feasibility and safety of extended-release naltrexone treatment of opioid and alcohol use disorder in HIV clinics: a pilot/feasibility randomized trial. *Addiction*. 2017;112(6):1036-44.
291. Mysels DJ, Cheng WY, Nunes EV, Sullivan MA. The association between naltrexone treatment and symptoms of depression in opioid-dependent patients. *Am J Drug Alcohol Abuse*. 2011;37(1):22-6.
292. Food and Drug Administration UF. Psychopharmacologic drugs advisory committee meeting; Vivitrol (naltrexone for extended-release injectable suspension), NDA 21-897. . 2010.
293. Earley PH, Zummo J, Memisoglu A, Silverman BL, Gastfriend DR. Open-label Study of Injectable Extended-release Naltrexone (XR-NTX) in Healthcare Professionals With Opioid Dependence. *Journal of addiction medicine*. 2017;11(3):224-30.
294. Digiusto E, Shakeshaft A, Ritter A, O'brien S, Mattick RP, Group NR. Serious adverse events in the Australian national evaluation of pharmacotherapies for opioid dependence (NEPOD). *Addiction*. 2004;99(4):450-60.
295. Kelty E, Hulse G. Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. *The International journal on drug policy*. 2017;46:54-60.
296. Williams AR, Barbieri V, Mishlen K, Levin FR, Nunes EV, Mariani JJ, et al. Long-term follow-up study of community-based patients receiving XR-NTX for opioid use disorders. *The American journal on addictions*. 2017;26(4):319-25.
297. Woody GE. Advances in the treatment of opioid use disorders. *F1000Research*. 2017;6.
298. Ramsey SE, Rounsaville D, Hoskinson R, Park TW, Ames EG, Neirinckx VD, et al. The need for psychosocial interventions to facilitate the transition to extended-release naltrexone (XR-NTX) treatment for opioid dependence: a concise review of the literature. *Substance abuse: research and treatment*. 2016;10:SART. S39067.
299. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database of Systematic Reviews*. 2011(9).
300. DeFulio A, Everly JJ, Leoutsakos J-MS, Umbricht A, Fingerhood M, Bigelow GE, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. *Drug and alcohol dependence*. 2012;120(1-3):48-54.
301. Jarvis BP, Holtyn AF, DeFulio A, Dunn KE, Everly JJ, Leoutsakos JMS, et al. Effects of incentives for naltrexone adherence on opiate abstinence in heroin-dependent adults. *Addiction*. 2017;112(5):830-7.
302. Everly JJ, DeFulio A, Koffarnus MN, Leoutsakos JM, Donlin WD, Aklon WM, et al. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: a randomized controlled trial. *Addiction*. 2011;106(7):1309-18.
303. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. *Addiction*. 2006;101(4):491-503.
304. Farabee D, Hillhouse M, Condon T, McCrady B, McCollister K, Ling W. Injectable pharmacotherapy for opioid use disorders (IPOD). *Contemporary clinical trials*. 2016;49:70-7.

305. Leslie DL, Milchak W, Gastfriend DR, Herschman PL, Bixler EO, Velott DL, et al. Effects of injectable extended-release naltrexone (XR-NTX) for opioid dependence on residential rehabilitation outcomes and early follow-up. *The American journal on addictions*. 2015;24(3):265-70.
306. Powell JE, Taylor D. Anger, depression, and anxiety following heroin withdrawal. *International journal of the addictions*. 1991;27(1):25-35.
307. Dean AJ, Saunders JB, Jones RT, Young RM, Connor JP, Lawford BR. Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence. *Journal of Psychiatry and Neuroscience*. 2006;31(1):38.
308. Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, et al. Anhedonia, depression, anxiety, and craving in opiate dependent patients stabilized on oral naltrexone or an extended release naltrexone implant. *The American Journal of Drug and Alcohol Abuse*. 2016;42(5):614-20.
309. Miotto K, McCann M, Basch J, Rawson R, Ling W. Naltrexone and dysphoria: fact or myth? *American Journal on Addictions*. 2002;11(2):151-60.
310. Mendelson JH, Ellingboe J, Keuhle JC, Mello NK. Effects of naltrexone on mood and neuroendocrine function in normal adult males. *Psychoneuroendocrinology*. 1978;3(3-4):231-6.
311. Miotto K, McCann MJ, Rawson RA, Frosch D, Ling W. Overdose, suicide attempts and death among a cohort of naltrexone-treated opioid addicts. *Drug & Alcohol Dependence*. 1997;45(1):131-4.
312. Crowley TJ, Wagner JE, Zerbe G, Macdonald M. Naltrexone-induced dysphoria in former opioid addicts. *The American journal of psychiatry*. 1985;142(9):1081-4.
313. Rea F, Bell JR, Young MR, Mattick RP. A randomised, controlled trial of low dose naltrexone for the treatment of opioid dependence. *Drug and alcohol dependence*. 2004;75(1):79-88.
314. Hollister LE, Johnson K, Boukhabza D, Gillespie HK. Aversive effects of naltrexone in subjects not dependent on opiates. *Drug and alcohol dependence*. 1981;8(1):37-41.
315. Petrakis IL, Poling J, Levinson C, Nich C, Carroll K, Rounsaville B, et al. Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. *Biological psychiatry*. 2005;57(10):1128-37.
316. Latt NC, Jurd S, Houseman J, Wutzke SE. Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting. *Medical Journal of Australia*. 2002;176(11):530-4.
317. Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, et al. Anhedonia, depression, anxiety, and craving in opioid dependent patients stabilized on oral naltrexone or naltrexone implant. *Journal of Neurology and Psychiatry named after S Korsakov (Zhurnal nevrologii i psikiatrii imeni SS Korsakova)*. 2018;118(1. Vyp. 2):26-33.
318. Ritter AJ. Naltrexone in the treatment of heroin dependence: relationship with depression and risk of overdose. *Australian & New Zealand Journal of Psychiatry*. 2002;36(2):224-8.
319. Wong MM, Brower KJ, Nigg JT, Zucker RA. Childhood sleep problems, response inhibition, and alcohol and drug outcomes in adolescence and young adulthood. *Alcoholism: Clinical and Experimental Research*. 2010;34(6):1033-44.
320. Ara A, Jacobs W, Bhat IA, McCall WV. Sleep disturbances and substance use disorders: A bi-directional relationship. *Psychiatric Annals*. 2016;46(7):408-12.
321. Doufas AG, Panagiotou OA, Panousis P, Wong SS, Ioannidis JP, editors. *Insomnia from drug treatments: evidence from meta-analyses of randomized trials and concordance with prescribing information*. Mayo Clinic Proceedings; 2017: Elsevier.
322. Stein C, Schäfer M, Machelska H. Attacking pain at its source: new perspectives on opioids. *Nature medicine*. 2003;9(8):1003.
323. DeLeo JA, Yeziarski RP. The role of neuroinflammation and neuroimmune activation in persistent pain. *Pain*. 2001;90(1):1-6.
324. Wang D, Sun X, Sadee W. Different effects of opioid antagonists on μ -, δ -, and κ -opioid receptors with and without agonist pretreatment. *Journal of Pharmacology and Experimental Therapeutics*. 2007;321(2):544-52.

325. Lewis SS, Loram LC, Hutchinson MR, Li C-M, Zhang Y, Maier SF, et al. (+)-naloxone, an opioid-inactive toll-like receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats. *The Journal of Pain*. 2012;13(5):498-506.
326. Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, Sholar PW, et al. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). *European Journal of Neuroscience*. 2008;28(1):20-9.
327. Price RC, Christou NV, Backman SB, Stone L, Schweinhardt P. Opioid-receptor antagonism increases pain and decreases pleasure in obese and non-obese individuals. *Psychopharmacology*. 2016;233(23-24):3869-79.
328. Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis & Rheumatology*. 2013;65(2):529-38.
329. Compton P. Pain tolerance in opioid addicts on and off naltrexone pharmacotherapy: a pilot study. *Journal of pain and symptom management*. 1998;16(1):21-8.
330. Welsch P, Sommer C, Schiltenswolf M, Häuser W. Opioids in chronic noncancer pain—are opioids superior to nonopioid analgesics? 2015.
331. Cruciani RA, Lussier D, Miller-Saultz D, Arbuck DM. Ultra-low dose oral naltrexone decreases side effects and potentiates the effect of methadone. *Journal of pain and symptom management*. 2003;25(6):491-4.
332. Chindalore VL, Craven RA, Yu KP, Butera PG, Burns LH, Friedmann N. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: a randomized, controlled trial of Oxytrex. *The journal of pain : official journal of the American Pain Society*. 2005;6(6):392-9.
333. Cepeda MS, Africano JM, Manrique AM, Fragosó W, Carr DB. The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. *Pain*. 2002;96(1-2):73-9.
334. Department of Health. National Guidelines for Pharmacological Treatment to Opioid Dependent, D.o.Health, Editor. 2010, Department of Health; Oslo. 2010.
335. Friedmann PD, Wilson D, Nunes EV, Hoskinson Jr R, Lee JD, Gordon M, et al. Do patient characteristics moderate the effect of extended-release naltrexone (XR-NTX) for opioid use disorder? *Journal of substance abuse treatment*. 2018;85:61-5.
336. Hser Y-I, Evans E, Grella C, Ling W, Anglin D. Long-term course of opioid addiction. *Harvard review of psychiatry*. 2015;23(2):76-89.
337. Sullivan MA, Bisaga A, Glass A, Mishlen K, Pavlicova M, Carpenter KM, et al. Opioid use and dropout in patients receiving oral naltrexone with or without single administration of injection naltrexone. *Drug and alcohol dependence*. 2015;147:122-9.
338. Sullivan MA, Garawi F, Bisaga A, Comer SD, Carpenter K, Raby WN, et al. Management of relapse in naltrexone maintenance for heroin dependence. *Drug and alcohol dependence*. 2007;91(2-3):289-92.
339. Rothenberg JL, Sullivan MA, Church SH, Seracini A, Collins E, Kleber HD, et al. Behavioral naltrexone therapy: an integrated treatment for opiate dependence. *Journal of substance abuse treatment*. 2002;23(4):351-60.
340. Kunøe N, Opheim A, Solli KK, Gaulen Z, Sharma-Haase K, Tanum L. Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacology and Toxicology*. 2016;17(1):18.
341. Tanum. Naltrexone vs Buprenorphine-Naloxone for Opioid dependence in Norway. 2012: ClinicalTrials.Gov. . 2012.
342. Kokkevi A, Hartgers C. EuropASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *European addiction research*. 1995;1(4):208-10.
343. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux P, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery*. 2012;10(1):28-55.

344. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International journal of surgery*. 2014;12(12):1495-9.
345. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of clinical psychiatry*. 1998.
346. Sobell LC, Sobell MB. Timeline follow-back. *Measuring alcohol consumption*: Springer; 1992. p. 41-72.
347. Feightner JW, Worrall G. Early detection of depression by primary care physicians. *CMAJ: Canadian Medical Association Journal*. 1990;142(11):1215.
348. Lipman RS, Covi L, Shapiro AK. The Hopkins Symptom Checklist (HSCL): factors derived from the HSCL-90. *Journal of affective disorders*. 1979;1(1):9-24.
349. Sandanger I, Moum T, Ingebrigtsen G, Dalgard O, Sørensen T, Bruusgaard D. Concordance between symptom screening and diagnostic procedure: the Hopkins Symptom Checklist-25 and the Composite International Diagnostic Interview I. *Social psychiatry and psychiatric epidemiology*. 1998;33(7):345-54.
350. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behavioral science*. 1974;19(1):1-15.
351. Pavot W, Diener E, Suh E. The temporal satisfaction with life scale. *Journal of Personality Assessment*. 1998;70(2):340-54.
352. Melzack R. The short-form McGill pain questionnaire. *Pain*. 1987;30(2):191-7.
353. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1(3):277-99.
354. Melzack R, Katz J. *The McGill Pain Questionnaire: Appraisal and current status*: Guilford Press; 2001.
355. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep medicine*. 2001;2(4):297-307.
356. Miller WR, Tonigan JS. Assessing drinkers' motivation for change: the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). *Psychology of addictive behaviors*. 1996;10(2):81.
357. Derogatis L, Lipman R, Covi I. The SCL-90: An outpatient psychiatric rating scale. *Psychopharmacology Bulletin*. 1973;9(1):13-28.
358. Derogatis LR, Savitz KL. The SCL-90-R, Brief Symptom Inventory, and Matching Clinical Rating Scales. 1999.
359. Parloff MB, Kelman HC, Frank JD. Comfort, effectiveness, and self-awareness as criteria of improvement in psychotherapy. *American Journal of Psychiatry*. 1954;111(5):343-52.
360. Murphy J. Psychiatric instrument development for primary care research: patient self-report questionnaire. Report on Contract. 1981(80M01428101D).
361. Nettelbladt P, Hansson L, Stefansson C-G, Borgquist L, Nordström G. Test characteristics of the Hopkins Symptom Check List-25 (HSCL-25) in Sweden, using the Present State Examination (PSE-9) as a caseness criterion. *Social psychiatry and psychiatric epidemiology*. 1993;28(3):130-3.
362. Munk-Jørgensen P, Fink P, Brevik J, Dalgard O, Engberg M, Hansson L, et al. Psychiatric morbidity in primary public health care: a multicentre investigation. Part II. Hidden morbidity and choice of treatment. *Acta Psychiatrica Scandinavica*. 1997;95(1):6-12.
363. Raskin A, Schulterbrandt JG, Reatig N, Chase C, McKeon JJ. Differential response to chlorpromazine, imipramine, and placebo: A study of subgroups of hospitalized depressed patients. *Archives of General Psychiatry*. 1970;23(2):164-73.
364. Rickels K, Lipman RS, Garcia C-R, Fisher E. Evaluating clinical improvement in anxious outpatients: A comparison of normal and treated neurotic patients. *American Journal of Psychiatry*. 1972;128(8):1005-9.
365. Hesbacher PT, Rickels K, Morris RJ, Newman H, Rosenfeld H. Psychiatric illness in family practice. *The Journal of clinical psychiatry*. 1980.

366. Khuon F, Lavelle J. Indochinese versions of the Hopkins Symptom Checklist-25: a screening instrument for the psychiatric care of refugees. *Am J Psychiatry*. 1987;144(4):497-500.
367. Carlson EB, Rosser-Hogan R. Mental health status of Cambodian refugees ten years after leaving their homes. *American Journal of Orthopsychiatry*. 1993;63(2):223.
368. Veijola J, Jokelainen J, Läksy K, Kantojärvi L, Kokkonen P, Järvelin M-R, et al. The Hopkins Symptom Checklist-25 in screening DSM-III-R axis-I disorders. *Nordic journal of psychiatry*. 2003;57(2):119-23.
369. Pernice R, Brook J. Refugees' and immigrants' mental health: Association of demographic and post-immigration factors. *The Journal of social psychology*. 1996;136(4):511-9.
370. Mollica RF, Poole C, Son L, Murray CC, Tor S. Effects of war trauma on Cambodian refugee adolescents' functional health and mental health status. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(8):1098-106.
371. Moum T. Mode of administration and interviewer effects in self-reported symptoms of anxiety and depression. *Social Indicators Research*. 1998;45(1):279-318.
372. Reading AE. Testing pain mechanisms in persons in pain. *Textbook of pain*. 1989;2:269-83.
373. Ljunggren AE. Descriptions of pain and other sensory modalities in patients with lumbago-sciatica and herniated intervertebral discs. Interview administration of an adapted McGill Pain Questionnaire. *Pain*. 1983;16(3):265-76.
374. Strand LI, Wisnes AR. The development of a Norwegian pain questionnaire. *Pain*. 1991;46(1):61-6.
375. Kim HS, Schwartz-Barcott D, Holter IM, Lorensen M. Developing a translation of the McGill pain questionnaire for cross-cultural comparison: an example from Norway. *Journal of advanced nursing*. 1995;21(3):421-6.
376. Ljunggren AE, Strand LI, Johnsen TB. Development of the Norwegian Short-Form McGill Pain Questionnaire (NSF-MPQ). *Advances in Physiotherapy*. 2009;9(4):169-80.
377. Grafton KV, Foster NE, Wright CC. Test-retest reliability of the Short-Form McGill Pain Questionnaire: assessment of intraclass correlation coefficients and limits of agreement in patients with osteoarthritis. *The Clinical journal of pain*. 2005;21(1):73-82.
378. Huskisson E. Visual analogue scales. *Pain measurement and assessment*. 1983:33-7.
379. Helsinki. Do. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama*. 2013;310(20):2191-4.
380. Kirkwood BRaS, J. A. C., . *Essential medical statistics*. "nd Edition. ed. 2003, Malden: Blackwell. : John Wiley & Sons; 2003.
381. Nunes EV, Lee JD, Sisti D, Segal A, Caplan A, Fishman M, et al. Ethical and clinical safety considerations in the design of an effectiveness trial: A comparison of buprenorphine versus naltrexone treatment for opioid dependence. *Contemporary clinical trials*. 2016;51:34-43.
382. Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. *Bmj*. 2010;340:c2697.
383. Farnier M, Freeman MW, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *European heart journal*. 2005;26(9):897-905.
384. Young JM, Feldman RA, Auerbach SM, Kaufman JM, Garcia CS, Shen W, et al. Tadalafil improved erectile function at twenty-four and thirty-six hours after dosing in men with erectile dysfunction: US trial. *Journal of andrology*. 2005;26(3):310-8.
385. Solomkin JS, Wilson SE, Christou NV, Rotstein OD, Dellinger EP, Bennion RS, et al. Results of a clinical trial of clinafloxacin versus imipenem/cilastatin for intraabdominal infections. *Annals of surgery*. 2001;233(1):79.
386. Dossing A, Tarp S, Furst DE, Gluud C, Wells GA, Beyene J, et al. Modified intention-to-treat analysis did not bias trial results. *Journal of clinical epidemiology*. 2016;72:66-74.
387. Abraha I, Cherubini A, Cozzolino F, De Florio R, Luchetta ML, Rimland JM, et al. Deviation from intention to treat analysis in randomised trials and treatment effect estimates: meta-epidemiological study. *bmj*. 2015;350:h2445.

