Opioid use disorder and long-acting opioid blockade. Patients' experiences with extended-release naltrexone treatment in a personal recovery process. A mixed-methods study.

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“The question is not how to get cured, but how to live.”

Joseph Conrad

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Anne Marciuch,

Oslo, February 2023

Summary

Background
Opioid use disorder (OUD) is a major global health problem with serious consequences. A relatively novel treatment approach in the treatment of OUD, extended-release naltrexone (XR-NTX) is an opioid antagonist, and it blocks the reinforcing, subjective and physiological effects of opioids over time (four weeks). While many studies have shown XR-NTX to be a safe, efficient and feasible treatment, less is known about how patients experience treatment and being blocked, why they discontinue treatment, and whether and how personal recovery occurs in such a context.

Recovery has become an increasingly important concept in the mental health and substance use disorder (SUD) fields. While recovery has been equated with the objective outcome of abstinence, there has been a growing interest in defining it in other terms (e.g., emphasizing psychosocial improvements or seeing it as a process). Personal recovery is defined as a deeply personal process of changing one's attitudes, values, feelings, goals, skills or roles, within the limitations of illness. Further conceptualizations have emphasized that personal recovery involves changes in connectedness, identity, meaning, empowerment and hope, constituting the CHIME framework.

Aims
Overall, this thesis aims to deepen understanding and knowledge of the treatment- and recovery process of people with OUD in XR-NTX treatment, specifically to illuminate central aspects of the processes. The specific aims were to explore how people with OUD experience treatment with XR-NTX over time, to better understand experiences leading to early discontinuation of treatment with XR-NTX and to examine the process of personal recovery in people with OUD receiving treatment with XR-NTX.

Material and Methods
This thesis employed a mixed-methods approach, with a partially mixed, sequential, equal status design. To obtain complementary and extended knowledge of the treatment and recovery process, both qualitative and quantitative methods were used. The thesis is connected to the Norwegian NaltRec study ("Long acting naltrexone for opioid addiction: the importance of mental, physical and societal factors for sustained abstinence and recovery"). The NaltRec study is a naturalistic, observational, multicenter open-label study of XR-NTX in the treatment of OUD, including 162 participants with OUD receiving monthly injections with XR-NTX. NaltRec is organized in four different work packages (WPs); relevant to this thesis are both WP 1 (the main prospective, observational cohort study, monthly questionnaire data used in Study 3) and WP 2 (qualitative sub-study, data used in Studies 1 and 2).

In Study 1, nineteen participants from the NaltRec study were interviewed using a semi-structured interview guide developed for WP2. Participants were in treatment with XR-NTX at the time of interview, and had been so continuously for at least 12 weeks, receiving at least 3 injections. This study employed qualitative content analysis.

In Study 2, the same interview guide was used to interview 13 participants who had chosen to discontinue XR-NTX treatment and who had received at least one injection and a maximum of four injections with XR-NTX. Study 2 employed thematic analysis, with a with a critical realist perspective.

Study 3 included 135 participants who had received at least one injection of XR-NTX. Linear mixed model was used to assess overall change in recovery, using the Questionnaire about the Process of Recovery (QPR). The QPR is widely used and is found to map the CHIME framework. Although there is no cutoff, higher scores indicate higher degrees of personal recovery. Growth mixture modeling was

used to identify groups following distinct trajectories of personal recovery. Groups were then compared for different baseline variables using ANOVA and χ^2-test.

Findings

Participants' experiences of treatment (Study 1, described in Paper I) emerged as a nonlinear process and centered on three main categories: 1) finding a new foothold and adapting to life, 2) connecting with self and others, and 3) finding meaning and maintaining hope.

The experiences of those deciding to discontinue treatment (Study 2, described in Paper II) were characterized by XR-NTX not meeting their expectations, which was central to the decision to discontinue treatment. Three themes were identified: 1) Entering treatment – *I thought I knew what I was going into*; 2) Life with XR-NTX – *I had something in me that I didn't want*; and 3) Leaving treatment – *I want to go somewhere in life.* Leaving treatment could be tied to a reacceptance of the opioid agonist treatment (OAT) or to reaching treatment goals. Either way, the motivation for abstinence from illicit substances remained.

There was a significant change in personal recovery during treatment (Study 3, described in Paper III), from baseline to 24, 40 and 52 weeks, but there was no change from baseline to 12 weeks.

Four groups following distinct recovery trajectories were identified; "initially low – increase" (G1) "initially average – no change" (G2), "initially high – no change" (G3) and "initially high – increase" (G4). Groups differed in terms of psychological distress, social support, use of benzodiazepines, previous participation in opioid agonist treatment programs, current pain, life satisfaction, employment, heroin craving and previous use of heroin. Overall, G1 had the highest burden (higher psychological distress, lower social support, etc.), and G4 the lowest.

In sum, the findings showed several important aspects pre-, mid- and post- treatment that both patients and treatment providers should be aware of regarding treatment with XR-NTX. Some of these aspects are specifically connected to the long-acting opioid blockade.

Conclusions and Implications

Utilizing a mixed-methods approach, this explorative thesis provides insight into the treatment and recovery process in XR-NTX treatment, as well as implications for further research and for the implementation of XR-NTX in Norway. The results suggest XR-NTX should be delivered as part of a flexible, individualized, long-term treatment approach, and with conscious awareness that a personal recovery process goes beyond the current treatment episode, where patients' initial, and changing, motivation and goals for treatment should be emphasized. While participants who stayed in treatment experienced many benefits, there are also considerable potential challenges, such as mental health issues (e.g., increase in symptoms), increased craving or substance use, that may arise during treatment, and may for some contribute to discontinuation of treatment. These and any other challenges should be addressed by clinicians during treatment. Discontinuation of treatment does not imply discontinuation of recovery goals, however. Attention to factors associated with different recovery trajectories may be important to facilitate the personal recovery process.

Norwegian summary

Bakgrunn
Opioidavhengighet er et globalt helseproblem, og har alvorlige konsekvenser for personen, familien og samfunnet forøvrig. Langtidsvirkende naltrekson (XR-NTX) er et relativt nytt tilbud i behandlingen av opioidavhengighet. XR-NTX gis som en intramuskulær injeksjon hver 4. uke, og blokkerer effektene av opioider. Flere studier har vist at XR-NTX er en trygg og effektiv behandling, men vi vet mindre om hvordan behandlingen oppleves; f.eks. hvordan pasienter opplever å bli blokkert fra å få effekt av opioider, hvorfor noen pasienter velger å avbryte behandlingen, samt om en tilnærming i tråd med begrepet personlig recovery er nyttig i en slik sammenheng.

Recovery (bedring eller bedringsprosess) er et viktig begrep innen områdene rus og psykisk helse. Mens recovery innenfor rusfeltet ofte sidestilles med rusfrihet og vedvarende avholdenhet fra rusmidler, har det vært en økende interesse for å definere det på andre måter, samt inkludere andre aspekter, som psykososiale forbedringer. Personlig recovery er definert som en dypt personlig og individuell prosess over tid. Prosessen inkluderer endring av egne holdninger, verdier, følelser, mål, ferdigheter og/eller roller, innenfor begrensningene av lidelsen. Recoverykonseptet er operasjonalisert ytterligere i CHIME-modellen som beskriver fem overordnede faktorer av betydning i en personlig recovery prosess; tilknytning og relasjoner til andre (Connectedness), håp (Hope), identitet (Identity), mening (Meaning), og kontroll over eget liv (Empowerment) som gir akronymet CHIME.

Målsetning
Det overordnede målet med avhandlingen var å få økt forståelse og kunnskap om behandlings- og recoveryprosessen til personer med opioidavhengighet i XR-NTX-behandling, samt å belyse sentrale aspekter ved disse prosessene. De spesifikke målsetningene var å utforske hvordan personer med opioidavhengighet opplever behandlingen med XR-NTX over tid; å bedre forstå erfaringer som fører til at pasienter velger å avbryte behandlingen, samt å undersøke den personlige recoveryprosessen hos pasienter med opioidavhengighet under behandling med XR-NTX.

Materiale og metoder
I denne avhandlingen ble det benyttet en mixed methods tilnærming, med et delvis blandet, sekvensielt, lik-status (partially mixed, sequential, equal status) design. Å benytte både kvalitative og kvantitative metoder ga mulighet til å etablere komplementær og utvidet kunnskap om behandlings- og recoveryprosessen. Avhandlingen er basert på data fra NaltRec-studien; en multisenter, naturalistisk, observasjonsstudie av XR-NTX i behandling av opioidavhengighet. NaltRec-studien inkluderte 162 deltakere med opioidavhengighet som fikk månedlige injeksjoner med XR-NTX. NaltRec-studien er organisert i fire ulike arbeidspakker (AP); hvor denne avhandlingens studier har hentet data og materiale fra to av disse. Studie 1 og 2 i avhandlingen inkluderte materiale fra NaltRec-studiens AP 2 (kvalitativ delstudie), mens studie 3 i avhandlingen inkluderte data fra NaltRec-studiens AP 1 (prospektiv kohortstudie, månedlige spørreskjemadata).

I studie 1 ble 19 deltakere fra NaltRec-studien intervjuet ved hjelp av en semistrukturert intervjuguide som ble utviklet for AP2. Ved intervjutidspunktet hadde deltakerne vært med i studien og mottatt behandling kontinuerlig i minst 12 uker, hadde fått minst 3 injeksjoner og deltok fortsatt i studien. Kvalitativ innholdsanalyse ble benyttet i denne studien.

I studie 2 ble den samme intervjuguiden brukt til å intervjue 13 deltakere som hadde valgt å avbryte XR-NTX-behandlingen etter å ha mottatt minst én, men maksimalt fire injeksjoner. Tematisk analyse med et kritisk realisme-perspektiv ble benyttet i denne studien.

I studie 3 ble 135 deltakere som hadde fått minst én injeksjon med XR-NTX inkludert. Lineær mixed modell ble brukt for å vurdere total endring i recovery, via "the Questionnaire about the process of recovery" (QPR). QPR er et mye benyttet instrument, og overlapper med faktorene i CHIME-rammeverket. I tråd med forståelsen av recovery som prosess, har ikke QPR en cut-off skåre, men høyere skårer indikerer høyere grad av personlig recovery. Videre ble growth mixture model (GMM) brukt for å identifisere grupper som fulgte distinkte løp for personlig recovery. ANOVA og $\chi 2$-test ble deretter brukt for å sammenlikne gruppene på forskjellige variabler ved baseline.

Funn

Deltakernes opplevelse av behandlingen (Studie 1, beskrevet i Paper I) var en ikke-lineær prosess, sentrert rundt tre hovedkategorier: 1) Finne nytt fotfeste og tilpasse seg livet, 2) Tilknytning til seg selv og andre, og 3) Finne mening og opprettholde håp. Behandlingen innebar både fordeler, ulemper og utfordringer.

Erfaringene til de som bestemte seg for å avslutte behandlingen (Studie 2, beskrevet i Paper II) var preget av at XR-NTX ikke svarte til deres forventninger, noe som var sentralt i beslutningen om å avslutte behandlingen. Tre temaer ble identifisert; 1) Inn i behandling – Jeg trodde jeg visste hva jeg gikk inn i; 2) Livet med XR-NTX – Jeg hadde noe i meg som jeg ikke ønsket; og 3): Å forlate behandlingen – Jeg vil noe med livet mitt. Valget om å avbryte behandlingen kunne være knyttet til en re-aksept av legemiddelassistert rehabilitering (LAR), eller knyttet til at man hadde oppnådd de målene man hadde med behandlingen. Uavhengig av hva avslutningen var knyttet til, opplevde deltakerne en fortsatt motivasjon for avholdenhet fra illegale rusmidler.

Det var en signifikant endring i personlig recovery under behandlingen med XR-NTX (studie 3, beskrevet i Paper III), fra baseline til henholdsvis 24, 40 og 52 uker, men ingen endring fra baseline til 12 uker. Fire grupper som fulgte distinkte forløp som beskrev recoveryprosessen ut fra skåringer i QPR ble identifisert; "opprinnelig lav– økning" (G1), "opprinnelig gjennomsnittlig– ingen endring" (G2), "opprinnelig høy– ingen endring" (G3) og "opprinnelig høy– økning" (G4). Det var forskjeller mellom gruppene mht. psykiske plager, sosial støtte og bruk av benzodiazepiner, deltakelse i LAR eller ikke før studiedeltakelse, nåværende smerter, livstilfredshet, sysselsetting, sug etter heroin og tidligere bruk av heroin. Totalt sett hadde G1 høyest belastning (høyere psykiske plager, lavere sosial støtte osv.), mens G4 hadde lavest belastning.

Oppsummert viste funnene at det er flere viktige aspekter før, under og etter behandling som både pasienter og behandlere må være oppmerksomme på når det gjelder behandling med XR-NTX. Noen av disse er spesifikt knyttet til langtidsvirkende opioidblokade.

Konklusjon og implikasjoner

Samlet sett gir denne eksplorative mixed method avhandlingen viktig kunnskap og innsikt i behandlings- og recoveryprosessen hos personer i XR-NTX-behandling. Videre har avhandlingen implikasjoner for implementering av XR-NTX i Norge, samt for videre forskning. Resultatene indikerer at XR-NTX bør gis som en del av en fleksibel, individualisert og langsiktig behandlingstilnærming. Behandlingsapparatet bør være bevisst på at en personlig recoveryprosess strekker seg utover den aktuelle behandlingsepisoden; både valg om å avbryte behandling og avslutning etter fullført XR-NTX behandling innebærer ikke at recoveryprosessen kan anses som fullendt. Pasientenes motivasjon og mål for behandlingen bør tillegges vekt, og kan også endres i løpet av behandlingen. Mens deltakere som var i behandling opplevde mange fordeler, innebærer behandling med XR-NTX også betydelige potensielle utfordringer, som psykiske helseproblemer (f.eks. økte psykiske symptomer), økt rus-sug eller rusbruk, som for noen kan bidra til at man velger å avbryte behandlingen. Disse og eventuelle andre utfordringer bør adresseres av klinikere som følger opp pasienten.

List of Papers

Paper I: Marciuch A, Brenna IH, Weimand B, Solli, KK, Tanum, L, Røstad B, Birkeland, B (2022). Patients' experiences of continued treatment with extended-release naltrexone: a Norwegian qualitative study. *Addiction Science & Clinical Practice* 2022;17(1):36. doi:10.1186/s13722-022-00317-2

Paper II: Brenna IH, Marciuch A, Birkeland B, Veseth, M, Røstad, B, Løberg, EM, Solli, KK, Tanum, L, Weimand, B (2022). 'Not at all what I had expected': Discontinuing treatment with extended-release naltrexone (XR-NTX): A qualitative study. *Journal of Substance Abuse Treatment*. 2022;136:108667. doi:10.1016/j.jsat.2021.108667

Paper III: Marciuch, A, Birkeland, B, Benth, JS, Solli, KK, Tanum, L, Mathisen, I, Weimand, B (submitted). Personal recovery among people with opioid use disorder during treatment with extended-release naltrexone.

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Abbreviations and Terms

AA	Alcoholics Anonymous
BDMA	Brain disease model of addiction
BUP-NX	Buprenorphine-naloxone
BZD	Benzodiazepines
DSM	Diagnostic and statistical manual
ICD	International classification of disease
LAR	Legemiddelassistert rehabilitering [Medication assisted rehabilitation] (see OAT/OMT)
MOUD	Medications for opioid use disorder
NA	Narcotics Anonymous
OAT	Opioid agonist treatment
OMT	Opioid maintenance treatment
OUD	Opioid use disorder
QPR	The Questionnaire about the Process of Recovery
RCT	Randomized controlled trial
SUD	Substance use disorder
WHO	World Health Organization
XR-NTX	Extended-release naltrexone

Terms Used in This Thesis

Paper and study: Generally "Paper I, II or III" is used when referring to either the published papers or the conducted Studies 1, 2 or 3. In addition, "Study 1, 2 or 3" is also used, when e.g., referring to the execution of a given study.

Participants and patients: When referring to the people participating in the studies, the terms "participants" and "patients" are used. People in OMT in Norway, and thusly participants in our studies, have patient status.

OAT and OMT: While the much-used term "opioid maintenance treatment" (OMT), may have negative connotations and is not preferred for use by some (1), OMT is still widely used, and I use the term when referring to the treatment *system* providing the OAT. "OAT" is used when referring to the agonist medication itself.

Recovery: The use of "recovery" and "personal recovery" is further expanded upon in Section 1.2.6.

Preface

I first heard about extended-release naltrexone (XR-NTX) in 2014 when the first study of XR-NTX in Norway was recruiting at the inpatient ward I then was working at. As a first impulse, I remember thinking, as did some of the participants in the qualitative studies presented in this thesis, that this must be a miracle drug. Blocking the effects of opioids in people with opioid use disorder (OUD) sounded almost too good to be true. Would the fact that opioids "would not work" mean that many, or even most, problems would be solved? Undoubtedly, this initial reaction was rather naïve, disregarding the complexity of OUD and the various reasons people use opioids, as well as the multitudinous problems they face, addiction to a substance being only one among them.

Upon further reflection, I reasoned that choosing to try this treatment must require a great deal of courage. People would need to willingly abandon the possibility of obtaining the high most of their lives was centered around chasing or give up the safety of the agonist medication and opioid maintenance treatment (OMT) system they had perhaps relied upon for many years. Even though XR-NTX really seemed like a miracle for some patients – enabling an escape from addiction, and building a new life (2) – other stories also emerged among clinicians about patients struggling to cope with life without opioids and services not prepared to meet their needs when blocked. Such accounts highlighted that people use drugs for various reasons, and that these reasons not only are rational to those people, but also hard to escape. Substance use can have many rationales, for example to manage emotional symptoms, escape existence or simply function, in addition to avoiding craving and withdrawal. People will likely need some assistance in managing these aspects of their lives when opioids no longer are the solution.

While my clinical background from the start led to a focus on the practical and real-life relevant aspects of XR-NTX, during the research process I became increasingly interested in the process these patients went through and how it related to the concept of recovery. Recovery has various meanings regarding understandings of illness, disease and health (3). While one, and perhaps the traditional, understanding relates to recovery as an outcome (to get well or to get rid of symptoms), another conceptualization (4) sees recovery as a personal process, focusing on the experiences of illness, peoples' context and their achievement of a life worth living. Recovery-as-outcome in the context of substance use disorders is closely connected to recovery as abstinence or reduced substance use.

The recommended and traditional treatment of OUD involves opioid agonist treatment (OAT) with (most commonly) the opioid agonists methadone or buprenorphine, replacing illicit or problematic short acting opioids such as heroin, as well as preventing withdrawal, reducing cravings and reducing harms related to opioid use, without causing a distinctive high (5). Despite the many benefits of this treatment option, many patients do not want OAT, for example because they want abstinence from *all* opioids or because of disadvantages of the OAT system, such as restrictions in personal freedom. What puts XR-NTX in a special position is its antagonist action, blocking the reinforcing, subjective and physiological effects of opioids over time, leading to the expectation that it will ensure abstinence. However, although results from the first Norwegian study (6) and from other studies had shown that XR-NTX treatment was not inferior to the first-line recommended treatment with buprenorphine, the reality for patients commencing this treatment could be more complex. Maybe it was not enough to know that XR-NTX works comparatively well in terms of how long people stay in treatment or how heavily they use opioids. Consequently knowledge of how people experience treatment and how it might help them to reach their goals was necessary – that is, how XR-NTX can

contribute to recovery. Furthermore, while retaining people in XR-NTX treatment over time is challenging (7), there is limited knowledge of why people discontinue treatment and how they experience treatment past the first few months. Furthermore, if the concept of personal recovery were to be applied in such a context, would there be detectable changes in personal recovery, and if so, what factors would be connected with such changes?

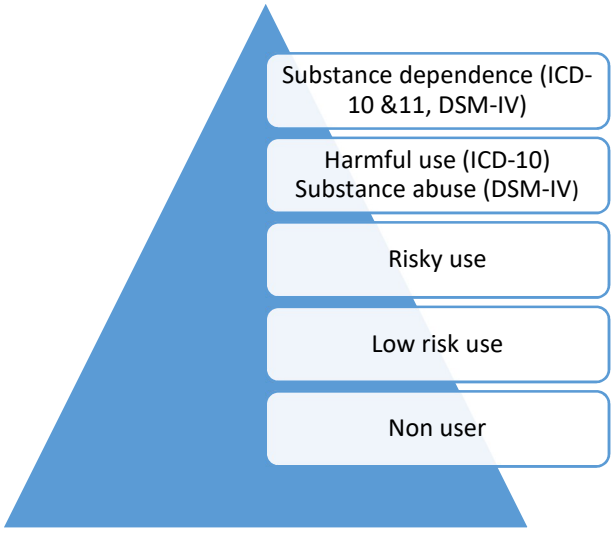
In my opinion, an approach that uses different angles and different methods is necessary to better understand the real-life usefulness and applications of XR-NTX treatment. This work, which includes patients' experiences with XR-NTX treatment, as well as an investigation of personal recovery and associated factors, addresses some of these questions and tries to shed some light on the treatment- and recovery process among people in XR-NTX treatment.

1. INTRODUCTION

1.1 Substance use disorders

The term “substance use disorder” (SUD), which overlaps with the term “addiction,” usually refers to a set of criteria indicating a problematic use or dependence on separate classes of psychoactive substances, such as opioids, alcohol or amphetamines. The term is adopted in the American Psychiatric Association’s diagnostic manual DSM-5 (8), and it encompasses the two previous categories of substance abuse and substance dependence, as severity is now assessed based on the number of criteria met. In the International classification of diseases (ICD-11), published by the World Health Organization (WHO) (9), a diagnosis of “substance dependence” overlaps with DSM-5’s substance use disorder. Central to either concept is a long-lasting problematic pattern of substance use that leads to clinically significant impairment or distress and is characterized by impaired control over the intake of the substance, craving, development of tolerance to the substance and withdrawal. The ICD applies the term “harmful use” for repeated substance use that does not fulfill the criteria for dependence syndrome. Figure 1 gives an overview of the ICD-11 and DSM-5, as well as their previous versions DSM-IV and ICD-10 diagnosis, and their relation to no use or clinically insignificant use.

Figure 1: The hierarchy of substance use disorders in DSM and ICD, adapted from Saunders (10)



SUDs have immensely negative effects on the affected individual, their family and society as a whole. They are associated with higher rates of physical- and mental health problems, mortality and crime. In addition, other negative effects include social isolation, stigma, reduced participation in and contribution to society, increased risk of experiencing physical and sexual abuse, poor living

conditions and other negative socioeconomic effects (11, 12, 13, 14, 15). An estimated 31 million years of healthy life worldwide is lost due to disability and premature death related to SUDs (11).

1.1.1 Understandings of substance use disorders

Historically, substance use disorders were seen as a moral failing of the people who had them, indicating a lack of willpower or bad choices and, thus, subjective responsibility. This likely contributed to much of the stigma surrounding SUDs. Since the last part of the 20th century, there has been an increased focus on SUD as a "brain disorder," culminating in Leshner's much-quoted assertion that "addiction is a brain disease" (16). This statement likely resonated with the optimism of the time that disorders of the brain could effectively be treated, as well as the increasing medicalization of many conditions. In a narrow biomedical model, or disease model, disease is seen as changes in biological structures or functioning, and treatment involves objectively measuring and normalizing these (3, 17). While such a model might acknowledge psychological or social factors, they are seen as less important (18).

A wide range of research has associated changes in brain function with substance use disorders and reported that through various mechanisms they play an important role in the development and maintenance of problematic substance use. For example, studies have demonstrated that cravings, tolerance or withdrawal have neural correlates and that persistent substance use can be associated with physical changes in the brain (19, 20, 21, 22). Specifically, the neurotransmitter dopamine and the motivational system are thought to have importance in the development of SUDs. Following the incentive sensitization theory of addiction, substance use increases dopamine levels, thereby influencing the wanting and liking of substances (23). This theory postulates that repeated exposure to addictive substances may contribute to brain changes in some individuals under some circumstances, which is thought to result in a neuro-adaptation that leads to decreased liking but increased wanting of the substance (24, 25, 26). Thus addiction may be, at least in part, a brain disease, but as Segal (27) questions, does it really matter? As Lewis (28, p. 11) notes,

> Every experience that is repeated enough times because of its motivational appeal will change [the brain]. Even if addictive habits are more deeply entrenched than other habits, there is no clear dividing line between addiction and the repeated pursuit of other attractive goals, either in experience or in brain function.

Arguably, the brain disorder model of addiction (BDMA) has helped to diminish stigma and raise the standing of SUDs by removing personal or moral blame, although some disagree, stating the reality is not either-or; SUDs can be neither a brain disease nor a moral failing (29, 30).

1.1.2 A biopsychosocial understanding

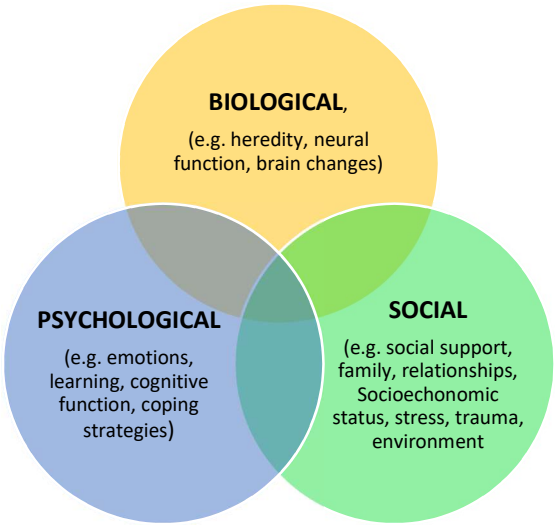
An overemphasis on addiction as a "brain disorder" represents a narrow focus, and is probably of little use to patients (31, 32). Correspondingly, the one-dimensional portrayal of addiction has received increasing criticism (30), as it obscures important dimensions (33), for example the equal importance of psychological and social factors, or that people use substances for a reason, representing the self-medication hypothesis (34). Consequently some critics have rejected the model, at least to the extent suggested (32, 35, 36, 37). Similarly, it has been argued that the BDMA is not sufficiently supported by either animal or neuroimaging evidence to the extent claimed by supporters of the model (37) and that the model has little practical utility.

Already in the 1970s the problems with a narrow biomedical model of illness were recognized (18). In 2014, *Nature* (38) published a letter by 94 addiction scholars disagreeing with a previous editorial statement that considering addiction as a brain disorder is uncontroversial. They further argued for the intertwined nature of addiction, where it "cannot be divorced from its social, psychological, cultural, political, legal and environmental contexts: it is not simply a consequence of brain malfunction" (38, p. 40).

Seeing SUDs solely as a brain disorder can be both deterministic and reductionist, possibly decreasing the individuals' agency ("It is my brain not me, so there's nothing I can do"), and might furthermore even question the possibility of recovery. Consequently, there has been an increasing acceptance that addiction is a complex, multifaceted and potentially long-lasting phenomenon. Although some have maintained the strong focus on addiction as a brain disease (39, 40), both defenders (31) and critics (e.g. 35) of the model seem to agree that a sole focus on addiction as a brain disorder is insufficient, but also that the recognition of neurobiological correlates or foundations does not negate the importance of other factors.

To understand complex phenomena, various viewpoints need to be considered. According to a biopsychosocial model (as illustrated in figure 2), biological, psychological and social factors play an important and intertwined role in the development and maintenance of substance use disorders (18). While biological factors such as brain chemistry or genetics contribute to the understanding of SUDs, other vital factors include psychological factors such as personality, mental health, self-efficacy or readiness to change and social factors such as family, environment and support. These factors cannot be separated, all playing an imperative role (18).

Figure 2: Example of factors of importance from a biopsychosocial understanding of substance use disorders



1.1.3 Substance use disorders: A chronic condition?

The conceptualization of addiction as a brain disease has contributed to the understanding of SUDs as chronic, relapsing and long lasting, underlining that there is no justification to distinguish SUDs from other chronic conditions such as diabetes or asthma (41). However, some critics of the BDMA (e.g. 33) have questioned the assertion of SUDs as chronic, for instance because some patients recover spontaneously or on their own, without any treatment. Many who meet diagnostic criteria quit using drugs as they age, and many without the use of professional help (42). Furthermore, there are concerns that a chronic illness conceptualization may undermine agency and motivation for recovery (43). Still, understanding SUDs as chronic, in the sense of "not acute" (rather than "incurable") does not automatically imply a BDMA, nor that they *must* be lifelong. Rather it indicates that addiction is, or may be, long lasting, and that relapse may occur (31). The fact that some people might experience a chronic, relapsing course does not negate that others do not, and vice versa. Addiction is heterogeneous, meaning there are many variations in symptoms, courses and paths to recovery. This conception aligns with the diagnostic understanding of SUDs in both DSM and ICD, where a subset of criteria constitute a diagnosis, enabling different combinations of criteria.

Traditionally, treatment systems have been organized more accordingly to an acute approach, where the patient seeks treatment, is assessed, receives treatment and then is discharged with the implicit understanding that the treatment is now finished (44). However, studies have shown that the natural development of addiction involves recurring cycles of treatment, relapse and abstinence, such that people seem to need multiple episodes of treatment over many years to sustain abstinence and other improvements (44, 45, 46, 47, 48, 49).

An understanding of SUDs as long lasting and heterogeneous has implications for how recovery should be understood. As will be further explained in Section 1.2.2, viewing SUD recovery as synonymous or overlapping with abstinence has been a common approach. The understanding of addiction as complex, multifaceted, and possibly long lasting (i.e., not acute) implies that recovery should be considered as such as well (44).

1.1.4 Opioid use disorder

Opioid use and opioid use disorder (OUD) are a major global health problem, causing great personal, economic and social health issues. Around the world, it is estimated that 61.3 million people used opioids in 2020, representing 1.2% of the total global population, and a doubling from the estimate from 2010. The number includes both illicit opiates such as heroin and prescription opioids such as those prescribed in opioid maintenance treatment (OMT) programs or as pain medication. The mortality rate for people with OUD is 6–20 times higher than that of the general population (49). Seventy-seven per cent of drug related deaths worldwide are estimated to be caused by opioids (11), while the number is 82% in Europe (50), making opioids the most lethal group of drugs. The rise in both the number of people diagnosed with OUD and in fatal and non-fatal overdoses has been rising steadily and globally over the past 40 years (51).

In North America the use of opioids has caused great concern in recent years, and the so-called "opioid epidemic" is related to increased use of opioid pain medications, as well as the increased spread and use of fentanyl, resulting in high opioid use and in high numbers of overdose deaths (11, 51).

The consequences of opioid use on society as a whole is considerable (52), and the societal burden includes costs related to healthcare and treatment, to prevention services, to the criminal justice system and to the social welfare system (53).

Despite treatment being widely available and free of charge to all citizens with OUD, Norway and other northern countries have seen a high number of opioid overdose deaths (50, 54). This has also led to a number of harm-reduction efforts, such as take-home naloxone and campaigns to increase peer use of naloxone in the prevention and acute treatment of overdoses (55). Recent numbers from the prescription registry have shown an increase in prescribed opioids in Norway, and the number of overdoses related to prescription opioids is rising (56, 57).