388. Gupta SK. Intention-to-treat concept: a review. *Perspectives in clinical research*. 2011;2(3):109.
389. Miller LE, Stewart ME. The blind leading the blind: use and misuse of blinding in randomized controlled trials. *Contemporary Clinical Trials*. 2011;32(2):240-3.
390. Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Archives of general psychiatry*. 2012;69(9):973-81.
391. Magura S, Lee JD, Hersherberger J, Joseph H, Marsch L, Shropshire C, et al. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. *Drug and alcohol dependence*. 2009;99(1-3):222-30.
392. Campbell R, Evans M, Tucker M, Quilty B, Dieppe P, Donovan J. Why don't patients do their exercises? Understanding non-compliance with physiotherapy in patients with osteoarthritis of the knee. *Journal of Epidemiology & Community Health*. 2001;55(2):132-8.
393. Saha C, Jones MP. Type I and Type II error rates in the last observation carried forward method under informative dropout. *Journal of Applied Statistics*. 2016;43(2):336-50.
394. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. *Journal of multidisciplinary healthcare*. 2016;9:211.
395. Banerjee A, Chitnis U, Jadhav S, Bhawalkar J, Chaudhury S. Hypothesis testing, type I and type II errors. *Industrial psychiatry journal*. 2009;18(2):127.
396. Mansournia MA, Higgins JP, Sterne JA, Hernán MA. Biases in randomized trials: a conversation between trialists and epidemiologists. *Epidemiology (Cambridge, Mass)*. 2017;28(1):54.
397. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*. 2008.
398. Pannucci CJ, Wilkins EG. Identifying and avoiding bias in research. *Plastic and reconstructive surgery*. 2010;126(2):619.
399. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection bias and information bias in clinical research. *Nephron Clinical Practice*. 2010;115(2):c94-c9.
400. Gerra G, Marcato A, Caccavari R, Fontanesi B, Delsignore R, Fertonani G, et al. Clonidine and opiate receptor antagonists in the treatment of heroin addiction. *Journal of substance abuse treatment*. 1995;12(1):35-41.
401. O'Connor PG, Fiellin DA. Pharmacologic treatment of heroin-dependent patients. *Annals of Internal Medicine*. 2000;133(1):40-54.
402. Johansson B, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical. 2015.
403. Aalen O. *Statistical methods in Medicine and Health Studies (Statistiske metoder i medisin og helsefag: Odd O)*. Aalen (red) Oslo: Gyldendal Academy (Gyldendal akademisk, Norway). 2006.
404. Del Boca FK, Noll JA. Truth or consequences: the validity of self-report data in health services research on addictions. *Addiction*. 2000;95(11s3):347-60.
405. Porta M. *A dictionary of epidemiology*: Oxford university press; 2014.
406. Nunan D, Aronson J, Bankhead C. Catalogue of bias: attrition bias. *BMJ Evidence-Based Medicine*. 2018;23(1):21-2.
407. Batista KBdSL, Thiruvengkatachari B, O'brien K. Intention-to-treat analysis: Are we managing dropouts and missing data properly in research on orthodontic treatment? A systematic review. *American Journal of Orthodontics and Dentofacial Orthopedics*. 2019;155(1):19-27. e3.
408. Pekarik G. Relationship of clients' reasons for dropping out of treatment to outcome and satisfaction. *Journal of Clinical Psychology*. 1992;48(1):91-8.
409. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *Journal of clinical epidemiology*. 2006;59(12):1331.
410. Elwood JM, Editor. *Casual Relationships in medicine*. Oxford; Oxford University Press; 1988. p 332. [press release]. Oxford University Press.1988.
411. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. *Gastroenterology and Hepatology from bed to bench*. 2012;5(2):79.

412. Mamdani M, Sykora K, Li P, Normand S-LT, Streiner DL, Austin PC, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *Bmj*. 2005;330(7497):960-2.
413. Altman DG, Bland JM. Treatment allocation in controlled trials: why randomise? *Bmj*. 1999;318(7192):1209-.
414. Walter S, Turner R, Macaskill P, McCaffery K, Irwig L. Beyond the treatment effect: evaluating the effects of patient preferences in randomised trials. *Statistical methods in medical research*. 2017;26(1):489-507.
415. Hulse GK, Ngo HT, Tait RJ. Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone. *Biological psychiatry*. 2010;68(3):296-302.
416. Rich-Edwards JW, Kaiser UB, Chen GL, Manson JE, Goldstein JM. Sex and gender differences research design for basic, clinical, and population studies: essentials for investigators. *Endocrine reviews*. 2018;39(4):424-39.
417. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *The Lancet*. 2005;365(9453):82-93.
418. Pocock SJ. *Clinical trials: a practical approach*: John Wiley & Sons; 2013.
419. Slack MK, Draugalis Jr JR. Establishing the internal and external validity of experimental studies. *American Journal of Health-System Pharmacy*. 2001;58(22):2173-81.
420. Benson J, Britten N. Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. *Bmj*. 2002;325(7369):873.
421. Kaptchuk TJ. Powerful placebo: the dark side of the randomised controlled trial. *The Lancet*. 1998;351(9117):1722-5.
422. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. *The Lancet*. 2001;357(9258):757-62.
423. Cartwright N. Are RCTs the gold standard? *BioSocieties*. 2007;2(1):11-20.
424. Deaton A, Cartwright N. Understanding and misunderstanding randomized controlled trials. *Social Science & Medicine*. 2018;210:2-21.
425. Jørgensen L, Paludan-Müller AS, Laursen DR, Savović J, Boutron I, Sterne JA, et al. Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews. *Systematic reviews*. 2016;5(1):80.
426. Muller SM. Causal interaction and external validity: Obstacles to the policy relevance of randomized evaluations. *The World Bank Economic Review*. 2015;29(suppl_1):S217-S25.
427. Caruana EJ, Roman M, Hernandez-Sanchez J, Solli P. Longitudinal studies. *Journal of thoracic disease*. 2015;7(11):E537-40.
428. Calabria B, Degenhardt L, Briegleb C, Vos T, Hall W, Lynskey M, et al. Systematic review of prospective studies investigating "remission" from amphetamine, cannabis, cocaine or opioid dependence. *Addictive Behaviors*. 2010;35(8):741-9.
429. Maters GA, Pool G, Sanderman R, Wempe JB, Fleer J. Identifying patients with COPD in need for psychosocial care through screening with the HSCL-25 and the CCQ mental state. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2018;15(1):60-4.
430. Glaesmer H, Braehler E, Grande G, Hinz A, Petermann F, Romppel M. The German version of the Hopkins Symptoms Checklist-25 (HSCL-25)—factorial structure, psychometric properties, and population-based norms. *Comprehensive psychiatry*. 2014;55(2):396-403.
431. Ashaba S, Kakuhi B, Vořechovská D, Perkins JM, Cooper-Vince CE, Maling S, et al. Reliability, validity, and factor structure of the Hopkins symptom Checklist-25: population-based study of persons living with HIV in rural Uganda. *AIDS and Behavior*. 2018;22(5):1467-74.
432. Reshvanloo FT, Saadati Shamir A. Construct validity and reliability of Symptom Checklist-25 (SCL-25). *Journal of Fundamentals of Mental Health*. 2016;18(1).
433. Lhewa D, Banu S, Rosenfeld B, Keller A. Validation of a Tibetan translation of the Hopkins symptom checklist-25 and the Harvard trauma questionnaire. *Assessment*. 2007;14(3):223-30.

434. Joukamaa M, Lehtinen V, Karlsson H, Rouhe E. SCL-25 and recognition of mental disorders reported by primary health care physicians. *Acta Psychiatrica Scandinavica*. 1994;89(5):320-3.
435. Fröjd K, Håkansson A, Karlsson I. The Hopkins Symptom Checklist-25 is a sensitive case-finder of clinically important depressive states in elderly people in primary care. *International journal of geriatric psychiatry*. 2004;19(4):386-90.
436. Savard MH, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*. 2005;14(6):429-41.
437. Morin CM. *Insomnia: Psychological assessment and management*: Guilford Press; 1993.
438. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *Jama*. 1999;281(11):991-9.
439. Savard MH, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. *Psycho-oncology*. 2005;14(6):429-41.
440. Chen P-Y, Yang C-M, Morin CM. Validating the cross-cultural factor structure and invariance property of the Insomnia Severity Index: evidence based on ordinal EFA and CFA. *Sleep medicine*. 2015;16(5):598-603.
441. Gerber M, Lang C, Lemola S, Colledge F, Kalak N, Holsboer-Trachsler E, et al. Validation of the German version of the insomnia severity index in adolescents, young adults and adult workers: results from three cross-sectional studies. *BMC psychiatry*. 2016;16(1):174.
442. Chaffee A, Yakuboff M, Tanabe T. Responsiveness of the VAS and McGill pain questionnaire in measuring changes in musculoskeletal pain. *Journal of sport rehabilitation*. 2011;20(2):250-5.
443. Melzack R, Wall P. *Textbook of Pain*. Churchill Livingstone. Edinburgh, pp49–64. 2005.
444. Meadows K, Bentzen N, Touw-Otten F. *Cross Cultural Health Outcome Assessment: A User's Guide*. 1996.
445. Strand LI, Ljunggren AE, Bogen B, Ask T, Johnsen TB. The Short-Form McGill Pain Questionnaire as an outcome measure: test-retest reliability and responsiveness to change. *European journal of pain*. 2008;12(7):917-25.
446. Ljunggren A. Discriminant validity of pain modalities and other sensory phenomena in patients with lumbar herniated intervertebral discs versus lumbar spinal stenosis. *Neuro-orthopedics*. 1991;11(2):91-9.
447. Dubuisson D, Melzack R. Classification of clinical pain descriptions by multiple group discriminant analysis. *Experimental neurology*. 1976;51(2):480-7.
448. Dudgeon D, Raubertas RF, Rosenthal SN. The short-form McGill Pain Questionnaire in chronic cancer pain. *Journal of pain and symptom management*. 1993;8(4):191-5.
449. Eich E, Reeves JL, Jaeger B, Graff-Radford SB. Memory for pain: relation between past and present pain intensity. *Pain*. 1985;23(4):375-80.
450. Hunter M, Philips C, Rachman S. Memory for pain. *Pain*. 1979;6(1):35-46.
451. Linton SJ, Melin L. The accuracy of remembering chronic pain. *Pain*. 1982;13(3):281-5.
452. Erskine A, Morley S, Pearce S. Memory for pain: a review. *Pain*. 1990;41(3):255-65.
453. *The Encyclopedia of Clinical Psychology*. The Encyclopedia of Clinical Psychology, first edition, Edited by Robin L. Cautin and Scott O. Lilienfeld. : John Wiley and Sons, Inc. Published 2015 by John Wiley and Sons, Inc. ; 2015.
454. Engstad T, Bønnaa KH, Viitanen M. Validity of self-reported stroke: the Tromsø Study. *Stroke*. 2000;31(7):1602-7.
455. Lampe FC, Walker M, Lennon LT, Whincup PH, Ebrahim S. Validity of a self-reported history of doctor-diagnosed angina. *Journal of clinical epidemiology*. 1999;52(1):73-81.
456. Paulhus DL, Vazire S. The self-report method. *Handbook of research methods in personality psychology*. 2007;1:224-39.
457. McDonald JD. Measuring personality constructs: The advantages and disadvantages of self-reports, informant reports and behavioural assessments. *Enquire*. 2008;1(1):1-19.
458. Fisher RJ. Social desirability bias and the validity of indirect questioning. *Journal of consumer research*. 1993;20(2):303-15.

459. Van de Mortel TF. Faking it: social desirability response bias in self-report research. *Australian Journal of Advanced Nursing, The*. 2008;25(4):40.
460. Gillham B. Developing a questionnaire: A&C Black; 2008.
461. Dodd-McCue D, Tartaglia A. Self-report response bias: Learning how to live with its diagnosis in chaplaincy research. *Chaplaincy Today*. 2010;26(1):2-8.
462. Jackson LA, Buxton JA, Dingwell J, Dykeman M, Gahagan J, Gallant K, et al. Improving psychosocial health and employment outcomes for individuals receiving methadone treatment: a realist synthesis of what makes interventions work. *BMC psychology*. 2014;2(1):26.
463. Abraham AJ, Rieckmann T, McNulty T, Kovas AE, Roman PM. Counselor attitudes toward the use of naltrexone in substance abuse treatment: A multi-level modeling approach. *Addictive behaviors*. 2011;36(6):576-83.
464. Haase KS, Kunøe N, Opheim A, Gaulen Z, Njå A-LM, Solli KK, et al. Interest in Extended Release Naltrexone among Opioid Users. *European addiction research*. 2016;22(6):301-5.
465. Dreifuss JA, Griffin ML, Frost K, Fitzmaurice GM, Potter JS, Fiellin DA, et al. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug and alcohol dependence*. 2013;131(1-2):112-8.
466. Sullivan M, Bisaga A, Pavlicova M, Choi CJ, Mishlen K, Carpenter KM, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *American Journal of Psychiatry*. 2017;174(5):459-67.
467. Sullivan MA, Bisaga A, Mariani JJ, Glass A, Levin FR, Comer SD, et al. Naltrexone treatment for opioid dependence: Does its effectiveness depend on testing the blockade? *Drug and alcohol dependence*. 2013;133(1):80-5.
468. Veilleux JC, Colvin PJ, Anderson J, York C, Heinz AJ. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. *Clinical psychology review*. 2010;30(2):155-66.
469. O'Brien CP, Gastfriend DR, Forman RF, Schweizer E, Pettinati HM. Long-Term Opioid Blockade and Hedonic Response: Preliminary Data from Two Open-Label Extension Studies with Extended-Release Naltrexone. *The American journal on addictions*. 2011;20(2):106-12.
470. Wardle MC, Bershad AK, de Wit H. Naltrexone alters the processing of social and emotional stimuli in healthy adults. *Social neuroscience*. 2016;11(6):579-91.
471. Miotto K, McCann M, Basch J, Rawson R, Ling W. Naltrexone and dysphoria: fact or myth? *The American journal on addictions*. 2002;11(2):151-60.
472. Zaaijer ER, van Dijk L, de Bruin K, Goudriaan AE, Lammers LA, Koeter MW, et al. Effect of extended-release naltrexone on striatal dopamine transporter availability, depression and anhedonia in heroin-dependent patients. *Psychopharmacology (Berl)*. 2015;232(14):2597-607.
473. Petke Z, Csorba J, Meszaros J, Vingender I, Farkas J, Demetrovics Z, et al. Changes in psychosocial symptoms of opiate users over six months with buprenorphine/naloxone substitution therapy. *Neuropsychopharmacologia Hungarica: a Magyar Pszichofarmakologiai Egyesulet lapja= official journal of the Hungarian Association of Psychopharmacology*. 2012;14(1):7-17.
474. Lukas SE, Dorsey CM, Mello NK, Mendelson JH, Lundahl LH, Sholar M, et al. Reversal of sleep disturbances in cocaine-and heroin-dependent men during chronic buprenorphine treatment. *Experimental and Clinical Psychopharmacology*. 1996;4(4):413.
475. Kupfer DJ, Reynolds CF. Management of insomnia. *New England Journal of Medicine*. 1997;336(5):341-6.
476. Lai HMX, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: a systematic review and meta-analysis. *Drug & Alcohol Dependence*. 2015;154:1-13.
477. Kunoe N, Lobmaier P, Vederhus JK, Hjerkin B, Hegstad S, Gossop M, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. *The British journal of psychiatry : the journal of mental science*. 2009;194(6):541-6.

478. Compton WM, Cottler LB, Ben Abdallah A, Phelps DL, Spitznagel EL, Horton JC. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. *The American journal on addictions*. 2000;9(2):113-25.
479. Alim T, Kumari S, Adams L, Saint Cyr DA, Tulin S, Carpenter Song E, et al. Craving and Depression in Opiate Dependent Mentally Ill African Americans Receiving Buprenorphine/Naloxone and Group CBT (Cognitive Behavioral Therapy). *Clinical Psychiatry*. 2017;03(02).
480. Swift RM, Stout RL. The relationship between craving, anxiety, and other symptoms in opioid withdrawal. *Journal of Substance Abuse*. 1992;4(1):19-26.
481. Yoburn BC, Purohit V, Patel K, Zhang Q. Opioid agonist and antagonist treatment differentially regulates immunoreactive μ -opioid receptors and dynamin-2 in vivo. *European journal of pharmacology*. 2004;498(1-3):87-96.
482. Kaada B, Torsteinbø O. Increase of plasma beta-endorphins in connective tissue massage. *General Pharmacology*. 1989;20(4):487-9.
483. Sprouse-Blum AS, Smith G, Sugai D, Parsa FD. Understanding endorphins and their importance in pain management. *Hawaii medical journal*. 2010;69(3):70.
484. Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. *Drug & Alcohol Dependence*. 2015;147:144-50.
485. Abrams D, Couey P, Shade S, Kelly M, Benowitz N. Cannabinoid–opioid interaction in chronic pain. *Clinical Pharmacology & Therapeutics*. 2011;90(6):844-51.
486. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007;129(3):355-62.
487. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. *Psychosomatic medicine*. 2002;64(5):773-86.
488. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain*. 2003;106(1):127-33.
489. Munce SE, Stewart DE. Gender differences in depression and chronic pain conditions in a national epidemiologic survey. *Psychosomatics*. 2007;48(5):394-9.
490. Keogh E, Herdenfeldt M. Gender, coping and the perception of pain. *Pain*. 2002;97(3):195-201.
491. Keogh E, Mansoor L. Investigating the effects of anxiety sensitivity and coping on the perception of cold pressor pain in healthy women. *European journal of pain*. 2001;5(1):11-22.
492. Sullivan MJ, Tripp DA, Santor D. Gender differences in pain and pain behavior: the role of catastrophizing. *Cognitive Therapy and Research*. 2000;24(1):121-34.
493. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain*. 2000;87(3):325-34.
494. Berkley KJ, Holdcroft A. Sex and gender differences in pain. *Textbook of pain*. 1999;4:951-65.
495. Cahill C, Morinville A, Hoffert C, O'donnell D, Beaudet A. Up-regulation and trafficking of δ opioid receptor in a model of chronic inflammation: implications for pain control. *Pain*. 2003;101(1-2):199-208.
496. Ballantyne J, LaForge S. Opioid dependence and addiction in opioid treated pain patients. *Pain*. 2007;129:235-55.