Opioids can induce intense pleasure and euphoria, as well as relieve pain and induce sedation. As for SUDs in general, the causes of OUD are multifactorial; genetics, neurobiology and environmental, social, physical and psychological factors contribute to the development and maintenance of OUD (58). Furthermore, the comorbidity of OUD and mental health disorders is high (59), most commonly

anxiety, depression and personality disorders, the symptoms of which may both be independent of or induced by the OUD and can complicate treatment (60). People with experiences of childhood trauma are more likely to develop OUD (61), and experiences of sexual or physical abuse and comorbid mental disorders are associated with persistent opioid use (49). Further, chronic pain among people with OUD is prevalent (62, 63). Concurrent use of opioids and other substances is common (64), and there are indications that people with OUD and polysubstance use are less likely to initiate and receive treatment with medications for OUD (MOUD) than are those without polysubstance use (65).

1.2 Recovery

Recovery has become an increasingly important concept for policymakers and in treatment evaluation in the fields of mental health and addiction: indeed, it has become "an organizing concept for addiction treatment" (66). While the Oxford dictionary (67) defines recovery as the process "of becoming well again after illness or injury" or "of improving or becoming stronger again," the term has diverse possible angles and understandings. Recovery can be defined as a process, or as an outcome, as objective, or subjective (68), arising from the varying viewpoints of health care professionals, family members, policy makers or people with experience of SUDs or mental illness themselves.

1.2.1 Why is the understanding of recovery important?

How recovery is understood has implications for how we understand SUDs (69), and vice versa. Since the early 2000s, the focus of the SUD field has shifted from pathology and intervention to recovery, as reflected in the increased interest in defining recovery and understanding recovery experiences, as well as what is needed to initiate and sustain recovery (66, 70, 71). This shift aligns with a similar shift in psychology, from a focus on pathology and illness to a positive psychology focusing on wellbeing, strengths and resources (72).

According to Bjornestad et al. (73), recovery is both a theoretical construct and an empirical object of inquiry. However, in the SUD field there is little consensus on how recovery should be conceptualized. The lack of a clear definition both hinders research and clinical practice and contributes to the great variability in reported treatment outcomes (74). Various definitions of recovery exist (75). Despite the need for a common definition of addiction recovery, a recent review states that the concept remains vague and that consensus is lacking on what SUD recovery means and how to measure it (76). Abstinence is commonly used interchangeably with recovery in the literature (77) and is the most common outcome in the treatment of SUDs (78, 79) together with retention in treatment, as being in treatment considerably increases the likelihood of favorable

outcomes (80). While there is agreement that recovery involves more than abstinence, abstinence is often used as a measure of treatment success (81). Still, various conceptualizations of what abstinence means exist (e.g., abstinence from a particular substance vs. all substances) or as to how long a person must maintain abstinence to be considered "recovered" (82).

If recovery is the goal of treatment and of patients, how it is understood is central to evaluating treatments and patients' processes. The development and conceptualization of recovery has been developed further in the field of serious mental illness than in the SUD field with the operationalization of clinical vs. personal recovery. Some (73) have proposed that the conceptualizations of recovery from serious mental illness may be applicable in the SUD field, which will be elaborated below. For example, certain core factors (e.g., increase in social connections and functioning) may be common across serious mental illness and SUDs.

1.2.2 Abstinence as recovery

The view that the solution to substance use problems is tied to abstinence from the substance dates back centuries, and was in the 1800s and early 1900s grounded in the rooted in the Temperance movement. Given a view of addiction as a moral problem involving poor decisions, the solution or cure becomes to make the right choice and stick to it: stop using. With the self-help movement of Alcoholics Anonymous (AA), recovery as a concept was introduced, describing people who maintained abstinence as recovering (83). While (total) abstinence is central in AA and other 12-step programs, such as Narcotics Anonymous (NA), AA also encompasses a focus on recovery as a process, involving not only abstinence but also "something more" (70).

Some argue that SUD recovery does not have to require abstinence, and that non-problematic use is possible. This is perhaps a particularly relevant discussion in the field of alcohol use disorders (AUD), where it is understood and accepted that some may choose to have a controlled use of alcohol, following treatment (84); likely tied to the social acceptability of alcohol consumption. Studies have also shown that among people previously diagnosed with AUD, a significant proportion can be classified as low-risk drinkers (85). Nevertheless regarding the use of illegal substances, where even limited use might have serious, detrimental effects, it is harder to imagine a limited, socially acceptable use, therefore it may be more difficult to wholly disregard abstinence as a factor in recovery.

While addiction is increasingly understood as a multifaceted phenomenon, abstinence remains among the most common outcome measures (86), and it seems to be the focus both in the research and in layman conceptions of SUD recovery. This emphasis on abstinence in recovery may be partially attributable to the lack of consensus regarding how recovery should be defined (87).

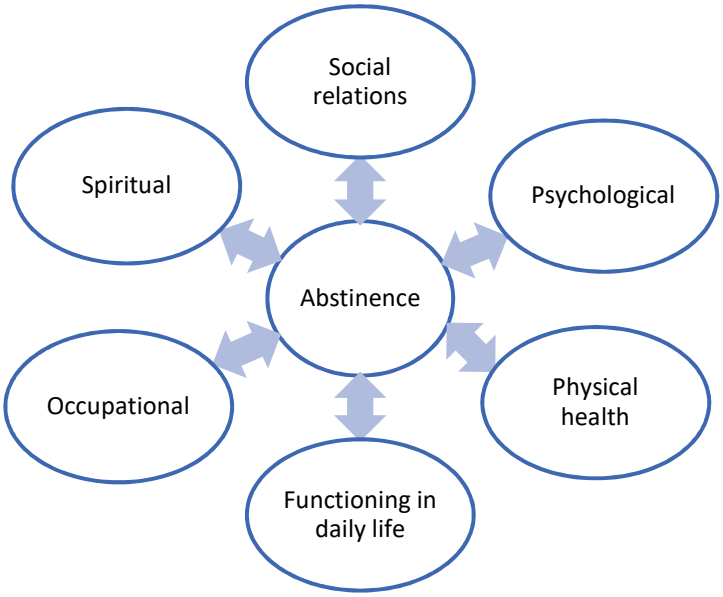
1.2.3 The importance of additional factors in recovery

While there are indications that many people who start treatment want abstinence (88), their associated aims also exceed abstinence, including improved relationships, meaningful activities, better health and material wealth (89). This recognition underlines the need to focus on factors other than abstinence, reflecting the complexity of patients' lives and pathways. Such factors may be improvements in overall quality of life or specific areas of life (e.g., wellbeing, psychological functioning, relationships or criminal activity). Nevertheless, it has also been pointed out that such recommendations to look beyond substance use and abstinence have been made for the last 20 years, without substantial change (86).

The emphasis on the importance of additional factors and outcome measures is underscored by recent and widely accepted definitions of recovery. A much-used definition from the Betty Ford Institute (90) emphasizes recovery as a "voluntarily maintained lifestyle characterized by sobriety, personal health and citizenship." Sustained abstinence is also underscored by others, such as the UK Drug Policy Commission's (UKDPC) characterization of recovery, further emphasizing recovery as sustained abstinence "which maximizes health and wellbeing and participation in the rights, roles, and responsibilities of society" (91, p. 6).

As can be seen in figure 3, which depicts the relationship between abstinence and various improvements, based on a model from Costello, Sousa, Ropp, and Rush (92), abstinence is thought to enable improvements in various areas, supporting further abstinence. Further, from their study exploring how people in aftercare following SUD treatment understand recovery, Costello et al.'s (2020) findings emphasize recovery as a process. In this process, abstinence is an important but not sufficient aspect, enabling and being enabled by other important aspects, and in turn increasing overall satisfaction with life. This conception aligns with others, emphasizing that while increased control over the intake of the problematic substance may be necessary (93) or even critical (74, 88, 94), it is not sufficient.

Figure 3: Recovery from addiction, adapted from Costello (92)



The role of abstinence is downplayed in other definitions, however, and the common ground in recovery in SUDs and mental health disorders is accentuated, such as the widely recognized working definition of the Substance Abuse and Mental Health Services Administration (SAMHSA) (95). Here recovery is defined as

> A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential.

This definition correlates significantly with health-related quality of life (96), and the definition has four key dimensions of recovery: health, home, purpose and community. SAMHSA notes that abstinence is one way to achieve other improvements, again emphasizing that abstinence is insufficient for recovery, meaning that someone who is abstinent but experiences no improvements would not be considered as in recovery. This is in contrast to recovery from an AA or NA-viewpoint mentioned previously, where “recovery is initiated only once abstinence has been achieved” (97, p. 5).

Using participatory approaches, studies have focused on domains and measurable indicators of recovery (98, 99, 100, 101) and ways to operationalize these. Understanding what facilitates and strengthens recovery is also an important perspective tied to the paradigmatic shift initially described, from pathology to strengths in psychology. The concept of recovery capital (102, 103), developed and gaining increasing momentum in the field of addiction, focuses on what is needed to achieve recovery from addiction. While the term does not seem to offer a clear definition of what recovery is, the perspective underlines recovery as individual or personal, and it emphasizes that

recovery exceeds abstinence. Recovery capital refers to the internal (e.g., family support) and external (e.g., access to healthcare) resources needed to support and sustain recovery. There are many possible dimensions of "recovery capital" (104) (e.g., personal recovery capital, family/social recovery capital and community recovery capital), and the application of this term is somewhat unsystematic (105).

Overall, an increased focus on factors related to wellbeing has been suggested, as "definitions of recovery that rely solely on abstinence (...) fail to capture the multidimensional and heterogeneous pathways to recovery that are evident" (106, p.1). As Laudet (107) writes, people with SUD seek help quitting drugs not as an end in itself, but as a means to escape the negative consequences of substance use and to secure a better life. The inclusion of other outcome measures, however, in many cases still means measuring objective end points (e.g., degree of or increase in life satisfaction or improvements in health) that may not capture the processual aspect of recovery. Furthermore, while it has been proposed that it is important to measure these, as well as abstinence, repeatedly over a treatment course (92), such outcomes still involve pre-determined facets, decided upon by people other than the patients themselves.

1.2.4 Personal recovery

The concept of personal recovery involves a shift in the understanding of recovery, viewing recovery as not only a result (e.g., abstinence or improvements in daily life), but also explicitly as a process. With roots in activism and human rights movements for people with psychosis, the concept was founded in the experiences of patients with serious mental illness, and it represents an alternative to a strictly medical understanding of illness. Increasingly used in the mental health field by policymakers, professionals and services, personal recovery is understood as "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills and/or roles" (4, p. 15). Personal recovery involves living a hopeful, satisfying and contributing life, even with the limitations caused by the disorder, and involves developing a meaningful life (4, 108).

Seeing recovery as personal underlines the importance of peoples' experiences of illness, as well as of their context, and emphasizes recovery as a process of healing. A personal recovery process rests on meaning, characterized by changes in connections with others, hope, changes in identity and empowerment, embracing individuality, complexity and diversity (4, 109). Further developing the concept, a systematic review (110) identified five key themes or processes supporting personal recovery: connectedness, hope, identity, meaning and purpose, and empowerment, establishing the widely used acronym CHIME.

It may be difficult to imagine SUD recovery without an aspect of abstinence or at least substance use reduction. However, if substance use is a symptom of SUD, a personal recovery framework contains the possibility of recovery without abstinence from the addictive substance, or at least of recovery less dependent of whether the substance is used or not– exactly because it is a process, and not an endpoint.

As there is a considerable overlap between the fields of mental health and SUDs, personal recovery has been proposed as the bridging principle between substance abuse treatment and mental health care (111). The comorbidity of SUDs and mental health problems is high (59, 60), and although not explicitly used in the SUD field, personal recovery has been examined in people with dual diagnosis, a term used for concurrent SUD and mental illness. Several studies have examined how people with dual diagnosis experience recovery, and a 2017 review (112) indicated that the themes in personal recovery seen as important by people with dual diagnosis in large overlap with the themes proposed in the CHIME framework.

Personal recovery has often been contrasted with clinical recovery (108), with the latter involving a symptom reduction or remission, along with improvements in various areas such as involvement in work or educational activity, financial independence or an active network (c.f. 113). While personal recovery is person centered, subjective and processual, clinical recovery is objective and outcome focused; the meaning is tied more to a strictly biomedical approach, connoting being cured or returning to normal, or recovery *in* vs. recovery *from* (114). As the focus on personal recovery marks a person's individual process in pursuit of a meaningful life, recovery cannot be achieved through an exclusively medical approach, since social and environmental aspects will be essential.

The traditional understanding of SUD recovery where abstinence is a central feature overlaps with the concept of clinical recovery, as it allows for the measurement of an outcome, that is change in the core feature of SUDs as well as related improvements. Table 1 contrasts the concepts of personal recovery and clinical recovery, based on Slade's (109) presentation.

Table 1: Clinical vs. personal recovery

Clinical recovery, abstinence focus	Personal recovery, process focus
An outcome or state Dichotomous – you either are abstinent or not	Process
Objective; Observable, defined by outside criteria	Subjective, context is important
Definition/measure does not vary between people	Individual – definition varies with people's goals
Getting rid of the disorder, No/few symptoms equals recovery. No substance use?	Living with the limitations of disorder Substance use possible, within the definition of the individual's goals

Studies of how people with SUDs understand and experience recovery (74, 115) highlight recovery as a personal, ongoing process, emphasizing factors overlapping with the CHIME framework (e.g., support and relationships, identity and meaning). As previously mentioned, people in recovery from SUDs emphasize many of these factors. Nevertheless, many also express having the goal of lasting abstinence (74, 88, 116).

Brophy et al.'s recent analysis (77) and resulting definition of recovery in SUDs proposes a definition somewhat overlapping with the definition of personal recovery, defining recovery as

> A person-centered, individualized process that can be measured by referents that suit the individual's own goals and objectives. What may constitute "recovery" and "recovered" requires definition by each individual. (p. 9)

Such a broad definition emphasizes the individual's definition of what recovery is, and what is emphasized in the individuals' process, rather than what can be objectively measured or what processionals or researchers define as recovery. Furthermore, for some, recovery may mean abstinence, while for others not.

While one criticism might be that the definition of personal recovery leaves a broad and varying definition of recovery, the multifaceted and varying paths of substance use disorders perhaps necessitates a recovery conceptualization that allows for individual adaptation.

1.2.5 Criticism of personal recovery

The personal recovery concept and movement has received some criticism, much tied to the focus on the individuality of the process. One critique is that recovery is emphasized as something happening in the individual, thus putting less emphasis on structural inequality and the collective responsibility of individuals' distress and problems (117). Furthermore, social recovery, with its focus on leading meaningful and active lives as citizens, is argued to be a key dimension of recovery (118). Being part

of, or belonging, is a fundamental human need (119), connected with improved health and wellbeing, as well as central in the recovery process of people with SUDs (120).

Thus, a criticism of personal recovery involves that the focus on the "personal" and "individual" aspects of the process disregards the importance of relationships, networks and social support in peoples' lives and in recovery. While support or connectedness might be a component in personal recovery, these factors are not necessarily central. *Relational recovery* is an approach to recovery recognizing the importance of social and relational factors (121), emphasizing that people are not independent of each other. Recovery is seen as a social and relational process, occurring through relationships and through people's interdependence on each other. Interestingly, healthcare providers may tend to focus more on the practical aspect and of the family supporting (clinical) recovery, "rather than the family's relational importance in personal recovery" (122). Nevertheless, while social relationships may be vital, they can also be experienced as a hindrance in recovery, as relationships may be both supportive and destructive, or they may be complicated by past experiences (123).

1.2.6 Conceptualization of recovery in this thesis

Based on the above, the focus in this thesis, further expanded in the thesis aims in section 2, will be on recovery *in* OUD (within the context of XR-NTX treatment), rather than *from* OUD. Consequently, in the following, I will use the term recovery in line with Anthony's definition of personal recovery, as well as the definition proposed by Brophy et al., underlining recovery as a process, with an emphasis on aspects experienced as important for the persons themselves. I will use "recovery" when referring to recovery as a concept (in the general or layman conception of recovery from illness) or when referring to less defined conceptualizations in the literature. I will use "personal recovery" or "recovery process" when referring to personal recovery in line with Anthony's (4) definition, or when recovery specifically has been defined as such in referenced literature. "Clinical recovery" will be used as outlined above.

1.3 Treatment of opioid use disorder

The numerous negative consequences of OUD together with the complexity of SUDs, underline the need for both time and multiple treatment episodes in achieving change (124), and emphasize the importance of available and effective treatments. Furthermore, a multifactor model of OUD and the many possible combinations of criteria for obtaining the diagnosis necessitate diverse and individualized approaches to the treatment of OUD.

The most common treatment options for OUD include abstinence-oriented treatments, brief inpatient withdrawal management ("detox") and MOUD, which can either be opioid agonist

treatment (OAT) or opioid antagonist treatment. Abstinence-oriented treatments and "detox" have poorer outcomes compared to MOUD (e.g., higher relapse rates) (80, 125) and are associated with increased risk of overdose after discharge (125, 126). They have, thus, not been found effective in sustaining abstinence. MOUD are considered central to the management of opioid dependence (80).

1.3.1 Discontinuation of treatment

As retention in OUD treatment is an important factor associated with favorable outcomes (80), understanding more about discontinuation of treatment is important to support and understand more about recovery in OUD. For example, the benefits of OAT strongly correlate with time spent in treatment, and early discontinuation from OAT corresponds to increased risk of relapse and overdose (127, 128), the benefits not frequently lasting after treatment ends (129).

Despite studies focusing on identifying the factors predicting discontinuation, few studies have focused on patients' perspectives on discontinuation. Research points to certain patient characteristics being associated with discontinuation from treatment, such as having younger age, not injecting drugs, polysubstance use or committing substance-related crime (130, 131, 132, 133). Still, factors related to the treatment process, such as motivation or satisfaction with treatment, have been suggested as more significant in a systematic review of discontinuation from SUD treatment (134). Certain aspects of services also seem to deter people with SUD from engaging with and staying in treatment (133). As central elements of discontinuation, studies have identified both individual reasons, such as loss of motivation or hope (135), and factors related to the treatment program, such as lack of flexibility or supportive staff (136). A Norwegian study exploring the reasons young adults leave in-patient SUD treatment found both individual and program-level factors to be important (137).

1.3.2 Opioid agonist treatment

OAT with methadone or buprenorphine is, and has long been, the recommended treatment for OUD by the WHO (138). Methadone is a synthetic, long acting, full opioid agonist that has been used in the treatment of OUD since the 1960s. Buprenorphine was developed later and is a partial agonist, meaning that it only partially activates opioid receptors. The standard of care is daily dosing of oral methadone or sublingual buprenorphine (with or without naloxone). In addition, monthly extended-release injectable buprenorphine has more recently been developed (138, 139, 140).

OAT is shown to reduce illicit opioid use, prevent relapse and reduce many of the negative consequences associated with illicit opioid use, such as overdoses mortality and criminal behavior (141, 142).

In line with the notion of OUD as a chronic and relapsing condition, OAT is recommended to not be time-restricted, and in many cases it is estimated to be life-long (138). However, many people with OUD express, as mentioned above, having a goal of abstinence, for some including ending the use of the medications prescribed through OMT (143). However, some patients may find it difficult to taper or discontinue medication and leave OMT, especially methadone, and leaving OAT can be complicated, for example, due to increased overdose mortality, reactions to the tapering (e.g., withdrawal symptoms and cravings), mental health challenges or anxiety related to the tapering (144, 145). As such, the discontinuation of OAT is often discouraged by treatment providers and was previously advised against by the Norwegian Directorate of health unless the patient could manage without opioids (146). A Norwegian qualitative study (147) showed that patients experience OAT as overruling and degrading and as a state of limbo between continued addiction and the process of recovery.

Furthermore, OAT, as well as the OMT program itself, is not without disadvantages. Discontinuation is common, especially in the first month of treatment (144). The use of non-opioid substances and alcohol during OAT is not uncommon (148, 149), and can complicate treatment (150). In addition, the OMT system places several restrictions on patients, due to the societal risks of medication diversion related to the potential lethal effects of the medication (151). For some, restrictions may apply, for instance urine drug testing or frequent pick-up and supervised intake of medication instead of take-home doses (152, 153, 154). While many of the restrictions lessen over time, patients must show at least stable control over substance use to achieve “benefits” like weekly or bi-weekly pick up of take home doses or only sporadic drug urine testing. Still, restrictions on personal freedom apply, as patients must follow pick-up appointments that they may feel hinder job or school attendance or their ability to travel freely abroad (155). The lack of control patients feel due to the restrictions placed on them may negatively influence the quality of life they experience (156). Consequently, some patients do not want to, or even cannot, stay in OMT due to their inability or lack of desire to conform to the rules of the OMT system, or because of the side effects of the medications, which can include sedation, headaches or constipation (157).

Finally, patients in OMT frequently face stigma (158). While there is an outside stigmatization of OMT (e.g., negative attitudes towards antagonist treatment or prejudice against “OMT patients”) that can bar a person from seeking out and remaining in treatment, the OMT system itself may further heighten the stigma they experience (155).

Treatment of OUD in Norway

In Norway, OAT is not the first choice when treating OUD, especially for young people, unless professionals judge it to be the most suitable treatment option (159). This is partially due to the addictive potential of the medication, as well as its potential but unknown long-term side effects, despite the known positive effects associated with methadone/buprenorphine treatment. However, not offering OAT to people who want it is unlikely to happen often in practice, as guidelines heavily emphasize the use of discretion and individual considerations in the choice of treatment, as has been further emphasized in the recently published updated guidelines (152). Although the national guidelines emphasize the active participation of the patient in treatment, the term "rehabilitation" is used rather than "recovery." In addition to OAT, people with problematic opioid use or OUD have access to municipal and specialized in-patient and out-patient treatment.

OAT is organized in the LAR system (*Legemiddelassistert rehabilitering*, meaning "Medication-assisted rehabilitation"), which oversees opioid agonist treatment, most commonly oral buprenorphine or methadone. Buprenorphine is the first choice of treatment, which around 60% of the OAT population receive (160). Overall, there seems to be an increase in the number of problem opioid users (not limited to injecting use) in OAT in Norway, from 50% estimated in 2013 (161) to 78% estimated in 2021 (162).

The goal of treatment is for the patient to achieve optimal health, functioning and quality of life, and the goals of the patient are central. In addition, central elements of treatment include support in various areas of life and the role of medications as *assisting* rehabilitation. This focus aligns with patients' expectations of many non-medical treatment outcomes of OMT such as employment, housing and the rebuilding of social relationships (155).

While a patient-centered approach is strongly represented in Norwegian guidelines, emphasizing patients' individual needs and the importance of considering patients' wishes when planning treatment, there is little specific focus on recovery.

1.4 Extended-release naltrexone

Naltrexone is an opioid antagonist used in the treatment of OUD (163). Naltrexone blocks the reinforcing, subjective and physiological effects of opioids (164, 165, 166) and can reduce cravings (166). The short acting oral naltrexone has been shown to have poor retention rates, low compliance and high drop-out (167), and it is generally not recommended other than as relapse prevention for people with no access to or interest in other treatment (138). Long-acting preparations of naltrexone exist in the form of implants and injections (163). One such formulation is extended-release naltrexone (XR-NTX).

Compared to OAT, treatment with extended-release naltrexone is a novel treatment approach and has shown promising results in recent years. Although not recommended as a first choice in the 13-year-old WHO guidelines (138), XR-NTX has been approved by the US Food and Drug administration since 2010 to treat OUD, recommended in the guidelines of the American Society of Addiction Medicine (153) and has been increasingly researched.

The antagonist effect of injectable, long-acting naltrexone, XR-NTX, lasts for four weeks. Treatment requires a full detoxification from opioids. In an early Russian randomized controlled trial (RCT), XR-NTX was compared with a placebo (168). While this study raised some concerns (169), for example, regarding the ethics of using a placebo as long as there are other well-researched options, the study showed that XR-NTX was superior to placebo in treating OUD. Nonetheless, these results may be less generalizable to settings outside Russia, as OMT is illegal and unavailable there.

Several studies, both naturalistic and observational studies and RCTs have then shown XR-NTX is associated with positive outcomes. XR-NTX has been shown to be a safe, effective and well-tolerated treatment, reducing cravings and the effects of heroin, reinforcing abstinence and being associated with a decrease in opioid and substance use, as well as with psychosocial improvements (7, 168, 170, 171, 172, 173, 174). Despite concerns, no increase in pain or levels of anxiety or depression (175, 176, 177) have been shown. Nevertheless, while depression often remits after treatment initiation, when it does not, it has been associated with more opioid use during treatment (178). A recent study (179) investigating injection opioid use in people receiving XR-NTX during and post-incarceration found that being in XR-NTX treatment was associated with reduced opioid injection use.

Some challenges related to XR-NTX treatment exist, perhaps contributing to lower utilization numbers found in a large comparative effectiveness retrospective study (180), which furthermore concluded that only methadone or buprenorphine treatment were associated with reduced overdoses. A systematic review (181) also found buprenorphine and methadone to be superior regarding retention rates. Relatedly, concerns connected to the usefulness of XR-NTX have mainly been related to its effectiveness in real-world settings (7). Particular issues include inducting patients into treatment and premature discontinuation of treatment. In the X:BOT trial described further below (171), 89% of relapses in the XR-NTX group were due to induction failures (171). A systematic review (7) found premature discontinuation of XR-NTX treatment to be common, with retention ranging from 15–74% in prospective studies and with low adherence rates (less than 10%) after 6 months. Nevertheless, the retention rates align with those found for OAT (182). Thus as for OAT, retention in treatment can be a challenge, and the need to follow up treatment with psychosocial interventions has been underlined (138, 183, 184).

Clinical trials have compared XR-NTX with buprenorphine, the first line recommended treatment, and shown equal treatment outcomes such as retention and opioid use. One such Norwegian 12-week XR-NTX RCT study (6) found that XR-NTX was as effective as buprenorphine-naloxone (BUP-NX) in maintaining abstinence from heroin and other illicit substances. In line with these results, a large US randomized trial, namely the X:BOT study (171), compared the effects of XR-NTX and BUP-NX, finding that BUP-NX and XR-NTX were equally effective on the outcomes measured (e.g., retention or overdose risk). Although retaining only about half of the patients at six months, retention rates were comparable in the two groups, as long as patients were taking medications. Overdose risk was found to be similar. However, a recent reanalysis of results from the X:BOT trial (185) although largely agreeing with the conclusions of the original paper, has indicated greater risk of overdose for XR-NTX than for BUP-NX. In a response (186), Lee et al. emphasized that "overdoses also occur during and after buprenorphine or methadone treatments" and that access and adherence to *all* MOUD treatment is vital. Furthermore, the researchers state the trial was not designed nor powered to show differences in overdose rates, so that although there were numerical differences, these were not found to be statistically significant. Notably, the original findings of Lee et al. align with those of Tanum et al. in Norway (6) regarding overdose risk.

When it comes to relapse to opioids, a reanalysis of the Norwegian XR-NTX RCT study data by the same research group (187) showed patients on XR-NTX had a substantially reduced risk of relapse compared to BUP-NX, in line with other findings (188), but contradicting findings from Lee et al. (171), where no difference in relapse risk was found. Furthermore another study (189) found BUP-NX to be more effective than implant XR-NTX in preventing relapse. Consequently, more high-quality research might be needed, in line with a systematic review and meta-analysis of naltrexone (not specifically XR-NTX) (190), which concluded that although injectable or implant formulations are more effective than oral ones and although "naltrexone appears to be an effective treatment in terms of retention in treatment and being opioid-free" (p. 9), these findings are not significant, and large-scale research is needed.

Most studies of XR-NTX have had limited time frames, normally one to six months, and there is no recommended standard duration of treatment (191). Some studies have followed patients for longer periods, however. For instance, the Norwegian XR-NTX RCT study (6) had both a nine-month follow-up (192) and a two-year follow-up (183), where participants in the original 3+9 month trial could choose to continue with XR-NTX for up to two more years. Fifty patients chose to continue treatment, for an average of 44 weeks. The results showed high treatment satisfaction, and 70% had no opioid relapse during the treatment period. While there are indications that improvements

decrease after the discontinuation of treatment (170, 193), if patients continue treatment after a study ends, there are indications they manage to stay abstinent (194).

1.4.1 Patients' experiences of XR-NTX

Patients' experiences of XR-NTX are not well understood, and the research on this subject is more recent. A study on patients' experiences of initiation and the initial period of treatment with XR-NTX (195) found that although patients viewed XR-NTX treatment favorably, there were certain barriers to initiating treatment, such as ambivalence and fears related to lack of familiarity with the medication or the perceived commitment to its long-acting duration. In line with previous research, the required full opioid detoxification was also a barrier and a vulnerable period for patients. As per a Ukrainian qualitative study (196) of preferences and attitudes towards XR-NTX among people who inject drugs, in addition to skepticism and misconceptions about how XR-NTX would work, concerns regarding the required opioid withdrawal were noted. This is in line with a qualitative study of the experiences of people participating in an RCT where XR-NTX was compared with treatment as usual (197), where misperceptions and apprehension about XR-NTX were also noted, especially concerning its long-acting effect. The importance of addressing patients' expectations of induction to treatment has also been emphasized (198). Hoffman et al.'s study (198), focusing on participants' perspectives on induction on XR-NTX, reported readiness for change as well as supportive characteristics of the induction as important among those completing induction. Ambivalence, concerns or preferences for other medications were emergent themes among those not completing induction.

For those overcoming these obstacles in Gauthier et al.'s study (195), once initiated, XR-NTX was viewed as an effective treatment, strengthening autonomy and affording a sense of freedom. For some it offered a new chance, having tried "everything else." Notably, the study did not include the perspectives of people discontinuing treatment after initiation.

Another study (199) explored the perceptions of MOUD among patients released from jail receiving either no medication, methadone, buprenorphine or XR-NTX (199). Overall, study participants were satisfied with XR-NTX. Notable barriers to treatment were socioeconomic (e.g., homelessness or economic insecurity) or related to exposure to heavy drug use in participants' surroundings. Many participants "tested the blockade" by using small amounts of heroin, and they described a lack of effect. The decision to discontinue XR-NTX was intentional, often driven by the desire to return to opioids or a confidence in further opioid abstinence without XR-NTX. In a study comparing participants' reasons to start and stop buprenorphine, methadone or XR-NTX treatment (200), the cost of XR-NTX, but also not wanting to be dependent on any medication were reasons to discontinue medications. Interestingly, while information from peers was important in learning about

methadone or buprenorphine, participants primarily leaned on information from healthcare providers regarding XR-NTX.

1.5 Knowledge gaps

Although a growing body of research indicates that XR-NTX is a safe, effective and well-tolerated treatment, there are gaps in knowledge as to patients' perspectives on treatment, as well as what role XR-NTX can play in peoples' personal recovery process. While some qualitative studies exist, they have focused on initiation and early treatment. Specifically, we know little about how patients experience treatment over time, the experiences that lead to treatment discontinuation, and whether the concept of personal recovery might be useful in such a context (e.g., if there are changes in personal recovery during XR-NTX treatment) and what factors might be associated with such change. Such a focus might contribute to a broader understanding of XR-NTX treatment, as previous research has understood and conceptualized recovery as clinical recovery, focusing on substance use reduction. Findings may also contribute to illuminate aspects of recovery in OUD and during XR-NTX treatment. As such, other conceptualizations of recovery (e.g., personal recovery) in XR-NTX treatment might be especially worth examining, because XR-NTX increases the probability of abstinence from opioids (over time and while on medication), and, thus, also creates a psychological, physical and temporal distance from the use of opioids, suggesting patients might have one less obstacle to tackle in their recovery process. Simultaneously, being blocked also means one has to give up the desired euphoric or sedative effects of opioids. Thus, the "blocking" might also involve great challenges that might hinder peoples' recovery process. Patients' reasons to discontinue XR-NTX treatment and their experience of treatment are important areas for further examination. Specifically, the need for a more detailed investigation of the psychological aspects of opioid receptor blockade has been pointed out (201).

2. AIMS

Overall, this thesis aims to deepen understanding and knowledge of the treatment- and recovery process of people with OUD in XR-NTX treatment, specifically to illuminate central aspects of these processes.

The specific aims were

- to explore and describe how people with opioid use disorder **experience treatment** with XR-NTX over time, including the possible benefits, challenges, and needs that arise during treatment (Paper I);
- to better understand **patients' experiences leading to early discontinuation of treatment** with XR-NTX. Specifically, we sought to explore participants' motivations for XR-NTX, experience of initiation and treatment, and rationale for leaving treatment (Paper II); and
- to examine the process of **personal recovery among opioid-dependent people receiving treatment with XR-NTX.** Specifically to explore 1) possible changes in personal recovery during the course of treatment; 2) whether there are groups of patients following distinct trajectories of personal recovery, and 3) whether baseline characteristics could predict belonging to such groups with different personal recovery trajectories (Paper III).

This thesis addresses the following research questions:

1. How do patients experience treatment with XR-NTX over time? (Paper I)
2. What are the benefits, challenges and needs that arise during treatment? (Paper I)
3. What are the experiences leading patients to early discontinuation of XR-NTX treatment? (Paper II)
    a. What are patients' motivations for treatment?
    b. How do patients experience treatment initiation and further treatment?
    c. What are patients' rationales for leaving treatment?
4. Are there changes in personal recovery during the course of treatment? (Paper III)
5. Can groups of patients following distinct trajectories of personal recovery be identified? (Paper III)
6. Will baseline characteristics predict belonging to such groups with different personal recovery trajectories? (Paper III)

3. MATERIAL AND METHODS

This section first presents the research setting to give an overview of the context of this thesis. The study methodology and its philosophical underpinning are then presented, followed by a presentation of the study design, recruitment, samples, data collection and analysis. Lastly, ethical considerations are addressed.

3.1 Setting

This thesis is based on data from a Norwegian clinical trial of XR-NTX in the treatment of OUD, the NaltRec study ("Long acting naltrexone for opioid addiction: the importance of mental, physical and societal factors for sustained abstinence and recovery").

The treatment of OUD in Norway is organized in municipal and specialized health care, the latter under TSB (interdisciplinary specialized treatment of SUD), where medicine, psychology and social work play an equally important part. MOUD treatment is organized within the specialized healthcare system, giving patient status to all patients receiving OMT. OAT is available for people with a diagnosis of OUD. While OMT clinics are situated in the specialized healthcare system, OMT is based on cooperation between the OMT center, general practitioners and social service centers. Although other options exist, the standard and recommended medications are methadone and buprenorphine with or without naloxone. Buprenorphine is often the first choice of medication, largely because it is considered safer regarding overdoses (202). While the study was conducted, XR-NTX was unavailable in Norway. Short-acting oral formulations of naltrexone were available, although indicated for alcohol use disorder and generally not recommended for the treatment of OUD outside of relapse prevention (203).

The NaltRec study is an observational, naturalistic, multicenter open-label study of treatment with extended-release naltrexone hydrochloride injectable suspension (Vivitrol®). While this thesis represents an independent part of the NaltRec study, decisions regarding recruitment, the overall sample, the type and amount of data collected and the overall study structure were made before this thesis began by the NaltRec project group.

Weimand et al. (2021) detail the NaltRec study, which was conducted at the addiction departments of hospitals in five urban areas (i.e., with populations over 40,000) in the southern, eastern, and western parts of Norway: Akershus University Hospital (the sponsor hospital), Sørlandet Hospital, Vestfold Hospital, Haukeland University Hospital, and Oslo University Hospital. The study catchment area included close to half of the Norwegian population. The fifth site (Oslo University Hospital) joined the study at a later date, and was not participating when the qualitative studies (Studies 1 and

2 in this thesis) were carried out. The NaltRec study is organized in four different work packages (WP); the relevant WPs for this thesis are WP 1 – the main prospective, observational cohort study, with monthly questionnaire data used in Study 3 of the present work – and WP 2; the qualitative sub-study, with data used in Studies 1 and 2 of this work. Data collection lasted from 2018–2021. Eligible participants who were in the OAT program, but who were not interested in XR-NTX were recruited as a control group to be compared to the XR-NTX group. The control group was recruited in the final phase of the NaltRec study and is not part of this thesis, so will not be further described.

3.2 Ethical approval

The current research was approved by the Regional Ethical Committee for Research South-East (#2018/132), by the Boards of Research Ethics at the participating hospitals and by the Norwegian Medicines Agency (EudraCT: 2017–004706–18). The study was registered at Clinicaltrials.gov # NCT03647774 on August 28, 2018, before the inclusion of the first participant on Sep 21, 2018. To confirm the requirements of Good Clinical Practice, the study was carried out in accordance with the international quality standards provided by the International Council of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (204). The study was conducted in accordance with the Ethical Principles of the Declaration of Helsinki (205).

3.3 Methodology

This thesis employed a mixed-methods approach using both qualitative and quantitative methods to investigate the treatment and recovery process of people in XR-NTX treatment. I therefore find it useful first to expand upon the mixed-methods approach, and the reasons to choose such an approach as well as its pragmatic underpinning.

3.3.1 A mixed-methods approach

Paradigms are worldviews including a set of philosophical and methodological assumptions (ontological, epistemological and methodological) (206). Quantitative and qualitative research methods have traditionally been seen as opposing paradigms, largely because of their divergent ***ontological*** (knowledge of existence or reality), ***epistemological*** (theory of knowledge) and ***methodological*** (rationale for the research approach or strategy, the inquiry logic) positions.

Quantitative methods are connected to a positivist and later post-positivist paradigm, concerned with objective data, hypothesis testing and generalizability, originating in a belief in the existence of an objective, independent reality that can be studied and measured. Qualitative methods, on the other hand, focus on experiences and the understanding of meaning, acknowledging that multiple and contradictory experiences of the same phenomenon – and, thus, multiple realities – can exist, forming a constructivist worldview (207, 208, 209). I will not elaborate the debate or paradigm wars

(206) between these two positions. The ontological, epistemological and methodological foundations of this thesis are shown in figure 5.

Mixed methods research has been referred to as “the third paradigm” in research (208). While some have argued that qualitative and quantitative paradigms are incompatible, a mixed-methods approach nevertheless combines them, acknowledging that knowledge is based on the reality of the world as well as constructed in the world we experience and live in (208). Mixed methods have seen increased application in various areas of research, specifically in health research, a field traditionally dominated by quantitative research (210). This increase may be due to the fact that mixed methods allow a researcher to move beyond the testing of single hypotheses and to provide insight into processes and mechanisms, giving a more comprehensive understanding of a topic.

Mixed methods involve “collecting, analyzing, and interpreting quantitative and qualitative data in a single study or in a series of studies that investigate the same underlying phenomenon” (211, p. 267). They thus involve mixing or integrating data that represent different scientific approaches to achieve a broader, more deepened understanding, or a more complete picture of the phenomenon being studied. Nonetheless, to be considered mixed method, findings must be mixed or integrated at some point (208). The mixing or integration can happen at different stages in the research process (e.g. when collecting, analyzing or reporting data) (207).

Both qualitative and quantitative data are collected in this thesis, which consists of three separate studies or phases investigating different aspects of the same underlying phenomenon (treatment- and recovery process). In the thesis qualitative and quantitative data are analyzed and interpreted both separately (in Studies 1, 2 and 3 individually) and together (in this thesis as a whole). There are several points of integration, both during the research process (see section 3.4, particularly) and in this thesis (see especially the findings and discussion section). Table 2 summarizes the studies in this thesis.

Table 2: Overview of included studies – methods, data collection, and sample.

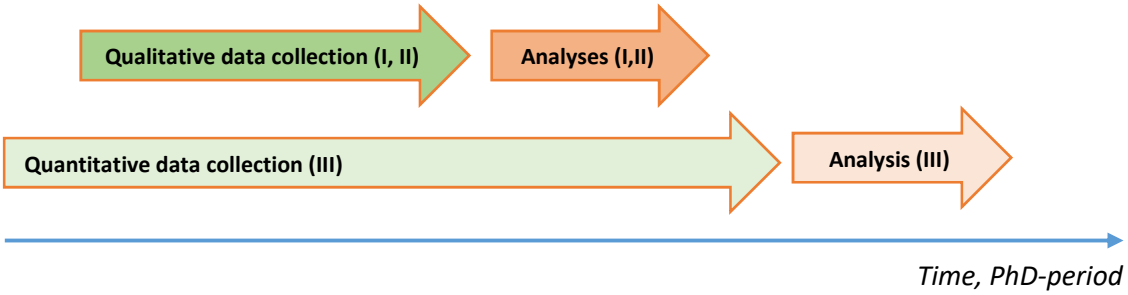
Study	Methods	Sample (see 3.6)	Data collection (see 3.7)	Data analysis (see 3.8)	Year of data collection
1 (Paper I)	Qualitative	19 patients in treatment with XR-NTX	Individual interviews	Content analysis	2019–2020
2 (Paper II)	Qualitative	13 patients who have discontinued XR-NTX treatment	Individual interviews	Thematic analysis	2019–2020
3 (Paper III)	Quantitative (longitudinal, cohort study)	138 patients in treatment with XR-NTX	Questionnaires, dep.variable: personal recovery	Growth mixture modeling (GMM)	2018–2021

3.3.2 Rationale or purpose of a mixed-methods approach

Using a mixed-methods approach can have several purposes and advantages beyond the methodological flexibility of using both qualitative and quantitative methods. As mentioned, it allows for an enhanced understanding of a phenomenon, or ensures that findings are grounded in or relatable to the experiences of participants (212). The purpose or goal of mixing methods can, thus, be said to be to "expand researchers' interpretations and explanations about the topic of interest and to draw data-based conclusions and inferences that are different than or potentially superior to the outcome derived by implementing a mono-method approach" (213, p 240).

In this thesis, the rationale for using a mixed-methods approach was to both give voice to participants and to explore their experiences of treatment and recovery (qualitatively), as well as to collect information on changes in and factors associated with the recovery process (quantitatively). Participants' experiences (qualitative phase) influenced the elaboration and systematic exploration of personal recovery among a greater group of people (quantitative phase), for instance by influencing the chosen focus and selection of variables from the available data. The choice of factors to explore was in part anchored in the qualitative findings, which in turn gave the quantitative results a foundation relevant for the real-world. Figure 4 illustrates the data collection and analysis over time, as described in Papers I–III.

Figure 4: Data collection and analyses over time

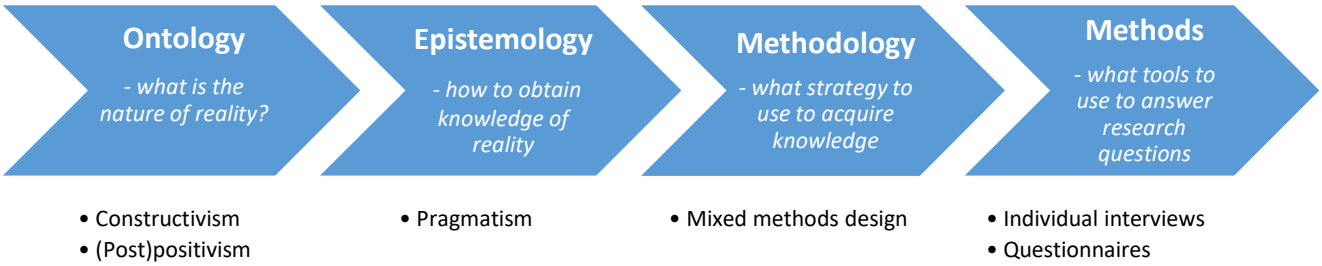


3.3.3 Pragmatic underpinning

The choice of a mixed-methods approach in this thesis was built upon the assumption that one type of research (either qualitative or quantitative) would be insufficient to address the main aim. The use of mixed methods can thus be argued have a pragmatic underpinning in this thesis. Pragmatism involves an emphasis on "what works" in research, focusing on the research question as the driving element and using any available methods to answer it. Thus, pragmatism does not involve any philosophical or epistemological dogmatism, rejecting the either-or choice between qualitative or quantitative perspectives or methods (206, 212). Rather, pragmatism entails an openness to the existence of multiple realities, which both qualitative and quantitative methods might shed light on.

In this thesis, pragmatism is used to suggest that there is more than one way to explore the treatment and recovery process of people in XR-NTX treatment, underlining the notion that different ways of doing so may uncover different aspects of the recovery process. As research is scarce on the recovery process and the experiences of patients in XR-NTX treatment, starting with the participants' experiences with the process of treatment with XR-NTX was reasonable. Figure 5 identifies the foundations of this thesis and of pragmatism as its theoretical underpinning or epistemological stance.

Figure 5: The ontological, epistemological and methodological foundations of this thesis



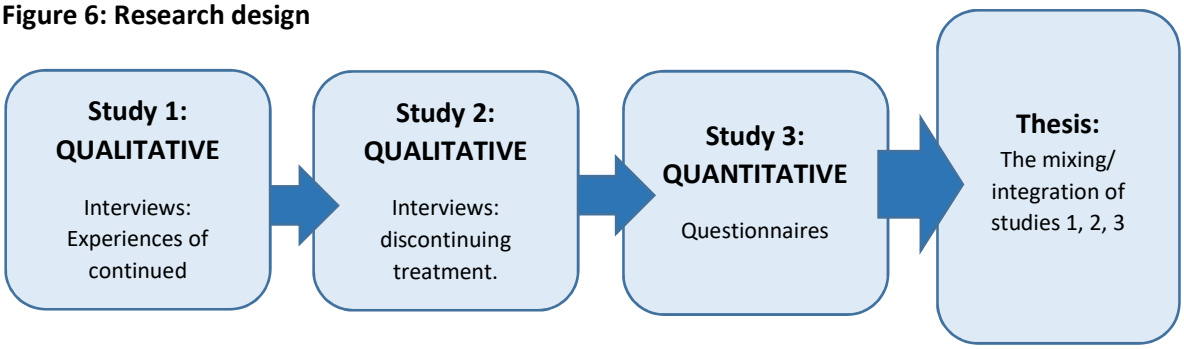
3.4 Mixed-methods design

Following the typology of Leech and Onwuegbuzie, which represents mixed-methods designs over three dimensions (level of mixing, time orientation and emphasis), this thesis has a partially mixed, sequential, equal status design (211), comprising two qualitative studies and one quantitative study. In addition, the design has elements of an emergent design, implying a flexibility and allowing changes to be made during the research process (207).

A ***partially mixed***, as opposed to fully mixed, design means that the quantitative and the qualitative parts were conducted before mixing. In this thesis was conducted separately, and the integration or mixing occurred after the separate studies were completed, as recorded in the findings/discussion

section in this thesis. A ***sequential***, as opposed to concurrent or simultaneous, design indicates that the qualitative and quantitative studies were conducted at different stages or times. In this thesis, Studies 1, 2 and 3 were performed consecutively. An ***equal***, as opposed to dominant, study is one in which qualitative and quantitative components have equal priority, meaning they contribute equally important insights. This thesis adopts a mixed-methods philosophy whereby qualitative and quantitative methods are thought to produce equally true or important insights. Figure 6 presents the research design.

Figure 6: Research design



3.4.1 Emergence

Traditionally, emergent mixed designs occur when a second approach (qualitative or quantitative) is added to a study because of the need for another perspective. However, emergent designs, as opposed to fixed designs, do not represent a clear dichotomy, but rather endpoints of a continuum (214). The term "emergent" also "describes situations in which the researcher makes adjustments to accommodate unexpected situations" (215). The design in this thesis, thus, has elements of an emergent design, as aspects of the study were not fully fixed in advance, allowing for new questions or angles.

This flexibility may in part be tied to the qualitative starting point. Qualitative methods are used to explore or understand something deeper (209), and they also should be interactive, allowing for new information to be integrated as the process progresses (216). To explore something one knows little about will likely require adjustments during the enquiry (e.g., in what questions to ask or what angles to take). This thesis involved a change from an initial focus on hindrances and enablers in XR-NTX treatment to a focus on recovery and process. This change was largely connected to what I learned during the first phase of research; that is, participants did not talk about "hindrances and enablers," but rather described a process or journey that XR-NTX initiated or was a part of. This focal point, in turn, influenced the overall questions I wanted to answer and led to a focus on recovery.

The first phase consisted of the qualitative exploration of the experiences of participants currently in treatment with XR-NTX, initially the only qualitative exploration planned. However, it became

evident that more knowledge was needed to reach the aim of exploring the experiences and the process of treatment and recovery; that is the experiences of those choosing to discontinue treatment. This recognition necessitated the addition of phase two in the thesis work, which consisted of qualitatively exploring data from a sample of participants who had started but chosen to discontinue treatment. The last quantitative study (3) had not been fully conceptualized beforehand, and the results from the two qualitative phases then influenced the focus on personal recovery in the quantitative phase. Restrictions in data points in the overall study meant that the initial plan to compare those staying in treatment and those discontinuing could not be carried out. This change in overall design is an example of emergence in this thesis, and it illustrates points of integration across the data sources.

In sum, the research design has allowed for multiple methods to explore different perspectives on recovery. The first phase (experience of treatment) revealed the need for the perspective of those choosing to discontinue treatment, leading to phase two with an in-depth investigation of those experiences. These two phases then inspired the third phase, which broadened the exploration to a larger sample, but at the same time narrowed the focus to personal recovery specifically. Thus, some integration or mixing occurred during the research. However, the predominant mixing will occur in this thesis, where the findings from the different phases are related and integrated.

3.5 Recruitment and inclusion

3.5.1 Overall NaltRec study and Study 3

The details regarding the recruitment and inclusion to the overall NaltRec study apply directly to Study 3 and are thusly described conjointly. Participants were recruited for the XR-NTX group in the NaltRec study through in- or outpatient clinics in the participating hospitals; through OAT counsellors or other treatment personnel, community health services, or study personnel at the detoxification units; or through newspaper articles or word of mouth.

Participants were required to sign a consent form prior to screening procedures described below, including consent to participate in the general study as well as in the various sub studies (e.g., qualitative individual interviews, collection of saliva DNA sample, consent to contact family or municipal health services for further interviews).

After signing the informed consent form and completing screening procedures, participants undertook a complete opioid detoxification. In accordance with national guidelines and international standards (146, 217), the detoxification was recommended to be undertaken at an in-patient ward. However, a few participants chose an outpatient detoxification, in some cases without the assistance of health services. After the required minimum of opioid-free days, participants received an injection

with XR-NTX, which they then subsequently received every four weeks together with various assessments, as per the study protocol (201). The overall study period was 24 weeks, with an optional 28 weeks.

Women of fertile age were required to provide a urine sample for pregnancy testing prior to the first injection, and they were required to use contraceptives while participating in the study. All participants not already in OAT were included in the OAT program before study participation, to ensure they would be entitled to counselling or interventions needed within the existing addiction treatment system.

Screening procedures prior to study participation

Screening procedures included the collection of baseline data, demographic factors and history of substance use, using the EuropASI interview (218), as well as an assessment of the inclusion and exclusion criteria. Participants had to be 18–60 years, have a DSM-IV diagnosis of opioid dependence and belong to the catchment area of one of the participating hospitals. The confirmation of a diagnosis of OUD, along with a screening for psychiatric disorders, was achieved using the Mini International Neuropsychiatric Interview 6.0 (MINI) (219), which was conducted at screening. A physician performed a physical examination for serious somatic disorders, and clinical blood and urine tests were taken, screening for serious illness such as HIV or hepatitis, as well as for pregnancy. Participants were excluded if they were pregnant or breastfeeding, had serious mental or physical disorders requiring extended attention, or had alcohol dependence.

3.5.2 Studies 1 and 2

For Studies 1 and 2, NaltRec study personnel mediated contact with participants who had previously given written informed consent to participate in individual interviews.

Inclusion criteria

For Study 1, the inclusion criteria were that participants had been in continuous treatment with XR-NTX for at least 12 weeks (i.e., received at least three injections) at the time of the interviews. For Study 2, the inclusion criteria were that participants must have received at least one injection with XR-NTX; and initially, that they also had chosen to discontinue treatment within the first 12 weeks of their treatment, receiving a maximum of three injections. However, due to recruitment issues we also included three participants who had received four injections. The period of twelve weeks was originally chosen pragmatically: we wanted participants to have some experience with treatment and for those staying in treatment to explore experiences past the initial period, but at the same time we wanted those discontinuing treatment to have not “too much” experience with it. The choice to

include participants who had received four injections was pragmatic and connected with difficulties recruiting enough participants, thus allowing for a sample size better aligned with the study's goals.

Recruitment

When recruiting, a purposive sampling strategy was planned; aiming for a balance in gender and geographic spread over the four sites present, as well as a distribution in the duration participants had been in treatment in Study 1. Both studies faced some recruitment difficulties.

Study 1 encountered difficulties recruiting enough females to achieve gender balance while maintaining site balance. In addition, some difficulties also arose in recruiting from the smallest site. Initially the research team aimed to recruit 20 participants: five from each of the four sites. Twenty was considered a feasible number of participants to recruit, given constraints on time and resources, as well as considered sufficient with regard to the topic and aim of the study and planned interview length (220). All participants initially contacted agreed to be interviewed. However, 10 participants withdrew consent or were subsequently unreachable. Subsequently we continued to strive for the best site distribution possible, which made it difficult maintain a gender balance.

There were further overall difficulties recruiting participants who had discontinued. As in Study 1, the initial goal was to recruit 20 participants. Because recruitment was difficult, we decided that participants who had received four injections could also be included. We attempted to contact 32 patients meeting inclusion criteria at the time of recruitment. Nineteen could not be reached or declined to participate. This was probably due to a general unreachability (e.g., no working phone), or to participants having moved on (e.g. not wanting to have anything to do with the study anymore or having returned to substance use). This also resulted in study staff conducting interviews with this group from a few weeks to several months after discontinuation, as well as in the inclusion of participants who had received four injections. In the end, 13 patients accepted participation.

3.6 Samples

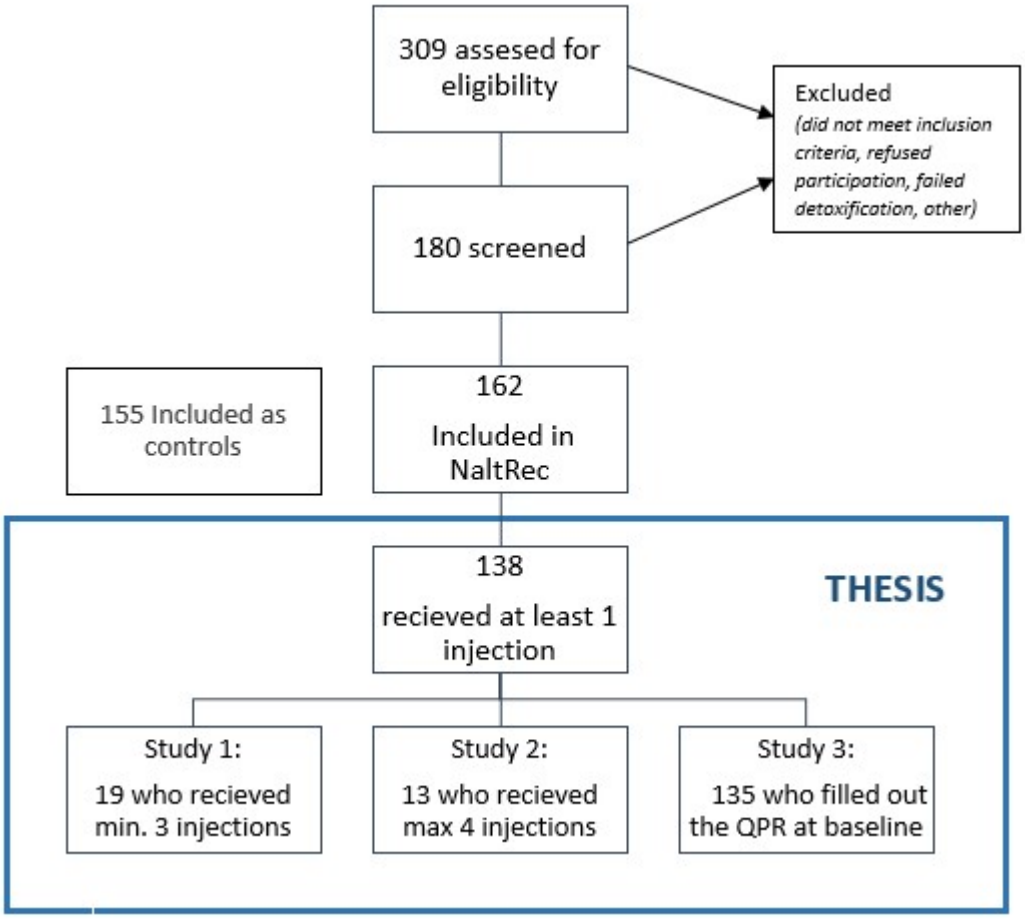
This section presents the samples for each study.

3.6.1 Overall sample

The overall NaltRec study included 162 persons with a previous diagnosis of opioid dependence according to the DSM-IV (221), who received treatment with XR-NTX. In addition, 155 were included as comparison controls. All XR-NTX participants were voluntarily seeking treatment with XR-NTX. Due to the exploratory nature of the study, power calculations were not performed. Initially the goal was to recruit 150 participants to receive treatment with XR-NTX: 309 participants were assessed for eligibility, of whom 180 were screened; finally the study included 162.

The three studies in this thesis had related samples, as all were drawn from the overall NaltRec population. For an overview of the samples, see figure 7.

Figure 7: Overview of the NaltRec study and the samples in this thesis



3.6.2 Study 1

Study 1 included 19 participants, 15 male and 4 female, with a mean age of 38 years (ranging from 22–55 years). Two participants did not identify as having Norwegian ethnicity. On average, participants had used opioids for 11.9 years (SD 9). Thirteen participants were in OAT when entering the NaltRec study. Participants had received between three and 12 injections at the time of the interview. One participant had received three injections, six had received 4–6 injections, eight had received 7–9 injections, and four had received 10–12 injections.

Although the sample in Study 1 had a gender imbalance (4 female of the 19 participants), as mentioned, due to difficulties recruiting females during the inclusion period, it reflects the gender imbalance present in the overall NaltRec study, which included 24% females. It is also consistent with the general gender imbalance both in OAT in Norway (222), and among Europeans with OUD seeking treatment (50), as well as the historically higher prevalence of SUD in men (223, 224).

3.6.3 Study 2

Study 2 included 13 participants, seven women, six men, aged 18–63 years (mean 38). All participants were white and identified as Norwegian. Nine were in OAT before entering XR-NTX treatment, and an additional two participants had prior experiences with OAT. All participants had prior experiences with opioid detoxification. Participants had, per the inclusion criteria, received one to four injections with XR-NTX; seven had received one, two had received two, one had received three, and three had received four injections before they decided to discontinue treatment.

3.6.4 Study 3

Study 3 included 135 participants who had received one injection and who also had filled out the Questionnaire about the Process of Recovery (QPR) at baseline. The mean age was 37.6 years with a SD of 9.4 years. Further, 22.2% were female, and 60% were in OAT programs before entering the study. Many (84.1%) had been previously been exposed to a traumatic event. On average, participants received between 9 and 10 injections with XR-NTX during the study period. Participants' baseline characteristics are reported in table 1 in Paper III.

3.7 Data collection

The data in this thesis were collected by both qualitative and quantitative methods, moving from the qualitative studies' explorations of the perspectives and experiences of a few people with OUD in XR-NTX-treatment, to the quantitative study's investigation of changes in the process of personal recovery among a larger group of people receiving XR-NTX. The collection of the qualitative data is presented first, followed by the quantitative data.

3.7.1 Qualitative data collection (Studies 1 and 2)

The qualitative data in this thesis were collected as part of WP2 within the NaltRec study. In a previous RCT of XR-NTX in Norway (6, 225), both study participants and user organizations expressed the importance of investigating the psychological aspects of this antagonist treatment, as well as the factors that may contribute to abstinence and recovery (201). This input contributed to the development of the qualitative WP in the NaltRec study.

Largely based on the objectives of the qualitative WP in NaltRec, a semi-structured interview guide with open-ended questions was developed. The interview guide was developed with input from co-researchers from RIO, which is a Norwegian users' association in the field of alcohol and drugs, and proLAR Nett, which is a national organization of people in OAT programs. Both those in treatment and those who had discontinued treatment were interviewed about their experiences with XR-NTX treatment using the same interview guide.

The interview was organized under 5 general topics: ***Motivation for treatment with XR-NTX*** ("Why did you want treatment with XR-NTX?"); ***Experience of being blocked from using opioids*** ("How did you experience being prevented from receiving effects from opioids?"); ***Barriers and facilitators to treatment with XR-NTX*** ("What made it easier or more difficult to be and/or stay in treatment with XR-NTX?"); ***Mental and physical health*** ("How does opioid abstinence influence your mental and physical health"); ***Support and follow-up*** ("What kind of health care and support did you receive/need?"); and ***Quality of life and recovery*** ("How has XR-NTX contributed to your recovery/quality of life?").

Each topic had three to six core questions, supported by prompts to allow for elaborations, and participants were asked to give examples to keep answers close to their everyday life. Participants were encouraged to speak freely, but it was ensured that all areas would be covered. Thus, while each interview aimed to include all the same questions or themes, the order could vary. Certain prompts were specific to those choosing to discontinue (e.g., "What made you choose to discontinue treatment?). Ultimately, participants were asked to share any additional comments or thoughts, and asked whether any important aspects had been overlooked in the interview. Although some had certain questions or comments, there was no indication of the latter.

Participants in the qualitative studies were interviewed once. Interviews were conducted by different staff (PhD students, researchers and study personnel) at the different sites. The person conducting the interview was not involved in the participants' follow-up in the NaltRec study, to ensure that participants would feel safe to share any information. Interviews were conducted at four of the five sites. All interviews in Study 1 and most interviews in Study 2 were conducted in person. Due to the COVID-19 situation, however, five of the interviews in Study 2 were conducted by phone. Each interview occurred in a private place at the respective individual site. Interviews lasted from 30–90 minutes.