PAPERS I-III

PAPER I

Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a 9-month follow-up to a 3-month randomized trial

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ABSTRACT

Background and aim This is a follow-up study of a previously published randomized clinical trial conducted in Norway that compared extended-release naltrexone (XR-NTX) to buprenorphine–naloxone (BP-NLX) over 3 months. At the conclusion of the trial, participants were offered their choice of study medication for an additional 9 months. While BP-NLX was available at no cost through opioid maintenance treatment programmes, XR-NTX was available only through study participation, accounting for why almost all participants chose XR-NTX in the follow-up. The aim of this follow-up study was to compare differences in outcome between adults with opioid dependence continuing XR-NTX and those inducted on XR-NTX for a 9-month period, on measures of effectiveness, safety and feasibility. **Design** In this prospective cohort study, participants were either continuing XR-NTX, changed from BP-NLX to XR-NTX or re-included into the study and inducted on XR-NTX treatment. **Setting** Five urban, out-patient addiction clinics in Norway. **Participants** Opioid-dependent adults continuing ($n = 54$) or inducted on ($n = 63$) XR-NTX. **Intervention** XR-NTX administered as intramuscular injections (380 mg) every fourth week. **Measurements** Data on retention, use of heroin and other illicit substances, opioid craving, treatment satisfaction, addiction-related problems and adverse events were reported every fourth week. **Findings** Nine-month follow-up completion rates were 51.9% among participants continuing XR-NTX in the follow-up and 47.6% among those inducted on XR-NTX. Opioid abstinence rates were, respectively, 53.7 and 44.4%. No significant group differences were found in use of heroin and other opioids. **Conclusions** Opioid-dependent individuals who elect to switch from buprenorphine–naltrexone treatment after 3 months to extended-release naltrexone treatment for 9 months appear to experience similar treatment completion and abstinence rates and similar adverse event profiles to individuals who had been on extended-release naltrexone from the start of treatment.

Keywords Antagonist treatment, craving, extended-release naltrexone, opioid use, recovery, treatment innovation, treatment of opioid dependence.

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INTRODUCTION

Treatment is the most important factor to prevent overdose death and other harmful effects of opioid abuse [1]. Opioid agonist maintenance treatment (OMT) is the World Health Organization (WHO) recommended option [2]. Despite the effectiveness of OMT [3] and its availability in many countries, it is utilized only by half of people with opioid

dependence in Europe [4]. There are opioid-dependent adults who prefer not to receive OMT with opioid agonist medications, and may consider opioid antagonist treatment an alternative [5–7].

Naltrexone is an opioid antagonist that competitively blocks euphoric effects of heroin and other opioids, thereby preventing relapse of opioid abuse and overdose deaths when used as prescribed [8–11]. It also reduces the craving

for opioids and alcohol [12,13]. Sustained-release formulations of naltrexone, both implantable and injectable, have shown promising results in maintaining abstinence from opioids and acceptable retention rates in studies with durations up to 6 months [14–19]. An injectable form of extended-release naltrexone (XR-NTX) administered once monthly is approved in the United States and in Russia [14,20,21]. Two recently published randomized clinical trials (RCT) from Norway and the United States compared the effectiveness of XR-NTX to buprenorphine–naloxone (BP-NLX) [22,23]. In the intention-to-treat population, the US study found BP-NLX to be superior to XR-NTX, due mainly to XR-NTX induction failure [22]. In the Norwegian study, which recruited participants after successful opioid detoxification and among the participants who were inducted successfully on study medication in the US study, similar retention, effectiveness and safety outcomes were reported [22,23].

The data on long-term use of XR-NTX are limited [3,24]. In a Russian trial, 62.3% of 114 participants completed 1-year follow-up [9]. In an American study, 55% of 38 health professionals received 12 XR-NTX injections [25]. In comparison, a review found retention rates between 26 and 85% at 12-month follow-ups for patients in opioid agonist treatment [24]. Sustained-release formulations of naltrexone are considered well-tolerated, with few serious side effects [11,21,26,27]. Severe injection-site reactions that require surgery may occur, but are not reported frequently [21]. Studies of sustained-release formulations of naltrexone have been criticized for the lack of post-treatment reporting of adverse events, including overdoses [28,29]. A recent study found no significant differences in rates of overdoses among people with opioid dependence treated with opioid agonist treatment or naltrexone implants, including after treatment cessation [30].

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

The overall purpose of the study was to assess the effectiveness, safety and feasibility of longer-term treatment with XR-NTX in a clinical setting. We aimed to: (1) compare participants continuing on XR-NTX following the 3-month RCT for potentially up to 12 total months treatment with those inducted on XR-NTX after the RCT for potentially up to 9 months treatment, and completers with non-completers with respect to (a) retention in XR-NTX treatment during a 9-month period, (b) opioid use, (c) craving scores and (d) treatment satisfaction; and (2) compare participants continuing XR-NTX with those inducted on

XR-NTX with respect to (a) use of other substances; (b) addiction-related problems and (c) reported adverse events.

According to the study protocol, participants could choose between receiving BP-NLX or XR-NTX during the 9-month follow-up period. Of the 122 participants who entered the follow-up, only five chose further treatment with BP-NLX while 117 chose XR-NTX. While OMT (including BP-NLX) is available at no cost in Norway, XR-NTX was only available through this study. The opportunity to receive XR-NTX was probably the most important motivating factor for study participation [23]. Due to the low number of participants choosing BP-NLX, no meaningful statistical or clinical comparisons could be performed using this group of five, leaving the 117 participants receiving XR-NTX as the natural focus of investigation. The rationale for comparing participants who continued XR-NTX to those inducted on XR-NTX was to investigate the clinical feasibility of XR-NTX induction. Participants who preferred BP-NLX were followed up at their sites' OMT clinics according to the national OMT guidelines.

METHODS

In the aforementioned Norwegian multi-centre RCT, 159 people with opioid dependence were randomized to receive XR-NTX or BP-NLX in a 1 : 1 ratio, after being tapered to a maximum of 4 mg buprenorphine [23]. Retention rates were non-inferior in the two groups and 105 completed the 3-month study (Fig. 1). Superiority analyses showed significantly lower use of illicit opioids and lower craving scores in the XR-NTX group. No significant differences were found between the treatment groups regarding most other illicit substance use. In the XR-NTX group, more adverse events were reported [23].

Design

This 9-month prospective cohort study was conducted following the 3-month RCT [34]. Participants consented to participate in the follow-up at conclusion of the RCT. In order to estimate effectiveness, safety and feasibility of XR-NTX in longer-term participants continuing XR-NTX ($n = 54$) and participants inducted on XR-NTX ($n = 63$) were compared with regard to retention in treatment, substance use, adverse events and other relevant outcomes (see below) every 4 weeks during the 9-month study period [23].

Setting

During the period from November 2012 to July 2015, opioid-dependent individuals were recruited for study participation in the RCT from five urban hospitals in Norway. RCT participants were offered to continue participation in the follow-up at week 12. Participants dropping-out of

Figure 1 Flow-chart for participants included in the study; participant flow in the preceding 3-month randomized controlled trial (RCT) [23] and in the present 9-month follow-up study. XR-NTX = extended-release naltrexone; BP-NLX = buprenorphine-naloxone

any treatment arm during the RCT period, but motivated for re-inclusion, were allowed induction on XR-NTX after week 12. The follow-up study was completed when the last patient completed participation in July 2016.

Participants

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

Measurements and outcomes

Participants were interviewed every fourth week using the Addiction Severity Index, European version [35] and self-reported craving for opioids and treatment satisfaction. Data were collected using the time-line follow-back method [36]. Any adverse events occurring during the study period and for up to 3 months after study discontinuation were reported.

Outcomes were: retention in treatment, measured in numbers of weeks in treatment and the number of participants completing the study; the number of participants abstinent from opioids during the study; the use of heroin and other illicit opioids, the use of cannabis, amphetamines and benzodiazepines; heavy alcohol use; injection use;

acquisitive crime and work, measured in number of days within the 4 weeks preceding each study attendance; money spent on drugs and alcohol within the 4 weeks preceding each study attendance, measured in Norwegian crowns (NOK); craving for heroin and treatment satisfaction within the 4 weeks preceding each study attendance measured by a visual analogue scale (VAS) with scores from 0–10; and the number of reported adverse events [34].

Study intervention

After week 12, participants chose medication based on their preferences. Those preferring XR-NTX are referred to in this paper: participants already receiving XR-NTX in the RCT continued their treatment. Participants who changed from BP-NLX to XR-NTX and those re-included in the study and inducted on XR-NTX in the follow-up were referred to a detoxification unit at week 12. The majority of participants were administered BP-NLX and tapered with a flexible standard 2 mg/day regimen. A small number of participants chose to discontinue opioid agonists without any tapering. After a minimum of 72 hours without any intake of opioids and if passing an injection of a 0.4 mg naloxone test dose, participants were given an intramuscular injection of 380 mg XR-NTX (Vivitrol®) in the buttock [34]. To relieve withdrawal symptoms such as vomiting, chills and insomnia in the detoxification phase, participants were prescribed pharmacological

treatment such as benzodiazepines, metoclopramide, valproate, quetiapine, clonidine and pregabalin, adapted individually according to clinical assessment. Participants were discharged from the detoxification units 1–7 days after the initial XR-NTX dose. Following induction, participants received a XR-NTX injection in an out-patient setting every fourth week throughout the study period. Counselling was not mandatory, but was offered to all participants at the study site as part of standard ancillary services. Counselling was adapted individually by clinicians at the OMT clinics or other out-patient clinics, as often as once every week but typically once or twice a month.

Research ethics

The study was approved by the South-East Regional Ethical Board for Medical Research Ethics (no. 2011/1320) and by the Norwegian Medicines Agency.

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

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

Statistical analyses

Statistical analyses were performed to compare outcomes between the participants continuing XR-NTX treatment ($n = 54$) and the participants inducted on XR-NTX ($n = 63$) and between completers and non-completers, in total 117 participants who received at least one injection of XR-NTX during weeks 12–48. Data were described as means and confidence intervals (CI) or frequencies and percentages. Kaplan–Meier survival curves were plotted and log-rank test performed to assess retention in treatment.

Differences between groups in 9-month changes in substance use, addiction-related outcomes and treatment satisfaction were assessed by linear mixed models with random effects for time and participants nested within sites. Fixed effects for time up to third-order handling non-linear patterns were included together with participant group and interaction between the group and time. A significant interaction would imply a difference in change between the

groups. The results were presented as observed means and 95% CI, and mean differences with 95% CI and P -values derived from linear mixed models.

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

Results with P -values < 0.05 were considered significant and all tests were two-sided. Analyses were performed using SPSS version 24 and SAS version 9.4.

RESULTS

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

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

Retention

After 9 months, 58 participants (49.6%) had attended all scheduled visits and received XR-NTX injections as prescribed (Fig. 2), meaning that 28 participants who continued XR-NTX (51.9%) completed a total of 12 months XR-NTX treatment and 30 who were inducted on XR-NTX (47.6%) completed a total of 9 months XR-NTX treatment (Fig. 1). The mean (95% CI) number of weeks in treatment in the follow-up was 25.6 (22.3–29.0) and 25.4 (22.4–28.4) among participants continuing XR-NTX and those inducted on XR-NTX, respectively, with no differences in retention between groups.

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

Use of opioids

There were no significant differences in the use of heroin or other illicit opioids between participants continuing XR-NTX and participants inducted on XR-NTX. The reduction from week 12 in heroin (other illicit opioids) use was significant to week 36 (week 24) among those continuing and week 48 (week 36) among those inducted on XR-NTX. During the 9-month study, 53.7% (29 of 54) of

Table 1 Life-time characteristics of participants.

Life-time characteristics	Participants continuing XR-NTX, <i>n</i> = 54 ^a	Participants induced on XR-NTX, <i>n</i> = 63 ^a
Age (years)	36.2 (33.9–38.4)	35.1 (32.9–37.2)
Women/men	10/44 (18.5%/81.5%)	18/45 (28.6%/71.4%)
HIV-positive	1 (1.9%)	1 (1.6%)
Hepatitis C seropositive	30 (55.6%)	31 (49.2%)
Injecting use, age at onset	22.5 (20.7–24.4)	19.0 (16.5–21.5)
Years of injecting use	10.6 (8.2–13.1)	9.4 (7.0–11.9)
Substance use, age at onset		
Heroin	22.5 (21.1–24.0)	21.4 (19.5–23.4)
Other illicit opioids	20.1 (17.3–22.9)	19.1 (16.1–22.1)
Cannabis	15.6 (14.6–16.6)	14.5 (13.7–15.3)
Polydrug	18.3 (16.8–19.8)	17.4 (15.7–19.1)
Benzodiazepines	19.4 (17.8–21.0)	18.2 (16.2–20.3)
Amphetamine	18.5 (17.2–19.8)	16.1 (14.7–17.4)
Alcohol for intoxication	14.1 (13.1–15.0)	12.9 (11.8–14.0)
Years of substance use		
Heroin	6.7 (5.5–7.8)	6.7 (5.2–8.1)
Other illicit opioids	1.6 (0.6–2.6)	3.1 (1.3–4.9)
Cannabis	8.9 (6.8–10.9)	11.1 (8.7–13.4)
Polydrug	10.3 (8.4–12.1)	9.9 (8.0–11.8)
Benzodiazepines	4.9 (3.4–6.5)	5.7 (3.4–8.0)
Amphetamine	7.1 (4.9–9.3)	6.4 (4.7–8.0)
Alcohol for intoxication	3.7 (2.2–5.2)	3.5 (2.4–4.6)

Characteristics of the 117 people with opioid dependence who received extended-release naltrexone (XR-NTX) in the study; *n* = 54 continuing XR-NTX treatment after an initial 3-month randomized controlled trial (RCT) and 63 who were induced on XR-NTX during the 9-month follow-up. Data collected at the time of inclusion in the RCT, week 0. ^aReported mean differences with corresponding 95% confidence intervals or number and percentage.

Figure 2 Retention in treatment for the 117 participants who received extended-release naltrexone (XR-NTX) in the follow-up study. *Kaplan–Meier survival curves for 54 participants continuing XR-NTX treatment in this follow-up study, and the 63 participants induced on XR-NTX [Colour figure can be viewed at wileyonlinelibrary.com]

participants continuing XR-NTX treatment, and 44.4% (28 of 63) of participants induced on XR-NTX reported abstinence from all opioids. Differences in heroin use were not significant between completers and non-completers, with completers reporting significant reduction in heroin use to week 32, while the reduction among non-completers was significant to week 24. However, completers and non-completers differed significantly in use of other opioids ($P = 0.018$), where non-completers reported significantly

higher use than completers up to week 16. Moreover, reduction in use of other illicit opioids was significant to week 16 among completers and to week 40 among non-completers. See Table 2 and Fig. 3 for more details.

Other outcome measures

There were significant differences between participants continuing XR-NTX treatment and those induced on

Table 2 Substance use and addiction-related problems.

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

Comparing number of days with substance use and addiction-related problems during the last 4 weeks between participants continuing extended-release naltrexone (XR-NTX) treatment and participant inducted on XR-NTX in the follow-up. ^aMean and confidence intervals (CIs) are descriptive numbers, not adjusted for repeated measurements or site effect; ^bmean differences with corresponding 95% CIs and *P*-values are derived from linear mixed models, adjusted for intraparticipant and intrasite correlations.

XR-NTX in heavy alcohol use ($P = 0.045$) and days of work ($P = 0.016$), where those inducted on XR-NTX reported more heavy alcohol use and more days at work at the end of the study period. Both groups reported a significant reduction in money spent on drugs up to week 32. No other differences or significant changes were found (Table 2).

Those inducted on XR-NTX reported significantly more heroin craving than participants continuing XR-NTX treatment ($P = 0.009$), but reduction in heroin craving

was only significant to week 16 among those inducted on XR-NTX. Participants continuing XR-NTX treatment reported higher satisfaction with the treatment ($P < 0.001$), which was increasing to week 24 in both groups. No differences in heroin craving or treatment satisfaction were found between completers and non-completers, with heroin craving remaining stable and treatment satisfaction increasing until week 24 in both groups (see Fig. 3).