Interviews were audio-recorded and transcribed by different study personnel. Transcriptions were stored at a secure server at the sponsor hospital. Respondents were given a fictive name in the transcripts and when reporting findings. Identifiable or sensitive information from interviews was not shared with others outside of the core research group working with the qualitative data, which consisted of two PhD-students and two researchers.

3.7.2 Quantitative data collection (Study 3)

The quantitative Study 3 draws directly on WP1 in the NaltRec study and has a longitudinal cohort design. Quantitative data were entered directly into the electronic case report form (CRF) program Viedoc. All data were kept on a secure server.

At baseline, participants were screened (see section 3.4.1) using the MINI interview (219), which also provided information on experience of previous traumatic events and PTSD diagnosis. Information on demographic data, substance use, education and work experience, living arrangements and relationships were gathered using the European version of the Addiction Severity Index (Europ-ASI) (218). Data was collected using a timeline follow-back (TFB) method (226). In addition, participants completed several questionnaires at baseline. The measurements used in Study 3 are presented below.

The main outcome in the study was the questionnaire about the process of recovery (QPR), which was completed at baseline, 12, 24, 40 and 52 weeks. Covariates were measured at baseline, and were selected for their importance to recovery, based on the literature, on the clinical knowledge and judgment of the authors, and on the qualitative Studies 1 and 2.

The questionnaire about the process of recovery (QPR)

The QPR is a widely used self-report measure of personal recovery. Originally, the questionnaire contained 22 items (227) and was developed and validated among people with psychosis. Subsequent evaluations have recommended using a 15-item version (228, 229). The measure has been translated and validated in different languages, including Swedish (230). The present study (III) used an available Norwegian translation of the 15-item version (231). The 15 items are scored on a 5-point scale from 0 (disagree strongly) to 4 (agree strongly). The total sum score, thus, ranges from 0–60, with higher scores indicating higher degrees of personal recovery. The English 15-item version of the QPR has shown high internal consistency with a Cronbach's alpha of 0.93 (228) or 0.89 (229), and high reliability and convergent validity (228, 232). A study estimating the minimal important difference (MID), that is the smallest meaningful change in score, suggested a within-person MID of 5 points (232). Shanks et al. (233) found the QPR to be the only measure of personal recovery to have all items map to the CHIME framework proposed by Leamy et al. (110).

The Europ-ASI

The sociodemographic variables as well as substance use variables were measured using the Europ-ASI (218).

The variables included number of close relationships, civil status, occupational status over the previous three years and four weeks, years of education, living situation, whom leisure time was spent with, and satisfaction with how it was spent. The variable "number of close relationships" was calculated based on a positive response in any of the six categories in question H14–19, where the respondent is asked about whether he has close relationships with anyone in six categories (father,

other family, friends etc.), giving a maximum score of 6 if the respondent has close relationships in all categories.

Regarding substance use variables, the substances studied were alcohol, heroin, methadone or buprenorphine, other opioids, benzodiazepines, cocaine, amphetamines, cannabis and multiple substances. Two variables were considered: use in the previous six months and number of days of use in the previous month for all the substances, as well as historical severity of substance use, assessed as years of regular use of the substance. Use in the previous six months was measured on a 5-point scale where 0 = no use; 1 = sometimes, but no more than 2–3 times a month; 2 = 1–3 times a week; 3 = daily or almost daily use; and 9 = never used the substance. The scores were then categorized into no use (score 0 + 9), occasional use (score 1), frequent use (score 2 + 3).

The Hopkins Symptom Checklist-25 (HSCL-25)

The HSCL-25 is a 25-item version derived from the well-known 90-item symptom checklist (234). The HSCL-25 is a widely used screening instrument, designed to identify common psychiatric symptoms or mental distress in the last two weeks. It consists of 10 items that assess anxiety symptoms, and 15 items that assess depressive symptoms, two of which are specifically somatic. The symptoms are measured on a 4-point scale ranging from 1 (not at all) to 4 (extremely). The global severity index (GSI) is the mean score of all items, and a GSI score above 1.75 has been set as a cut off, indicating clinical levels of mental distress (235, 236). The questionnaire has been translated into many languages, and has shown very good internal consistency, with Cronbach alpha scores ≥ .90, as well as robust validity and reliability (237, 238).

The Interpersonal Support Evaluation List (ISEL-12)

The ISEL-12 (239, 240) is a modified version of the original 40-item version of the scale. The ISEL-12 consists of three subscales with four items in each, and the total score of the 12 items describes functional or perceived availability of support, both daily and in crises. The items are scored on a 4-point scale ranging from 0 (definitely false) to 3 (definitely true). All items are summed to give a total score ranging from 0–36. There is no general cut-off for high versus low perceived social support; however, scores above the mid-point of the scale (for the 12-item version a score of 18) are thought to indicate a more positive than negative view of the social support available (241). The ISEL-12 has been used in several countries, including Norway, showing acceptable reliability and validity, and yielding adequate to high Cronbach's alpha scores (242, 243, 244).

Present life satisfaction

The Temporal Satisfaction with Life Scale (TSWLS) assesses global cognitive judgments of one's life satisfaction (245). The scale includes the 5 "present" satisfaction items used I this study, as well as

past and future satisfaction. The scale is derived from the Satisfaction with Life Scale (SWLS) (246). Participants indicated how much they agree or disagree with each of the five items using a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). The original SWLS has been shown to have strong internal consistency with a Cronbach's alpha of 0.87 (246).

Craving

Craving was measured with the question, "How much have you thought about heroin the last month" – which participants were asked to rate on an 11-point scale ranging from 0 (not at all) to 10 (constantly/very much). The question has been used previously to measure craving (c.f. 225).

Current experience of pain

Experience of pain was measured using the single-item numeric pain rating scale (NRS) (247), which measures pain intensity, and is shown to be a valid and reliable scale (248). Participants were asked to mark their "current pain" on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable). The question was presented with other questions concerning pain.

3.8 Data analysis

In the following, the different analyses in the three studies are presented.

3.8.1 Qualitative analyses

The analytical process began after the data collection was finished. In both qualitative studies, analyses were conducted by four researchers (henceforth, "the core research group"), who consisted of health professionals from nursing, social work and psychology, and who had research or clinical experience with substance use problems, or personal experience with substance use problems in the family. The first author of each paper led the analysis in their respective study.

Because there was little former knowledge of the studied phenomenon (249), an inductive approach was deemed appropriate in both Studies 1 and 2. Such an approach facilitates the search for central concepts in the material, rather than using previous knowledge or theories as basis for the analysis.

The NVivo software (250) was used to code and organize the data.

Study 1

Study 1 employed qualitative content analysis to explore the experiences of patients in treatment with XR-NTX. Content analysis was used because it is well suited to analyze written material, and is a systematic way to attain a broad and condensed description of a phenomenon under study (249). The analysis was data-driven, aiming to identify central themes describing the process of treatment from the patients' perspective.

Informed by the approaches described by Elo and Kyngäs (249) and Graneheim and Lundman (251), I listened to all interviews, and I read and re-read the transcripts several times to obtain a sense of the whole body of data. The text was then coded, using an inductive content analysis. The codes represented condensed units of meaning in the text (where e.g., "I had such a headache after starting" could be coded as "adverse effects"). The coding of the first interviews were crosschecked by my main supervisor and co-author (BW). After the initial coding, a map of all the codes was made, and the codes were compared, grouped and regrouped, looking for similarities, relations or differences. The interviews and the codes were then discussed between the researchers in the core research group. The codes were sorted into subcategories and categories, providing a description of participants' experiences that was as full as possible. The organization and reorganization was discussed several times among the researchers. The final conceptualization, naming of the three main categories and hierarchical organization were done in collaboration. The interviews were read over several times in the process, and the final categories were kept in mind during the final review of the transcripts to ensure categories reflected participants' accounts and experiences. Figure 8 depicts the analysis process.

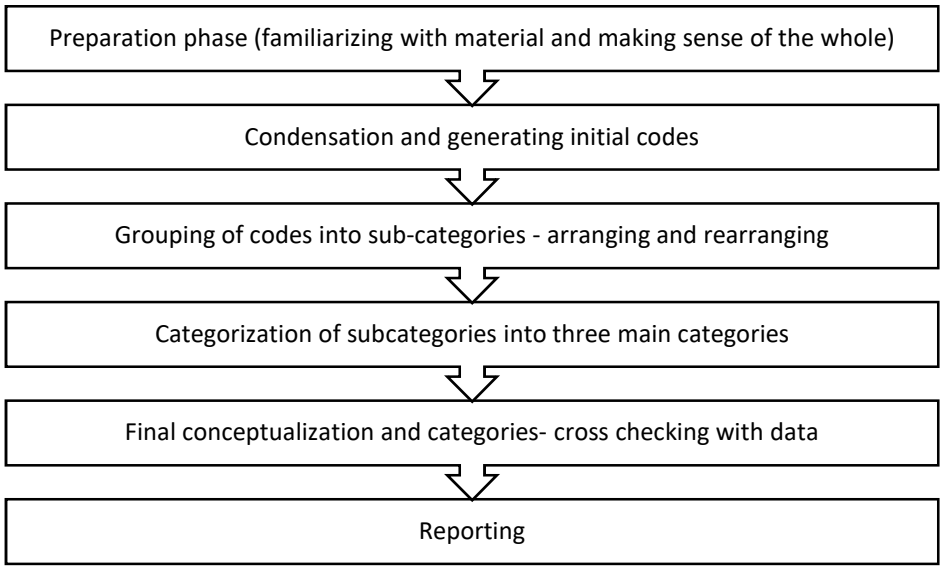
Study 2

In Study 2, the thematic analysis was informed by the critical realist approach described by Maxwell (252).

The steps of the analysis process were similar to those in Study 1. However, as the central aim was to explore pathways leading to discontinuation, the analysis and categorization of inductive codes also involved the creation of narrative summaries for each participant, inspired by Maxwell (252). In the presentation of findings, the themes were presented as a chronological narrative and distinct trajectories of treatment outcomes.

The analysis was led by the first author (IHB) of the study. I listened to many of the interviews, and read all transcripts once, as well as read all narrative summaries. As in Study 1, the core research group was involved throughout the analysis process, among whom the coding, the arrangement of codes and categories, and the final conceptualization were regularly discussed.

Figure 8: The process of analysis in Study 1, in accordance with the descriptions of Elo and Kyngäs (249) and Graneheim and Lundman (251).



3.8.2 Quantitative analysis

In quantitative Study 3, a study-independent statistician was involved in the analyses. Analyses were conducted in STATA v16. The study aimed to explore changes in personal recovery, the different trajectories of personal recovery and associated factors during XR-NTX treatment.

Data were described using means and confidence intervals (CIs) or frequencies and percentages. To assess changes in overall QPR score, a linear mixed model with random intercepts and fixed effects for time, coded as dummy, was used. Growth mixture model (GMM) was further applied to identify possible unobserved groups of participants following distinct QPR trajectories (253). GMM can be used to identify homogenous groups within a sample based on individual profiles by applying statistical criteria. As criteria, this study used Bayes Information Criterion, reasonable group size, high average within-group probabilities, and non-overlapping 95% confidence intervals (CI) for the trajectories.

After being identified, groups were further compared using ANOVA (for continuous variables) or χ^2-test (for categorical variables) for the baseline variables. Groups were compared pairwise in post hoc analyses. The choice of variables was based on the clinical knowledge and judgment of the authors, the previous qualitative studies, and factors emphasized in the literature as important for recovery.

Sensitivity analyses were performed employing non-parametric tests due to group size. All tests were two-sided, and p-values under 0.05 were considered statistically significant.

3.9 Author's role in the overall study

I was responsible for collecting quantitative data at Akershus University hospital. This responsibility included recruiting and informing potential participants and clinicians, as well as screening and follow-up with participants. I coordinated the participants' study start up, scheduled, and performed participant visits (interviews and questionnaires as well as collecting urine samples) and updated case report forms and electronic medical records. I contributed to the qualitative study by making the first draft of the interview guide, conducting qualitative interviews with participants and transcribing interviews (Study 1), as well as by being responsible for coordination of the qualitative interviews and the transcription process. My contributions in the analysis in the studies is described above (section 3.8), and my role as researcher is further expanded upon in section 6.5 where preunderstanding and reflexivity are addressed.

3.10 Ethical considerations

Research involving human beings inherently involves ethical challenges, as the main goal is to gain knowledge that will have a future benefit, not primarily to benefit those participating in the research (254). Thus, such research also involves strict regulations, ensuring the integrity of the individual. Ethical issues and their consideration are an important part of the research process. The main principles of human biomedical research are voluntary participation, the right to withdraw, and the minimization of harm (254), and these will be discussed. Some considerations specific to the qualitative studies (I, II) will be discussed in closing.

Autonomy and informed consent

All participation in the overall study, and thus in studies I, II and III, was voluntary and informed. Before agreeing to participation and signing the consent form, all participants were given thorough written and oral information in a separate meeting, where the comprehensive information regarding the study, medication, possible risks, participation and procedures was given. Participants were also informed of their right to withdraw from the study at any time and assured that refusal to participate or a later withdrawal from the study would have no negative consequences. Participants gave written consent to participate in the different parts of the study, such that they could, for example, opt out of participating in the in-depth interviews or DNA sample collection, but still participate in the main study. Regarding participation in the qualitative interviews, participants were informed that not everyone signing a consent form would be subsequently contacted.

Although a strength for the clinical relevance of the study, recruitment was naturalistic, meaning close to how the choice of treatment approach could or would be made in a real-world setting. Thus, many participants were referred to the study and recommended the treatment by their OAT

counsellor or therapist, which may have contributed to feeling pressured to participate or participating because recommended by professionals. This possibility was mitigated, however, by the comprehensive information given before the participants' study start.

Right to withdraw

The study period of the overall NaltRec study lasted for a year for those choosing to complete the full study, thus, participants provided much information, answered many questions and met for many study visits. Although the study's potential benefits outweigh this potential inconvenience for the individual, such a study may still be trying for some. Backing out once starting might be difficult, and issues such as gratitude or sense of debt might make participants agree to more than they are genuinely comfortable with. This might influence participants to say *yes*, or not say *no*, out of a sense of obligation. For some, this might have made them agree to the sub-studies (e.g., give a saliva sample or participate in the qualitative interviews). This point may be illustrated by a quote from a participant upon ending the qualitative interview: "It's been OK (…), but I won't do more interviews, this is the last. (…). I'm beginning to feel I've paid my dues."

Regarding the main study, some might have felt they needed to continue in the study to continue obtaining the medication. This touches upon the issue of unequal balance – the study provides something the participants want (the medication), and to keep getting it, they cannot in reality withdraw from the study. On the other hand, many participants expressed gratitude and wanted to give something back or to contribute to new knowledge that would benefit others. This fits well with other research showing that for people with SUDs the main motivation to participate in a study is often the expected benefits for themselves as well as for others (255). In addition, feeling one has been able to pay one's dues might contribute to a positive sense of self. Nonetheless, these issues are important to be mindful of during the research process, and the research team regularly reflected upon them.

The importance of repeatedly and explicitly underlining that further participation was voluntarily, and that a given consent could be withdrawn, was underlined by a participant who, when asked why he chose to participate in the qualitative interviews, expressed that he thought he "had to" to continue in the main study, because he had signed the consent form to do so.

Minimizing harm

XR-NTX has potential adverse effects, which participants were informed of beforehand, and these were monitored closely during the study. Because XR-NTX is a long-acting opioid agonist, which could have possible consequences for other treatment-requiring opioids, study participation was recorded in participants' electronic medical records. The date of the last injection and the telephone number

for the doctor on call were also noted in the record, in addition to participants receiving a card with the same information to keep in their wallet. Participants were also emphatically informed of the increased overdose risk if they discontinued treatment and used opioids, information that was repeated to any participants considering discontinuing.

Another ethical concern is related to the potentially negative effects of sensitive questions. Issues related specifically to the qualitative interviews are discussed below. However, the quantitative interviews and questionnaires also covered sensitive issues, such as previous and current substance use, mental health, relationships and conflicts, criminal activity, and so forth. It was stressed that the information was confidential, would not be shared within the treatment system, and would have no consequences for the participant. In some cases, therapists wanted to know participants' results from the routine urine drug test provided at each study visit, and such information would be routinely denied to reduce any pressure participants might feel to provide these results. Overall, sensitivity and respect in the data collection were emphasized throughout the research process, and participants were informed that they could decline to answer especially difficult questions if they needed.

There are also certain considerations regarding participation in a study employing a novel, potentially attractive treatment. XR-NTX was unavailable in Norway outside of the NaltRec study, so study participation was the only way to obtain XR-NTX. Furthermore, the treatment was limited to a year. Although participants were informed of this limitation, many hoped the treatment would be approved for regular use during this year, and likely many had not reflected upon what the absolute limitation in time would actually mean (i.e., what they would do "after" or if they needed more time). Relatedly, an ethical concern might be the starting of a treatment in a treatment system not prepared to receive and address the needs of participants arising during and after study treatment, when the study follow-up finishes. However, to join the study, referral to the existing OAT program was required, ensuring that participants would receive adequate follow-up at the end of the study. This also made certain that participants could withdraw from the study at any time and be ensured opioid agonist treatment within the OAT system, as well as access to counselling and referral to other necessary services.

Confidentiality

Participants were informed that all study data was confidential, and accordingly, participants' names were not linked to the data. The quantitative data were directly entered into an electronic database and stored on a secure server, where each participant was given a number. For the qualitative studies, no names, backgrounds or other identifiable data were recorded during transcription. Audio

files were encrypted and kept on a secure part of the hospital server, reserved for such information. The written transcripts were stored anonymously on another secure server, with referral to the participants' number in the study.

Participation in the qualitative interviews

People with SUDs may be a particularly vulnerable group, as stigma, social exclusion and mental health issues are common.

Many of the data collected, and many aspects related to SUDs are sensitive in nature. While participants provided sensitive information in the quantitative questionnaires, in the qualitative interviews participants shared further information on their own experiences and on potentially particularly difficult and sensitive periods of their lives. Especial strain might be caused by asking people who have discontinued treatment to review the process they went though and their reasons for discontinuing treatment. For some participants, as described in Paper II, their accounts involved both sensitive and harrowing experiences. On the other hand, these experiences are important to explore and describe. Thus, special care was taken to ensure that participants could not be identified from their interviews, including the use of fictive names and the removal of any other identifiable information (e.g., places or other names). In addition, it was ensured interviews were not carried out by personnel tied to the participant's site, to ensure participants would feel free to share experiences regarding issues pertaining to the study or study personnel. No information from interviews was shared with clinical or study staff afterwards. Interviewers were urged to avoid asking unnecessary questions and to focus on the interview guide, aiming to ensure that participants would not end up sharing more than they wanted and more than was needed in the research.

In both qualitative studies, the researchers asked questions respectfully and stressed that participants could chose not to answer questions if they wanted. No participants reported not wanting to answer any questions. In addition, participants were asked how they had experienced participation, whether they wanted to add anything and whether sharing had felt comfortable. Overall, participants reported they had experienced the interviews as positive and meaningful, allowing them to "give back" or to process their experiences. However, since such interviews can expose the vulnerability of participants or even trigger further negative thoughts or feelings in them, participants were informed that they could contact either study personnel at their study site or representatives from the participating user organizations after the interviews if needed.

4. FINDINGS

The following section presents the results of the three studies in this thesis, according to the overall aim of the thesis. To illuminate the treatment and recovery process of patients receiving long-term opioid blockade through XR-NTX treatment, and central aspects, the findings are presented in two steps.

First, the findings from each study are presented, then findings across studies are presented in a joint summary focusing on the aspects or experiences of the treatment process relevant to recovery.

An overview of the focus and research questions in the three studies is presented in table 3.

Table 3: Overview of the three studies and research questions

	Study 1	Study 2	Study 3
Title of Paper (I-III)	Patients' experiences of continued treatment with extended-release naltrexone – a Norwegian qualitative study (I)	*'Not at all what I had expected':* Discontinuing treatment with extended-release naltrexone (XR-NTX): A qualitative study (II)	Personal recovery during treatment with extended-release naltrexone (III)
Research questions included in the thesis	How do patients experience treatment with XR-NTX over time? What are the benefits, challenges and needs that arise during treatment?	What are the experiences leading patients to early discontinuation of XR-NTX treatment? Specifically: What are patients' motivation for treatment? How do patients experience initiation and further treatment? What are patients' rationale for leaving treatment?	Are there changes in personal recovery during the course of treatment? Can groups of patients following distinct trajectories of personal recovery be identified? Will baseline characteristics predict belonging to such groups with different QPR-trajectories?

4.1 Paper I

The aim of this study was to explore how people with OUD experience being in continuous treatment with XR-NTX. Previous research concerning XR-NTX treatment has demonstrated a knowledge gap concerning participant's perspectives on treatment, especially beyond the initial phase of treatment. This study explored how the process of treatment, and indirectly recovery, was experienced by participants, focusing on the possible benefits, challenges and needs that arise during treatment.

Participants' experiences of treatment emerged as a nonlinear process, and centered around three main categories: 1) Finding a new foothold and adapting to life, 2) Connecting with self and others, and 3) Finding meaning and maintaining hope. With the exception of the subcategory "approaching the unknown," which centers on the beginning of treatment, these issues are apparent throughout the treatment period. Figure 1 in Paper I illustrates the categories and subcategories.

Different challenges, needs and benefits arose throughout the treatment process. One important benefit was a decrease in cravings. Patients experienced that because opioids would not work, there was "no point" in thinking about them. Thus, opioids were no longer at the forefront of one's mind all the time, which could be unburdening or liberating. In addition, receiving XR-NTX could feel safe, with the medication working as a safety net guarding against opioid relapse. Nevertheless, having to "deal with life" without the possibility of escape into opioid intoxication could also feel like a prison with no escape from difficulties that might arise. Especially the start of treatment was described as challenging for several participants, involving emotional onslaught, and at odds with the expectation of XR-NTX treatment as a miracle, fixing "the problem" (i.e. the OUD).

The benefits of treatment included better sleep, improved physical health, improved cognitive capacity, an opportunity to participate in society (e.g., through obtaining a job), the building or re-building of an identity away from that of an "addict" and increased hope for the future, as well as a sense of increased meaning in life. Nevertheless, these areas could also involve challenges, including persistent pain and sleep disturbances following induction to treatment, or uncertainty about one's present identity. In addition, participants underlined not expecting too much too fast in terms of achieving changes in life; rather, acclimatizing to being abstinent was a sufficient initial challenge.

Changes in mental and emotional functioning were positive for some (i.e., being more in contact with emotions and having "normal" reactions), but could also involve the loss of one's primary coping or escape strategy.

Being blocked from the effects of opioids, thus, proved especially challenging for those struggling emotionally or psychologically, and an important hindrance in treatment involved the emergence of a heavy use of non-opioids. This could also threaten hope, which participants expressed was otherwise generally strengthened throughout treatment. During XR-NTX treatment, participants expressed feeling more hope for the future, as well as experiencing life as more meaningful.

Findings furthermore highlight the needs of patients throughout treatment. Support is necessary especially in the beginning of treatment, but also throughout treatment, and in the form of professional treatment or follow-up as well as the presence of the person's network of friends and family. Participants also mentioned wanting to give or receive peer support from others with

previous experience of XR-NTX treatment. In addition, having something to do was emphasized as important, and as a way to feel a part of society.

Apprehension about ending of treatment, could involve both an uncertainty about how the future would look once XR-NTX treatment was finished, and a fear of having to go back to OMT.

4.2 Paper II

This study aimed to explore participants' experiences of XR-NTX treatment discontinuation, specifically participants' motivation for XR-NTX, experiences of initiation and treatment, and rationale for leaving treatment.

The main themes are 1) entering treatment, illustrated by the quote "I thought I knew what I was going into"; 2) life with XR-NTX: "I had something in me that I didn't want"; and 3) leaving treatment: "I want to go somewhere in life." Themes and subthemes are illustrated in figure 1 in Paper II.

The findings are presented as a chronological narrative of the treatment process, where the first two themes describe the linear process for all participants, entering treatment and then living with XR-NTX, whereas the third theme, leaving treatment, involves two different trajectories illustrated by the two subthemes of opioid abstinence versus reacceptance of OMT – nevertheless ending in the same outcome: belief in a life without illicit substance use. The analysis highlighted the overarching theme of XR-NTX not meeting participants' expectations.

Both the participants' reasons for starting treatment and how the transition from opioids was tolerated had a bearing on how treatment was experienced, and subsequently the outcome of the treatment process.

Participants started treatment with an explicit goal of ending opioid use, whether illicit or prescribed, seeking to either leave or avoid OAT. XR-NTX could be both the next step in a yearlong recovery process, and a way to resolve dissatisfaction with OMT, e.g. avoid the side effects of the medication, or the challenging control measures of the system. Guarding against the effect of opioids, XR-NTX was a way to discontinue opioids safely.

Participants' experiences varied regarding the transition to XR-NTX, as several felt rushed into treatment or through the opioid tapering prior to starting XR-NTX. A feeling of unpreparedness contributed to the difficulties of the treatment experience, with participants feeling unprepared for the mental and physical reactions or side effects following the first injection, raising concerns of the lack of tailored treatment offered. Unrealistic expectations or lacking information also contributed to the feeling of unpreparedness.

The experiences of being in treatment with XR-NTX were characterized by unexpected (unwanted) effects and by a lack of expected (wanted) effects. The former could involve events such as a relapse to illicit substance use due to the distress of starting XR-NTX; a shock for those without any illicit use for years, while the latter could involve a lack of a blocking of craving or opioid effect.

Being on XR-NTX could also mean a disruption to daily life, with XR-NTX leading to continuous challenges preventing usual activities or a sudden lack of the typical activities related to substance use.

The needs for healthcare and support varied greatly, but such help was generally stressed as important, with some participants stating that better help might perhaps have prevented treatment discontinuation.

Participants' experiences of leaving XR-NTX treatment followed one of two typical trajectories, either the achievement of personal treatment goals or a reacceptance of OMT. Interestingly, some participants discontinued treatment early because they felt they had reached their goal to end all opioid use (whether illicit or through OMT), and they did not see XR-NTX as further necessary. For the majority of participants, however, the negative experiences connected to XR-NTX treatment made them re-evaluate and renew their acceptance of OMT. This reacceptance could be a disappointment at first, however, life without opioids had proven to be more difficult than initially expected, seeing a need for further opioid medication. Nevertheless, regardless of treatment trajectory, participants expressed a strong belief in a life without illicit substance use, either staying in OMT or after a limited period of stabilizing in OMT.

4.3 Paper III

The personal recovery concept founded in the mental health field describes recovery as a personal and dynamic process towards living a satisfying life, even with the limitations posed by one's disorder.The purpose of this exploratory study was to examine personal recovery in people with OUD, receiving extended-release naltrexone; specifically to investigate changes in personal recovery during treatment, identify groups of participants following distinct trajectories of recovery, and the characteristics predicting group-belonging.

As measured with the QPR (227), personal recovery was examined in 135 participants receiving XR-NTX, with a baseline measurement of QPR and selected factors, and four subsequent measurements of QPR over one year. There is no cut-off in QPR, as the questionnaire measures a personal process and not a "hard outcome," but in general, higher scores indicate higher degrees of personal recovery. Table 4 shows the overall sample size and QPR scores at the different time points.

Table 4: Sample sizes and QPR scores at the different time points

QPR score, time	*N*	M	SD
Baseline	135	40.5	10.3
12 weeks	92	42.3	9.9
24 weeks	78	43.1	10.5
40 weeks	58	45.2	8.0
52 weeks	39	47.5	8.6

We found that there was an overall significant change in QPR score during the course of treatment. The change was significant from baseline to weeks 24, 40 and 52, respectively, whereas no other changes between other time points were significant.

While the overall change in QPR was significant, as described, the results of the growth mixture model (GMM) showed there were four groups following distinct recovery trajectories. The four groups were "initially low – increase" (G1), "initially average – no change" (G2), "initially high – no change" (G3) and "initially high – increase" (G4). The two "change groups" were rather small (n= 12 in G1 and n= 10 in G4), while the two "no-change groups" were larger (n=48 in G3 and n=65 in G3). Figure 2 in Paper III visualizes the results of the GMM, with the four trajectory groups and the development of personal recovery over time presented in a graph.

As indicated by the average probability (0.80 or higher for three of the groups, see table 3 in Paper III), the groups were rather homogenous, as also confirmed by the essentially non-overlapping 95% confidence intervals for the group trajectories. Table 3 in Paper III shows the group sizes and the QPR mean baseline score as well as presents the results of the GMM. At baseline, the QPR scores differed significantly between groups. G1 had a QPR score below the mid-point of 30 at baseline, while G4 had a score close to the maximum score of 60.

Constituting the majority of participants, the two "no change" groups (G2 and G3) showed no significant change in personal recovery during treatment. However, the initially lowest scoring low-increase group (G1) experienced the largest change in personal recovery during treatment. In addition, the high-increase group (G4), which initially had the highest score, around 30 points higher than G1, also experienced a significant increase. The no-change groups (G2 and G3) had initial scores of mid-30s (G2) to mid-40s (G3), and these were approximately stable (i.e., no change) through the course of treatment.

A number of variables were examined in relation to the four personal recovery trajectories.

No significant differences appeared between trajectories on sociodemographic variables, such as age, gender, civil status or years of education. Variables differing between groups comprised OAT status prior to study participation, life satisfaction, psychological distress, current pain, social support, working in the previous month, heroin craving, heroin use with the previous six months, benzodiazepine (BZD) use in the previous six months and the previous four weeks, and multiple substance use in the previous six months and in the previous four weeks. Baseline variables of the four trajectory groups can be seen in table 4 in Paper III.

There were no differences, however, in rating the need for help with psychological/emotional problems or prior experience of traumatic events or PTSD diagnosis. Regarding substance use variables, years of regular use did not differ between groups for any of the substances. No differences between groups were found on use of alcohol, other opioids, cocaine, amphetamines or cannabis. For opioids, use in the previous four weeks did not differ between groups.

Post hoc tests were employed to explore which groups differed on the variables showing significant differences. G1 had higher values than G4 on variables where a lower score is positive, such as psychological distress or heroin craving, and lower values on variables where a higher score is positive, such as satisfaction with life or social support. In general, but not consistent for all variables, G1 had the lowest/highest (i.e., "least favorable") scores, and the scores then increased/decreased from G1 to G2 to G3 to G4, with the latter having had the highest/lowest (most favourable) scores. As an example, a lower social support, or a higher mental distress score at baseline was associated with lower QPR score at baseline, regardless of subsequent development in personal recovery or lack thereof. The different scores for the respective groups can be seen in tables 4 and 5 in Paper III.

On all significant variables, post hoc tests showed that the low-increase group (G1) differed significantly from the high-increase group (G4), except on the variable of having worked in the previous four weeks and use of multiple substances. For the working variable, the average-no change group (G2) differed significantly from both the high-no-change (G3) and high-increase (G4) groups (with 10.4% working in the previous week in G2 vs. 30.8% and 40.0 % in G3 and G4, respectively). Further, psychological distress was the variable differing between all groups, except between the high – no change and the high – increase groups (G3 and G4). The low-increase group was the group differing most from the other groups on the variables measured, and individuals in this group reported more psychological distress, less life satisfaction and more craving for heroin than all the other groups at the beginning of treatment. The results of the post hoc tests can be seen in table 5, which expands on the information in table 6 in Paper III by including information on the non-significant p-values, non-significant values in red. As can be seen some values are close to a

significance level of 0.05. Non-significant results should be made available, as labeling non-significant results as "negative" might be misleading. It is also important to remember the choice of a cut-off for the significance level (0.01 or 0.05) is arbitrary, and non-significant results should be included when presenting results, as they might make clear that evidence is inconclusive (256).

Table 5: Results of post-hoc analyses. Pairwise comparisons between personal recovery trajectory groups. *Numbers are p-values*

Variable	G1 vs. G2	G1 vs. G3	G1 vs. G4	G2 vs. G3	G2 vs. G4	G3 vs. G4
In OAT prior to study participation	*0.605*	*0.108*	*0.019*	*0.084*	*0.020*	*0.128*
Psychological distress (SCL-25)	*0.006*	*<0.001*	*<0.001*	*0.003*	*0.002*	*0.119*
Social support (ISEL)	*0.594*	*0.002*	*0.013*	*<0.001*	*0.006*	*0.767*
Current pain	*0.065*	*0.006*	*0.011*	*0.321*	*0.078*	*0.140*
Working previous 4 weeks	*0.830*	*0.109*	*0.078*	*0.010*	*0.019*	*0.560*
Life satisfaction (TSWLS)	*0.005*	*0.001*	*0.009*	*0.062*	*0.085*	*0.522*
Craving for heroin	*0.040*	*0.003*	*0.005*	*0.100*	*0.143*	*0.593*
Heroin, use last 6 mos., *n* (%)	*0.096*	*0.020*	*0.003*	*0.447*	*0.085*	*0.165*
BZD use last 6 mos.	*0.262*	*0.061*	*<0.001*	*0.255*	*<0.001*	*0.011*
BZD days of use last 4 weeks	*0.160*	*0.002*	*0.003*	*0.022*	*0.023*	*0.167*
Multiple substances last 6 mos.	*0.740*	*0.179*	*0.011*	*0.064*	*0.006*	*0.038*
Multiple substances last 4 weeks	*0.619*	*0.023*	*0.061*	*0.010*	*0.058*	*0.420*

G1: "initially low– increase", G2: "initially average– no change", G3: "initially high– no change" G4: "initially high– increase"

4.4. Joint summary and comprehensive understanding of findings

Overall, this thesis aimed to deepen understanding and knowledge of the treatment and recovery process of people with OUD in XR-NTX treatment, specifically to illuminate central aspects of these processes.

Findings related to the main aim are summarized in table 6, which offers a joint summary of findings. Integration or mixing is achieved through juxtaposing results from the three studies, and each study contributes a piece regarding important aspects for patients and their treatment and recovery process during XR-NTX treatment. The integration is done in this way because the studies illuminate different aspects and different time points in the process, rather than illuminating the same aspects.

Summarized, the findings revealed several important aspects that both patients and treatment providers must be aware of regarding treatment with XR-NTX. These issues might include both pretreatment aspects and issues arising during treatment as well as be related to what happens after treatment.

Findings from table 6 show that before treatment, patients' motivation, realistic expectations as well as realistic and balanced information are important for patients' recovery and treatment process. Here, the two qualitative studies converge and elaborate on each other. Further, several baseline characteristics (paper III) are associated with further recovery, meaning that patients' situation before entering treatment is of significance for further recovery during treatment. While these factors are not mentioned by participants related to the pre-treatment phase – thus, not explicitly experienced by patients as vital when entering, or before entering, treatment – the factors found in Study 3 seem to be relevant during treatment, and appear when participants discuss how treatment is experienced. For example, psychological distress is an important pre-treatment variable associated with further recovery trajectory that is also important in participants' accounts of the experience of treatment (i.e., during treatment). Other central aspects of importance for patients in their process of recovery are substance use and its function, as well as various treatment needs. There are, however, also several factors during treatment experienced as central for participants that were not measured in Study 3. Many of these are related to the delivery or characteristics of the treatment itself, or directly to how treatment or being blocked is experienced.

Study 3 shows 60% are in OMT prior to study participation and that OMT status is associated with subsequent recovery trajectory – with the high-increase group (G4) having the highest percentage of people in OMT. At the same time, leaving or avoiding OMT is the most expressed motivation for XR-NTX.

During treatment there is an increase in personal recovery, measured by the QPR (III). This increase converges with information from participants in treatment (I), emphasizing changes and improvements in the aspects of personal recovery from the CHIME framework. While the increase in personal recovery is significant in a longer treatment perspective, there is no change from pre-treatment to 12 weeks (III). This is the time point when most participants in Study 2 discontinued treatment at the latest, and, thus, is supported by the fact that patients discontinuing to a lesser degree discuss factors related to CHIME (II). For those choosing to discontinue, their treatment is characterized rather by negative experiences and challenges, rather than improvements, and their process is characterized by broken expectations.

The quantitative Study 3 showed that low initial QPR score is associated with a larger burden (e.g., more psychological distress, more pain, more craving, lower life satisfaction) at baseline, but then subsequently a large increase in recovery. This finding is not further expanded in the qualitative studies, but it might align with the finding (I) that not all patients with burden in terms of mental health problems experienced being in treatment (i.e., being blocked) as difficult.

The finding of four trajectory groups (III) further support the heterogeneity of participants accounts (I and II). How recovery develops is not best described by an overall trend for the whole group – but neither is the "splitting" in those staying in treatment and those discontinuing. We did not find anything to support that the stayers and discontinuers are in different trajectory groups, as the total number of injections during treatment does not differ between groups. Furthermore, the nature of qualitative data highlights differences in patients' experiences, which is also supported by the quantitative finding that an overall increase in personal recovery is not representative for all patients, and that looking at subgroups add interesting perspectives.

Figure 9, presented after the joint summary of findings, summarizes the factors important for patients and their treatment and recovery process.

Table 6: Joint summary of findings

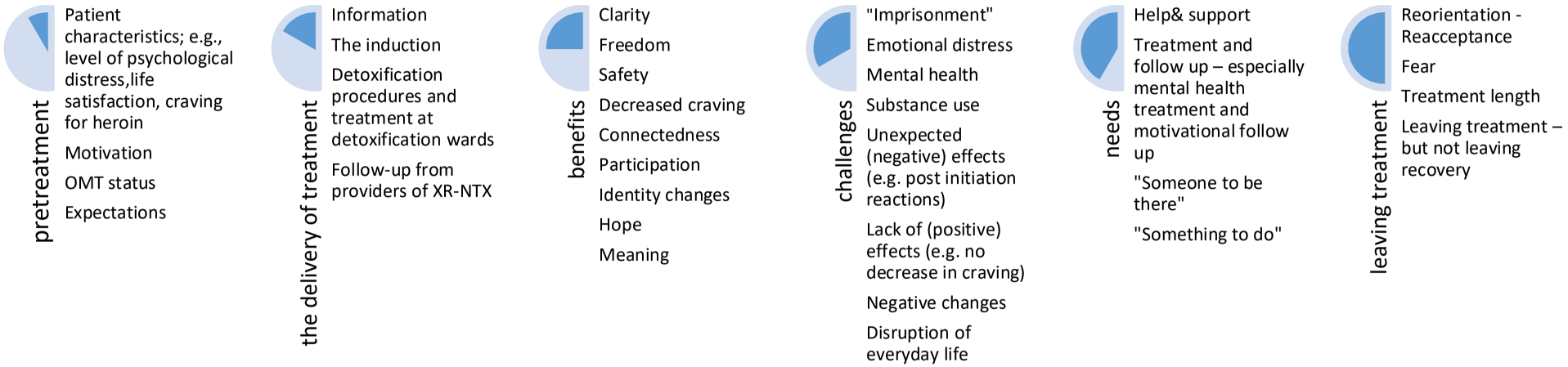
Time	Aspect	Paper I	Paper II	Paper III
Pre-treatment	Motivation	• Leaving OMT • Freedom from opioids or OMT – in a safe way	• Ending all substance use • Leaving or avoiding OMT • The expectation of others – the right thing to do	• OMT status associated with subsequent recovery trajectory, overall, 60% were in OMT prior to XR-NTX • Substance use (except heroin and BZD) not significantly associated with recovery trajectory
	Expectations	• Expecting a miracle • The unknown – unsure of what to expect	• XR-NTX as a step further in the recovery process • Expectations of those around • "I thought I knew what I was going into"	• Overall recovery score at baseline around 40 • Recovery score between trajectory groups at baseline varies from 20 to 50 (Midpoint is 30 points)
	Information, preparation	• Lack of information? Entering something unknown	• Lack of information + Feeling rushed -> unpreparedness • Realistic information is vital	
	Pretreatment variables			Pretreatment variables predicting recovery trajectory: • OAT status • life satisfaction • psychological distress • current pain • social support • working the last month • heroin craving • heroin use • BZD use • multiple substance use Not associated with recovery trajectory: Trauma/PTSD Psychosocial variables

Initiation and early treatment		• "The emotions hit me like a train" – especially hard emotionally • Adverse reactions; side effects or withdrawal • Needs: support	• "Hitting a rock wall at 360 km/h" • Rushed, unhelpful help, chaotic • Increase in symptoms of underlying conditions • Relapse to substance use due to the distress of starting XR-NTX	N at baseline: 135 N at 12 weeks: 92 43 (31.8%) discontinued within the first three months
During treatment	Experience of being blocked	• Freedom • Safe, safety net, something holding me back <from opioids>, but also a prison • "No point in thinking about opioids" • Having to deal with life without the possibility to escape • Expectations of a miracle could turn to broken hope	• Destabilizing • Suddenly thinking about opioids	
	Emotional function/ Mental health	• Mental health difficulties can make handling being blocked hard • Positive aspect of "getting emotions back" • Still needing a way to suppress emotions, to cope with mental challenges –struggling emotionally	• Increase in underlying mental conditions • Positive aspect of "getting emotions back" • Increase in symptoms in underlying PTSD	• Mental health at baseline significantly associated with recovery trajectory • 84.1% reporting exposure to traumatic event
	Substance use	• Testing the blockade • A limited use of some substances, typically cannabis For some: • Searching for something that dulls • Using previously unused substances when things are difficult • Relapse to illicit substance use	• Testing the blockade – XR-NTX not blocking buprenorphine • Relapse to illicit substance use – connected to emotional and physical status	• Before treatment use of heroin and BZD differs between groups – use of other substances does not differ

During treatment, cont.	Personal recovery; CHIME	Patients experience changes/improvements in: • Connectedness – strengthened relationships and being part of society • Hope • Identity • Meaning • Empowerment ⇩ Important aspects of experiences of patients in treatment with XR-NTX	• CHIME domains not explicitly mentioned • Hope is broken "Now I've tried everything, and even this is not working" • Experiences more characterized by difficulties	• Using the QPR shows a significant increase from baseline to 12 months, but NOT to 3 months; thus, change in QPR not significant for those discontinuing treatment (II) • Majority of participants do not experience QPR change
	Treatment characterized by	• Benefits and challenges • Adjustment	• Broken expectations • Frustration • Disruption of daily life • Unexpected, negative side effects and lack of anticipated effects of XR-NTX	• Increase in personal recovery overall, however the majority did not experience any increase in personal recovery • Four distinct groups with different trajectories
	Needs	• "Something more than just the injection" • Having something to do – however, not expect too much • Support from friends/family • Monthly study visits useful • Treatment - of underlying conditions, and new problems surfacing	• Healthcare • Unwillingness to involve family • Outpatient care and follow up • Supplementary treatment necessary • Lack of adequate psychosocial support	• Working last 4 weeks before treatment associated with trajectory – high-no increase (G3) and high-increase (G4) significantly more likely to be working than average-no increase (G2)

After treatment /future	Treatment length	• Fears of ending treatment, uncertainty about the future • Treatment length needs to be individualized – possibility of prolonging more than a year	• Individualized – ending treatment when goals are reached • Ending treatment if need to reevaluate goals	• Total number of injections (i.e. how long one stayed in the study) was not associated with group-belonging
	Future goals	• Continued abstinence from all opioids • Current treatment episode "is it"	• Reevaluation of goals • Reacceptance of OMT or preparation for new episode with XR-NTX in the future • Continued abstinence from illicit substance use	

Figure 9: Relevant aspects in patients' treatment and recovery process during XR-NTX



5. DISCUSSION OF FINDINGS

The overall aim of this thesis was to deepen understanding and knowledge of the treatment and recovery process of people with OUD in XR-NTX treatment, specifically to highlight central aspects of these processes from the perspective of people undergoing treatment. Accordingly, what aspects are relevant when proposing XR-NTX as a treatment option for patients, and how can treatment be understood in a personal recovery framework?

This section discusses the main findings across the three studies included in this thesis, related to the overall aim. The discussion will focus on the two parts of the main aim: the treatment process, focusing on patients' experiences of treatment (Paper I, II), and the recovery process in XR-NTX treatment (Paper I, II, III). Except for the final section, focusing explicitly on personal recovery, each section is illustrated by direct or synthesized quotations from the interviews with participants (Paper I, II).

5.1 Pre-treatment: Motivation, hopes and expectations

Participants (I, II) expected NTX to provide abstinence from opioids through blocking their effect and reducing cravings, in line with how other studies describe patients perceiving XR-NTX (195, 199).

5.1.1 Motivation

"I don't want to be addicted to anything."

Both participants staying in treatment and those discontinuing treatment (I, II) expressed their main motivation was to end opioid use, and some explicitly to end or avoid being enrolled in OAT. This is in line with questionnaire data indicating many patients in OMT want to become abstinent from all opioids (143). While one barrier to OAT in general is thought to be related to its availability, studies have shown that when treatment is offered for free, many still do not enter OAT (257, 258). This lack of uptake has been linked to patients not wanting abstinence (259), but there are also indications that patients *do* want abstinence when seeking treatment (88). As abstinence from opioids is the implied premise of XR-NTX, the group of people seeking XR-NTX treatment might represent a subgroup of patients with OUD especially motivated to seek abstinence. As participants were both in and without OAT when entering treatment, our findings also show that XR-NTX reaches patients not previously in treatment, but who *also* have the goal of abstinence.

Some participants expressed previous negative experiences with OAT, such as feeling unfree, which is in line with overall findings in the literature and described in the background section. The desire of participants (I, II) to avoid or escape OAT is understandable in light of the dissatisfaction many patients may have with OAT, and in line with a study showing that a common reason to seek

transition from OAT to XR-NTX is the desire to be free from all opioids (260). Despite that OAT has many benefits, a previous review (261) has emphasized the different perceptions of OAT patients. While some see this treatment as a means to obtain stability and recovery, others have described experiencing it as a limbo and continued addiction or dependence (147, 261, 262). Among our participants, both views were represented and may have influenced how treatment was experienced, as well as the following treatment paths.

It may also be important to take note of what participants gave as the reason to discontinue OAT and start XR-NTX. While many emphasized the desire for freedom, no longer being controlled by the demands of OMT or escaping adverse effects of the medication, some also expressed external pressure, where others' expectations played a role. As previously noted; many patients might feel it is expected to eventually discontinue OAT (263), involving a misconception that it is the right next step, a sign of doing well or of recovery. At the same time, research has underlined the significance of internal motivation for abstinence (262). This emphasizes the importance of exploring not only patients' motivation for XR-NTX, but also what lies behind that motivation. While some have emphasized that a view of OUD as an incurable condition requiring lifelong treatment might become a self-fulfilling prophesy that denies people the right to "reject the institutional identity of being a chronic addict" (264 p. 881), the opposite can be equally problematic. As has been presented in the introduction, "chronic" does not have to mean incurable, and the fact that some people need long-lasting agonist treatment does not negate others needing other approaches. Considerable stigma and misconceptions are connected to OAT (e.g., that people in OAT are still addicts or need to discontinue OAT to be in recovery), which may propel people prematurely into discontinuation of OAT (265). Furthermore, a question remains of whether abstinence (from all opioids) is always what people want or only what they are told it is right to want, or even what they must pursue to escape stigma. Patients in OAT are shown to have goals unrelated to substance use, which are as important to meet as the goal of abstinence (259). Still, the choice of XR-NTX could be understood as a resistance to the understanding of opioid dependence as a chronic disease requiring long-lasting treatment and, thus, freedom from a potentially deterministic view of OUD.

5.1.2 Previous attempts at reaching the goal

"I am too weak to resist opioids."

As previously discussed, participants wanted abstinence from all opioids. Interestingly, patients with an explicit goal to "stay or get clean" have previously been shown to have worse outcomes in treatment, namely more use of opioids (259). One hypothesis posed by Rosic et al. (259) is that patients with a more severe OUD could have an increased likelihood of experiencing worse

outcomes, but at the same time to report goals related to opioid use. This is somewhat in line with participants' (I, II) previous experiences. Participants described several previous attempts at detoxification from illicit opioids, or at tapering OAT medication, without reaching sustainable abstinence. Discontinuing OAT can be difficult; few succeed, and many relapse to opioid use (266). It is thus understandable that participants wanted the help XR-NTX provides when discontinuing OAT or opioids and sustaining that discontinuation (i.e. abstinence). Correspondingly, it has been recommended that patients wishing to discontinue buprenorphine should be advised to consider XR-NTX (267). In line with our findings, while transitioning from buprenorphine to XR-NTX aligns with patient autonomy, the patients' motivation for changing treatment, as well certain pre-treatment characteristics such as severity of use are important to take into consideration and may require additional care. For some, a longer period of stabilization on buprenorphine prior to transition to XR-NTX might be advisable (260).

5.1.3 Final opportunity – last hope

"I have tried everything else."

For many participants, going into XR-NTX meant a last hope, having tried everything else without succeeding. This is in line with the accounts of participants in Gauthier et al.'s (195) study. The hope placed on XR-NTX was that it would be the thing to turn their lives around. While hope was important for all, it seemed like those staying in treatment (I) were unwilling to let go of treatment despite difficulties. One participant among those struggling (Paper I), however, expressed that XR-NTX treatment was too hard, wanting to give up, thus conveying a sense of hopelessness and broken hope. On the other hand, participants (Paper II) seemed more often characterized by great disappointment, but not necessarily hopelessness.

Hope is an important aspect in human lives and has many facets and definitions. It is connected to goals, agency and self-efficacy beliefs (268, 269), and a realistic optimism, i.e. more than waiting for a miracle. Hopelessness on the other hand, is a cognitive experience of having no possibility of further positive change and problem-solving, defined in terms of helplessness and a negative outcome expectancy (270). While thoroughly disappointed and sometimes even angry, participants choosing to discontinue (II) were overall not characterized by a hopelessness depriving them of further possibilities, but rather a reorientation and the pursuit of other solutions to reach their goals.

Overall, hope was an important force in treatment, tied to the expectations and motivation to seek XR-NTX in the first place (I, II). Furthermore, hope is seen as a central factor in the recovery processes (271), and in the CHIME model as one of the five central processes or factors (110), overlapping with its importance in our findings.

5.1.4 Expectations

"It sounded like a miracle, really."

Positive expectations are shown to foster motivation, and motivation is related to action towards change. However, if the expectations are closer to fantasies (i.e. wishful positive thinking) than positive expectations (i.e. realistic positive expectations), they can negatively affect the desired outcome (272). Thus, it is possible to hypothesize that some of the participants' expectations better aligned with what Oettingen and Mayer (272) describe as fantasies than realistic beliefs, as exemplified by the conceptualization of XR-NTX as a miracle. Previous research has shown patients' expectations of OAT to be important to their satisfaction with treatment, and high expectations may contribute to patients' dissatisfaction (155).

The question is whether participants had reflected sufficiently on what abstinence entails and what XR-NTX provides. Simply put, XR-NTX promises to block the effects of opioids, thereby, safeguarding abstinence. However, participants seemed to conceptualize this in terms of abstinence leading to further improvements, jumping to the conclusion XR-NTX in itself would change their lives. This conception aligns with how people with OUD can conceptualize successful recovery, with abstinence being at the heart of other changes (92). Other studies (197) have also shown that people starting XR-NTX will often have expectations of outcomes not directly related to the medication. For these changes to happen, however, our results suggest that additional help and support is necessary, as will be further discussed in section 6.5.

It is no wonder that such expectations existed, and some were likely connected to what was the dominating public narrative. While participants might know someone that was unhappy with XR-NTX in the previous Norwegian study (6), the media coverage focused on stories of changed or saved lives through XR-NTX treatment, and few of these stories, if any, problematized aspects of what it would mean to be blocked (see, e.g. 2, 273). Such a strong belief in XR-NTX as a last resort, a life changing tool or even a miracle might have further enforced itself through mechanisms such as confirmation bias (274), where information confirming the existing image of XR-NTX is emphasized, or therapeutic misconception, where a person underestimates the risk and overestimates the benefit from participation in a clinical trial (275, 276). Some of these difficulties seem attributable to inadequate information as well as a lack of addressing expectations prior to study commencement. Participants expressed wanting more time to make the decision to start XR-NTX, as well as better and more realistic information from study personnel, which especially those in Study 2 did not experience was the case. This is in line with findings that patients in general often report they want more information, or that the information they receive from healthcare providers does not meet their

needs (277). When expectations were then not met, the sum of unmet expectations participants in Study 2 experienced seemed to be too great of a hurdle to overcome.

5.2 In treatment: Benefits and changes, unfulfilled expectations and challenges

While the accounts of those discontinuing treatment were largely characterized by unmet expectations and unremitting challenges, those staying in treatment to a greater degree also emphasized the benefits of treatment, perhaps due to having previously likened treatment with XR-NTX to entering something unknown, reflecting a more open attitude.

5.2.1 Benefits and changes – stigma, identity and participation

"It's a whole new life."

For some, the positive expectations regarding life with XR-NTX turned out to be true. Many of the improvements described by participants (I) are seen as important for people with OUD, and also in line with studies showing XR-NTX treatment to be associated with improvements in overall quality of life (278). In general participants in Study 1 described being in treatment with XR-NTX (i.e., being blocked) as safe. XR-NTX could be a crutch or a safety net, guarding against relapse. XR-NTX also increased a sense of freedom, both from needing opioids and from the OAT system, echoing previous findings (195, 199).

XR-NTX was described (I) as life-changing, leading to improvements in various areas, such as better health and cognitive capacity, decreased craving, increased sense of meaning, being able to participate in society and improved relationships. Participants (I) described a changing of identity and sense of self, which was initially potentially challenging, but was described as a positive process. The latter can be understood in light of the much studied concept of self-stigma, which can be said to represent the opposite: Self-stigma occurs when people with SUD internalize the public stigma and experience shame based on negative stereotypes, leading to changes in identity, isolating individuals and making recovery less likely (279).

The marginalization and discrimination that people with OUD and in OAT face can deter them from entering treatment, achieving abstinence and further recovering (155). Overcoming stigma is an important part of the personal recovery process (4). For patients (I), it was clear that XR-NTX represented something other than OAT in this regard, allowing them to pursue "normality" and an identity outside of that of a "drug user." Although after commencing treatment, some saw XR-NTX as disruptive to their daily lives (II), for many the opportunity to move away from a negative identity and participate in society was a strong facilitator in their process. Having something meaningful to do (e.g., a job) was underlined as vital, contrasting a previous life focused almost exclusively on

substance use. The importance of meaningful activities such as employment or education has previously been underlined, largely because they provide both social arenas and a sense of purpose and belonging (280). Related to this is the term "mattering," which can be understood as a fundamental psychological need involves both feeling valued and adding value (281). This is reflected in our findings. While participants described the importance of, for example, a job in feeling valued and in lessening stigma, the desire to contribute and help others (e.g., through peer support) was also emphasized. Many studies have underlined the positive impact of peer support in SUD treatment and recovery (282). Davidson (283) has proposed that recovery is a byproduct of micro-affirmations, that is, small and ordinary gestures conveying dignity and shared humanity. It would seem that XR-NTX opens up arenas for more such affirmations, from family and friends, community and society, and that this may play a central part in the recovery process of people. Indeed, as previously described in the introduction, a sense of community, belonging and social relationships have been proposed as a central aspect of the recovery process.

5.2.2 Unmet expectations

"I thought I knew what I was going into."

The challenges of those choosing to discontinue treatment were largely connected to broken expectations, related to XR-NTX not working as expected, for instance regarding blocking opioids and reducing craving, but also disrupting daily life and rendering participants unrecognizable to themselves.

Participants described some disappointment in how the induction to treatment and further treatment was organized, contributing to a sense of distress and frustration. Lack of realistic information, as well as adequate follow up and the negative consequences this can have is emphasized by our findings. Overall, the detoxification and initial treatment phase was described as hard (I, II), in line with other research proposing the initiation to treatment to be the biggest obstacle to XR-NTX treatment (7). The lack of individual tailoring was especially emphasized, and it has previously been linked to less successful transition or detoxification (284). Patients in a previous study (198) who completed a successful induction to XR-NTX reported the environment during withdrawal to be supportive, with important aspects including caring staff and access to medications to ease pain and discomfort. This is in contrast to the experiences described by some participants in Study 2; despite completing detoxification, many reported not receiving the help they needed at the detoxification wards. It cannot be stressed enough that the induction and the first period of treatment is a vulnerable period for patients, where they should not be left on their own unless they specifically do not want any service involvement. Although detoxification fear (145) and worries of

tapering (285) is not unknown, and may have contributed to exacerbate the negative experiences of detoxification and induction, for some, especially those in Study 2, the reactions could be long lasting, prohibiting reorientation to a life in which the effects of opioids were blocked, as described by participants in Study 1.

Some participants reported that they did not experience XR-NTX blocking opioids, in particular buprenorphine. This contributed to some of the disappointment participants expressed, eliminating the premise and breaking the promise of XR-NTX treatment and further contributing to them ending treatment (II). This "non-blocking" is thoroughly discussed in Paper II. Overall, it may seem that the accounts of those in Study 2 were to a greater degree characterized by difficulties, in line with what has been proposed as missing in the CHIME-model (286).

5.2.3 Craving

"I couldn't think about anything else than opioids."

Craving is generally understood as "an intrusive and overwhelming strong desire or compulsion to use a drug because of the memory of the pleasant rewarding effects superimposed on a negative emotional state" (287, p. 1). Craving is thought to be central to the motivation in addiction (288), and strongly associated with the return to substance use (289), and it is also recognized as an important aspect of substance use diagnoses (8, 9). Our results further underline that craving is a subjective experience that varies between individuals.

Several participants in Study 2 reported not experiencing reduced craving, at odds with what participants expected, as well as previous research findings comparing XR-NTX with placebo or buprenorphine treatment (6, 168, 171). However, it is in line with a 9-month follow-up of patients in XR-NTX treatment, showing that those discontinuing treatment reported higher craving than those staying in treatment. While those in Study 1 reported, overall, not thinking about opioids, or thinking less about opioids because there was no point in thinking about them, many in Study 2 reported thinking about opioids "all the time," and felt that the reduction in craving was not "working as promised." While it may be difficult to explain this difference, biological differences in opioid and/or opioid blockade effect, and subsequent craving, (290, 291) or psychological mechanisms such as varying degrees of cognitive bias might be at play (292). As an example, greater attention to opioid-related cues among those with higher degrees of craving might again further amplify craving. Attentional bias for heroin cues has been demonstrated in people with OUD, and it is thought to represent a vulnerability to relapse to substance use (293). Individual differences in attention bias can also predict substance use (292, 294). The four trajectory groups differed in reported degree of

craving before treatment (Paper III). Thus, craving and how it is experienced are relevant factors in the treatment and recovery process.

While it is easy to (mis)understand the reduction in craving as something that the medication in itself provides, XR-NTX blocks the euphoric, and therefore *reinforcing,* effects of opioids. Conditioning plays an important role in the development of SUDs, and OUD, as the positive, euphoric effects of opioids act as a positive reinforcement for further use (295). Thus, the blocking of reinforcing effect plays a vital role in reducing craving; no reinforcement means an extinction of behavior, in line with reinforcement and operant conditioning models, postulating that drug-seeking behavior will cease (extinguish) if the use is not reinforced by euphoric drug effects (296). While it may be hypothesized that the "no-craving effect" thus will have to be connected to use of the substance with no subsequent effect, our results indicate that perhaps it is enough to *anticipate* that there will be no effect, as also participants who did not report "testing the blockade", experienced no craving. Patients' testing of whether the blockade really works is well known from previous studies (199, 297).

Our results indicate that an important reason XR-NTX is perceived as an effective treatment lies in the uncompromising belief that opioids will not work. This belief may in part be connected to people acknowledging they cannot resist opioids on their own: they need outside enforcement to remain abstinent. This lower self-efficacy might be what made them seek treatment in the first place, in line with findings showing that more hope, or higher self-efficacy beliefs, are connected to a lower probability one will seek treatment (269). Moreover, the detrimental and concerning consequences of experiencing an effect of opioids (buprenorphine) while on XR-NTX (II) are emphasized, as it reinforces further substance use and potentially undermines the usefulness of XR-NTX. This highlights an ethical dilemma, and raises a potential question; should people be told buprenorphine potentially will "work" for some? Not telling them is unethical; on the other hand, announcing such will perhaps undermine the potential benefit of treatment. Still, several participants in Study 2, in contrast to Study 1, reported knowing of the possibility of an effect of buprenorphine.

5.2.4 Substance use

"I know I like to escape from myself."

Regarding use of non-opioid substances there were variations: Some expressed wanting to end all substance use (a desire more prevalent among participants in Study 2), while others felt that recreational use was within their goal. In contrast to the widely accepted abstinence focus in OUD treatment, some suggest that the potential benefits of substance use should not be disregarded in treatment of SUDs (298). For some, these positive aspects are worth some continued use. Some

substance use has also been found to not be inconsistent with a recovery process for some people (299). The use of substances other than opioids and benzodiazepines prior to the start of treatment were not associated with further recovery (III) in our study.

While participants in Study 1 seemed to have a goal of opioid abstinence, participants in Study 2 instead saw absolute abstinence from all psychoactive substances as a prerequisite to achieve their goals. This seems to be in line with the varying goals people with OUD may have going into treatment. While frequent substance use is not uncommon in OAT (300, 301), and use of non-opioids seems to diminish to a lesser degree (148), non-opioid use is also shown to diminish over time (302). In a comparison of BUP-NX to XR-NTX, the latter has been shown to be associated with a greater decrease in use of opioids, but no differences in the use of other substances (6). The qualitative findings (I, II) provide some nuances.

Participants (I) reported an overall decrease in substance use, and the use of non-opioids was generally viewed as being harmless or recreational. This was in our studies however not true for all, and many participants in Study 2 as well as some in Study 1 reported a harmful and escalating use of non-opioids, which they conveyed could stand in the way of a further recovery process. This use can be understood as if one were unable to attain opioids, other substances might provide some of the sought effect, in line with the self-medication hypothesis (34). Furthermore, use of multiple substances may reflect different motivations and usages of substances, for instance social or event-specific use or use to enhance one's energy, to calm one or to counteract withdrawal from other substances (303, 304).