Figure 3 Estimated mean number of days of use of (a) heroin, (b) other opioids, (c) mean craving scores and (d) mean treatment satisfaction. (a,b) Mean number of days with use of heroin (a) and other opioids (b) last 4 weeks; (c,d) visual analogue scales were used to assess craving (c) (0–10 with 0 indicating none and 10 indicating very strong) and treatment satisfaction (d) (0–10 with 0 indicating very low and 10 indicating very high). *Significant differences between completers and non-completers, $P < 0.05$; **significant differences between completers and non-completers, $P < 0.01$; ***significant differences between completers and non-completers, $P < 0.001$; \$significant differences between ‘continuing extended-release naltrexone (XR-NTX)’ and ‘induced on XR-NTX’, $P < 0.05$; \$\$significant differences between ‘continuing XR-NTX’ and ‘induced on XR-NTX’, $P < 0.01$; \$\$\$significant differences between ‘continuing XR-NTX’ and ‘induced on XR-NTX’, $P < 0.001$ [Colour figure can be viewed at wileyonlinelibrary.com]

Safety and tolerability

A total of 62 (53%) participants reported at least one non-serious adverse event (Table 3). Participants induced on XR-NTX reported 37 and participants continuing XR-NTX reported 25 adverse events ($P = 0.198$).

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

Adverse events caused seven participants to discontinue treatment due to: withdrawal-like symptoms (two), psychological reactions (two), need for opioid agonist pain treatment (one), seizure (one) and insomnia (one).

Five participants reported a serious adverse event requiring hospitalization; two due to infections, one planned

surgery and two serious injection-site reactions requiring surgery. All participants recovered completely, and except for those who experienced the injection-site reactions, all continued XR-NTX treatment. One participant died of internal injuries after an accident. No opioid overdoses were reported. No serious adverse events, including no overdose fatalities, were reported among the participants during the first 3 months following their completion of the study.

DISCUSSION

Of the 143 participants who took at least one dose of study medication in the 3-month RCT, 117 (81.8%) chose to continue on XR-NTX or be induced on XR-NTX in the 9-month follow-up study. Only five participants (3.5%) chose to either continue on BP-NLX or transition from XR-NTX to BP-NLX in the follow-up. As BP-NLX is available in Norway at no cost in the OMT programmes, while

Table 3 Adverse events.

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

Adverse events reported among the 117 participants receiving extended-release naltrexone (XR-NTX). Several participants are registered with multiple adverse events. ^aIncludes 20 participants who were re-included and started XR-NTX in the follow-up; ^bFisher's exact test; ^cNo serious adverse events were reported during the first three months after the study discontinuation. ^dgamma hydroxybutyrate (GHB); ^eone participant died in an accident.

XR-NTX was not registered for use and available only for study participants, it is likely that study participation was motivated by the possibility to obtain XR-NTX [23]. Half the participants (49.6%) completed all XR-NTX injections and follow-up interviews in the 9-month study, and no differences were reported between participants continuing XR-NTX and those inducted on XR-NTX. There was no difference in opioid use between the groups, and a non-significant reduction in opioid use was reported during the study. Abstinence from opioids was reported by 53.7% of those continuing and 44.4% of those inducted on XR-NTX. During the 9 months, participants inducted on XR-NTX reported significantly more days with heavy alcohol use and more days working than participants who continued XR-NTX. Participants continuing XR-NTX reported significantly less heroin craving and higher treatment satisfaction than those inducted on XR-NTX. Adverse events were reported by 53% of the participants, and the majority of these were related to withdrawal symptoms during induction on XR-NTX.

Retention rates reported in studies of medication-assisted treatment for opioid dependence vary considerably, e.g. between 26–85% at 1-year follow-ups in OMT [24]. In our study, 49.6% of the participants completed the follow-up with XR-NTX, and thus within the range of findings in studies of OMT. Two studies of XR-NTX reported retention rates of 55 and 62.3% after 1 year in treatment [9,25]. Differences in study designs, the availability of OMT medication and the inclusion criteria limit comparison between our study and previous studies of XR-NTX. The study

design did not include any mandatory supplementary interventions. We suggest that implementing such interventions could improve retention in XR-NTX treatment. In contrast to the findings from a longer-term study in Russia, we found no differences in the retention rates between participants who continued on XR-NTX from the RCT phase and those inducted on XR-NTX in the follow-up study [9].

Consistent with other studies of sustained-release naltrexone, participants reported reduced use of illicit opioids during the study period [9,11,15,16,19,22,26,38,39]. Fewer participants inducted on XR-NTX reported full abstinence from opioids, and we suggest this may be a result of participants 'testing the blockade' when starting the XR-NTX treatment, as seen in other studies [10]. Opioid use remained at a low level in both groups (Table 2).

Similar to the preceding RCT phase [23] and other XR-NTX studies [19,25], the majority of the adverse events were withdrawal-related and reported following the first administration of XR-NTX [21]. While we administered the first XR-NTX injection after a minimum 72 hours of complete abstinence from any opioids, other studies have recommended a longer period of abstinence [9,40,41]. Extending the number of opioid-free days would have reduced the amount of adverse events and eased the induction phase. However, while participants were encouraged to extend the number of opioid-free days, some expressed concern they would not be able to endure more than 72 hours without opioids and requested a rapid but more unpleasant induction. As XR-NTX was only available

through study participation and participants volunteered for complete abstinence from opioid agonists, this may have enhanced participants' motivation to complete the induction phase.

No opioid overdoses were reported during the study or within 3 months after study discontinuation. This may reflect the effectiveness of XR-NTX in blocking the opioid receptors and thereby preventing overdoses [20], as well as being an indication of the participants' high motivation for an opioid-free treatment. The safety profile of XR-NTX in our study corresponded with previous findings in other longer-term studies [9,25].

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

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

In summary, there were no differences between participants continuing XR-NTX and participants inducted on XR-NTX in this 9-month follow-up study concerning retention in treatment and use of opioids, suggesting feasibility for induction and continuation of XR-NTX treatment in a clinical setting.

Trial registration

<http://clinicaltrials.gov> no. NCT01717963, first registered: 28 October 2012. Protocol version no. 3C, 12 June 2012.

Declaration of interests

None.

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References

1. Degenhardt L., Bucello C., Mathers B., Briegleb C., Ali H., Hickman M. *et al.* Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction* 2011; **106**: 32–51.
2. World Health Organization (WHO). *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. Geneva: WHO; 2009. Available at: http://www.who.int/substance_abuse/activities/treatment_opioid_dependence/en/ (accessed 13 June 2018) (Archived at <http://www.webcitation.org/708vX88MD> on 13 June 2018).
3. Connery H S. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harv Rev Psychiatry* 2015; **23**: 63–75.
4. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *European Drug Report: Trend and Developments*. Lisbon: EMCDDA; 2015. Available at: <http://www.emcdda.europa.eu/publications/edr/trends-developments/2015> (accessed 13 June 2018) (Archived at <http://www.webcitation.org/708vrYPMh> on 13 June 2018).
5. Larney S., Zador D., Sindich N., Dolan K. A qualitative study of reasons for seeking and ceasing opioid substitution treatment in prisons in New South Wales, Australia. *Drug Alcohol Rev* 2016; **36**: 305–10.
6. Vanderplasschen W., Naert J., Vander Laenen E., De Maeyer J. Treatment satisfaction and quality of support in outpatient substitution treatment: opiate users' experiences and perspectives. *Drugs Educ Prev Pol* 2015; **22**: 272–80.
7. Notley C., Blyth A., Maskrey V., Craig J., Holland R. The experience of long-term opiate maintenance treatment and reported barriers to recovery: a qualitative systematic review. *Eur Addict Res* 2013; **19**: 287–98.
8. Herbeck D. M., Jeter K. E., Cousins S. J., Abdelmaksoud R., Crèvecoeur-MacPhail D. Gender differences in treatment and clinical characteristics among patients receiving extended release naltrexone. *J Addict Dis* 2016; **35**: 305–14.
9. Krupitsky E., Nunes E. V., Ling W., Gastfriend D. R., Memisoglu A., Silverman B. L. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. *Addiction* 2013; **108**: 1628–37.
10. Sullivan M. A., Bisaga A., Mariani J. J., Glass A., Levin F. R., Comer S. D. *et al.* Naltrexone treatment for opioid dependence: does its effectiveness depend on testing the blockade? *Drug Alcohol Depend* 2013; **133**: 80–5.
11. Kunoe N., Lobmaier P., Ngo H. T., Hulse G. Injectable and implantable sustained release naltrexone in the treatment of opioid addiction. *Br J Clin Pharmacol* 2014; **77**: 264–71.

12. Maremmani I., Rovai L., Maremmani A. G. I., Bacciardi S., Rugani E., Massimetti E. *et al.* Antagonist opioid medications in mental illness: State of art and future perspectives. *Heroin Addiction Relat Clin Problems* 2015; **188**: 394.
13. National Academy of Science-National Research Council (NAS-NRC). Clinical evaluation of naltrexone treatment of opiate-dependent individuals: Report of the national research council committee on clinical evaluation of narcotic antagonists. *Arch Gen Psychiatry* 1978; **35**: 335–40.
14. Krupitsky E., Nunes E. V., Ling W., Illeperuma A., Gastfriend D. R., Silverman B. L. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Lancet* 2011; **377**: 1506–13.
15. Hulse G. K., Morris N., Arnold-Reed D., Tait R. J. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. *Arch Gen Psychiatry* 2009; **66**: 1108–15.
16. Kunøe N., Lobmaier P., Vederhus J. K., Hjerkin B., Hegstad S., Gossop M. *et al.* Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. *Br J Psychiatry* 2009; **194**: 541–6.
17. DeFulio A., Everly J. J., Leoutsakos J. M., Umbricht A., Fingerhood M., Bigelow G. E. *et al.* Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. *Drug Alcohol Depend* 2012; **120**: 48–54.
18. Crits-Christoph P., Markell H. M., Gibbons M. B., Gallop R., Lundy C., Stringer M. *et al.* A naturalistic evaluation of extended-release naltrexone in clinical practice in Missouri. *J Subst Abuse Treat* 2016; **70**: 50–7.
19. Lee J. D., Friedmann P. D., Kinlock T. W., Nunes E. V., Boney T. Y., Hoskinson R. A. Jr. *et al.* Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med* 2016; **374**: 1232–42.
20. Bigelow G. E., Preston K. L., Schmittner J., Dong Q., Gastfriend D. R. Opioid challenge evaluation of blockade by extended-release naltrexone in opioid-abusing adults: dose-effects and time-course. *Drug Alcohol Depend* 2012; **123**: 57–65.
21. Gastfriend D. R. Intramuscular extended-release naltrexone: current evidence. *Ann NY Acad Sci* 2011; **1216**: 144–66.
22. Lee J. D., Nunes E. V. Jr., Novo P., Bachrach K., Bailey G. L., Bhatt S. *et al.* Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* 2017; **391**: 309–18.
23. Tanum L., Solli K. K., Latif Z. E., Benth J. S., Opheim A., Sharma-Haase K. *et al.* Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry* 2017; **74**: 1197–205.
24. Timko C., Schultz N. R., Cucciare M. A., Vittorio L., Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: a systematic review. *J Addict Dis* 2016; **35**: 22–35.
25. Earley P. H., Zummo J., Memisoglu A., Silverman B. L., Gastfriend D. R. Open-label study of injectable extended-release naltrexone (XR-NTX) in healthcare professionals with opioid dependence. *J Addict Med* 2017; **11**: 224–30.
26. Comer S. D., Sullivan M. A., Yu E., Rothenberg J. L., Kleber H. D., Kampman K. *et al.* Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006; **63**: 210–8.
27. Garbutt J. C., Kranzler H. R., O'Malley S. S., Gastfriend D. R., Pettinati H. M., Silverman B. I. *et al.* Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; **293**: 1617–25.
28. Wolfe D., Carrieri M. P., Dasgupta N., Wodak A., Newman R., Bruce R. D. Concerns about injectable naltrexone for opioid dependence. *Lancet* 2011; **377**: 1468–70.
29. Larney S., Gowing L., Mattick R. P., Farrell M., Hall W., Degenhardt L. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. *Drug Alcohol Rev* 2014; **33**: 115–28.
30. Keltz E., Hulse G. Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone. *Int J Drug Pol* 2017; **46**: 54–60.
31. Nunes E. V., Krupitsky E., Ling W., Zummo J., Memisoglu A., Silverman B. L. *et al.* Treating opioid dependence with injectable extended-release naltrexone (XR-NTX): who will respond? *J Addict Med* 2015; **9**: 238–43.
32. Hser Y. I., Evans E., Grella C., Ling W., Anglin D. Long-term course of opioid addiction. *Harv Rev Psychiatry* 2015; **23**: 76–89.
33. McLellan A. T., McKay J. R., Forman R., Cacciola J., Kemp J. Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring. *Addiction* 2005; **100**: 447–58.
34. Kunøe N., Opheim A., Solli K. K., Gaulen Z., Sharma-Haase K., Latif Z. E. *et al.* Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacol Toxicol* 2016; **17**: 1–10.
35. Kokkevi A., Hartgers C. EuropASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. *Eur Addict Res* 1995; **1**: 208–10.
36. Sobell L. C., Sobell M. B., Litten R. Z., Allen J. P. *Timeline Follow-back: a Technique for Assessing Self-reported Alcohol Consumption*. Totowa, NJ: Humana Press; 1992.
37. World Medical Association (WMA). WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects. Available at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/2013> (accessed 13 July 2017) (Archived at <http://www.webcitation.org/6wsyQO5Tu> on 13 July 2017).
38. Krupitsky E., Zvartau E., Blokhina E., Verbitskaya E., Wahlgren V., Tsoy-Podosenin M. *et al.* Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Arch Gen Psychiatry* 2012; **69**: 973–81.
39. Lobmaier P. P., Kunøe N., Gossop M., Katevoll T., Waal H. Naltrexone implants compared to methadone: outcomes six months after prison release. *Eur Addict Res* 2010; **16**: 139–45.
40. Cousins S. J., Denering L., Crevecoeur-MacPhail D., Viernes J., Sugita W., Barger J. *et al.* A demonstration project implementing extended-release naltrexone in Los Angeles County. *Subst Abuse* 2016; **37**: 54–62.
41. Sullivan M., Bisaga A., Pavlicova M., Choi C. J., Mishlen K., Carpenter K. M. *et al.* Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *Am J Psychiatry* 2017; **174**: 459–67.
42. Nunes E. V., Lee J. D., Sisti D., Segal A., Caplan A., Fishman M. *et al.* Ethical and clinical safety considerations in the design of an effectiveness trial: a comparison of buprenorphine versus naltrexone treatment for opioid dependence. *Contemp Clin Trials* 2016; **51**: 34–43.

PAPER II

Anxiety, Depression, and Insomnia in Opioid-dependent Individuals Randomized to Treatment with Either Extended-release Naltrexone or Buprenorphine-Naloxone: A 3 Months Randomized Clinical Trial and A Subsequent 9 Months Follow-Up Study

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Key Points

Question

Will treatment with injectable extended-release naltrexone hydrochloride unmask or reinforce symptoms of anxiety, depression or insomnia compared with daily sublingual buprenorphine-naloxone hydrochloride in newly detoxified, opioid-dependent individuals?

Findings

In this open-label, randomized clinical trial including 159 opioid dependent users, both treatments were equally effective in reducing symptoms of anxiety and depression, but symptoms of insomnia was significantly more reduced in the extended-release naltrexone group. All symptoms were further improved by longer-term extended-release naltrexone treatment.

Meaning

Comorbid symptoms of anxiety, depression or insomnia in opioid-dependent individuals should not prevent switching from opioid agonist treatment to long-acting naltrexone in abstinence-motivated individuals.

Abstract

Importance: Extended-release naltrexone hydrochloride is a promising alternative treatment for opioid addiction, but has never been compared with opioid agonist treatment with regard to reported symptoms of anxiety, depression, and insomnia.

Objective: To investigate if extended-release naltrexone hydrochloride may unmask or reinforce current comorbid symptoms of anxiety, depression and insomnia compared with opioid agonist treatment.

Design: A prospective clinical study of opioid-dependent individuals randomized to 12 weeks of treatment with either extended-release naltrexone hydrochloride or buprenorphine-naloxone hydrochloride followed by a nine month open treatment study with either drug, chosen by the participant.

Setting: Outpatient addiction clinics at five urban hospitals in Norway.

Participants: Opioid-dependent men and women aged 18-60 years.

Intervention: Extended-release naltrexone hydrochloride was administered as injections (380 mg) every 4 weeks, or daily oral-buprenorphine-naloxone hydrochloride in flexible 4-16 mg doses daily.

Main Outcome and Measures: Symptoms of anxiety, depression and insomnia were assessed every 4 weeks using the Hopkins Symptom Checklist-25, and the Insomnia Severity Index.

Results: 159 participants were randomized to treatment with either extended-release naltrexone hydrochloride (n=80) or buprenorphine-naloxone hydrochloride (n=79), and 105 participants (66.0%) completed the trial. The treatment groups showed similar age and gender distribution (mean (SD) 36.4 (8.8), versus 35.7 (8.5) years; 76.3% versus 68.4% males) and years of heroin use (mean (SD) 6.9 (5.8) and 6.7 (5.2)).

In the RCT period, no overall differences could be detected between the treatment groups in trend in anxiety and depression scores, but the insomnia scores were significantly lower

($p=0.008$) in extended-release naltrexone hydrochloride group (effect sizes (95% CI); -0.14 (-0.47; 0.19), -0.12 (-0.45; 0.21) and -0.32 (-0.65; 0.02) respectively).

In the follow-up period, no overall differences could be detected in anxiety, depression and insomnia scores between participants continuing with and -participants switching -to extended-release naltrexone hydrochloride (effect sizes (95% CI); 0.04 (-0.34; 0.42), -0.04 (-0.42; 0.33) and 0.04 (-0.33; 0.42), respectively).