Increasing and harmful use of non-opioids carried progressive disadvantages similar to those the use of opioids had previously carried. While such use seemed in part to contribute to an increasing disappointment among participants in Study 2, participants in Study 1 still wanted to continue XR-NTX, underlining the strength of their hope. Regardless, escalating non-opioid substance use during XR-NTX treatment is a serious warning sign that a patient is struggling with opioid blockade, that additional measures are needed and that there is an increasing risk of discontinuation. Furthermore, such a use will complicate a patient's recovery process, raising the question of whether freedom from opioids may carry too great of a cost for some.

5.2.5 Emotional struggle

"All the emotions suddenly hit me like a train."

Our findings indicate that difficulties regulating emotional and mental health challenges play an important part in how XR-NTX treatment is coped with. Previous research has shown that addressing mental health problems in people with OUD increases the likelihood of a stable reduction in

substance use, as well as in the face of stressful events (305). In studies of XR-NTX, furthermore, mental distress has been highlighted as an important area of focus (306).

While a great benefit of XR-NTX was the safety regarding preventing relapse and the freedom from both opioid addiction and the OMT system, it could also have a cost, being experienced as a prison with no way to escape when escape was needed (I). Stress is linked to increased craving and substance use, and people using naltrexone might experience particular vulnerability in this regard (296). While opioids could not work as an escape, non-opioids could. The harmful and "out of hand" use of non-opioids that some described can, thus, be understood as an attempt to manage life difficulties or psychological or emotional challenges. This understanding aligns with an understanding of mental disorders or symptoms as attempts at solving difficulties (307), and that people use substances for a reason, for instance to self-medicate (34).

Emotion regulation plays an important part in SUDs. People with difficulties regulating emotions are more likely to use substances as a way to alleviate negative emotional states (308), and the use of substances may reinforce further use because the positive effects of substances also may distract from unpleasant emotions. People with SUDs have been shown to have greater difficulties with emotion regulation, and deficits in emotion regulation are associated with more severe substance use (309). Furthermore, substance use in itself can be understood as regulation of emotion (310). Emotion regulation is thought to be a cardinal, trans-diagnostic feature of mental disorders in general, including SUDs (311, 312). SUDs and mental health disorders have a high comorbidity (59, 313), and mental health disorders might contribute negatively to the course and treatment of OUD (314). Previous experiences of traumatic events or abuse are associated with OUD (315) as well as with persistent opioid use (49).

Psychological distress was high in the majority of participants, meaning above the cutoff for clinically significant distress (Paper III). The exploration of personal recovery (III) also highlights psychological distress as an important factor associated with further recovery trajectory. Most (84.1%) participants had previously been exposed to a traumatic event. The number is high, but in accordance to other literature (316, 317). There is also an association between emotion regulation and trauma (318). We do not know specifically whether participants (Paper I and II) had been diagnosed with a mental health condition, but some participants described that when mental health and functioning worsens or fluctuates, the need for escape is great. This illustrates the importance of understanding the reasons people use substances and the importance of supporting the development of alternative strategies. If a person's most common coping strategy is to use opioids, it is difficult for that person

to suddenly lack the opportunity, and for many, the "easiest" option is to find some other substance by which to escape.

Generally, coping strategies are understood as the efforts aimed to manage the internal or external demands of the person or of the environment (319). Coping strategies can be adaptive, characterized by engagement and dealing with stressors or emotions, or maladaptive, characterized by disengagement to avoid a situation or emotions (320). The use of substances is in itself sometimes considered a maladaptive coping strategy (321), or it can be the precursor to the development of SUDs. Furthermore, there seems to be a relationship between the use of adaptive coping strategies and lower substance use, whereas the use of adaptive strategies in general is lower among people with SUDs (322, 323, 324).

In Papers I and II, some participants reported increased symptoms of existing mental health challenges, such as PTSD or ADHD. Others on the other hand reported better emotional or mental health, e.g. connected to being able to feel and react "normally." The present research, thus, provides important nuances to previous findings of improved symptoms of anxiety, depression and insomnia (175) during XR-NTX treatment. While these previous findings are quantitative, our findings highlight individual differences.

Not all participants with underlying mental health conditions seemed to struggle. Participants in Studies 1 and 2 also reported that getting their emotions back had a positive aspect, namely being able to react or no longer feeling flat. Although the reasons some struggle while others do not are unclear, emotion regulation might be the underlying factor. As the focus in many mental health and SUD treatment approaches is emotion regulation strategies (325) the degree of difficulty with emotion regulation might connect, for example, to whether previous treatment is received and how well strategies for emotion regulation have been addressed.

To sum up, the treatment process was characterized by both difficulties and improvements, and pretreatment aspects such as patients' motivations and expectations are important to consider thoroughly before entering treatment. Benefits include changes in health, identity and meaning in life. The two main "obstacles" in treatment, namely substance use and emotion regulation, seem to be connected. Hope, a somewhat elusive concept is also a vital aspect of treatment.

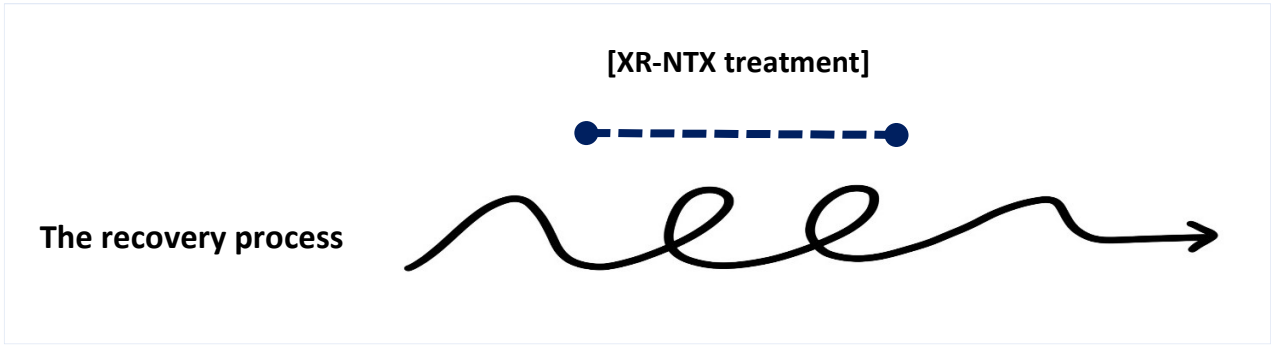
5.3 Ending treatment – but not an end to recovery

"The road continues..."

The descriptions from participants (I, II) highlight the difficulties and potential setbacks characterizing XR-NTX treatment, and the different trajectories leading to and from the treatment episode. Our

findings, thus, suggest that recovery is an ongoing, nonlinear process that extends beyond the present treatment period. Some described having been in treatment for many years, having achieved many improvements, while others described previously struggling or that the treatment previously available to them did not meet their preferences. Accounts illuminate that recovery did not start when entering XR-NTX treatment, neither did it end when the treatment ended, whether at the predetermined point or during the first three months. Recovery as an ongoing process is in line with conceptualizations of recovery in SUDs described in the introduction (see e.g. 77, 92), as well as the concept of personal recovery. The XR-NTX treatment process or episode may, thus, be understood as a part of a larger (personal) recovery process, as illustrated in figure 10. Several of the aspects central to the treatment process described above underline this point; people's motivations, hopes or underlying difficulties do not appear and disappear with the XR-NTX treatment episode.

Figure 10: Recovery as a non-linear, ongoing process, surpassing the treatment period



This point is further underlined by the findings in Paper III of varying, and for some, high recovery scores pre-treatment. Thus, for some, NTX may be a late step in the recovery process, already having made achievements in recovery; for others, it may be the opposite. This variation might be in line with the varying proportion of participants previously in OAT in the four trajectory groups. While both high and low OAT participation was associated with significant changes in recovery (both the low-increase [G1] and high-increase [G4] groups), the high-increase group (G4) with the highest recovery score initially had the highest OMT participation, at 90% in OMT prior to study participation. This result is in line with research showing OMT is associated with many improvements and increased functioning, as mentioned in the introduction. Furthermore, the number of total injections (meaning how long one stayed in the study), was not associated with group belonging. This would support the qualitative findings (II) that treatment discontinuation does not have to equal low or no recovery, and that how long one stays in XR-NTX treatment is not associated with belonging to, for example, the increase or no-increase groups in recovery.

Another important finding (Paper II) was that although participants chose to discontinue treatment, they did not let go of their goal of long-term abstinence. This may research showing that people require multiple treatment attempts, supporting the notion of viewing OUD as a long lasting condition (49). Some participants envisioned returning to XR-NTX again in the future, some foresaw going back to OAT for shorter or longer periods, and some felt they were "done" and had reached their goal of ending all opioid use. The latter view is in line with the findings of Velasquez et al. (199), and tied to a sense of feeling "cured." While such a belief was problematized by Velasquez et al. as a false belief in self-efficacy, it may as well be an expression of recovery, emphasizing the persons' individual process and preference. Our results thus underline that the individual motivations of people do not always match the predefined goals set by treatment providers, and participants' self-defined definitions of successful treatment are heterogeneous. This highlights the usefulness of a definition of recovery in line with personal recovery, as will be further discussed in section 6.4.

For some, XR-NTX treatment allowed for a clarification of goals or a reorientation, such as a reacceptance of OAT. While participants in both qualitative studies described avoiding or leaving OMT and opioid use as pivotal in their motivation for XR-NTX, participants who had discontinued treatment (II) experienced XR-NTX as having clarified their perspectives, for some meaning a reacceptance of OMT, either as a short term solution or as their end point in the recovery process, and involving a changing of goals. In contrast to other findings (199), the participants (Paper II) who chose to discontinue treatment did not state they discontinued treatment to return to illicit opioid use. Those staying in treatment, however, seemed to have an implicit understanding that the XR-NTX treatment would be their last treatment period, which for some might have contributed to a sense of hopelessness if the difficulties were great. Nevertheless, such an understanding did not mean the end of recovery, participants anticipated challenges lying ahead after the end of treatment, illustrating that recovery surpasses the treatment episode.

A conceptualization of recovery as ongoing and long-lasting emphasizes that treatment providers should not be so afraid of discontinuation. While we know that staying in treatment has positive correlates (80), we also know that a substantial proportion discontinue OUD treatment, whether OAT, XR-NTX or non-medical treatment (7, 49). The treatment systems need to be in tune with these realities, offering support for patients' needs during treatment and offering the opportunity for treatment when patients are ready for it. People's goals might not always overlap with the goals of treatment providers (259), with people seeking treatment to reach their goals, not to finish the treatment period per se. While the question of what makes someone "drop out" is an intuitive one, this thesis suggests it is perhaps not a useful one Furthermore, from a recovery-as-process perspective, whether treatment is successful or not does not depend on whether it is completed.

Rather, we should be asking what people hope to achieve, what they need to get there, and whether a given treatment can help them along the way. As such, the perspective of personal recovery is a useful one focusing on the individual lived experience.

5.4 Personal recovery

As elaborated in the background section, personal recovery is often contrasted with clinical recovery. While clinical recovery focuses on an outcome or an endpoint, personal recovery is an individual process, conceptualized through five factors: Connectedness, Hope, Identity, Meaning and Empowerment. The following will discuss how patients' experiences of XR-NTX treatment coincide with such a conceptualization of recovery.

In the SUD field, clinical recovery has been closely related to abstinence. As this research confirms, what XR-NTX in essence provides is in large connected to the concept of clinical (or objective) recovery. XR-NTX ensures abstinence, and through abstinence, people can achieve improvements in other areas. In line with such expectations, several studies (6, 168, 170, 171) have shown XR-NTX reduces use of opioids during treatment, and is associated with other measurable improvements, such as life satisfaction (278). However, as also underlined by this research, a sole focus on for instance reduced opioid use, disregards an important piece of information, namely peoples' experiences of OUD, treatment and recovery. The needs expressed by patients (e.g., for connections) further highlight the need for such a perspective.

While clinical recovery leans heavily on quantitative research, personal recovery is qualitative in nature, because it by definition is a subjective, unique process. In reality, we can access knowledge of personal recovery only via the person him or herself, as personal recovery per definition is unique and deeply personal. Thus while quantifying a subjective process can be complicated (109), resonating with some of the epistemological considerations raised regarding the use of mixed methods, I would argue that we need both qualitative and quantitative approaches to understand more about treatment and recovery, and that these approaches complement each other. The findings (Paper III) based on a quantitative measure of personal recovery, thus, add to the understanding of the personal recovery process during XR-NTX treatment.

Personal recovery contrasts the idea of a "hijacked brain" that has been used as a powerful image to explain the role the brain plays in addiction, as well as the brain disease model of addiction (33, 326). The analogy of hijacking implies someone coming from the outside, taking control by violent means and against one's will. While an understanding of the biological foundation of SUDs is important, and although the brain plays an important part in addiction, it does so in all aspects of our lives. The brain "controls everything," but we rarely question, for instance, whether a person chooses what to wear

or rather if their brain does. Seeing SUDs as a matter of choice has, however, been connected to seeing them as moral failings, putting the blame or responsibility on the person. Still, there seems to be a misconception that it has to be either-or: either choice or disease. As mentioned in the introduction, SUDs can be so much better understood in light of many perspectives. Thus they are both diseases of the brain, with social and psychologically foundations, and may even involve an element of choice, or agency. While I will not go further into the disease vs. choice debate, understanding medical diseases as affected by the choices the person makes is rather uncontroversial. The difficulty in the equation is that addictive substances constrict or limit the room for action. However, such a limitation does not entail a complete absence of room for action or choice. The perspective of personal recovery adds a dimension of agency, of hope and of empowerment, and it promotes the message that even if the brain is hijacked, there is a possibility to make the best of it.

5.4.1 The CHIME-model

As previously described, Leamy et al. (110) summarized the key components of personal recovery in the acronym CHIME: Connectedness, Hope, Identity, Meaning and Empowerment. How does experiences of the XR-NTX treatment process correspond with this? I would argue, based on the above discussion, some of the mechanisms by which XR-NTX furthers personal recovery arguably operate by promoting the CHIME factors. Furthermore, XR-NTX can indeed be understood in light of a personal recovery framework. As blocking the effect of opioids, and, thus, abstinence, is the main "function" of XR-NTX, and also understood by patients as the main mechanism, XR-NTX unarguably supports clinical recovery. However, is such an understanding sufficient in the understanding of XR-NTX treatment? What role may it play in recovery as a process?

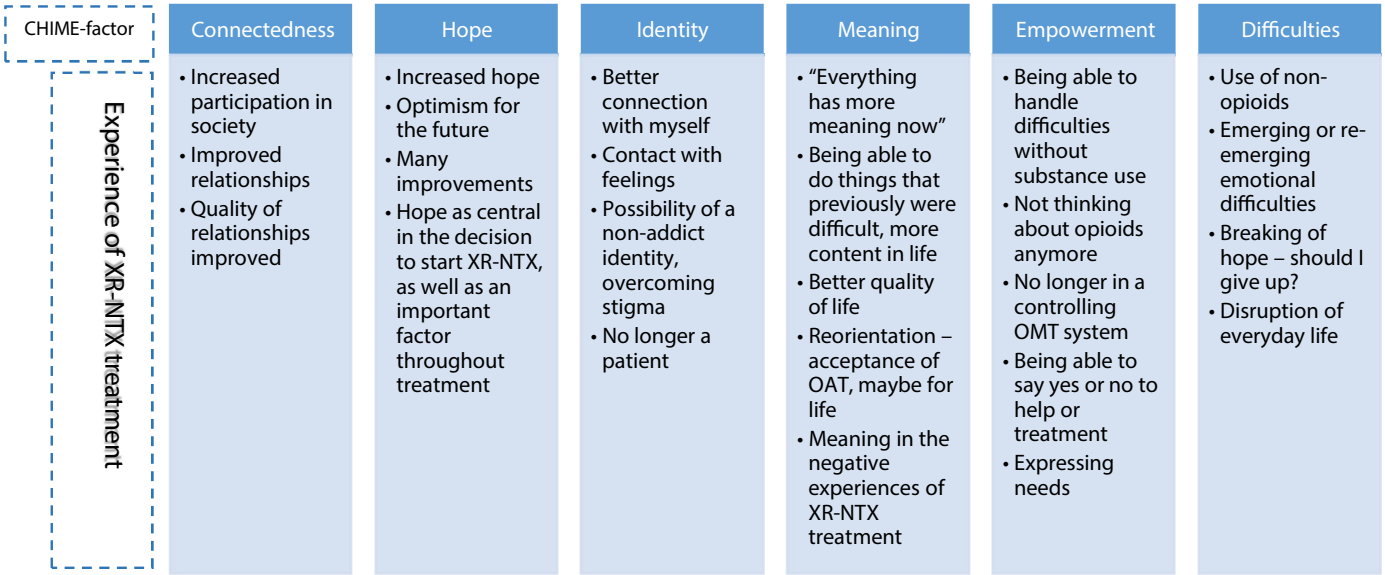
The CHIME framework seems applicable to the XR-NTX treatment setting because of the overlaps between mental health and SUDs previously described, as well as its focus on psychosocial recovery rather than strictly medical recovery. Several studies have examined how people with both substance use and mental health disorders experience recovery, and a 2017 review (112) showed the themes people with dual diagnosis see as important for their personal recovery in broad overlap with the themes identified in the CHIME framework (108). Furthermore, the domains of CHIME highlight what people with OUD or in OAT lack or need: connectedness, hope, identity, meaning and empowerment. In addition, the domains of the framework are broad and general, and they should be applicable across settings.

During treatment, patients experienced many changes due to the support XR-NTX provides in regard to ensuring abstinence from opioids one month at a time, including changes in identity, participation

in and contribution to society and community, increased hope and the experience of a meaningful life. Thus, the findings highlight factors outside of the mechanism of treatment (blocking of opioid receptors) as important to personal recovery. When relating the thesis findings to the CHIME framework, the findings align with the central factors of personal recovery (110). To aid the demonstration of these similarities, the findings interpreted in light of the CHIME framework are presented in figure 11. In addition, our findings show that the expanded framework, including difficulties (CHIME-D) (286), is also relevant to consider, as evident by the challenges patients faced during treatment. While it is relevant to ask whether the "difficulties" category can be understood as lack of Connectedness, Hope, Identity, Meaning in life, or Empowerment, difficulties were an important part of the process, warranting a separate category.

As we did not specifically ask about CHIME factors or have a personal recovery frame in the interviews, the results are solely data driven, and they suggest that the CHIME factors indeed feature in recovery in XR-NTX treatment.

Figure 11: CHIME-factors and their relations to patients' experiences (Paper I and II) of XR-NTX



A study (74) asking people with SUDs in self-defined recovery what recovery means to them found that most define recovery in terms of abstinence, but in line with our findings, also as a process of self-change and reclaiming of the self. Treatment represents only one of the paths to recovery (327). Research regarding SUDs and personal recovery specifically is limited, but one study examining personal recovery among members of Narcotics Anonymous (328) found connectedness to be a central aspect. While perhaps not dominant to XR-NTX treatment, as many other aspects were stated in our findings, connectedness still seems to play an important role, as highlighted by the possibility

of and improvements to social connections discussed previously. Dekkers et al. (328) argue that changes in identity, hope, meaning and empowerment can occur only through relations to others (i.e. connectedness). Another study (120) also focused on the role of community in the personal recovery process of young adults with SUDs, emphasizing the importance of community approaches in promoting personal recovery. This seemed less clear in our results. Moreover, while connectedness was important and while there is much to support that recovery *is* a relational process (121), some of the changes and processes for our participants seemed to occur on an individual level, for example in strengthened self-efficacy beliefs. This variation may be connected to XR-NTX as a treatment specifically helping to ensure abstinence and, through that mechanism, allowing people other improvements or letting them recognize what more they need. For participants, while abstinence was insufficient – and while treatment highlighted the need for "other things," such as someone" being there," in line with research highlighting the importance of other people in recovery (329) – XR-NTX was still what was emphasized as important and helpful to initiate or accelerate recovery, at least for participants staying in treatment (I).

5.4.2 XR-NTX and the process of personal recovery

As Study 3 shows, there are changes in personal recovery during XR-NTX treatment. While the study cannot make any causal inferences as will be further described in the next chapter, we can hypothesize that XR-NTX facilitates and contributes to personal recovery. This supposition is in line with findings of XR-NTX being associated with improvements such as in life satisfaction (278). Contrary to the findings in studies of how recovery in SUD can be understood, where better functioning typically occurs after longer periods of time (330), our qualitative findings indicate that for patients in XR-NTX, improved functioning can happen rather quickly, possibly because XR-NTX quickly reduces the harmful use of opioids. However, changes in personal recovery as measured by the QPR might require some time, as we did not find significant changes at three months.

We identified four distinct recovery trajectories for patients. This is in line with and underlines the argument made in the qualitative studies, namely that treatment trajectories are diverse and individual and that looking at subgroups and individual voices may bring new insights. Most of participants (the two no-change groups; G2 and G3) did not experience any increase in personal recovery during treatment. It is difficult to discern why, but it is possible that for some, the recovery process will require more time (331). Furthermore, for some people it might be more useful to consider particular subdomains of the QPR better aligned with personal goals than total QPR score (332). For two of the groups (the low-increase [G1] and high-increase [G4]) the increase in personal recovery was linear and significant. Both groups provided interesting insights. Despite initially considerably high QPR scores, the high-increase group (G4) experienced an increase in personal

recovery, indicating that people already in the process of recovery have something to gain by seeking XR-NTX. As previously mentioned, our findings demonstrate that G4 also had the highest proportion of OAT. While the association of OAT with high recovery scores is unsurprising, considering the benefits OAT can have in improving peoples' lives (80, 138), it also underlines that further recovery is possible, even for those with high recovery scores or already in OAT. In addition, those with the initially lowest recovery scores (the low-increase group, G1) and highest burden experienced the greatest increase in personal recovery, underlining that these patients also have much to gain by commencing XR-NTX treatment.

There are certain characteristics present before the start of XR-NTX treatment that are relevant for further recovery, underlining factors outside of XR-NTX as important for recovery trajectories. There were no differences in demographic factors between groups, meaning that age, education or gender, for instance, did not predict trajectory group. Participants in the low-increase group (G1), with the lowest QPR score initially, experienced a higher degree of burden; they experienced more psychological distress and pain, had lower life satisfaction and social support scores, were more likely to exhibit more heroin and benzodiazepine use and were less likely to be in OAT. The latter is in line with previous results from Norway; participants who were not in OMT before entering an XR-NTX study exhibited more severe addiction-related problems (333).

5.5 The needs of patients – suggesting a personal recovery perspective

"…I needed help, I needed everything. "

As has been discussed, the XR-NTX treatment process can be understood as a part of an overall process of personal recovery. Our findings (I, II) show that participants initially conceptualized stopping opioid use as "enough" to achieve their goals or recovery. While participants did not explicitly discuss recovery as such, aspects of their accounts and experiences align with a process more than they do with an end-point. As our results further emphasize, people in XR-NTX treatment need something in addition to the mediation itself, something more than abstinence via opioid blockade (i.e., something more than clinical recovery). Improvements in social relationships, changes in identity, and belonging and contribution to society were among the aspects emphasized as important to recovery. This is in line with a personal recovery perspective, as well as is supported by previous research (74, 92, 334).

During treatment, the needs of participants varied greatly, both between people and for a given person over time. This finding accords with notions of SUDs as heterogeneous, as presented in the background section. As previously mentioned, the need for realistic information prior to the start of treatment was emphasized. Furthermore, participants emphasized the need for healthcare,

preferably treatment of underlying mental health challenges. This need aligns with other research emphasizing the importance of treating concurrent mental problems when treating SUDs (49, 314), as well as the importance of mental health treatment for recovery to be successful (335). In OAT, lack of access to psychological support is seen as a barrier to clinical recovery (261). Some participants also emphasized the need for motivational help, emphasizing that blocking opioid receptors is not sufficient for patients to manage the psychological and motivational aspects of SUDs. This focal point would align with a developmental perspective of how new behaviors are learned, underlining the importance of not only "breaking the habit" of substance use, but also learning new habits or skills (28) (e.g., how to regulate emotions without substance use). While outside factors such as stable housing, economy and so forth have been emphasized as important in recovery or as an aspect of recovery capital (104), this was only infrequently mentioned by our participants. While this finding does not negate the importance of such factors, it could reflect the Norwegian welfare system which provides a minimum standard of living such as housing, benefit payments or free healthcare, so that participants to a lesser degree worried about such issues.

People who seek treatment might be characterized by greater vulnerability, including a greater degree of lifetime adversity, greater severity of use and more obstacles (336), which can also be described as less recovery capital (103), corresponding with the low-increase group (G1) (Paper III). Interestingly, participants in G1 had the greatest increase in personal recovery during treatment. Although we do not know whether and how these other factors changed, this group with the greatest vulnerability, or in other terms, the lowest recovery capital, seemed to benefit much from treatment in terms of personal recovery. Likewise, the group with the least vulnerability (the high-increase group, G4) also benefited significantly. These might represent two groups of patients requiring varying amounts of additional support. Drawing on White and Cloud's conceptualizations (103), not only problem severity (which traditionally has been the major consideration) but also degree of recovery capital (or vulnerability) should be regarded when considering treatment needs. Thus, a person with high problem severity but high recovery capital might need less treatment effort than someone with lower problem severity but little recovery capital (103).

5.5.1 A relational aspect

"Before I was just there, now I am with them"

In addition to the need for healthcare and structured psychosocial support related to the treatment itself, the need for relationships and support was apparent in participants' accounts, underlining the relational aspect of recovery (121). Participants emphasized needing others such as friends and family and that their connection with others was important. The findings (I) suggest there was a

changing in the *quality* of relationships, XR-NTX treatment enabled better connections with others. This also surpassed the aspect of receiving practical help and support (122), and although this was mentioned by some, participants stressed the importance of having someone there. Interestingly, and in line with findings that relationships may also frustrate recovery (123), participants in Studies 1 and 2 were hesitant to involve family and friends directly in the XR-NTX treatment. The reasons for this hesitance varied, but for some it seemed related to a wish for autonomy, for others not wanting to involve others in their struggle, or to disappoint them if struggling. While it is easy to appreciate the positive aspects of relationships for recovery, it might be worth considering the possible negative aspects relationships can have, as highlighted, for example, by a study of peer relationships in residential addiction treatment (337). In the study, interpersonal differences and negative role models undermined social capital. Moving away from substance-using peers can often be important in achieving abstinence and other improvements, and a history of associating with substance-using peers can be a risk factor for substance use (338). On the other hand, self-help groups are often an important component of SUD treatment, and many people struggling with SUDs express wanting support from peers sharing some of their experiences (282, 339), or even to be a source of support for others, as was also expressed by participants in our qualitative studies. Thus, for some patients, facilitating peer support will be an important part of treatment, and for some perhaps a starting point if family or friends are not, or are not wanted to be, involved in the treatment process.

Although definitions vary, social support can be conceptualized according to objective aspects of social networks, such as number of relationships, or functional aspects, such as the perceived availability of specific support (242). Social support is shown to positively impact overall wellbeing and both physical and psychological health (340), and has been shown to be related to recovery (341) and sustained abstinence (342). Low levels of social support are connected with higher levels of stigma (343). We measured perceived social support, and lower social support at baseline was associated with lower QPR score at baseline, regardless of subsequent development in personal recovery or lack thereof. However, perceived social support, although it varied between trajectory groups (Paper III), was for all groups above the "midpoint" at baseline, indicating that, overall, people had a perception of adequate social support prior to entering treatment. The relatively high social support scores might be understood in light of social/relational recovery capital (344); the participants in our study already had some social support in place. Social capital (i.e., relationships, employment, stable living arrangements, etc.) play a vital role in recovery and ending substance use (345). Still, at baseline, 30–50% (III) reported spending their leisure time mostly alone. Furthermore, neither how leisure time was spent nor any of the other social or relational variables (e.g., number of close relationships) differed between groups, warranting further exploration of these aspects.

6. METHODOLOGICAL CONSIDERATIONS

This section presents reflections on the thesis and the three studies' methodological strengths and limitations. In this regard, trustworthiness of the qualitative methods and the validity and reliability of the quantitative methods will be reviewed.

In general, ***validity*** concerns the soundness of the research design and the methods used. External validity, or ***generalizability,*** concerns whether findings are meaningful beyond the specific context or population of the study (346). ***Internal validity*** refers to whether the observed findings represent the truth in the studied population, rather than methodological errors (347), that is, whether the inferences made in a study are sound. ***Reliability*** refers to consistency and accuracy (i.e., whether results can be reproduced), and is often related to a measure (207). Generalizability, validity and reliability are traditionally tied to quantitative research. Thus the term ***trustworthiness*** was developed in qualitative research, covering many of the same issues as validity and reliability (348). Discussions of how to judge quality in mixed methods are relatively recent, and there are different approaches and a lack of consensus (207, 214). An important aspect is the critical appraisal of the individual qualitative and quantitative components (207).

In the following, I will first discuss certain general considerations related to the use of mixed methods. Then, using Guba's term of trustworthiness (348), I discuss issues specifically related to the qualitative studies. Issues related to the quantitative study will be discussed in terms of validity and reliability. Then, issues related to the thesis as a whole and mixing of the two (qualitative and quantitative methods, respectively) will be discussed. Finally, I will elaborate upon and discuss the influence of my background and preunderstanding of the research.

6.1 Mixed Methods: Utilizing strengths and weaknesses of qualitative and quantitative methods

Despite the lack of agreement as to how to assess quality in mixed methods research, knowledge of and rigorous use of both qualitative and quantitative methods is important (214), and the individual parts of mixed methods studies can be evaluated using criteria for qualitative and quantitative studies, respectively (207). Considerations related to the qualitative and quantitative methods used will be discussed in the following sections. Using mixed methods involves utilizing the strengths and weaknesses of each method; the mixing should result in "complementary strengths and non-overlapping weaknesses" (208, p. 19).

Qualitative designs can provide deepened insight and are rich in context, but they are not suited to generalize to a broader population, as quantitative methods are. While quantitative methods allow

for generalization to a broader context, they lack the insight into individual experiences and context that qualitative methods might offer (208). In this thesis, the qualitative studies provided rich and in-depth, contextual knowledge of how people may experience XR-NTX treatment and the paths that may lead to discontinuation, which would not be attainable through quantitative methods. In addition, I wanted specifically to investigate personal recovery, which had appeared as a potentially important concept in the interviews. The use of quantitative methods allowed for the investigation of changes in personal recovery across the group, rather than individual experiences, as well as associations between personal recovery and other factors across participants. The use of the QPR allowed for a deductive approach, addressing personal recovery directly, and asking a larger group of people the exact same questions. While this approach meant the loss of possibility of in-depth investigation on what might be important nuances, such nuances were present in the qualitative studies. Accordingly, mixed methods complement the strengths and compensate for the weaknesses of each of the methods used. Hence, mixed methods and can strengthen the overall validity or increase the credibility of the research, "because the product will be superior to mono-methods studies" (208).

6.2 Trustworthiness in the qualitative studies (1 and 2)

Different strategies to assess the quality of qualitative methods exist. Guba (348) has described four actions to increase trustworthiness: credibility, transferability, dependability, and confirmability, and these were followed in the qualitative studies. The following elaboration concerns Studies I and II.

6.2.1 Credibility

Credibility concerns confidence in the truth of data, and it was pursued by using open-ended questions, as well as by allowing participants to add to or expand any information regarding their experiences in the interviews. To ensure that participants could freely discuss any aspects of their experience, it was ensured that the interviews were not conducted by anyone involved in the recruitment or follow up of that particular participant in NaltRec, and at a sheltered place. This was done to enable the participants to freely discuss experiences related to the study or study personnel or to raise any concerns or dissatisfactions. All interviews were audio-recorded and transcribed verbatim. During analyses, interpretations were regularly discussed among the four researchers involved in the qualitative analyses, and they were tested against the interview material. There was an openness to alternative interpretations, and discussion continued until an agreement was made. One weakness, however, was that the study did not employ member checking. Member checking involves testing data, interpretations, conclusions, etc. with members of the group from which the data was originally obtained. This is a recommended and much used technique to establish credibility (348).

A further possible limitation is that follow-up interviews were not conducted, which could have safeguarded what is considered an important validation strategy in qualitative research (349), and would have allowed for increased credibility, for instance in that participants could elaborate or add to the initial interview, as well as elaborate on information given by others (member checking). However, the choice of one interview was also expected to provide sufficient in-depth exploration of each participant's experiences. In Study 1, we sought to interview participants at different times, ensuring variability in length of treatment and allowing for a longitudinal exploration of the experiences of treatment. Regarding the validity of retrospective data, we can assume that such longitudinal exploration might carry certain challenging aspects, such as those related to the possible stresses the participants experienced during the initial period of the trial, influencing what is emphasized or recalled. Further, we do not know whether participants in Study 1 stayed in treatment past the time of the interviews, and thus, whether their experiences might be more closely related to those of the participants in Paper II, even though all participants (I) identified as "in treatment" when interviewed. In Study 2, interviews were conducted over a wider range of time after the participants' final injection, thus, also potentially influencing recall of events or perspectives of XR-NTX.

6.2.2 Transferability

Transferability regards whether findings will be applicable in other contexts or groups. Thick descriptions, that is, rich contextual information, are a way to establish transferability (348). For this purpose, the provided descriptions were as rich as possible regarding the participants, the setting and the context of the studies in both the individual papers and this thesis. One such contextual information is the treatment of SUDs in Norway, as the treatment context of SUDs will differ between countries, and may thus influence transferability to a given context. Furthermore, rich descriptions of the study allow for transferability outside of the study, as they allow for judgments as to whether conclusions are transferable to other settings, times or people, outside that of the study. According to Guba (348), "one needs to know a great deal about both the transferring and receiving contexts" (p 81). Thus, the researcher of a study needs to provide sufficiently thick descriptions so that those who seek to transfer findings can judge the transferability. In my opinion, the provided information offers sufficient detail to enable one to judge whether the results will be transferable to a given context or not, and thus maintaining transferability.

6.2.3 Dependability

Dependability refers to consistency, showing that findings are consistent and can be repeated. Dependability was strengthened by using the same interview guide in both Studies 1 and 2. However, a possible threat to dependability was the use of several interviewers, which may have influenced the information brought forth by differences in interview styles, experiences or pre-understandings.

An in depth interview is not an objective event, and the information is created in the interaction between interviewer and respondent (350). Thus, each interviewer had their own contribution to the interview, and this contribution was not constant over interviews. In addition, the "quality of interview improves with the increasing skill of interviewer" (350), an effect that was perhaps minimized, as each interviewer did only a portion of the interviews. One possible limitation is, thus, that I conducted only some of the interviews in Study 1 and that I conducted none in Study 2. However, to counteract this, I listened to all interviews in Study 1, some in Study 2, and read all transcripts. Furthermore, several of the other researchers in the core research group performed interviews with both those staying and those discontinuing treatment. The use of content analysis, which is well suited for analysis of written material (249), was also chosen, such that the loss of sensory information in the interview situation would not be critical. A further possible weakness is the lack of any external audits, that is having researchers not involved in the studies examine the research process. Still, the possible threats mentioned should not make results unrepeatable, and are, thus, not a direct threat to dependability; rather, they are issues that may have influenced the data collection and that are important to recognize.

6.2.4 Confirmability

Confirmability relates to the objectivity of the researcher or the results, the degree of neutrality. Confirmability was sought by open and regular discussions of each researchers' preconceptions in the core research group. The investigators in this group had weekly meetings, which also encouraged reflection on how background and preconceptions could influence interpretations and understandings. Further, quotations were used to confirm categories, and to cover as many participants' experiences as possible. The findings in the two studies were compared, as well as with other relevant studies of recovery processes.

One way to establish confirmability is researcher reflexivity (348). In the thesis' preface, I have briefly described my background, and my preunderstanding will be further expanded upon in section 6.5, as this relates to the thesis as a whole. In the core-research group, biases and preconceptions were regularly discussed, as was the influence of different professional and personal backgrounds.

6.3 Validity and reliability of the quantitative study (3)

Study 3 sought to clarify whether there would be changes in personal recovery during XR-NTX treatment, if groups following distinct trajectories could be identified and, if so, whether baseline characteristics could predict group belonging.

Bias, which is to say, systematic errors that can occur at different points in the research process (351, 352), can contribute to results not corresponding with reality, skewing the data in a certain direction

(353). As such, they are important in assessing the soundness of research, and they threaten a study's validity. Bias can distort both the inferences made (internal validity) and their generalization (external validity) (353). Generalizability will be discussed in more detail in relation to the thesis as a whole (section 5.4.1).

6.3.1 Design

Study 3 has a longitudinal, observational, design. This design allowed for an examination of personal recovery over time, in a sample where this has not previously been studied. However, one limitation of such a design is that causal inferences cannot be made (e.g., regarding the changes in personal recovery). We found associations between certain characteristics and personal recovery, but we cannot determine whether these, or something else, causes such change. Further, as the factors associated with personal recovery were measured only at baseline, we do not know how the associated characteristics developed during the course of treatment and how this development could influence or be associated with the personal recovery process.

6.3.2 Recruitment and sample

Another issue relates to the sample (N= 135) in Study 3. As we wanted to investigate people in treatment, only 138 of the recruited 162 (to the NaltRec study) were relevant to the study. Further, three participants did not fill in the QPR at baseline, so were excluded from the analysis. We do not know why these 24 included in the NaltRec study chose not to start treatment after being included, although induction problems are well known (7), and neither why three participants did not fill in the QPR. These may represent a threat to the validity of Study 3, e.g. if there were systematic differences in personal recovery between these and those participating.

As described in section 3.6, the sample for Study 3 closely relates to the overall NaltRec sample. The overall group size was judged acceptable, given the design, and the goal of recruiting at least 150 participants in the overall NaltRec study was met. While "the statistical procedures underlying GMM are large sample techniques," there is no rule regarding sample size when performing GMM; rather, sample size should be evaluated in relation to the study in question (354). Since the two change-groups that emerged (Paper III) consisted of only 10 and 12 participants, respectively, it is possible that certain differences between groups were not identified (false negatives or type II errors) or that significant findings represented false positives (type I error) (355). One example is the variable "working last 4 weeks" – where only one participant in G1 had a positive response. The difference between G1 and the other groups, in particular G3 and G4, were not significant, although being larger percentwise than the significant difference between G2 and G3 and G4, respectively. This is likely due to low statistical power, meaning that the chances of detecting a true effect are reduced.

Low statistical power also increases the likelihood of type II errors, that is, false-negatives or failing to reject a false null hypothesis (356).

However, given the exploratory nature of Study 3, the analysis provided preliminary findings, hinting at possible patterns that may be interesting to examine further.

Selection towards treatment (selection bias)

The choice of study population is important especially for the generalizability of results to a context outside of the study, and the selection of participants can be influenced by various factors (357). In the NaltRec study – and thus Study 3, as well as Studies 1 and 2, further discussed in section 6.4.1 – participants were not randomly selected. The people choosing to participate can be characterized as a self-selected sample, in that they might, for example, be especially focused on recovery, motivated for XR-NTX treatment, willing to try a novel and less known treatment despite the availability of other treatment options, especially dissatisfied with OAT, or motivated in some other way. Furthermore, many participants were referred to the study by their treatment providers. There may have been some selection bias in that clinicians or treatment providers judged which patients to refer or recommend the treatment and study participation. Thus, it is possible some patients were recommended not to contact the study, or even did not receive information about it. The patients referred were both those judged to benefit from participation, as well as those who had tried "everything else," the latter implying that XR-NTX was proposed as a last resort. The aforementioned issues may all influence the generalizability of the study. Still, the generalizability to a similar context (people being able to choose XR-NTX treatment as one of many options for OUD) may not be problematic, as selection of treatment in the real world is never random, and thus paralleling selection in the overall study.

We lack information regarding the people who chose not to participate in the overall NaltRec study, and, thus, in Study 3. Such non-response can be a bias. To counteract any systematic reason that some people chose not to participate, it is recommended to increase the sample size (358). We initially planned to include 150 people in the NaltRec study, and included 162, which probably also increased the *N* for Study 3. However, as recruitment and participation were very close to a real-world setting, as previously described, non-response is probably not a threat to generalizability.

Attrition

Attrition bias refers to possible systematic differences between those who leave a study and those who continue (359). This is a possible bias in Study 3, and may have influenced findings, as we do not know whether there are any systematic differences between those discontinuing and those staying in treatment. Interestingly, the qualitative results (II) indicate discontinuation could both be linked to

a lower treatment effect and a high treatment effect. Discontinuation is not central in Study 3, and in the GMM, participants discontinuing are included until discontinuation, meaning that all available data points are included. The participants discontinuing, however, reduce the sample at certain time points, which influences the confidence interval, that is, the interval is wider than it would be if all were participating. A wide confidence interval can indicate that the sample was too small and that precise inferences cannot be made (360).

6.3.3 Data collection

Regarding the measurement of baseline characteristics, these might have been influenced by the current situation of each participant, for instance excitement to start a new treatment, intoxication or withdrawal influencing cognitive capacity.

Different clinician and staff were involved in filling out and completing questionnaires and interviews, and while questionnaires were mostly filled out by participants themselves, there could be variations in how much help participants needed (e.g., due to problems concentrating or reading), which may have influenced how questionnaires were filled out or understood. Inter-rater reliability was not examined, which is a limitation of the study. However, training was given on the instruments used if staff was not previously familiar with the use, and instructions on how to fill out was included in questionnaires. An advantage of using an electronic case report form (Viedoc) was that all answers were filled directly in, thus minimizing errors in the input, as well as in punching and regarding missing data. The limited amount of missing data minimize bias, thus strengthening the validity (358).

The impact of the global Covid-19 pandemic on the data collection also must be mentioned. During periods of lock-down, most data collection procedures and follow up were carried out by phone, with participants visits limited to receiving the injection of XR-NTX. In addition to the pandemic situation in general possibly affecting the experience of recovery for some participants, it may also have influenced how participants experienced XR-NTX treatment specifically, and possibly how long they stayed in the study.

Information bias

Information bias refers to bias related to systematic differences in the information in a study and occurs during data collection (351). While self-report measures are especially vulnerable for such bias, they also allow for the collection of more detailed information than, for example, biological measures or registry data. Information from self-reports regarding substance use has acceptable validity compared to biological measures (361, 362) and should, thus, not be problematic in this regard. A comparison made in the NaltRec study research group (unpublished material) furthermore

showed high overlap between urine drug tests and self-reports (between 99.4% and 93.6% overlap when looking at the different substances tested).

Recall bias, a type of information bias (363) pertaining to participants not remembering previous events accurately or omitting details (364), may have been an issue in both baseline interviews and subsequent visits. All measures used in Study 3 were based on patient reports, and the TFB method used may lead participants to under- or overestimate their substance use (365). This indicates that recall bias might have been at play. Furthermore, social desirability may have occurred, since the answers given may have been susceptible to participants answering or presenting themselves in a preferred way, or in a way they believed the interviewer would prefer (366). The risk of desirability bias increases with face-to-face interactions (367). Such biases and their potential effect on results are difficult to assess. While there are reasons the self-reports of people with SUDs may be inaccurate, such bias often relates to perceived negative consequences associated with reporting in a certain way, for example, cessation of treatment or legal action (361). We attempted to reduce such systematic bias in our study by underlining that no answers, including information of substance use, would influence participation or treatment, neither in the study nor in the regular treatment system.

Choice of covariates

While the chosen characteristics or baseline variables in Study 3 cover a wide area, there is a possibility that some important factor that would have differentiated between trajectories was overlooked and, thus, was not measured. For example, we had no useful or detailed measure of previous treatment experiences, type of treatment received (other than current OMT-status) or background variables other than those being included. As this study is explorative, the research group still found it valuable to carry out as described. Furthermore, the variables that were included were assessed relevant based upon clinical experiences.

6.3.4 Statistical analyses in an exploratory study

As Study 3 is an exploratory study, we did not test a specified hypothesis, but rather examined several possible associations, generating hypotheses. The results should therefore be interpreted cautiously and require further research. Furthermore, it is important to keep in mind that no adjustment for multiple testing was made. Multiple testing increases the risk of false positives (type I errors). However, adjusting for multiple testing is not necessary in exploratory research, and some even prefer exploratory study data to be analyzed without adjusting for multiple testing (368). Nevertheless, it is then important to recognize that any significant results are exploratory results and that adjustments have not been made. To confirm the results of Study 3, hypotheses will need to be tested in confirmatory studies.

6.3.5 Measurements – reliability and validity

Reliability concerns the consistency of a measure, while the validation of a measure ensures that it measures what it is supposed to measure (207).

All of the measures used in Study 3 were previously used and validated, with good psychometric properties, which I consider a strength. The validity, reliability and alpha scores of the included measures have been described in chapter 3. In the following, I discuss relevant issues regarding the measurements not already mentioned in section 3.7.2.

Since the internal consistency (alpha scores) of the measures was satisfactory, we did not carry out any psychometric evaluations. Furthermore, the main outcome variable of personal recovery (QPR) is translated to Norwegian (231), and has been used in Norway in mental health samples (369, 370, 371), where psychometric evaluations have shown a one-factor solution, with a Cronbach's alpha of 0.91 (370). Still, the QPR is, to our knowledge, not previously used, and thus not validated, in a SUD setting, meaning we cannot be sure the measure is meaningful or fully covers the concept of personal recovery in such a population. There are, however, arguments that the personal recovery concept, and the QPR, is meaningful in contexts outside of serious mental illness (328, 372). To sum up, the validation of the QPR in a SUD setting, and in a Norwegian setting, is necessary.

For the measure of life satisfaction (TSWL), the five "present items" were used; one of the three factors constituting the full scale (past, present, future) (245). The three factors constitute three correlated but discrete constructs (373). Utilizing only the present items might be a problem in judging the overall (temporal) satisfaction with life. However, the past and future items were developed from the present questions (374), and the five "present items" were taken from the original satisfaction with life scale, which consisted of these five present items (SWLS) (246). This scale has been shown to have a strong internal consistency and moderate temporal stability (Cronbach's alpha of 0.82) (246, 375).

For the Europ-ASI, many of the selected questions included were demographic (e.g., years of education, living arrangements and number of friends) or related to substance use. The ASI is widely used in SUD treatment and to assess substance use, and it is seen as a valid assessment tool (376). While some have taken a more critical stance towards the ASI (28), much of the critique is related to the use of composite scores, which were not employed in the current study.

Craving was measured with the single item "how much have you thought about getting high on heroin in the last month," indicated on a 0–10 scale. Although this single-item has previously been used to measure craving (225), it measures only the cognitive component of the experience. A

potential threat to construct validity could be whether "craving" is effectively operationalized and whether the question measures the concept as intended.

6.4 Considerations for the thesis as a whole – the mixed methods study

A minimum criteria suggested by Creswell and Plano Clark (214) includes the rigorous collection and analysis of both qualitative and quantitative data, intentionally integrating the two types of data, logical research designs and the framing of the procedures within theory and philosophy. These aspects have previously been expanded upon, both in this chapter and in chapter 3. However, concerning the last criterion of Creswell and Plano Cark, while the thesis study ***is*** framed within the philosophy of pragmatism, it is not framed in an overall theory. While I consider this thesis' focus on personal recovery to represent such a frame, the thesis is exploratory in nature, seeking to explore openly the treatment process and patients' experiences with treatment, and further restrictions in theoretical perspective, especially if predetermined, might have narrowed the focus too much.

The research group involved in the studies in this thesis have extensive experience with both qualitative and quantitative approaches, which made it feasible to include both approaches. I also took courses in qualitative, quantitative and mixed methods to ensure competence. One constraint of mixed methods has been linked to the cost and additional effort such an approach requires (207). My stance is that although the use of both qualitative and quantitative methods indeed involves additional time and effort, and despite that conducting a single-method study may have been less time consuming, the use of both qualitative and quantitative methods strengthens the relevance and validity of the overall thesis, contributing broader perspectives to the topic under study.

6.4.1 Relevance in a real world setting

The NaltRec study had a naturalistic design, which is a major strength for the thesis as a whole, because the context is close to a real-world setting, where patients can choose XR-NTX as one of many treatment options; accordingly, it is both transferable and generalizable beyond the setting of a clinical study. The group of patients seeking participation in the NaltRec study is likely relatable to patients seeking XR-NTX treatment in a real-world setting. The fact that patients were recruited from different parts of Norway, as well as from different sectors (in-patient, outpatient and municipal services), is also a strength, and increases the generalizability of the findings.

An inherent aspect of a naturalistic design is higher generalizability, at the cost of lower internal validity. The issue of internal validity versus generalizability is longstanding, and internal validity has traditionally been seen as the overriding goal, at least in experimental research. This tendency has been tied to the reasoning that if our inferences are not sound, why worry about generalizing the results. However, a different perspective may be, perhaps especially salient in light of the increasing

emphasis of evidence based practice, what is the point of sound inferences if they are not applicable to a real world setting (207), a view which I share. According to Polit and Beck (207), one solution to this conflict is "to emphasize one and sacrifice the other," (p. 221) as is the case in Study 3 and the thesis.

Being able to generalize findings to a population outside of the study sample is a critical concern for quantitative studies (207). Naturalistic studies have the advantage of mimicking real life, increasing generalizability, but at the cost of lower internal validity (377), because for example there is less control over factors than in an RCT such as few exclusion criteria, or less standardization and room for individual adjustments. In the overall NaltRec study, such adjustments could include that study personnel accommodated patients who were late or who could not attend visits within the visit windows or that participants during the study could obtain other treatment both in- and out-patient if needed. Participants "lived their lives," and there was little control over potential factors influencing the treatment situation, just as it would be in the real world.

Regarding generalization in qualitative research, qualitative researchers often prefer to use the term "transferability" (discussed above), stating that generalizations are not possible, as phenomena are time and context specific. Instead, transferability may be possible depending on the degree of similarity (348, 378, 379). As Gobo (378) writes, qualitative research does not aim to "generalize to some finite population, but to develop some theoretical ideas that will have general validity." Nevertheless, descriptions and knowledge of the context are relevant, and a real-world context would strengthen transferability beyond the study context.

While the overall findings in this thesis should be generalizable to similar settings, caution should still be taken regarding generalizability to the larger context of people with OUD, or other contexts, such as other countries, other SUD-groups or other treatments. The findings point to issues or areas of importance during XR-NTX treatment, and while they may be relevant to SUD-recovery in general, people receiving XR-NTX are probably distinct in that they are blocked from using their main substance (opioids), ensuring one less obstacle in the recovery process. I nevertheless believe the findings in this thesis are easily generalizable to a XR-NTX context, especially in Norway and similar countries. Generalizations to other countries will require more caution, as the treatment setting and people's reasons to pursue XR-NTX might differ substantially.

The issues related to the samples have been previously discussed and need to be considered when judging the generalizability and transferability of the thesis's findings. Relating to the qualitative samples, certain issues not previously discussed are worth mentioning here. Because recruitment was challenging, those who chose to participate in Study 2 might have to a greater degree have

reconciled with the resolution of their XR-NTX treatment process. Likely, people with more distressing outcomes (e.g., returning to illicit substance use) might have been impossible to reach or unwilling to participate. This may have skewed the information obtained in the study in a more positive direction. In Study 1, we do not know who the 10 participants choosing not to participate were and why they chose so. Perhaps they discontinued treatment, or perhaps their experiences would have been more negative than the experiences of those choosing to participate. However, one strength of Study 1 is that both those satisfied and those disappointed by treatment participated, nuancing the experience of the treatment process. On a general note, we cannot know whether important nuances in how treatment and recovery is experienced were missed. Nevertheless, this lack of certainty does not imply that the findings are not trustworthy. The fact that some experiences might be missed does not mean that the experiences obtained in the studies are not relevant or that transferability is weakened.

The use of a mixed-methods approach increases the overall generalizability of the research, not in the sense of statistical generalization, but what Yin (380) calls *analytic generalization.* While statistical generalization is tied to "postpositivist notions about the representativeness of a sample in characterizing a larger universe or population" (380, p. 656), analytic generalization concerns generalizability at a higher level of abstraction. That is, not whether a study's findings pertain "to a large number of like-venues but whether it has produced key ideas potentially applicable to a myriad of other situations" (Ibid.). I would argue that this is exactly what this thesis contributes: the specific factors relevant in treatment and recovery are not necessarily all relatable to a given context, but the underlying ideas and concretization of what may be relevant in a treatment and recovery process involving XR-NTX are probably applicable to "a myriad" of situations.

Gender balance

The fact that the overall NaltRec sample had a greater proportion of men compared to women (24% women) influenced the gender balance in the samples in the individual studies, especially Studies 1 and 3, as Study 2 had a particular focus on recruiting females. One explanation of the low number of women recruited may be that it reflects the actual gender distribution in OAT in Norway (160) and Europe (50). Gender bias might have been a particular issue in Study 3, where the proportion of females was too low to explore any gender differences and where a weakness might be less generalizability to females.

The qualitative studies employed a purposive sampling strategy, intending to "maximize the range of information uncovered" (348, p. 86). In Study 2, we succeeded in recruiting a large percentage of females, ensuring a wide range of information regarding the experiences of females. A previous

study showed that women face different challenges than do men in OUD treatment, for example related to mental health and stigma (381). It is, however, important to underline that gender was not specifically investigated in the qualitative studies. The gender proportions are, however, specified in the studies as well as in this thesis.

6.4.2 The mixed methods design and development across phases

This thesis had a partially mixed, sequential, equal status mixed methods design, as described in chapter 3. Some elaboration regarding design, especially time orientation, must be made. In the thesis, data were provided sequentially, with the qualitative studies followed by the quantitative. Usually, "sequential" implies that findings from one method (e.g., the qualitative) are used to develop the design of the following method, allowing the researcher to decide what more is needed to advance understanding based on the previous phase, or oppositely, that quantitative findings are explained or further expanded upon by subsequent qualitative research (206, 212). In this thesis, however, the development across phases can be questioned, partly attributed to the fact that the decision as to what quantitative data should be collected was already made, and started, before the qualitative study was initiated, thus limiting the possibilities for changes in design and data collection in the quantitative study. Thus, restrictions in data points and available data in the NaltRec study meant certain approaches were not possible. For instance, the idea to compare personal recovery among those staying in treatment with those discontinuing before three months was impossible due to an insufficient number of data points, those discontinuing only having baseline measures of recovery, for example. The qualitative studies still influenced some of the focus in the quantitative study by highlighting participants' process and aspects resonating with the concept of personal recovery, rather than other measures of recovery. As the questionnaire about the process of recovery (QPR) was among the quantitative measures already collected, and fit well with what we found in the qualitative studies, this was chosen as the focus for the quantitative study. As Polit and Beck (207) write, having a name for the design is of less importance than having a rationale for structuring the research process in a given way. When developing the rationale for this thesis, I started broadly, allowing for a wide, qualitative exploration of experiences of treatment. This development then lead to the need to expand my knowledge of the experiences of those discontinuing. Further, the two qualitative phases led to the need for a quantitative exploration of personal recovery. During the process, the overall aim was also adjusted accordingly, in interaction with the research. At the same time, the aim also influenced the choice of methods and focus. This illustrates the interactivity as well as the emergence of the design (216), allowing for a back-and-forth process whereby the aim was adjusted to fit with the three studies and vice versa. Together, the three studies and two perspectives allowed for an enhanced exploration of the thesis' main aim,

and I, thus, consider the mixed design a strength of this thesis. Furthermore, the transparency as to issues with the design, connected to conducting a mixed design within the limitations of a larger study, is a further strength of the thesis (e.g., of the choices made and the development across phases), and the interactivity somewhat resonates with pragmatism, in "doing what works."

However, the independence of the two strands can, in a sense, be an unutilized potential. Allowing for a greater degree of mixing in the data collection and interpretations – for example, by letting the qualitative findings steer what more data should be collected, by developing specific quantitative measures (e.g., a questionnaire), or by doing analysis simultaneously – might have allowed for a greater degree of mixing, strengthening the validity of the thesis. At the same time, this may have led to other limitations, such as validity or reliability issues with developing and using a new instrument. Nevertheless, the quantitative study was built on the previous qualitative studies, as the qualitative studies (I, II) guided which of the large pool of quantitative data to pursue further. While the quantitative data was collected throughout the collection and analysis of qualitative data, the *processing and analysis* of the quantitative data was not commenced before the qualitative phases were finished, as shown in figure 4 (data collection and analyses over time) in chapter 3. The use of quantitative data from a larger sample allowed us to reach all participants who had started XR-NTX treatment, focusing specifically on personal recovery. In addition, it enabled a greater degree of generalizability.

6.4.3 Samples

In line with my understanding of Creswell and Plano Clark (214), I would argue that a strength of this thesis is that the three samples are from the same overall study. All samples (I, II, III) are subsamples of the overall NaltRec sample, allowing for both comparisons and relations between results, and an understanding of the results within the same context. On the other hand, one could argue that the sampling from the same overall study context might be a limitation, in that the perspective is broadened neither beyond this particular setting nor beyond the participant's perspective. While the data included is both qualitative and quantitative, all the methods still investigate subjective phenomena.

6.4.4 The integration and the inferences

Viewing each study separately, the research simply involves using different methods. I will argue, however, that looking at the studies (I, II and III) together and as a whole, with the overarching focus on the treatment and recovery process, qualifies this thesis as mixed-methods research, whereby an integration has taken place. Furthermore, this integration has provided a more complete picture of the treatment and recovery process of people in XR-NTX treatment. When judging mixed methods

research, “there is a separate set of expectations for a mixed methods study beyond what is needed for quantitative and qualitative research” (214, p. 377). Much of this relates to how elements of the study fit together, and how the qualitative and the quantitative findings are integrated. As has previously been described, the overarching question in mixed methods studies is whether an integration of the qualitative and quantitative strands has occurred and contributed to strengthening the inferences about the studied phenomenon (207).

To be “truly mixed,” and not just “multiple methods,” the mixing must involve something *more* than using different methods. Aspects of this have been previously discussed and relate, in part, to the development across Studies 1, 2 and 3. Based on the need for further elaboration of patients’ experiences of treatment, Study 2 was included, focusing on experiences of discontinuation. The responses of Studies 1 and 2 contributed to the choice of focus in Study 3, suggesting the concept of personal recovery as meaningful and highlighting the need for a larger sample. In the integration, the findings from all phases are seen as one and related to each other. Table 6 and figure 9, in particular, provide an integration of findings and something “more” than what the individual studies provide on their own.

6.5 Preunderstanding and reflexive comments

In quantitative research, interviewer bias is thought to occur where the characteristics of the researcher (e.g., experience, personality, demographics) influence how participants respond. In this regard, I find useful the stance, taken from qualitative perspectives, that it is not a question of *whether* the researcher influences participant responses, but rather, *how* she influences it, and how this influence affects the research (e.g. validity of inferences) (216). In quantitative research, the threat is seen as lessened the more structured the interview is, as the interviewer is more likely to influence direction and to probe in an open interview and only minimally in self-administered questionnaires (207, 382). In the quantitative study, the use of different interviewers may have increased the impact of interviewer bias, as each interviewer influenced the interview situation uniquely. However, the use of multiple interviewers can, on the other hand, be thought to have reduced bias as long as different interviewers were biased in “different directions.” Nevertheless, the absence of interview data other that the ASI interview or MINI, and no use of unstructured interview data, as well as training on the different measures, minimized any such influence.

Preunderstanding and reflexivity are relevant terms in qualitative research (216). The influence of the researcher has been previously touched upon, and it is seen as important to reflect on during the research process. The goal in a qualitative study “is not to eliminate this influence, but to understand it and to use it productively” (216, p. 165). Thus, such an understanding can be an advantage in that

it can provide valuable knowledge, but on the other hand it can also lead to misinterpreting data and threaten the validity of qualitative conclusions if the researcher selects data that fit existing goals or preconceptions, or select data that "stand out" to her (216). When the researcher is able to take different perspectives, question preconceptions and offer different interpretations, this subjectivity is not necessarily a weakness, but can be a strength. I therefore find it useful to reflect on my background and preunderstanding. Certain related issues have been previously discussed (e.g., the importance of regular discussions with the researchers most involved in qualitative data collection and analysis).

Preunderstanding

Substance use disorders, opioid use disorders and their treatment, as well as reflections concerning addiction and recovery as phenomena, are themes and fields of which I have knowledge from a professional standpoint. As a psychologist working with SUDs for the five years previous to starting the work within the thesis, and working with mental health issues for several years prior, I have an understanding of the field as a whole, treatment options, the difficulties and challenges people with SUDs may face and exemplifications of peoples' process of change. From my work, where I have met numerous people with SUDs, their families and other professional network, I have knowledge of the lives of people struggling with addiction and the variations in circumstances and conditions that can exist, as well as possible thought processes regarding change, quitting drugs and resisting cravings. Being a therapist to people in OAT has given me insight into how the restrictions and control measures can be experiences on one hand, but on the other, the circumstantial necessity of such measures.

On a more general basis, through my overall working experience, I have seen the resilience and strength that can exist in people, but also how dark life can be. I have a strong belief in people and tend to emphasize resources and strengths, rather than pathology. For people with SUDs, I have been concerned with the need for psychological treatment and the importance of recognizing the co-occurrence of SUDs and mental health disorders. The importance of factors outside of treatment, such as relationships, living conditions or meaningful activities, have also been repeatedly underlined to me through my work, and thus something I see as vital for people to be able to instigate change.

Self-reflection about how my preunderstanding influences the research has been an important part of the process. Furthermore, I have made an effort to make my preunderstanding a valuable resource rather than a blind spot, leading me to misunderstand, not see things that are there or see things that are not there. During my work with the thesis, especially in the qualitative studies (I, II) and in the analysis and understanding of findings, I have regularly discussed findings and

interpretations with supervisors and other colleagues. The research team was from different disciplines (medicine, social work, nursing and psychology), such that issues related to preconceptions, both my own and others', have been reflected upon in relation to the material. Different perspectives have also helped to identify or clarify perspectives (e.g., in why I understood findings as I did).