No significant gender differences between the two treatment groups were detected.

Conclusion and Relevance: Comorbid symptoms of anxiety, depression or insomnia in opioid-dependent individuals should not prevent switching from opioid agonist treatment to long-acting naltrexone in abstinence-motivated individuals.

Trial Registration: [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01717963) identifier: NCT01717963

Introduction

Opioid-dependent individuals fulfilling the criteria for substance use disorder (SUD) have an increased prevalence of life-time psychiatric disorders compared with the general population¹⁻³ often in combination with insomnia.^{4,5} Grant et al (2004) reported that 20% of all the persons in the general population in US with a current SUD had at least one current independent mood disorder and at least one current independent anxiety disorder.⁶

Epidemiological studies also report a lifetime history of substance-use disorder among approximately 24-43% of individuals with anxiety disorders.⁷

Both anxiety and depression have a negative impact on the course and treatment outcome in opioid use disorder.^{8,9} Agonist treatment with methadone or buprenorphine or residential treatments have shown positive effects on co-existing anxiety and depressive symptoms, but the data have not been consistent,^{8,9,10} with regards to the type of substance used, frequency of intake or poly drug-use period¹¹⁻¹⁵

Insomnia is frequently related to an increased risk of psychiatric morbidity,¹⁶ and it has been estimated that 10-15% of individuals with chronic sleep disturbances have underlying substance use problems.¹⁷ Larger scale studies on the prevalence and impact of insomnia in this population are still lacking.

Long-acting naltrexone (XR-NTX) is shown to be a promising treatment for opioid dependence,¹⁸⁻²¹ but until now no study has had focused on changes in anxiety, depression, or insomnia after induction of such treatment compared to treatment with an opioid agonist. Naltrexone inhibits the action of heroin and other opioid agonists by a competitive blocking of the mu, delta and kappa opioid receptors, and lacks abuse potential or any risk of diversion, and it provides a prolonged period of abstinence from opioids with a high level of protection from relapse and overdose.

Our hypothesis was that XR-NTX may unmask symptoms of psychiatric distress concealed by daily intake of opioids. The main aim and end points of this study was to assess the change in psychiatric distress reported as symptoms of anxiety, depression, and insomnia in opioid-dependent individuals randomized to either short-term treatment with XR-NTX or buprenorphine-naloxone (BP-NLX) followed by a longer-term treatment. As exploratory analyses, associations between anxiety/ depression and insomnia, and sex differences and the use of illicit substances were assessed.

Material and Methods

Methods

This study consisted of a 12 week randomized clinical trial assigning patients to treatment with either XR-NTX intramuscular injection in the gluteal region every fourth week or daily, sublingual BP-NLX using a permuted block algorithm provided by an external authority, and a 36 week open follow-up study with either drug chosen by the participant. A written informed consent was signed by all the participants. The primary endpoints of the study were changes in anxiety, depression, and insomnia scores in the randomized part of the study and during longer-term treatment. Participants were assessed for these symptoms every four weeks from baseline to week 48 using the Hopkins Symptom Checklist-25 (HSCL-25) and the Insomnia Severity Index (ISI).

The study was performed according to Protocol version # 3C, June 12, 2012 at all participating sites and approved by the Regional Committee for Medical and Health Research Ethics South East Norway (# 2011/1320), the Norwegian Medicines Agency, and the Boards of Research Ethics at the participating hospitals.²⁰

The HSCL-25 is a screening instrument developed for the assessment of change in anxiety and depressive symptoms in the course of clinical treatment.²²⁻²⁵ It has robust validity

and reliability and can distinguish between normal and neurotic individuals.^{26,27} The questions are graded from “not at all” (=1) to “extremely” (=4). The the patient version of the Insomnia Severity Index is a seven-element self-reporting questionnaire developed to assess insomnia in the last 4 weeks, and has shown robust psychometric properties.^{16, 28} The ISI measures the latency of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, daytime functioning affected by sleep difficulties, sleep problems apparent to others, and anguish caused by sleep difficulties. The scoring is done on a 5-point rating scale, where 0 = no problem and 4 = a very severe problem.

Participants & setting

Patients were included between November 1, 2012 and July 10, 2015 from outpatient clinics and detoxification units at five urban addiction clinics in Norway. Eligible participants were men and women, aged 18-60 years old who had opioid dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders (Fourth edition). Criteria for exclusion were other drug or alcohol dependence and serious somatic or psychiatric psychotic illness that, according to hospital records and our clinical judgement, interfered with study participation. Females of childbearing age could not be pregnant or lactating and agreed to use contraceptive methods. Study personnel (Z.H.L., K.K.S., A.O., K.S-H.) screened patients for psychiatric disorders using the M.I.N.I. Interview 6.0;²⁹ while, a physician examined patients for serious somatic disease. Eligible patients were referred to a detoxification unit following screening. Participants were not paid or compensated for taking part in the study with the exception of reimbursement for travel expenses. Ethnicity was defined by the participants and was assessed to show if the study participants followed the ethnical distribution of the general population.

After individually-adapted detoxification, patients were randomly assigned to commence treatment with either individually-dosed BP-NLX, 4-24 mg/day (target dosage 16 mg/day), or XR-NTX, 380 mg every fourth week for the following twelve weeks. All per protocol participants were invited to enter a 36-week follow up study, either continuing their randomized treatment or switching to their preferred medication. Participants who dropped out of the randomization phase could be re-included in the follow-up study after a new detoxification. The procedure and selection of participants are described elsewhere.^{20,30} Drop-outs were defined as not meeting for the assessment within 3 days of scheduled date or terminating the study medicine or refusing to receive the next injection.

Statistical Analyses:

Main analyses assessed the differences between the two treatment groups in trend in three outcome measures- anxiety, depression, and insomnia- by estimating a linear mixed model with fixed effects for the group, non-linear time, and the interaction between group and time for each measure.

Three exploratory analyses were carried out. Associations between anxiety/depression scores and substance abuse (heroin, other opiates, benzodiazepines/sedatives, amphetamine, and cannabis) were assessed by linear mixed models with fixed effects for non-linear time and substance use. Next, main analysis stratified by gender were repeated by including additional fixed effects for gender and three-way interaction between group, gender and time, as well as all lower-order interactions into linear mixed model. Associations between insomnia score and anxiety/depression were examined by the same linear mixed models as in main analysis with additional fixed effects for anxiety/depression score, and three-way interactions between time, group and score; and all lower-order interactions.

All linear mixed models included random intercepts for participants and additional fixed effect for the period (RCT or follow-up) followed by interactions between period and relevant variables. Autregressive covariance structured was employed. The cluster effect on site level was negligible and not included into the models. All analyses were carried out on ITT sample using SAS v 9.4. Results with p-values below .05 were considered statistically significant.

Results:

Among the 232 participants assessed for eligibility, 165 were included in the study and 159 were randomized to treatment with either XR-NTX (n=80) or BP-NLX (n=79). The reasons for exclusion or not being randomized after inclusion were refusal to participate (n=51; 69.9%), not meeting inclusion criteria (n=9; 12.3%), failed detoxification (n=6; 8.2%), and other reasons (n=7; 9.6%). At week 12, 105 (66.0%) participants had completed the randomized part of the study. No significant difference in treatment retention between the groups could be detected.. Most participants (n=117 of 122) preferred XR-NTX when entering the follow-up study after week 12. These data were therefore based on XR-NTX participants only, those who continued with XR-NTX and those who switched from BP-LNX to XR-NTX. At week 16, n=8 participants dropped out or failed detoxification, leaving 109 participants in the follow-up study. In both groups 29 participants completed the study (n=58; 10 women , 48 men) (figure 1). Four participants were HIV positive while 86 (54.1%) had positive hepatitis C tests. The mean daily dose of BP-NLX was 11.2 mg (range 6-24 mg). Participants characteristics are reported in Table 1.

XR-NTX and BP-NLX participants, respectively, showed similar age distribution (mean (SD), 36.4 (8.8) and 35.7 (8.5)), gender distribution (male n=61 (76.3%) and n=54 (68.4%), female n=19 (23.6%) and n=25 (31.6%)), years of heroin use (mean (SD), 6.9 (5.8) and 6.7 (5.2)), ethnicity (white (90.0% and)88.6%) and other social characteristics corresponding to

data from the national registry on opioid-dependent substance users in Norway. Descriptive statistics for both treatment groups are presented in Table 1. Among the XR-NTX continuers mean age was 36.0 (SD 8.3), and in the BP-NLX switch group 35.4 (SD 9.7).

At baseline, mean (SD) anxiety, depression and insomnia scores were 18.6 (6.8), 31.1 (10.3) and 12.9 (8.1), respectively. The scores were moderately to highly intercorrelated; anxiety and depression 0.73; anxiety and insomnia 0.58; and depression and insomnia, 0.56.

Men and women, respectively, showed similar age distribution (mean (SD) 36.2, (8.9) and 35.6 (7.9) years), years of heavy heroin use (mean (SD) 6.7 (5.5) and 6.9 (5.3)), years of heavy use of other illicit opioids (mean SD 2.8 (5.5) and 3.0 (7.6)), and age at onset of injection use (mean (SD) 21.2 (7.8) and 21.0 (8.6) years).

Randomized Clinical Trial Period

We were not able to show any overall differences between the XR-NTX and BP-NLX groups in trend in anxiety and depression scores, but the insomnia score was significantly lower in XR-NTX group ($p=0.008$) (figure 2). The difference would remained significant also after adjustment for multiple testing. The estimated effect sizes were small and 95% confidence intervals (CI) relatively narrow; -0.14 (-0.47; 0.19) for anxiety, -0.12 (-0.45; 0.21) for depression and -0.32 (-0.65; 0.02) for insomnia scores.

Since there were no differences between the treatment groups shown, the associations between the anxiety/depression scores and illicit substance abuse were assessed for all participants together. The anxiety score was not related to the use of heroin. For one day extra use of other opiates, amphetamine, benzodiazepine or cannabis, anxiety score increased significantly by on average 0.17 ($p=.002$), 0.08 ($p=.013$), 0.10 ($p<.001$) and 0.05 ($p=.019$), respectively. The depression scores were significantly higher by on average 0.14, 0.27, 0.17, 0.20 and 0.15, respectively, for one extra day use of heroin ($p<.001$), other opiates ($p=.003$),

benzodiazepines ($p < .001$), amphetamine ($p = .001$), and cannabis ($p = .001$). When adjusted for substance use, the trend in anxiety and depression scores remained unchanged.

The study was not able to show any overall sex differences in trend in anxiety, depression and insomnia scores between the 2 treatment groups. although increases in anxiety and depression scores were significantly associated with higher insomnia score (anxiety mean 0.36; 95% CI, 0.28-0.45; $P < 0.001$), no difference was found between treatment groups.

We found only weak correlations between craving for opioids and anxiety, depression and insomnia scores. In addition, among participants who completed the study, we did not find any significant differences but found a small overall difference between the groups for insomnia scores (0.02; 95% CI, -0.56 to -0.06; $P = 0.02$).

Follow-up Study Period

No overall differences in anxiety, depression and insomnia scores were detected between participants continuing with XR-NTX from the RCT and participants switching from BP-NLX to XR-NTX after week 12 (Figure 2). The estimated effect sizes were 0.04 (-0.34; 0.42) for anxiety, -0.04 (-0.42; 0.33) for depression and 0.04 (-0.33; 0.42) for insomnia scores.

When assessing all participants as 1 treatment group, higher mean anxiety scores were significantly associated with 1 day extra use of heroin (0.11; 95% CI, 0.02-0.20; $p = 0.01$), benzodiazepine (0.13; 95% CI, 0.09-0.17; $p < 0.001$), amphetamine (0.16; 95% CI, 0.10-0.22; $p < 0.001$), and cannabis (0.06; 95% CI, 0.02-0.11; $p = 0.004$) and a higher depression scores were significantly associated with 1 day extra use of heroin (0.25; 95% CI, 0.11-0.40; $p = 0.001$), benzodiazepine (0.25; 95% CI, 0.18-0.32; $p < 0.001$), amphetamine (0.30; 95% CI, 0.20-0.39; $p < 0.001$), and cannabis (0.13; 95% CI, 0.06-0.20; $p < 0.001$). We found no association between the use of other opioids and depression or anxiety scores.

Increases in the anxiety and depression scores were significantly associated with higher insomnia scores (mean 0.65; 95% CI, 0.41-0.84 and mean 0.43; 0.30-0.57, respectively; $p < 0.001$) in the follow-up period with no differences detected between treatment groups. Our analyses did not show any overall sex differences in the trends for anxiety, depression and insomnia scores between the 2 groups of participants.

Discussion

To the best of our knowledge, this is the first study comparing the effects of XR-NTX injections vs. daily oral BP-NLX treatment on comorbid symptoms of anxiety, depression, and insomnia assessed by the SCL-25 inventory. The levels of anxiety and depression were positively correlated with the use of illicit substances in both study periods, and were positively associated also to the degree of insomnia. Based on our findings, we postulate that opioid agonist treatment with BP-NLX has no advantage over XR-NTX with regard to comorbid symptoms of anxiety, depression, or insomnia in abstinence-motivated, opioid-dependent individuals.

Previous reports have discussed anhedonia, depression, and reduced pleasure after induction of either XR-NTX or oral naltrexone in subjects with and without SUDs.^{31,32,33,34} However, our findings are in line with a study by Krupitsky et al. that reported gradual improvements in anxiety, depression, anhedonia, and insomnia over time in participants treated with either oral NTX or XR-NTX implant.³³ Both Zaaijer et al.³⁵ and Mysels et al.³⁶ reported a significant improvement in depressive symptoms on NTX treatment but Mysels et al. found no improvement in anxiety symptoms, and a transient worsening of late insomnia. A study by Dean et al. showed improvement in depressive symptoms only, and a worsening of anxiety symptoms with oral NTX.³⁷

Among opioid-dependent substance users, anxiety and depressive symptoms are heavily influenced by the use of other substances.³⁸ A 10-year prospective study of patients on OMT¹⁰ found that high and stable scores of anxiety and depression corresponded well with substantial difficulties in reducing the abuse of benzodiazepines and cannabis. This outcome is in line with our finding of a higher use of illicit substances in participants reporting more symptoms of anxiety and depression. While no improvement was noticed in the above mentioned study at any point of time, our results showed improvements in anxiety, depression, and insomnia already a few weeks after beginning either study treatment. Our study also showed reductions in the use of opioids and other illegal substances in both treatment groups. This outcome is in accordance with a study by Comer et al. reporting a reduction in illicit opioid use among participants treated with XR-NTX compared with placebo injections,¹⁹ general treatment aftercare,³⁹ or oral NTX treatment.⁴⁰ However, it is difficult to know if the observed improvements in symptoms of anxiety, depression, and insomnia were merely a reflection of the reduced use of illicit-substances or a positive pharmacological effect of XR-NTX treatment per se.

It is assumed that there is a complex interplay between the use of illicit substances and sleep disturbances, anxiety, and depressive symptoms. A number of studies report that opioid agonists have psychotropic effects on mood, sedation, and anxiety, and that buprenorphine and BP-NLX are useful in the palliation of such symptoms in opioid-dependent individuals.⁴¹⁻⁴⁵ Depressed opioid-dependent individuals have also reported a reduction in symptoms following methadone treatment.³⁴ This is in line with our data on the BP-NLX participants, but our results also suggest that this effect can be obtained with an opioid antagonist such as XR-NTX.

Sleep problems are regarded as a risk factor for, a consequence of, and a complication of both depression and opioid dependence. Studies have suggested that depression and

insomnia may share a common etiology or may simply co-exist¹⁷ and that depression and anxiety disorders independently affect sleep among illicit substance users.^{46,47} One study reported improved sleep patterns and insomnia with opioid agonist treatment.⁴⁸ We assume that the improvement in anxiety and depressive symptoms and possibly the reduction in substance abuse may have led to this reported improvement in insomnia.⁴⁹

The majority of the participants that dropped out from the randomized part of the study due to side effects were randomized to BP-NLX. Most of these patients were initially motivated to receive treatment with XR-NTX, which may have influenced the drop-out rate among patients receiving BP-NLX.

Limitations and Strengths

Self-reporting questionnaires were used to detect symptoms of depression, anxiety, and insomnia. A possible weakness with such questionnaires is that there will be variations in the participant's understanding of questions, their introspective ability to provide an accurate response to a question, and their understanding of rating scales. Even though these questionnaires were used under supervision of study personnel (Z.H.L., K.K.S., A.O., and K.S.-H.), the assessment of changes in symptoms over time can be compromised at many points due to these factors. In addition, the HCL-25 describes symptoms of anxiety and depression but is not a diagnostic tool. Our data cannot describe any prevalence of ongoing anxiety or depressive disorders on a diagnostic level, but merely describes symptoms of distress perceived and reported in terms of anxiety and depressive symptoms.

Another limitation is that we did not confirm reported drug use by urine samples in the follow-up period. However, analyses performed in the randomized part of the study showed a high correlation between the reported use of illicit substances and urine analyses results.

Current psychiatric disorders were not exclusion criteria, except for psychotic disorders and other severe psychiatric illnesses that would most likely make participation in the study difficult. Finally, an even distribution of participants in the XR-NTX and BP-NLX groups reduced the possibility of bias in observed improvement in both treatment groups.

Conclusions

Since treatment with XR-NTX and BP-NLX showed equal improvements in anxiety, depression, and insomnia assessed by the HCL-25, such symptoms should not preclude the choice to leave opioid agonist treatment and be inducted to treatment with XR-NTX. There was a close relationship between higher HCL-25 scores and more frequent use of illicit substances.

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Additional contributions: All data analyses were conducted by the study-independent statistician Jūratė Šaltytė Benth, PhD (Akershus University Hospital and University of Oslo). Zhanna Gaulen, MSc (Department of Addiction Medicine, Haukeland University Hospital), Anne-Lill Mjoelhus Njaa, MSc (Center for Alcohol and Drug Research, Stavanger University

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References:

1. Landheim AS, Bakken K, Vaglum P. Gender differences in the prevalence of symptom disorders and personality disorders among poly-substance abusers and pure alcoholics - Substance abusers treated in two counties in Norway. *European Addiction Research*. 2003;9(1):8-17.
2. Hintz T, Mann K. Comorbidity in alcohol use disorders: focus on mood, anxiety and personality. *Dual Diagnosis. The Evolving Conceptual Framework*. 2005;172:65-91.
3. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. *Jama*. 1990;264(19):2511-2518.
4. Benca RM. Sleep in psychiatric disorders. *Neurologic clinics*. 1996;14(4):739-764.
5. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. *Archives of general psychiatry*. 1992;49(8):651-668.
6. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of general psychiatry*. 2004;61(8):807-816.
7. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. *Depression and anxiety*. 2000;12(s 1):69-76.
8. Brooner RK, King VL, Kidorf M, Schmidt CW, Bigelow GE. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Archives of General psychiatry*. 1997;54(1):71-80.
9. Rounsaville BJ, Weissman MM, Crits-Christoph K, Wilber C, Kleber H. Diagnosis and symptoms of depression in opiate addicts: Course and relationship to treatment outcome. *Archives of General Psychiatry*. 1982;39(2):151-156.
10. Ravndal E, Lauritzen G. Rusmisbruk, angst og depresjon etter 10 år: En prospektiv undersøkelse av stoffmisbrukere med og uten LAR-behandling. *Nordic Studies on Alcohol and Drugs*. 2015;32(5):495-508.
11. Verthein U, Degkwitz P, Haasen C, Krausz M. Significance of comorbidity for the long-term course of opiate dependence. *European addiction research*. 2005;11(1):15-21.
12. Tómasson K, Vaglum P. The 2-year course following detoxification treatment of substance abuse: the possible influence of psychiatric comorbidity. *European archives of psychiatry and clinical neuroscience*. 1997;247(6):320-327.
13. Öjehagen A, Schaar I. The process of recovery among severely mentally ill substance abusers: a long-term follow-up of a multicentre study in connection with the psychiatric care reform initiated by the Department of Social Affairs. *Stockholm: Department of Social Affaires*. 2004.
14. Schaar I, Öjehagen A. Severely mentally ill substance abusers: an 18-month follow-up study. *Social psychiatry and psychiatric epidemiology*. 2001;36(2):70-78.
15. Nishimoto RH, La Faune YG. The course of depressive symptoms over time for women who completed drug treatment. *Journal of substance abuse treatment*. 1997;14(2):123-131.
16. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601-608.
17. Stein MD, Herman DS, Bishop S, et al. Sleep disturbances among methadone maintained patients. *Journal of Substance Abuse Treatment*. 2004;26(3):175-180.
18. Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. *Addiction*. 2013;108(9):1628-1637.
19. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Archives of general psychiatry*. 2006;63(2):210-218.

20. Tanum L, Solli KK, Benth JŠ, et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. *JAMA psychiatry*. 2017;74(12):1197-1205.
21. Lee JD, Nunes Jr EV, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X: BOT): a multicentre, open-label, randomised controlled trial. *The Lancet*. 2017.
22. Murphy J. Psychiatric instrument development for primary care research: patient self-report questionnaire. *Report on Contract*. 1981(80M01428101D).
23. Parloff MB, Kelman HC, Frank JD. Comfort, effectiveness, and self-awareness as criteria of improvement in psychotherapy. *American Journal of Psychiatry*. 1954;111(5):343-352.
24. Hesbacher PT, Rickels K, Morris RJ, Newman H, Rosenfeld H. Psychiatric illness in family practice. *The Journal of clinical psychiatry*. 1980.
25. Winokur A, Winokur DF, Rickels K, Cox DS. Symptoms of emotional distress in a family planning service: stability over a four-week period. *The British Journal of Psychiatry*. 1984;144(4):395-399.
26. Rickels K, Lipman RS, GARCIA C-R, Fisher E. Evaluating clinical improvement in anxious outpatients: A comparison of normal and treated neurotic patients. *American Journal of Psychiatry*. 1972;128(8):1005-1009.
27. Sandanger I, Moum T, Ingebrigtsen G, Dalgard O, Sørensen T, Bruusgaard D. Concordance between symptom screening and diagnostic procedure: the Hopkins Symptom Checklist-25 and the Composite International Diagnostic Interview I. *Social psychiatry and psychiatric epidemiology*. 1998;33(7):345-354.
28. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep medicine*. 2001;2(4):297-307.
29. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry*. 1998;59 Suppl 20:22-33;quiz 34-57.
30. Kunøe N, Opheim A, Solli KK, Gaulen Z, Sharma-Haase K, Tanum L. Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacology and Toxicology*. 2016;17(1):18.
31. O' Brien CP, Gastfriend DR, Forman RF, Schweizer E, Pettinati HM. Long-Term Opioid Blockade and Hedonic Response: Preliminary Data from Two Open-Label Extension Studies with Extended-Release Naltrexone. *The American journal on addictions*. 2011;20(2):106-112.
32. Wardle MC, Bershad AK, de Wit H. Naltrexone alters the processing of social and emotional stimuli in healthy adults. *Social neuroscience*. 2016;11(6):579-591.
33. Krupitsky E, Zvartau E, Blokhina E, et al. Anhedonia, depression, anxiety, and craving in opiate dependent patients stabilized on oral naltrexone or an extended release naltrexone implant. *The American Journal of Drug and Alcohol Abuse*. 2016;42(5):614-620.
34. Miotto K, McCann M, Basch J, Rawson R, Ling W. Naltrexone and dysphoria: fact or myth? *The American journal on addictions*. 2002;11(2):151-160.
35. Zaaier ER, van Dijk L, de Bruin K, et al. Effect of extended-release naltrexone on striatal dopamine transporter availability, depression and anhedonia in heroin-dependent patients. *Psychopharmacology*. 2015;232(14):2597-2607.
36. Mysels DJ, Cheng WY, Nunes EV, Sullivan MA. The association between naltrexone treatment and symptoms of depression in opioid-dependent patients. *Am J Drug Alcohol Abuse*. 2011;37(1):22-26.
37. Dean AJ, Saunders JB, Jones RT, Young RM, Connor JP, Lawford BR. Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence. *Journal of Psychiatry and Neuroscience*. 2006;31(1):38.

38. Lai HMX, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990 – 2014: a systematic review and meta-analysis. *Drug & Alcohol Dependence*. 2015;154:1-13.
39. Kunoe N, Lobmaier P, Vederhus JK, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. *The British journal of psychiatry : the journal of mental science*. 2009;194(6):541-546.
40. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. *Arch Gen Psychiatry*. 2009;66(10):1108-1115.
41. Petke Z, Csorba J, Meszaros J, et al. Changes in psychosocial symptoms of opiate users over six months with buprenorphine/naloxone substitution therapy. *Neuropsychopharmacologia Hungarica: a Magyar Pszichofarmakologiai Egyesulet lapja= official journal of the Hungarian Association of Psychopharmacology*. 2012;14(1):7-17.
42. Williams JT, Christie MJ, Manzoni O. Cellular and synaptic adaptations mediating opioid dependence. *Physiological reviews*. 2001;81(1):299-343.
43. Bodkin JA, Zornberg GL, Lukas SE, Cole JO. Buprenorphine treatment of refractory depression. *Journal of clinical psychopharmacology*. 1995;15(1):49-57.
44. Zheng W, Wakim R, Geary R, et al. Self-reported Sleep Improvement in Buprenorphine MAT (Medication Assisted Treatment) Population. *Austin journal of drug abuse and addiction*. 2016;3(1).
45. Schuman-Olivier Z, Albanese M, Nelson SE, et al. Self-treatment: illicit buprenorphine use by opioid-dependent treatment seekers. *Journal of Substance Abuse Treatment*. 2010;39(1):41-50.
46. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep medicine reviews*. 2002;6(2):97-111.
47. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *Jama*. 1989;262(11):1479-1484.
48. Lukas SE, Dorsey CM, Mello NK, et al. Reversal of sleep disturbances in cocaine-and heroin-dependent men during chronic buprenorphine treatment. *Experimental and Clinical Psychopharmacology*. 1996;4(4):413.
49. Kupfer DJ, Reynolds CF. Management of insomnia. *New England Journal of Medicine*. 1997;336(5):341-346.
50. Brady KT, Grice DE, Dustan L, Randall C. Gender differences in substance use disorders. *The American journal of psychiatry*. 1993;150(11):1707.
51. Compton WM, Cottler LB, Ben Abdallah A, Phelps DL, Spitznagel EL, Horton JC. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. *The American journal on addictions*. 2000;9(2):113-125.

Figure 1: Consort Flow Chart

*Additional 5 patients continued with the Bp-NLX treatment but were not included in the analysis.

Figure 2

Changes in anxiety-, depression-, and sleep score in the randomized part of the study and in the follow-up period.

Time trend in Mean Anxiety Subscale, Mean Depression Subscale of the HSCL-25 and Insomnia Severity Index among participants randomized to XR-NTX or BP-NLX treatment from baseline to week 12, and during the follow-up period from week 16 to week 48, using a linear mixed model. Values in parenthesis indicate minimum and maximum values on each scale. Bars in the graphs are 95% confidence intervals. The colors discriminate between participants continuing on XR-NTX (red line) and participants switching from BP-NLX to XR-NTX after week 12 (blue line).

Table 1. Lifetime and Baseline Clinical Characteristics of Participants Randomized into Treatment with extended-release naltrexone or buprenorphine-naloxone

Lifetime Characteristic			Extended-Release Naltrexone (n=80)		Buprenorphine-Naloxone (n=79)			
Age, mean (SD), y			36.4 (8.8)		35.7 (8.5)			
Sex, No. (%)								
Male			61 (76.3)		54 (68.4)			
Female			19 (23.6)		25 (31.6)			
White, No. (%)			72 (90.0)		70 (88.6)			
Injecting (intravenous) users, No. (%)			72 (90)		64 (81)			
HIV positive, NO. (%)			2 (2.5)		2 (2.5)			
Hepatitis C Seropositive, No. (%)			44 (55.0)		42 (53.2)			
Years of substance use, Mean (SD)								
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)			
Descriptive statistics for Anxiety, Depression and Insomnia score (total) within treatment groups at each time point								
Week	BP- NLX	XR- NTX	Total Anxiety Score, Mean (SD)		Total depression Score, Mean (SD)		Total Insomnia score Mean (SD)	
	(N)	(N)						
			BP-NLX	XR-NTX	BP-NLX	XR-NTX	BP-NLX	XR-NTX
0	79	80	18.2 (6.7)	19.0 (6.9)	31.6 (10.3)	30.6 (10.2)	12.9 (8.0)	13.4 (8.2)
4	71	69	16.4 (5.4)	18.2 (6.8)	27.5 (9.5)	28.7 (10.1)	13.4 (7.8)	12.3 (7.3)
8	57	56	16.8 (6.8)	16.3 (5.7)	27.7 (8.9)	25.5 (9.7)	11.3 (7.5)	9.8 (7.6)
12	49	56	16.3 (5.4)	16.1 (5.6)	28.4 (8.5)	26.0 (9.3)	12.8 (7.4)	9.2 (7.3)
			Switch Group	Maintenance Group	Switch Group	Maintenance Group	Switch Group	Maintenance Group
12	61	56	18.2 (6.6)	16.1 (5.7)	30.5 (9.6)	25.9 (9.4)	13.7 (7.8)	9.1 (7.5)
16	59	50	18.1 (7.4)	15.3 (5.0)	28.3 (10.0)	25.9 (9.0)	13.2 (8.7)	9.2 (7.2)
20	50	45	16.6 (7.1)	15.3 (5.4)	26.1 (9.8)	24.7 (9.9)	11.8 (8.4)	7.9 (7.1)
24	44	44	16.0 (6.9)	15.6 (6.0)	25.0 (9.7)	24.8 (8.6)	9.4 (7.6)	7.1 (6.5)
28	41	38	15.8 (7.2)	14.4 (5.1)	26.0 (11.1)	23.9 (9.2)	10.4 (8.3)	7.6 (7.0)
32	37	33	15.5 (7.4)	15.2 (5.9)	25.1 (10.4)	24.5 (9.2)	8.7 (7.6)	7.4 (7.4)
36	33	35	16.7 (7.1)	16.1 (6.0)	27.8 (10.8)	26.2 (10.3)	11.0 (8.3)	9.1 (7.9)
40	31	30	15.5 (6.5)	13.3 (4.3)	26.2 (10.7)	22.8 (7.1)	9.5 (8.5)	7.5 (7.0)
44	28	32	15.5 (7.1)	14.1 (4.7)	26.6 (9.6)	23.0 (7.8)	10.6 (9.1)	8.0 (7.4)
48	29	29	16.2 (7.8)	13.7 (5.6)	25.6 (10.7)	21.5 (6.4)	9.6 (8.0)	6.6 (6.1)

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PAPER III

**No increased pain among opioid-dependent individuals treated with extended-release
naltrexone or buprenorphine-naloxone: A 3-month randomized study and 9-month
open-treatment follow-up study**

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Running head: Effect of XR-NTX on pain in opioid-dependence

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Abstract

Background and Objectives

It is presently unclear whether extended-release naltrexone hydrochloride treatment induces pain or aggravates existing pain among individuals with opioid use disorders. We assessed changes in pain among individuals receiving treatment with either extended-release naltrexone hydrochloride or buprenorphine-naloxone hydrochloride.

Methods

This randomized prospective open-label clinical study included 143 participants (aged 18–60 years) with opioid dependencies, recruited from outpatient addiction clinics at five urban hospitals in Norway. After in-patient detoxification from opioids, patients were randomized to 12-week treatment with either long-acting naltrexone (380 mg intramuscularly injected every four weeks) or buprenorphine-naloxone (flexible 4–16 mg sublingual doses daily). This phase was followed by a 9-month open-treatment study with the participant's choice of either naltrexone or buprenorphine-naloxone. Changes in pain were assessed every 4 weeks using the Norwegian Short-Form of McGill Pain Questionnaire.

Results

Throughout the study period, we found no increase in mean sensory pain, affective pain, or present pain intensity on the McGill Pain Questionnaire, in either treatment group, including the subgroups of participants with chronic pain. Participants who switched from buprenorphine-naloxone to extended-release naltrexone treatment after week 12 reported no increase in pain intensity during longer-term treatment. Women experienced significantly more affective pain symptoms than men ($p = .01$).

Discussion and Conclusions

Among individuals with opioid use disorder, switching from daily opioid use to long-acting naltrexone did not induce pain, or aggravate mild-to-moderate chronic pain.

Scientific significance

In opioid-dependent individuals, mild-to-moderate chronic pain was not influenced by opioid agonist or antagonist treatment.

INTRODUCTION

The incidence of chronic pain has significantly risen in the Western population over the last 50 years.¹ An estimated 80 million Americans experience chronic pain that affects various aspects of their lives.² The International Association for the Study of Pain (1986) defines chronic non-cancer pain as “pain that lasts past the normal time of healing” , which is three months or more.³ The World Health Organization reviewed pain conditions among patients in primary care, and found that 22% of the included patients experienced pain lasting over six months.¹

Opioids are among the most frequently prescribed medications for pain treatment. Over recent years, growing awareness of chronic pain as a potentially disabling condition has led to increased opioid prescriptions for chronic pain.⁴ However, relatively liberal opioid prescription practices have promoted severe public health problems in the US.¹³ Since 1990, opioid prescriptions for non-medical conditions have increased over three-fold, representing nearly epidemic levels.¹³ Moreover, hospital admissions due to opioid use increased by 400% from 1998 to 2008.⁵⁻⁸ Significantly increased use of prescribed opioids has also been reported in other countries.¹²

A recent survey indicates that up to 8 million Americans use opioids for long-term management of chronic pain.⁹ The evolving use, and possible misuse, of prescribed opioids may be partly explained by their easy availability and by marketing-induced conceptions that opioids are physically harmless and pose no major risks of dependence or addiction.^{10,11} However, recent studies demonstrate that long-term use of prescribed opioids increases the risk of substance-use disorder development.⁵ Moreover, there is an ongoing controversy about the insufficient evidence supporting opioids long-term adequacy and effectiveness for chronic pain.² Additionally concerns have been raised regarding opioids’ side effects,

induction of tolerance, and addictive properties, which present medical challenges in individuals who suffer from chronic pain but develop opioid dependence.⁷

Previous studies demonstrate that extended-release naltrexone (XR-NTX) shows promise for treating opioid dependence.^{12,13} Naltrexone inhibits the action of heroin and other opioid agonists by competitively blocking the mu and kappa opioid receptors, and has been proposed as an alternative treatment for maintaining opioid abstinence.^{6,14} In contrast to opioid agonists, naltrexone lacks abuse potential and any risk of diversion. It offers a prolonged period of opioid abstinence, and strong protection from relapse. However, no study to date has examined how such treatment influences long-term pain conditions.

The present study aimed to assess changes in pain symptoms in opioid -dependent individuals that received short-term treatment with XR-NTX compared to buprenorphine-naloxone (BP-NLX), followed by longer-term treatment with XR-NTX.

MATERIALS AND METHODS

Methods

We performed a randomized, prospective, open-label clinical study with two treatment phases. In the first phase, we conducted a 12-week randomized clinical trial, in which participants received treatment with either XR-NTX administered every fourth week, or sublingual BP-NLX administered daily. Treatments were assigned following a permuted block algorithm provided by an external authority.

In the second phase, we conducted a 36-week follow-up study, in which participants chose treatment with either drug. Week 12 was considered baseline for the 36-week follow-up study. Only five participants chose BP-NLX during the follow-up period. Such a small group size prevented further comparisons between the treatment groups. Therefore, we

divided the XR-NTX participants into two groups: individuals who continued with XR-NTX from the RCT phase of the study (maintenance group), and participants who switched from daily BP-NLX treatment to XR-NTX after week 12 and those who were re-included in the follow-up phase after dropping out of the RCT phase (switch group).

During both phases, participants were assessed for pain symptoms every fourth week using the Norwegian validated short form of the McGill Pain Questionnaire (NSF-MPQ).⁸ The NSF-MPQ^{15,16} is commonly used for self-reported pain, and shows high reliability and validity.¹⁷ The questionnaire has three different components: pain descriptors, present pain intensity (PPI) scale, and visual analogue scale (VAS). The 15 pain descriptors include a sensory subscale comprising 11 pain-related words, and an affective subscale comprising 4 pain-related words. Descriptors were rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The PPI scale is a vertical 6-point ordinal scale, with anchors of 0, indicating no pain, and 5, indicating excruciating pain. The VAS ranks the average pain intensity on a 100-mm horizontal line, with anchors of 0, indicating no pain, and 100, indicating the worst possible pain. At each assessment, participants were instructed to report pain intensity during the last 5 days.

All participants provided their written informed consent. At all participating sites, the study was performed according to the Protocol, version #3C, of June 12, 2012. The study was approved by the Regional Committee for Medical and Health Research Ethics, South East Norway (#2011/1320), the Norwegian Medicines Agency, and the Boards of Research Ethics at the participating hospitals.

Participants & setting

Participants were recruited from outpatient clinics and detoxification units at five urban addiction clinics in Norway between November 1, 2012 and July 10, 2015. Eligible

participants were men and women, of 18–60 years of age, with opioid dependence (DSM-IV). Criteria for exclusion were dependence on another drug or alcohol, serious somatic or psychiatric illness that might interfere with study participation, and pregnancy or lactation. Participating females of childbearing age agreed to use contraceptive methods during the study period. Although chronic pain was not an exclusion criterion, eligible subjects with severe chronic pain were not encouraged to participate. Study personnel screened patients for psychiatric disorders using the M.I.N.I. Interview 6.0.¹⁸ A physician examined patients for serious somatic disease.

Following screening, eligible participants were referred to an individually adapted in-patient detoxification plan. Participants were randomly assigned to receive either BP-NLX at an individualized dose of 4–24 mg daily (target dosage, 16 mg/day) or XR-NTX at a dose of 380 mg every fourth week for 12 weeks. For most participants, randomization occurred after detoxification. All included participants took at least one dose of study medication and attended at least one assessment (Modified Intention-To-Treat population).

The participants were invited to enter the 36-week follow-up study, during which they could either continue with the same treatment or switch to the other medication. Participants who dropped out of the randomization phase were invited to be re-included in the follow-up study. All participants who initiated XR-NTX treatment at re-inclusion after week 12 were referred to in-patient detoxification. Participants were not paid or compensated for participating in the study, except for reimbursement of travel expenses. The procedure and selection of participants have been described elsewhere.^{6,19}

Statistical analysis

Data are presented as mean and standard deviation (SD), or as frequency and percentage. To assess whether the two treatment groups differed regarding trends in the NSF-MPQ components (PPI, VAS, and sensory and affective pain scores), we estimated a linear mixed model with random intercepts for participants for each variable. The site effect was negligible; therefore, the models were not adjusted for site. Models included fixed effects for non-linear time, treatment group, and the interaction between time and treatment group. A significant interaction would imply that the two treatment groups differed in the ways the outcome variables developed.

To identify potential distinct groups of participants having similar profiles of NSF-MPQ components, we estimated group-based trajectory models. We identified groups of patients using a number of criteria; Akaike's Information Criterion (where a smaller value indicates a better model), reasonable sample size for each group, non-overlapping 95% confidence intervals (CIs) for each trajectory representing a group of participants, and average within-group probabilities of about 0.80 or higher. The identified groups were compared in terms of a number of parameters by estimating bivariate nominal regression models. The results are presented as odds ratios with corresponding 95% CIs.

The methods applied handle unbalanced data sets by including all available observations, also from drop-outs. Statistical analyses were performed using SPSS v25, STATA v14, and SAS v9.4. Results with *p* values below .05 were considered statistically significant.

RESULTS

A total of 232 individuals were assessed for eligibility, of whom 165 were included in the study and 159 were randomized to treatment with XR-NTX ($n = 80$) or BP-NLX ($n = 79$). Of the 73 excluded individuals, 51 refused to participate, 9 did not meet inclusion criteria, 6 failed detoxification, and 7 were excluded due to other reasons. The 159 participants with a mean age of 36 years were randomized to treatment (113 males and 46 females),⁶ Of these participants, 143 took at least one dose of study medication and attended at least one assessment (Modified Intention-To-Treat population) and were included in this study. After 12 weeks, 105 participants had completed the randomized part of the study. The number of patients retained in treatments did not significantly differ between the two randomized groups. Since the baseline assessment was performed just prior to or during detoxification, we used week 4 as the first assessment in our analyses. At week 4, 81 participants reported chronic pain, and 55 reported no pain (7 assessments missing). At week 12, 52 participants reported chronic pain, and 53 reported no pain. Among participants who completed the follow-up period, at week 48, 58 participants reported no pain and 54 continued to report chronic pain symptoms. The use of other illicit substances, including cannabis, did not significantly differ between participants reporting pain and those reporting no pain. The PPI and VAS scores were highly correlated from week 4 to week 48, with a correlation coefficient ranging from 0.46 to 0.90.

12-week randomized trial

Among participants with a present pain condition that had persisted for at least three months prior to the study the number reporting no pain slightly increased from week 4 to week 12 (see Table 1) in both groups. The mean PPI, VAS, sensory pain, and affective pain

scores did not show statistically significant improvements from week 4 to 12 within treatment groups (Figure 1). Assessed pain did not differ between the treatment groups.

36-week follow-up study

In the follow-up phase of the study, 117 of the 122 participants chose XR-NTX. In XR-NTX maintenance group there was a slight increase in the number of participants reporting no-pain on PPI while there was a slight decrease in the number of participants reporting no-pain on VAS. A slight increase in the number of participants reporting no-pain both on PPI and VAS score was shown in the XR-NTX switch group (Table 1). There was no significant improvement in pain score over time, in terms of mean sensory, affective, PPI and VAS scores within the XR-NTX maintenance and switch groups (Figure 1). Assessed pain did not differ between the XR-NTX maintenance and switch groups.

Trajectories of reported pain

The treatment groups did not significantly differ with regards to overall trends in reported pain components (XR-NTX versus BP-NLX, or XR-NTX continuers versus switchers). Thus, we pooled all participants into a single group and performed group-based trajectory modeling.

We identified three distinct trajectories in PPI scores (Figure 2a). The low PPI group reported low PPI scores (average PPI, 0.2) at week 4, and showed a small but significant improvement in PPI scores throughout the entire study period. The low-moderate PPI group reported moderate pain scores (average PPI, 1.5) at week 4, and showed a significant improvement to week 48 (average PPI, 1.0). The high-moderate PPI group showed somewhat higher moderate pain scores (average PPI, 2.0) at week 4, and exhibited no significant change through week 48. Participants who were negative for hepatitis C were more likely to exhibit a low PPI than a high-moderate PPI ($p = .048$; Table 2).

VAS pain score analysis also revealed three trajectories (Figure 2b). The three groups significantly differed from each other at week 4, and showed no significant changes throughout the study period. The low VAS group experienced no pain at week 4, and remained pain free. The low-moderate VAS group experienced mild pain (average VAS, 2.0) at week 4, and reported a slight decrease in pain throughout the study. The high-moderate VAS group experienced moderate pain (average VAS, 5.2) at week 4, and reported a non-significant reduction of pain towards the end of the study period. These three groups did not differ in any of the considered demographic characteristics (Table 2).

Analysis of affective pain (AP) scores revealed two trajectories (Figure 2c). Low AP group showed a low mean affective pain score of 1.2. The moderate AP group showed a moderate mean affective pain-score of 4.3 at week 4, which non-significantly declined towards the end of study period. Women were significantly more likely to experience higher affective pain ($p = .01$).

We also identified two trajectories in sensory pain (SP) scores (Figure 2d). The low SP group showed a mean sensory pain score of 3.2 at week 4, which significantly declined towards the end of the study. The moderate SP group displayed a moderate mean sensory pain score of 10.5 at week 4, with no significant improvement over time. These two groups did not differ with regards to any of the considered demographic characteristics (Table 2).

DISCUSSION

In the randomized part of the present study, we found that individuals with opioid dependencies reported no significant differences in pain after terminating their use of illicit opioids or prescribed opioids, and starting treatment with either XR-NTX or BP-LNX. Moreover, in the follow-up phase, no increase of pain was reported among participants who switched from daily BP-NLX to XR-NTX treatment. In fact, longer-term XR-NTX treatment

was not associated with decrease in pain intensity over time. We also found that women experienced more affective pain than men, and participants' positive for hepatitis C more commonly reported mild-to-moderate pain than low or no pain. Overall, our present results challenge the perceived notion that an opioid antagonist, such as XR-NTX, is likely to aggravate long-standing pain in individuals with opioid dependencies. Our findings also raise questions regarding whether opioids can provide adequate analgesic efficacy in individuals with opioid dependencies who experience chronic mild-to-moderate pain.

This is the first study to compare the effects of XR-NTX and BP-NLX on chronic mild-to-moderate pain among individuals with opioid dependencies. Thus, our present results improve our understanding of the role of opioid receptors in chronic pain. Indeed, among the participants with chronic pain at the start of the study, none experienced pain aggravation upon XR-NTX treatment. Moreover, our findings suggested that opioid treatments had very limited analgesic efficacy in opioid-addicted individuals. In agreement with our present results, Compton et al.²⁰ Previously reported that opioid-dependent individuals experience improved pain tolerance upon receiving NTX treatment. Welsch et al.^{21,22} performed a systematic review of 10 randomized controlled trials on pain treatment efficacy, and concluded that opioid and non-opioid analgesics do not significantly differ in efficacy or reduction of chronic pain. Moreover, their data did not support the notion that chronic non-cancer pain requires opioid treatment.²² Other studies have concluded that opioid agonist and antagonist treatments are equally effective in reducing chronic pain among individuals with opioid dependencies, but that antagonist treatments have a few advantages over agonist treatments.²¹ Importantly, different mechanisms underlie the analgesic effects induced by opioid antagonists versus opioid agonists.²³

Data suggest that long-standing pain conditions are associated with increased prevalence of prescribed and illicit opioid use.^{5,24} Other studies describe persistent chronic

pain in individuals who have either developed opioid dependencies or used opioids for prolonged periods.²⁵ The opioid antagonist XR-NTX is not generally considered an adequate treatment for opioid-dependent individuals with chronic pain, due to concerns that blocking opioid receptors could worsen pain symptoms or trigger recurrent acute or chronic pain conditions. Thus, in our present study, we did not encourage participation of individuals with severe chronic pain, but rather recruited those who reported either no pain or mild-to-moderate long-standing pain. Consequently, our findings may not be generalizable to opioid-dependent individuals who experience severe chronic pain. Future studies should explore how such individuals tolerate XR-NTX treatment with the therapeutic goal of opioid abstinence or opioid use harm reduction.

Prior studies report increased cannabis use in individuals with long-term pain with or without opioid dependence.^{26,27} Here we found that cannabis use did not significantly differ among participants experiencing chronic pain compared to those reporting no pain throughout the study period. Therefore, the slight decrease in pain intensity reported by participants receiving XR-NTX treatment cannot be explained by increased cannabis use.⁶

Chronic pain is associated with nervous system inflammation due to tissue damage, abnormal immune system reactivity, or nerve injury.²⁸ A number of studies propose that chronic pain mainly arises from a state of neuro-inflammation that can be maintained by dynamic interplay between the hypothalamic–pituitary–adrenal (HPA) axis, stress, and neuro-immune functions.²⁹ Thus, long-standing pain might be maintained by peripheral and central nerve inflammatory or degenerative processes,^{28,29} and opioid receptors do not seem to play a major role in this pain mechanism. Low-dose naltrexone (LDN) treatment reportedly reduces pain in a number of chronic pain conditions thought to involve inflammatory processes. In this context, naltrexone may exert anti-inflammatory effects via a pathway that does not involve its opioid antagonist activity.³⁰ We speculate that this potential

anti-inflammatory effect of XR-NTX might partly explain the minor pain reductions and lack of pain aggravation that we observed in the trajectories of mild-to-moderate chronic pain in our study participants.

Our present observations may have also been related to the fact that chronic naltrexone administration is associated with sustained elevations in beta-endorphin levels in individuals with opioid dependencies.³¹ Prolonged opioid exposure leads to neuronal system changes at both the receptor and cellular levels, which may increase pain sensitivity and modulate pain perception among opioid-dependent individuals.³² Consequently, individuals who use opioids for prolonged periods are at risk of experiencing increased pain, new types of pain, pain relapse, and pronounced pain in response to acute injury.³² In chronic pain states, opioid agonists inhibit endogenous production of both opiate peptides and mu-opioid receptors, thus promoting further development of hyperalgesia, tolerance, and addiction.³³

We postulate that the slightly improved or unchanged intensity of mild-to-moderate long-standing pain reported in the XR-NTX study group is likely due to a combination of factors. The reduced use of illicit substances and lifestyle changes could have contributed to opioid receptor up-regulation, increased beta-endorphin levels, and a potential reduction of chronic nervous system inflammation. Moreover, chronic inflammatory pain conditions can cause up-regulated delta opioid-receptor expression,³⁴ which is not substantially blocked by XR-NTX.²⁸

Patients with chronic pain commonly present with psychiatric co-morbidities, most frequently depression, anxiety, or substance-use disorders.³⁵ Our study participants reported reduced use of illicit substances, and improved anxiety and depressive symptoms over time.⁶ It is likely that these reported improvements in mental distress might have contributed to the participants' perceived improvement of chronic pain³⁵ (paper accepted for publication).

None of our study participants dropped out due to pain issues. Compared to participants who completed the study, those who prematurely terminated the study did not differ in pain severity, character, or pattern. The number of participants who prematurely left the study should not significantly influence our results. Moreover, the models applied handle unbalanced data by including all available observations, including those from drop-outs.

Study limitations

One potential weakness of this study is that the NSF-MPQ is a self-reporting questionnaire; thus, the results may be influenced by variability among participants with regards to their understanding of the questions, their introspective ability to provide accurate responses to the questions, and their understanding of rating scales. Although the questionnaires were completed under the supervision of study personnel, these factors may compromise the assessment of changes in symptoms at multiple points over time. Another limitation was that we had no previous knowledge or record of participant pain conditions before inclusion in the study. Therefore, pain histories could not be verified with medical records. Notably, most of the medical records that we obtained for study participants after enrollment did not include comments regarding pain symptoms.

Conclusions

Based on our present findings, we conclude that treatment with the opioid agonist BP-LNX was not superior to treatment with the opioid antagonist XR-NTX treatment in terms of reducing chronic mild-to-moderate pain in abstinence-motivated individuals with opioid dependencies. Study participants who successfully switched from opioid agonist treatment to XR-NTX treatment did not experience any increase in pain.

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Author Contributions: Dr. Kunoe and Dr. Tanum had full access to all of the study data, and take responsibility for the data integrity and the accuracy of the data analysis.

Study concept and design: Tanum, Kunoe.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Latif, Tanum, Šaltytė Benth.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Latif, Solli, Šaltytė Benth..

Obtained funding: Tanum, Opheim, Kunoe.

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Study supervision: Tanum, Kunoe.

Additional Contributions: All data analyses were conducted by the study-independent statistician Jūratė Šaltytė Benth, PhD (Akershus University Hospital and University of Oslo). Zhanna Gaulen, MSc (Department of Addiction Medicine, Haukeland University Hospital), Anne-Lill Mjoelhus Njaa, MSc (Center for Alcohol and Drug Research, Stavanger University Hospital), and LinnWergeland Digranes, BSc (Department of Addiction Medicine, Akershus

University Hospital), contributed to data collection. They received no financial compensation. Alkermes, Inc. supplied extended-release naltrexone for the study.

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Declaration of interests

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Trial registration

Clinicaltrials.gov #NCT01717963, first registered: Oct 28, 2012. Protocol version # 3C, June 12th 2012.

REFERENCES

1. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *Jama*. 1998;280(2):147-151.
2. Solanki DR, Koyyalagunta D, Shah RV, Silverman S, Manchikanti L. Monitoring opioid adherence in chronic pain patients: Assessment of risk of substance misuse. *Pain Physician*. 2011;14(2):E119-E131.
3. Merskey HE. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. *Pain*. 1986.
4. Manchikanti L, Benyamin R, Datta S, Vallejo R, Smith H. Opioids in chronic noncancer pain. *Expert review of neurotherapeutics*. 2010;10(5):775-789.
5. Ling W, Mooney L, Hillhouse M. Prescription opioid abuse, pain and addiction: clinical issues and implications. *Drug and alcohol review*. 2011;30(3):300-305.
6. Tanum L, Solli KK, Benth JS, et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. *JAMA psychiatry*. 2017;74(12):1197-1205.
7. Solis K. Ethical, legal, and professional challenges posed by “controlled medication seekers” to healthcare providers, part 2. *American Journal of Clinical Medicine*. 2010;7(2):86-92.
8. Melzack R, Katz J. *The McGill Pain Questionnaire: Appraisal and current status*. Guilford Press; 2001.
9. Reuben DB, Alvanzo AA, Ashikaga T, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. *Annals of internal medicine*. 2015;162(4):295-300.
10. Jamison RN, Serrailier J, Michna E. Assessment and treatment of abuse risk in opioid prescribing for chronic pain. *Pain research and treatment*. 2011;2011.
11. Kuehn BM. Prescription drug abuse rises globally. *Jama*. 2007;297(12):1306-1306.
12. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Archives of general psychiatry*. 2006;63(2):210-218.
13. Krupitsky E, Nunes EV, Ling W, Gastfriend DR, Memisoglu A, Silverman BL. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. *Addiction*. 2013;108(9):1628-1637.
14. Lee JD, Nunes Jr EV, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X: BOT): a multicentre, open-label, randomised controlled trial. *The Lancet*. 2017.
15. Ljunggren AE, Strand LI, Johnsen TB. Development of the Norwegian Short-Form McGill Pain Questionnaire (NSF-MPQ). *Advances in Physiotherapy*. 2009;9(4):169-180.
16. Melzack R. The short-form McGill pain questionnaire. *Pain*. 1987;30(2):191-197.
17. Grafton KV, Foster NE, Wright CC. Test-retest reliability of the Short-Form McGill Pain Questionnaire: assessment of intraclass correlation coefficients and limits of agreement in patients with osteoarthritis. *The Clinical journal of pain*. 2005;21(1):73-82.
18. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry*. 1998;59 Suppl 20:22-33;quiz 34-57.
19. Kunøe N, Opheim A, Solli KK, Gaulen Z, Sharma-Haase K, Tanum L. Design of a randomized controlled trial of extended-release naltrexone versus daily buprenorphine-naloxone for opioid dependence in Norway (NTX-SBX). *BMC Pharmacology and Toxicology*. 2016;17(1):18.
20. Compton P. Pain tolerance in opioid addicts on and off naltrexone pharmacotherapy: a pilot study. *Journal of pain and symptom management*. 1998;16(1):21-28.

21. Welsch P, Sommer C, Schiltenswolf M, Häuser W. Opioids in chronic noncancer pain—are opioids superior to nonopioid analgesics? 2015.
22. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Jama*. 2016;315(15):1624-1645.
23. Yoburn BC, Purohit V, Patel K, Zhang Q. Opioid agonist and antagonist treatment differentially regulates immunoreactive μ -opioid receptors and dynamin-2 in vivo. *European journal of pharmacology*. 2004;498(1-3):87-96.
24. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *Jama*. 2008;300(22):2613-2620.
25. Ballantyne JC, LaForge SK. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129(3):235-255.
26. Degenhardt L, Lintzeris N, Campbell G, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. *Drug & Alcohol Dependence*. 2015;147:144-150.
27. Abrams D, Couey P, Shade S, Kelly M, Benowitz N. Cannabinoid–opioid interaction in chronic pain. *Clinical Pharmacology & Therapeutics*. 2011;90(6):844-851.
28. Stein C, Schäfer M, Machelska H. Attacking pain at its source: new perspectives on opioids. *Nature medicine*. 2003;9(8):1003.
29. DeLeo JA, Yezierski RP. The role of neuroinflammation and neuroimmune activation in persistent pain. *Pain*. 2001;90(1):1-6.
30. Younger J, Noor N, McCue R, Mackey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis & Rheumatology*. 2013;65(2):529-538.
31. Kaada B, Torsteinbø O. Increase of plasma beta-endorphins in connective tissue massage. *General Pharmacology*. 1989;20(4):487-489.
32. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med*. 2008;9(4):444-459.
33. Sprouse-Blum AS, Smith G, Sugai D, Parsa FD. Understanding endorphins and their importance in pain management. *Hawaii medical journal*. 2010;69(3):70.
34. Cahill C, Morinville A, Hoffert C, O'donnell D, Beaudet A. Up-regulation and trafficking of δ opioid receptor in a model of chronic inflammation: implications for pain control. *Pain*. 2003;101(1-2):199-208.
35. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007;129(3):355-362.

Table 1: Descriptive statistics of Present Pain Intensity, Visual Analogue Scale, Affective Pain and Sensory Pain among study participants in the randomized and the follow-up period of the study.

Week	XR-NTX				BP-NLX			
	PPI		VAS		PPI		VAS	
	Total	% No Pain	Total	% No Pain	Total	% No Pain	Total	% No Pain
4	63	41.3	64	37.5	73	39.7	72	40.3
8	63	39.7	68	35.3	72	43.0	67	41.8
12	49	57.1	49	51.0	56	44.6	56	41.0
	XR-NTX (Maintenance Group)				XR-NTX (Switch Group)			
16	52	50	52	48.1	62	40.3	62	40.3
20	53	50.9	51	47.1	59	47.5	61	45.9
24	56	46.4	52	46.2	57	45.6	60	43.3
28	53	43.4	52	38.5	61	44.3	60	45.0
32	53	54.7	51	43.2	59	50.8	61	50.8
36	57	47.4	56	42.9	56	53.6	56	48.2
40	53	52.8	54	48.1	58	50.0	57	45.6
44	58	51.7	53	45.3	56	50.0	57	47.4
48	56	53.6	55	45.4	56	50.0	56	44.6
	AP		SP		AP		SP	
	Total	% No Pain	Total	% No Pain	Total	% No Pain	Total	% No Pain
4	64	46.8	65	36.9	73	42.5	72	37.5
8	64	57.7	69	43.5	71	49.3	66	42.4
12	49	46.9	49	44.9	56	48.2	56	39.3
	XR-NTX (Maintenance Group)				XR-NTX (Switch Group)			
16	52	51.9	52	44.3	62	38.7	62	32.3
20	53	52.8	51	45.1	59	50.8	61	44.3
24	56	35.7	52	55.7	58	29.3	60	46.7
28	54	51.8	53	41.5	61	40.9	60	46.7
32	54	55.6	52	38.5	59	52.5	61	47.5
36	57	52.6	56	41.1	56	57.2	56	50.0
40	54	55.6	53	52.8	57	52.6	58	51.7
44	56	66.1	54	46.3	57	52.6	58	50.0
48	56	62.5	54	51.8	56	60.7	57	43.8

*PPI (present pain intensity), VAS (visual analogue scale), AP (affective pain), SP (sensory pain), XR-NTX maintenance group (participants who continued with the XR-NTX after week 12), XR-NTX switch group (participants who switched from BP-NLX to XR-NTX treatment after week 12).

*Missing values PPI and VAS respectively (week 4= 7, week 8= 8, week 16 = 3, week 20 = 5, week 24= 4 and 5, week 28 = 3 and 5, week 32 = 5, week 36 = 4 and 5, week = 40 = 6, week 44 = 3 and 7, week 48 = 5 and 6).

Table 2: Results of regression analyses (bivariate model) of group-affiliation among study participants in the randomization and follow-up period of the study.

	PPI			VAS		
Lifetime Charactersitics		OR (95% CI)	p-value		OR (95% CI)	p-value
Sex, No. (%)						
Female)	30 (78.9)					
Low	35 (79.5)	2.67 (0.96; 7.42)	0.060	33 (78.6)	2.48 (0.94; 6.59)	0.067
Low-moderate	50 (43.5)	2.29 (0.90; 5.80)	0.081	34 (79.1)	2.10 (0.82; 5.39)	0.120
High-moderate – ref.		1		48 (64.9)	1	
Age, mean(SD) , y	35.7 (7.3)					
Low	35.6 (9.0)					
Low-moderate	36.5 (9.0)	0.98 (0.93; 1.03)	0.328	36.1 (7.4)	0.99 (0.94; 1.04)	0.627
High-moderate – ref.		0.97 (0.93; 1.02)	0.280	35.7 (9.7)	0.99 (0.94; 1.04)	0.564
Injecting (i.v) users, No. (%)						
Low	10.1 (12.2)					
Low-moderate	10.2 (12.7)	0.99 (0.96; 1.03)	0.788	9.9 (11.8)	0.99 (0.96; 1.02)	0.595
High-moderate – ref.	11.3 (12.8)	0.99 (0.96; 1.03)	0.693	10.0 (13.0)	0.99 (0.96; 1.03)	0.479
Hepatitis C, No. (%)						
Low	21 (58.3)	2.37 (1.01; 5.56)	0.048	21 (52.5)	1.78 (0.78; 4.06)	0.167
Low-moderate	18 (40.9)	1.25 (0.55; 2.82)	0.595	19 (44.2)	1.30 (0.57; 2.97)	0.537
High-moderate – ref.	28 (37.3)	1		27 (37.5)	1	
Years of heroin use, mean (SD)						
Low	7.2 (3.8)					
Low-moderate	6.2 (3.8)	0.99 (0.92; 1.07)	0.824	7.1 (3.7)	0.99 (0.92; 1.06)	0.771
High-moderate – ref.	7.0 (6.9)	0.95 (0.88; 1.03)	0.224	6.1 (3.8)	0.95 (0.87; 1.03)	0.196
		1		7.0 (7.0)	1	
	AP			SP		
Sex, No. (%)						
(Female – ref.)						
Low – ref.	79 (78.2)	1		76 (74.5)	1	
Moderate	36 (62.1)	0.36 (0.17; 0.78)	0.010	39 (68.4)	0.63 (0.29; 1.36)	0.238
Age, mean (SD), y						
Low – ref.	37.0 (8.5)	1		36.7 (8.5)	1	
Moderate	34.5 (8.6)	0.96 (0.92; 1.00)	0.078	35.0 (8.8)	0.98 (0.93; 1.02)	0.253
Injecting (i.v) users, No. (%)						
Low – ref.	10.0 (12.2)	1		10.5 (12.4)	1	
Moderate	12.0 (13.2)	1.01 (0.98; 1.04)	0.491	11.1 (13.0)	0.99 (0.97; 1.03)	0.968
Hepatitis C, No. (%)						
Low – ref.	41 (42.3)	1		43 (43.9)	1	
Moderate	26 (46.4)	1.10 (0.54; 2.23)	0.802	24 (43.6)	0.89 (0.44; 1.82)	0.749
Years of heroin use, mean (SD)						
Low – ref.	7.0 (5.4)	1		6.8 (5.0)	1	
Moderate	6.4 (5.6)	0.99 (0.92; 1.05)	0.678	6.8 (6.2)	1.02 (0.95; 1.08)	0.636

PPI (present pain intensity), VAS (visual analogue scale), SP (sensory pain), AP (affective pain)

Figure1:

Title: Changes in the pain score among study participants both in the randomization period and follow-up period of the study

Legend:

Changes in the pain score measured by 4 components of McGill pain questionnaire, A:

Present Pain Intensity (PPI), B: Visual Analogue Scale (VAS) C: Affective Pain Score (AP),

D: Sensory Pain Score (SP) among participants randomized to XR-NTX (black line) or BP-

NLX (red line) treatment from week 4 to week 12 and between participants continuing on

XR-NTX (red line) and participants switching from BP-NLX to XR-NTX (black line) from

week 16 to week 48 in the follow-up period.

Figure2:

Title: Trajectories of pain components of McGill pain questionnaire among all study participants pooled as one group from week 4 to week 48

Legend:

Trajectories of different components of McGill Pain Questionnaire from week 4 to week 48.

All participants were pooled as one group and were further divided on basis of their pain levels. In Present Pain Intensity (PPI) (A) and Visual Analogue Scale (VAS) (B), three groups of participants were made, while in Affective Pain (AP) (C) and Sensory Pain (SP) (D), two groups of participants were made. Each line represents the changes with time in pain score in one particular group.

APPENDIX

The Hopkins Symptoms Check List–25, Norwegian Version

Når smerter og andre plager har vart en tid, blir en gjerne sliten og oppgitt. Dette gir ofte slike plager som nevnt nedenfor. Samlet blir disse her brukt som mål på at en er legemlig og psykisk presset. Vurder hvor mye hvert symptom har vært til plage eller ulempe for deg de siste 14 dagene (til og med i dag). Sett ring rundt tallet som passer best. Husk å sette en ring rundt aktuelt tall for hver plage/hvert symptom.

(sett ring rundt tallet)	Ikke i det hele tatt	Litt	En god del	Svært mye
1. Plutselig skremt uten grunn.	1	2	3	4
2. Føler du deg engstelig.	1	2	3	4
3. Føler du deg svimmel eller kraftløs.	1	2	3	4
4. Nervøs eller urolig.	1	2	3	4
5. Hjerterbank.	1	2	3	4
6. Skjelving.	1	2	3	4
7. Føler deg anspent eller opphisset.	1	2	3	4
8. Hodepine.	1	2	3	4
9. Anfall av redsel eller panikk	1	2	3	4
10. Rastløshet, kan ikke sitte rolig	1	2	3	4
11. Føler deg slapp og uten energi.	1	2	3	4
12. Anklager deg selv for ting.	1	2	3	4
13. Har lett for å gråte.	1	2	3	4
14. Tap av seksuell interesse/opplevelse.	1	2	3	4
15. Dårlig appetitt.	1	2	3	4
16. Vanskelig for å sove.	1	2	3	4
17. Følelse av håpløshet mht. framtiden.	1	2	3	4
18. Føler deg nedfor.	1	2	3	4
19. Føler deg ensom.	1	2	3	4
20. Har tanker om å ta ditt eget liv.	1	2	3	4
21. Følelse av å være fanget.	1	2	3	4
22. Bekymrer deg for mye.	1	2	3	4
23. Føler ikke interesse for noe.	1	2	3	4
24. Føler at alt krever stor anstrengelse.	1	2	3	4
25. Føler at du ikke er noe verd.	1	2	3	4

The Insomnia Severity Index, Norwegian Version

Navn: _____ Dato: _____

1. Vær vennlig å angi hvor store vansker du har med søvnen nå for tiden (de siste 2 ukene)?

	Ingen	Milde	Moderate	Alvorlige	Veldige
a. Vansker med å sovne inn:	0	1	2	3	4
b. Vansker med å holde meg sovende	0	1	2	3	4
c. Vansker med at jeg våkner for tidlig	0	1	2	3	4

2. Hvor fornøyd/misfornøyd er du med ditt nåværende søvnmonster?

Veldig fornøyd	Fornøyd	Nøytral	Misfornøyd	Veldig misfornøyd
0	1	2	3	4

3. I hvilken grad mener du at ditt søvnproblem forstyrrer din daglige fungering (for eksempel tretthet på dagtid, evne til å fungere på arbeid/daglige gjøremål, konsentrasjon, hukommelse, humør, etc.)?

Forstyrrer ikke i det hele tatt	Litt	Noe	Mye	Forstyrrer i veldig stor grad
0	1	2	3	4

4. Hvor synlig tror du det er for andre at du har søvnproblemer som svekker din livskvalitet?

Ikke synlig i det hele tatt	Litt	Noe	Mye	Synlig i veldig stor grad
0	1	2	3	4

5. Hvor bekymret/plaget er du over ditt nåværende søvnproblem?

Ikke bekymret i det hele tatt	Litt	Noe	Mye	Bekymret i veldig stor grad
0	1	2	3	4

Skåringsinstruksjon:

Summere alle ledd ($1a + 1b + 1c + 2 + 3 + 4 + 5$).

Total spennvidde: 0-28.

Fortolkning:

0-7 = Ingen klinisk signifikant insomni

8-14 = Subterskel insomni

15-21 = Klinisk insomni (moderat)

22-28 = Klinisk insomni (alvorlig)

Norwegian version of Mc-Gill Pain Questionnaire

Institutt for samfunnsmedisinske fag
Seksjon for fysioterapivitenenskap
Universitetet i Bergen

Norsk kortform av McGill Pain Questionnaire (NSF-MPQ)

Pasientens navn: _____

Dato: _____

Ordene under kan brukes for å beskrive din smerte nå for tiden. Ett eller to beslektede ord er brukt på hver linje for å beskrive smertens kvalitet. Vennligst sett kryss for hvert enkelt ord eller ordpar ved det tallet som passer best.

		Ingen	Svak	Moderat	Sterk
BANKENDE	(Throbbing)	0	1	2	3
ILENDE - JAGENDE	(Shooting)	0	1	2	3
STIKKENDE - PRIKKENDE	(Stabbing)	0	1	2	3
SKARP - SKJÆRENDE	(Sharp)	0	1	2	3
KRAMPELIGNENDE	(Cramping)	0	1	2	3
GNAGENDE	(Gnawing)	0	1	2	3
BRENNENDE - SVIENDE	(Hot - Burning)	0	1	2	3
VERKENDE - MURRENDE	(Aching)	0	1	2	3
TYNGENDE - TRYKKENDE	(Heavy)	0	1	2	3
ØM - SÅR	(Tender)	0	1	2	3
SPRENGENDE - REVNENDE	(Splitting)	0	1	2	3
SLITSOM - UTMATTENDE	(Tiring - Exhausting)	0	1	2	3
KVALMENDE	(Sickening)	0	1	2	3
SKREMMENDE	(Fearful)	0	1	2	3
PINEFULL - GRUSOM	(Punishing - Cruel)	0	1	2	3

Sett ett kryss på linjen under for å angi dine smerter nå for tiden:

Ingen smerte

Verst tenkelige
smerte

Sett kryss ved ett av ordene under for å angi dine smerter nå for tiden:

0	Ingen smerte	(No pain)	_____
1	Svak	(Mild)	_____
2	Ubehagelig	(Discomforting)	_____
3	Plagsom	(Distressing)	_____
4	Fryktelig	(Horrible)	_____
5	Uutholdelig	(Excruciating)	_____