During the PhD-period, I had a combined position (75–25%) working both as a PhD-student and as a clinical psychologist at the outpatient clinic in which I had previously worked full-time. Working in both research and the clinic during the work with this thesis had both advantages and disadvantages. On one hand, it was very useful for the background of the study, and it enabled me to see findings in a larger context and relate them both to SUDs in general and to the experiences of people in OAT. I also had access to the different perspectives of patients in OAT, therapists and other treatment staff and the general attitudes in the field. This may have contributed to strengthening the relevance of the research and linking it to actual issues or needs in the field. However, it could also be challenging occupying the positions as clinician and researcher or trying to shift positions. This could be especially challenging when asked, for example, to talk to people at my clinic about the study, or in making sure interviews did not take the form of therapeutic conversations.

It is also worth keeping in mind the participants also may have their own preconceptions of how the interview will proceed, as well as differing positions (e.g. that of a patient vs. that of one contributing to knowledge creation). The fact that qualitative interviews were conducted at the study site, where participants also received injections, may have contributed to enforcing the "patient position." Furthermore, the place where the qualitative interviews took place was in many cases also the same place where the quantitative data collection took place. As the quantitative data collection was characterized by seeking short and concrete answers, sometimes even having to stop participants from sharing further reflections, it may have influenced patients' preconceptions of the qualitative interview situation.

Reflexivity

Reflexivity may be understood as a self-awareness of how the researcher influences the research process, a sort of self-appraisal or self-critique. In qualitative studies, it is viewed as a means to add credibility to the research (383). Although I did not keep a journal during the whole research process as have been recommend (348), I tended to write down occasional notes and reflections, discuss with supervisors and engage in continuous internal reflection on how my background and preconceptions influenced the research process.

As previously mentioned, excluding preunderstanding from the research process is impossible. Thus, the reflections on my own preconceptions are important to clarify my preunderstanding. In the following, I attempt to reflect on and exemplify some of these preconceptions, as well as how they may have influenced the research process.

A closeness to the studied phenomena was inevitable, as I have studied the field I previously was working in, from which I have an extensive experience. With regard to my own preunderstanding, I entered the study with previous knowledge of the patient group. Treatment of SUDs and OUD, recovery and treatment processes were issues I was familiar with beforehand and probably also contributed to my interest in the topic. Furthermore, my clinical background likely contributed to the aspiration to make the research clinically relevant and as close to reality as possible. In this regard, the naturalistic design of the overall study was a good fit. From working with the group of people with SUDs, their experiences, needs and challenges has been something that engages me, and contributed to the study being a source of continuous inspiration and engagement. I believe this preunderstanding to be strength in that it enabled me to understand the complexity of the studied phenomena. Not understanding too fast, and taking a position of non-expert was also a stance I had with me from my clinical work, which I believe was an advantage in the research.

An important question was whether my professional background could have affected how and what participants chose to share in the interview and if it may have made me "too familiar" with the field. I believe my background may have contributed to facilitating good conversations, and it may be an advantage in that I am familiar with talking about difficult topics with people, or understand aspects of the "drug using life." However, my previous experience is with clinical, therapeutic conversations, which may be similar, but still different from research interviews. I had to be aware not to ask participants to disclose more than was needed within the context of the interview scope, as well as to try to avoid adopting the position of therapist or helper, not getting "too close" or understanding too quickly. In this regard Moen and Middelthon (209) have developed the term "productive distance" which I found useful – that is the need to keep both a distance and a proximity to what is studied to be able to understand fully.

Regarding my experience within the field, I initially saw it as almost exclusively positive, helping me understanding the context quickly and enabling me to relate to and understand patients' experiences and difficulties. However, upon reflection, I also understood my preconceptions could steer what I saw or emphasized in the material, for example noticing or emphasizing participants' narratives that were closer to those I had previously heard through my work, emphasizing mental health or psychological processes. In the interviews, my background probably influenced the questions I asked

and the answers I expected. For example there can be a risk of thinking I understand because I have "heard it before," which can stand in the way of real understanding or capturing unique experiences, or may mean some issues remain underexplored.

To counteract this possibility, I made an effort to notice the instances in which I was surprised, as this may indicate preconceptions being challenged. For example, when the first participant I interviewed told me he did not find being blocked difficult at all, I was surprised and devoted some time to try to understand this. My preconception was that being blocked would surely be difficult, maybe even unbearable, and his experience was at odds with this expectation. It was also important to me to foster an attitude of openness and curiosity, noticing experiences different to those I had previously encountered in the clinic. The use of follow-up questions, as well as asking whether I had understood correctly, or relating how I had understood something was also important in the interview setting. When working with the material (e.g., listening to recordings or reading transcripts), I made conscious efforts to be conscious of my preunderstanding and background and their influence on how the material was interpreted. I also checked categories against the material as a whole and discussed interpretations or categorizations with the other researchers involved. Furthermore, the experiences of those struggling are more emotional and evocative than those expressing "everything is OK," and perhaps closer to what patients' tend to bring to a therapist (or what a therapist might find interesting), which made me conscious to the importance of emphasizing both sides.

7. CONCLUSIONS AND IMPLICATIONS

7.1 Concluding remarks

Overall, this thesis aimed to better understand the treatment and recovery process of people with OUD in XR-NTX treatment, specifically to illuminate central aspects of these processes. This aim was based on a lack of knowledge of patients' experiences of XR-NTX treatment, expanding the understanding of treatment and recovery in XR-NTX beyond a conceptualization of recovery emphasizing abstinence (clinical recovery), which has been central in previous research. The thesis has shown that XR-NTX treatment may be life changing, but at the same time involves serious challenges that will need to be taken into consideration, and that people will need various, individualized support (I, II). Personal recovery increased during a year of XR-NTX treatment (III), and followed distinct trajectories highlighting a heterogeneity among participants and in recovery. Factors such as benzodiazepine use, psychological distress or social support before the start of XR-NTX treatment may be especially relevant for subsequent recovery, and clinicians should map these. Together the results of the thesis give an increased understanding of the XR-NTX treatment process.

A conceptualization of recovery as personal recovery fits well with participants' experiences (I), but a focus on difficulties in addition to changes in connectedness, hope, identity, meaning and empowerment (CHIME) may be necessary to capture the whole picture (I, II). The experiences of those choosing to discontinue treatment were characterized by disappointment, unmet needs and unfulfilled expectations, and XR-NTX not supporting their goals (II). Nevertheless, a discontinuation of XR-NTX treatment did not mean a discontinuation of recovery goals, highlighting recovery as an ongoing process transcending the current treatment episode. Thus, whether patients continue or discontinue treatment per se is less vital, as the process continues regardless. People might need longer or shorter times than a year on XR-NTX, or several treatment episodes. While the need for individualized length related to prolonging treatment was emphasized in Paper I, Paper II emphasized that for some, treatment can, or should, be short. In Paper III, we showed that the longer people were in treatment, the more their recovery score increased. All these eventualities should be considered, and treatment tailored to individual needs. Some might be close to their recovery plateau after a year, while others might still have much to benefit from continuing treatment, in terms of personal recovery. Others may not experience any increase in personal recovery, and for some, leaving treatment might be the right thing to do.

Abstinence and discontinuation of opioids (i.e., clinical recovery) was the implied premise of XR-NTX, as well as peoples' explicit motivation for choosing this treatment. However, the experiences of participants highlight that while abstinence from opioids is what is initially sought, it is not sufficient,

as is apparent from the needs surfacing during treatment. Being abstinent (or blocked from using the drug of choice) may enable people to initiate change, yet recovery is experienced more as a process than as a measurable endpoint. XR-NTX in itself does not equal recovery, but it may enable the process of recovery. Furthermore, there is no single path to recovery. The recovery process is unique and personal, and thus highly heterogeneous in that people may take different paths and need different support. While “all roads may lead to Rome” (i.e., recovery), peoples' journeys are unique, and each pathway will be different, as is the destination of the journey.

The use of a mixed-methods approach provides insights into the recovery process during XR-NTX treatment, and offers a comprehensive picture of XR-NTX treatment, focusing on aspects and issues of this treatment previously not explored. As the qualitative and the quantitative parts counterbalance and corroborate one another, the overall validity of results is strengthened. The naturalistic design ensures findings are highly clinically relevant, at least should XR-NTX be offered as a regular treatment in Norway. In such a case, insights from the thesis will be important in implementing and planning XR-NTX as a treatment option, which will be further discussed in the following section.

7.2 Implications

Should XR-NTX be made available in Norway?

This thesis offers insights relevant to the implementation of XR-NTX as a treatment for OUD. For many, existing available treatments are not in line with their goals, nor with further recovery. While there are also serious challenges surfacing during XR-NTX treatment, the findings of this thesis support a recommendation to implement XR-NTX in Norway. For potential patients, XR-NTX represents something contrasting other available treatments such as OAT, and as such brings hope of a different and improved life.

While our findings indicate that XR-NTX may not be feasible for *all* patients with OUD, it can easily be argued it is important to have a variety of treatment options for people with OUD. Even though only a small number should want XR-NTX, it remains relevant as a treatment option, and it can importantly impact the lives of those choosing it. For some, XR-NTX is just what they want, and need, to improve their life and advance recovery. The naturalistic nature of the overall NaltRec study also means there was no selection other than a self-selection and that XR-NTX was of interest for the people participating in the study and, thus, relevant in a real-life setting.

Looking at OUD treatment and recovery in OUD as a continuous, lasting process, not constricted to a specific treatment episode, XR-NTX might have an important function at different times during this process. As findings underline, the recovery process of people is not linear, and several treatment

episodes with different treatment modalities will for many be part of the process. A treatment episode with XR-NTX may be just what is needed for a person to realize the need for OAT, or OAT might be a useful precondition for XR-NTX, facilitating the usefulness of XR-NTX. Thus both policy makers and service providers need to see treatment of OUD not in terms of individual treatment episodes, but in light of recovery as an ongoing, long-lasting process.

How should XR-NTX be delivered? Implication for services and clinicians

This research indicates the motivation, goals and preferences of patients are important to consider when choosing or proposing XR-NTX as a treatment, as well as during the course of treatment. This is in line with both personal recovery and a patient-centered approach. Patients' goals need to be included as an integral part of treatment, and should be an important area of focus. Furthermore, as this research shows, although goals might be or seem clear when entering treatment, they can change, and clinicians should be sensitive to such. This includes when such goals are in contrast to treatment providers' goals.

A number of pretreatment variables are associated with subsequent recovery trajectory (e.g., mental distress, social support, craving or use of benzodiazepines). When considering treatment with XR-NTX, it can be useful for clinicians to be aware of and assess these before treatment, as they might be associated with further recovery (trajectory). Clinical awareness of such factors will be important to monitor and facilitate further successful personal recovery. Furthermore, both those with a high level of burden or vulnerability (e.g. high psychological distress, pain, lower social support etc.) and those already in a recovery process (high initial QPR score) or with low burden (lower psychological distress, lower benzodiazepine use, etc.) may have much to gain by commencing XR-NTX in terms of personal recovery.

When planning treatment, it is vital that patients receive adequate and realistic information, and sufficient time to make up their mind as to whether XR-NTX is something they want to attempt. Rushing patients into making the decision is counterproductive, as is a rushed tapering of opioids prior to the start of treatment. The seriousness of OUD makes it easy to understand patients' anticipation of XR-NTX being able to change their lives. Addressing patient motivation, as well as the underlying reasons for a motivation to start XR-NTX together with expectations related to the treatment will also be beneficial.

The induction to treatment and the first weeks of treatment are a period of great vulnerability for patients, and clinicians and services will need to offer increased support and help. A detailed treatment plan might be advisable. Patients will also need to be informed that the first few weeks may be especially difficult, so that they are prepared.

Treatment with XR-NTX needs to be followed by psychosocial interventions. During treatment, attention to mental health and substance use, both opioid and non-opioid, is important, and it can be a sign of a patient struggling, needing reinforced help. As different patients will experience treatment differently, addressing the varied and diverse challenges patients will face is vital. Regardless, both follow-up and social support are important during treatment, as summarized concisely and articulately by one of the participants of Study 1 (not included in Paper I):

> It's extremely important with the follow-up services around you, it really is. I think there are very few people who will make it without having any more follow-up than just getting the injection once a month, and no other follow-up.

Such help may include therapy, motivational support, or health care targeted at emerging pain or sleep disturbances, or other difficulties. Support outside of the treatment setting is also important, and although it in many instances will include family or friends, many will not want to involve them directly in the treatment. As such, peers with personal experience with XR-NTX treatment are important, both as a source of support and as an opportunity for patients to matter to others. Clinicians and treatment systems can, and should, facilitate such peer support, such as by establishing peer support groups, which may be particularly important in the context of XR-NTX treatment.

While previous research has noted a lack of a recommended duration of treatment, the findings in this thesis emphasize that treatment length will need to be individually adapted to patient needs. Furthermore, findings highlight the diversity of treatment trajectories and that treatment needs to be individualized, and comprehensive, where different treatment modalities can be tried at different times, as well as repeatedly. Moreover, treatment systems need to be accepting of patients not completing treatment, because some will want to discontinue early, and probably rightly so. However, systems should facilitate and nurture hope and provide and facilitate help and support so that people do not discontinue for reasons such as lack of support or a deteriorating situation.

7.3 Recommendations for future research

This thesis has contributed knowledge on the treatment and recovery process of people in XR-NTX treatment, and what may be of importance during treatment. Thus, the findings are relevant should XR-NTX treatment be implemented in the regular treatment system in Norway. In such a case, implementation research will be vital. As described in the previous section, patients will need more than just the injection, and an investigation of, for example, the importance of different additional measures and their influence on treatment will be important.

Future studies should consider the outcome in XR-NTX treatment not only in terms of clinical recovery (i.e., reduced opioid use), but also in terms of the recovery process happening during treatment. There have been some previous recommendations of what outcomes to emphasize in SUDs (e.g., social relations, psychological and physical health, and life satisfaction). Although the CHIME framework provides useful insights into the understanding of the process of recovery and can be used as a lens to understand the experiences of patients in XR-NTX treatment, the framework is not directly transferable to a SUD setting. While abstinence is seen as an important aspect of recovery in OUD, it is not a part of the CHIME model. As such, the question of how personal recovery best can be understood and measured in the SUD field remains. In addition, this thesis shows that there is a need for further exploration of the use of the CHIME framework and the instrument QPR in the SUD field.

While participants' experiences, as described, correspond with a personal recovery conceptualization, the QPR has not previously been validated in Norway, nor in a SUD setting. Thus, should this measure be used, there is a need for validation. Further research of the use of QPR in a SUD setting is also important. For example, comparing the QPR with existing measures of recovery in SUDs might be useful. Furthermore, qualitatively exploring the trajectories found in Study 3, as well as deductively investigating personal recovery in a qualitative sample might offer some further nuances.

There is a further need for comprehensive studies examining courses of OUD treatment as they occur in the real world. Focusing on those discontinuing treatment versus those staying in treatment may not always be useful in tailoring treatment to patients. Those discontinuing may do so because the treatment is not a good fit, or because they are, or feel, cured, and discontinuation needs to be seen as not a failure. However, a comprehensive study of the first three months of XR-NTX treatment and the reasons to discontinue treatment and associations with other parameters may still be useful. We were not able to compare those discontinuing treatment with those staying in treatment because of few data points for those discontinuing.

Longitudinal studies allowing for the investigation of the relationship between personal recovery and factors such as psychological distress, life satisfaction and social support or other covariates are needed, exploring how they develop during treatment and predict recovery, as are longitudinal examinations of overall treatment trajectories and the role of XR-NTX within them. The role of emotion regulation and mental health in XR-NTX treatment remains to be examined, along with how it contributes to the course of treatment. Another interesting issue is that of opioid effect during XR-NTX treatment, indicated in the qualitative Study 2, which needs to be further examined. More

knowledge of how patients experience and understand craving, as well as the mechanisms of changes in craving during XR-NTX treatment are also needed. Further examination of the role of social capital and relationships may also be warranted, and other measures than social support may need to be employed.

An in-depth qualitative investigation of patients' experiences after ending treatment with XR-NTX might offer further valuable insights into longer term trajectories, as well as experiences of patients after ending treatment. An important question that remains to be answered is whether improvements gained during treatment remain after treatment end, as well as how patients think about and experience "life after XR-NTX" and what their needs after ending treatment might be. Other research suggests relapse to opioid use is a common occurrence after ending treatment, which would support longitudinal investigations of treatment trajectories. We do not know whether any achieved improvements will last after treatment completion, and while our findings may lead to hypothesize that this is the case, neither do we know to what degree patients after XR-NTX relapse to opioid use, sustain abstinence or return to OAT.

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Papers I-III

I

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RESEARCH Open Access

Patients' experiences of continued treatment with extended-release naltrexone: a Norwegian qualitative study

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Abstract

Background: The opioid antagonist extended-release naltrexone (XR-NTX) in the treatment of opioid use disorder (OUD) is effective in terms of safety, abstinence from opioid use and retention in treatment. However, it is unclear how patients experience and adjust to losing the possibility of achieving an opioid effect. This qualitative study is the first to explore how people with opioid dependence experience XR-NTX treatment, focusing on the process of treatment over time.

Methods: Using a purposive sampling strategy, semi-structured interviews were undertaken with 19 persons with opioid use disorder (15 men, four women, 22–55 years of age) participating in a clinical trial of XR-NTX in Norway. The interviewees had received at least three XR-NTX injections. Qualitative content analysis with an inductive approach was used.

Findings: Participants described that XR-NTX treatment had many advantages. However they still faced multiple challenges, some of which they were not prepared for. Having to find a new foothold and adapt to no longer gaining an effect from opioids due to the antagonist medication was challenging. This was especially true for those struggling emotionally and transitioning into the harmful use of non-opioid substances. Additional support was considered crucial. Even so, the treatment led to an opportunity to participate in society and reclaim identity. Participants had strong goals for the future and described that XR-NTX enabled a more meaningful life. Expectations of a better life could however turn into broken hopes. Although participants were largely optimistic about the future, thinking about the end of treatment could cause apprehension.

Conclusions: XR-NTX treatment offers freedom from opioids and can facilitate the recovery process for people with OUD. However, our findings also highlight several challenges associated with XR-NTX treatment, emphasizing the importance of monitoring emotional difficulties and increase of non-opioid substances during treatment. As opioid abstinence in itself does not necessarily equal recovery, our findings underscore the importance of seeing XR-NTX as part of a comprehensive, individualized treatment approach.

Trial registration: Clinicaltrials.gov # NCT03647774, first Registered: Aug 28, 2018.

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Keywords: Extended-release naltrexone, Opioids, Opioid use disorder, Treatment of opioid dependence, Recovery, Qualitative, Patient experience

Background

The opioid antagonist extended-release naltrexone (XR-NTX) blocks the effects of opioids and is a promising, safe and effective [1], treatment for patients with opioid use disorder (OUD) [2–4]. By its long-acting effect it offers an opportunity for persistent abstinence from all opioids, including agonist medication prescribed through opioid treatment programs (OTPs). OUD is a chronic, relapsing disorder with serious consequences for the individual, their families and society, and illicit opioid use is a major global public health problem, taking an ever-increasing number of lives annually [5–8]. Despite promising results from clinical trials, many patients choose to discontinue XR-NTX treatment prematurely [9, 10], which may somewhat limit the clinical usefulness. Relatedly, the question regarding what patients need to be able to continue treatment and stay abstinent, in addition to being blocked in itself, remains unexplored. Such knowledge is crucial to tailor treatment and reach more people with OUD, and thus prevent the harmful effects of opioid addiction for the individual, family, and society. Many individuals with substance use disorders (SUD), hereunder OUD, use the substance as a means to escape reality and regulate emotions [11], underlining the importance of understanding how patients adjust to having the effects of opioids blocked.

Traditionally, recovery from OUD has been understood as abstinence [12], but likely also involves something beyond mere abstinence, such as improvements in health and wellness [13]. Achieving long-term abstinence from opioids can require both time and multiple efforts [14–16], highlighting the complex nature of opioid dependence and the importance of effective treatments. Medication for opioid use disorder (MOUD), with the opioid agonists buprenorphine or methadone, has long been the recommended treatment for opioid use disorders by the World Health Organization [17], and has been shown to reduce illicit opioid use, prevent relapse and reduce mortality [18–21]. In Norway the medical treatment of OUD is organized in an OTP system, overseeing treatment with opioid agonists, most commonly buprenorphine or methadone. Opioid antagonist treatment is currently not available except in clinical trials. Generally, and especially for young people, agonist medication is not the first choice of treatment for OUD in Norway, unless professionals judge it to be the most suitable and safe option [22]. In addition to MOUD, non-medication treatment for OUD is also available, e.g. in-patient detoxification or therapeutic treatment and out-patient counselling, despite studies showing that abstinence-oriented treatments have poorer outcomes than agonist treatment [23] when it comes to sustained abstinence and overdose risk after discharge [21, 24].

Despite being safe and effective [17], agonist medication, as well as the OTP system itself, is not without disadvantages. Use of illegal substances and alcohol alongside agonist treatment is not uncommon [25, 26] and poses risks to retention and long-term opioid abstinence [27]. Patients receiving agonist medication are frequently stigmatized [28], and control measures (e.g. daily pick up of medication, supervised intake or regular drug urine testing) are often mandatory [29], due to the need for control over the potential harmful societal effect of medication dispersion. In a Norwegian study [30], patients described the OTP system as overruling and degrading; a limbo between recovery and continued addiction. Also, not all patients manage to stay in, or even want agonist MOUD, e.g. due to non-conformity to the demands of the system, inability "play by the rules" [31], or side-effects of the medication, such as constipation, headaches or sedation [32]. For some, lasting abstinence [33, 34] and abstinence from *all* opioids, including opioid agonist medication, is the treatment goal [35].

XR-NTX treatment involves "being blocked" from the reinforcing, physiological and subjective effects of opioids over time [36, 37], which can reduce opioid use and sustain abstinence [9]. At the same time, being blocked also means giving up the desired (e.g. euphoric or sedative) effects of opioids. Still, XR-NTX is an option for people with OUD seeking abstinence from both illicit and prescribed opioids within the safety of treatment. The effects of opioids are blocked for a considerable, fixed length of time (approximately 4 weeks), which for many patients likely is important in contributing to a distance from opioids both psychologically, physically and temporally.

Several studies with XR-NTX have shown positive results. A previous randomized controlled trial [2] demonstrated that XR-NTX is as safe and effective as buprenorphine-naloxone (an opioid agonist). The results were consistent with other studies [4, 38–41], showing a decrease in opioid and substance use, improvements on psychosocial variables, and less opioid craving [3, 42–44]. The need for XR-NTX to be reinforced by psychosocial

interventions or psychological treatment [45–47] has been emphasized, while a lack of psycho-social follow-up has been linked to treatment discontinuation [44].

Despite these promising results, few qualitative studies examining patients' perspectives on XR-NTX exist. In one study [48] of patients' perceptions of medications for OUD following release from jail, XR-NTX was perceived as a helpful, relapse-preventing intervention, albeit with limitations. A study examining patients' perspectives on initiating treatment with XR-NTX [49], found detoxification, ambivalence, and fears regarding antagonist treatment to be barriers to treatment initiation. A recent study of induction to treatment among patients living with HIV and OUD [50] emphasized the importance of addressing patients' expectations regarding induction to improve initiation rates. This is in line with a recent qualitative study focusing on patients discontinuing treatment [51]. The study indicated unfulfilled expectations as central to discontinuation, but also emphasized that the motivation for abstinence from illicit opioids remained after discontinuation.

No study, to our knowledge, has focused on patients' experience of staying in treatment with XR-NTX well past the initiation phase. The aim of this study was to explore and describe how people with opioid use disorder experience treatment with XR-NTX over time, including the possible benefits, challenges, and needs that arise during treatment. This study offers a unique opportunity to further the understanding of what makes patients continue treatment or what obstacles need to be overcome, and thus, how to facilitate treatment initiation and course, and increase utilization.

Methods

This study employed an explorative and descriptive qualitative design. Analysis was not pre-registered, and the results should be considered exploratory. A semi-structured interview-guide with open-ended questions was developed (AM, BW) with input from co-researchers from "RIO-en landsdekkende brukerorganisasjon på rusfeltet" ("RIO-a Norwegian users' association in the field of alcohol and drugs"), and proLAR Nett ("Pro-OTP Network"), a national organization of people in OTPs. Interviews were analyzed using an inductive content analysis inspired by Elo and Kyngas [52], and Graneheim and Lundmann [53].

This qualitative study is a sub-study of the Norwegian, naturalistic, multicenter, clinical treatment study "Long acting naltrexone for opioid addiction: the importance of mental, physical and societal factors for sustained abstinence and recovery" (NaltRec). The overall NaltRec study included 162 persons, 39 female, and 123 male, aged 18–65 years, with a diagnosis of OUD. All participants were voluntarily seeking treatment with XR-NTX, and were recruited through OTP counselors or other health care workers either at addiction clinics or in the community health services, by study personnel at the detoxification units, or through newspaper articles.

After inclusion to the trial, participants went through complete detoxification from opioids, before receiving an injection of XR-NTX which they subsequently received every 4 weeks during the 24 + 28 week study period, together with multiple assessments. The NaltRec study was conducted at five urban (population > 40.000) addiction clinics throughout the southern part of Norway. The fifth site joined the study at a later date than the first four, and was not present when the qualitative sub-study was carried out. The catchment areas included close to half of the total population in Norway. Treatment with XR-NTX was not generally available in Norway when the study was conducted. For further details on the NaltRec study, see Weimand et al. [1].

The qualitative sub-study of NaltRec consisted of interviews with 32 participants; 13 who had received at least one injection, but chose to discontinue treatment before 12 weeks, and 19 who chose to continue treatment for at least 12 weeks (receiving at least 3 injections), constituting the sample for the present study. Both samples were interviewed using the same interview guide. 102 (63%) of the original sample of 162 in the NaltRec study chose to receive at least 3 injections. Study personnel mediated contact with participants in NaltRec who had given written consent to be individually interviewed, and met the inclusion criteria of being in continuous, active XR-NTX treatment for at least 12 weeks (three injections) after inclusion at the time of interview. Participants were informed that not all consenting to be interviewed would actually be contacted. When recruiting we used a purposive sampling strategy. The selection of participants was strategic, based on inclusion criteria, as well as aimed to include a balance in gender, and geographic spread in the four sites participating when recruiting. All patients contacted initially agreed to be interviewed. However there were 10 patients who either withdrew consent, or who we were unable to reach subsequently. We had initially aimed to interview 20 patients, as 20 participants were considered feasible to recruit within available time and resources, and also sufficient with regard to the topic and scope of the study, as well as the planned length of each in-depth interview which allowed for ample information from each participant.

We conducted interviews with 19 participants—15 male and four female. Although our sample had a gender imbalance, due to difficulties recruiting females during the inclusion period, it reflects the gender imbalance present in the overall study (24% female), as well as the

gender imbalance in OTPs in Norway [54] and among treatment seeking individuals with OUD in Europe [7], as well as the historically higher SUD prevalence in men [55, 56]. The mean age was 38 years (range = 22–55 years). Thirteen participants were in OTPs prior to NaltRec study participation. Participants had received between three and 12 injections at the time of the interview (Table 1).

The interviews focused on different themes relating to the participants' experience of receiving XR-NTX; "Motivation for XR-NTX-treatment", "Experience of being blocked", "Barriers and enablers in XR-NTX-treatment", "Mental and physical health", "Care and support", and "Quality of life and recovery". Each topic consisted of three to six "core questions" supported by prompts to allow for details and elaboration. To keep the exploration close to participants' everyday life, we asked for examples. Interviews were conducted face to face in a private room by the core research group (AM, IHB, BB, BW) and trained personnel, and lasted 60–90 min. All interviews took place between April 2019 and February 2020. Only one interview was conducted with each participant on account of choices made in the overall study, as well as due to restrictions in time and resources. However, we also expected this design would give us the opportunity to go in-depth into each informant's reflections regarding both past and present experiences with XR-NTX. In addition, a variability in length of treatment between individuals was sought, ensuring longitudinal examination of the experiences of treatment.

Table 1 Participant characteristics

Characteristic	Total N = 19
Age, mean (range), years	37.95 (22–55)
Sex, n (%)	
Male	15 (78.9)
Female	4 (21.1)
Ethnicity, n (%)	
Norwegian	17 (89.5)
Other	2 (10.5)
In OTPs previous to study participation, n (%)	13 (68.4)
Most common living arrangements last three years, n (%)	
Alone	12 (63.2)
With partner	4 (21)
With parents or other family	3 (15.8)
Currently living with someone with problematic drug/alcohol use, n (%)	0 (0)
Years of completed education, mean (SD)	13.4 (2.5)
Age at start of regular opioid use (yr), mean (SD)	25.4 (9.0)
Length of regular opioid use (yr), mean (SD)	11.9 (7.0)
XR-NTX injections received, mean (range)	7 [3–12]
Number of XR-NTX injections received at interview time, n	
3	1
4–6	6
7–9	8
10–12	4

Interviews were audio-recorded and transcribed verbatim (AM, IHB, study personnel). Transcripts were imported into NVivo 12 [57] for systematic coding. To ensure credibility and the trustworthiness of findings, two of the core research team members (AM, BW) analyzed the findings. Theoretical saturation [58] was not considered as the material was analyzed after the data collection phase was finished.

An inductive approach [52, 53] was used for coding, keeping codes close to the text. Subsequently, codes were grouped into categories, based on the common denominators that were identified. Codes were reorganized several times to achieve "a full description" of the participants' experiences, and consensus between three of the authors (AM, BW, BB). Categories were thoroughly discussed, and after scrutinizing and re-organizing, we reached agreement in grouping the categories under three themes. In reporting the findings, quotations have been selected to illustrate findings and to ensure trustworthiness.

Ethical approval for the NaltRec trial, including the present study, was granted by the Norwegian Regional Ethical Committees for Medical and Health Research Ethics (REK) committee South East A (# 2018/132), by the personal data protection representative for each of the sites, and by the Norwegian Medicine Agency (NOMA), EudraCT Code 2017-004,706-18. The trial is registered on Clinicaltrials.gov # NCT03647774. It was first registered on Aug 28, 2018, before first participant inclusion on Sep 21, 2018 [1]. All participants gave written, informed consent for their participation.

Interviews were conducted by personnel not involved in the follow-up of the interviewed participant in NaltRec. No information from interviews was shared with clinical or study staff. Interviews were transcribed verbatim, anonymized, and stored at a secure server at the sponsor hospital. Participants were given fictitious names in both the transcripts and in the quotes included in this article.

Findings

When exploring participants' experiences with XR-NTX, three themes were formulated: "Finding a new foothold and adapting to life"; "Connecting with self and others"; and "Finding meaning and maintaining hope." (Fig. 1). These were derived from organizing and grouping the sub themes together into themes describing important aspects of the treatment process, and are considered to

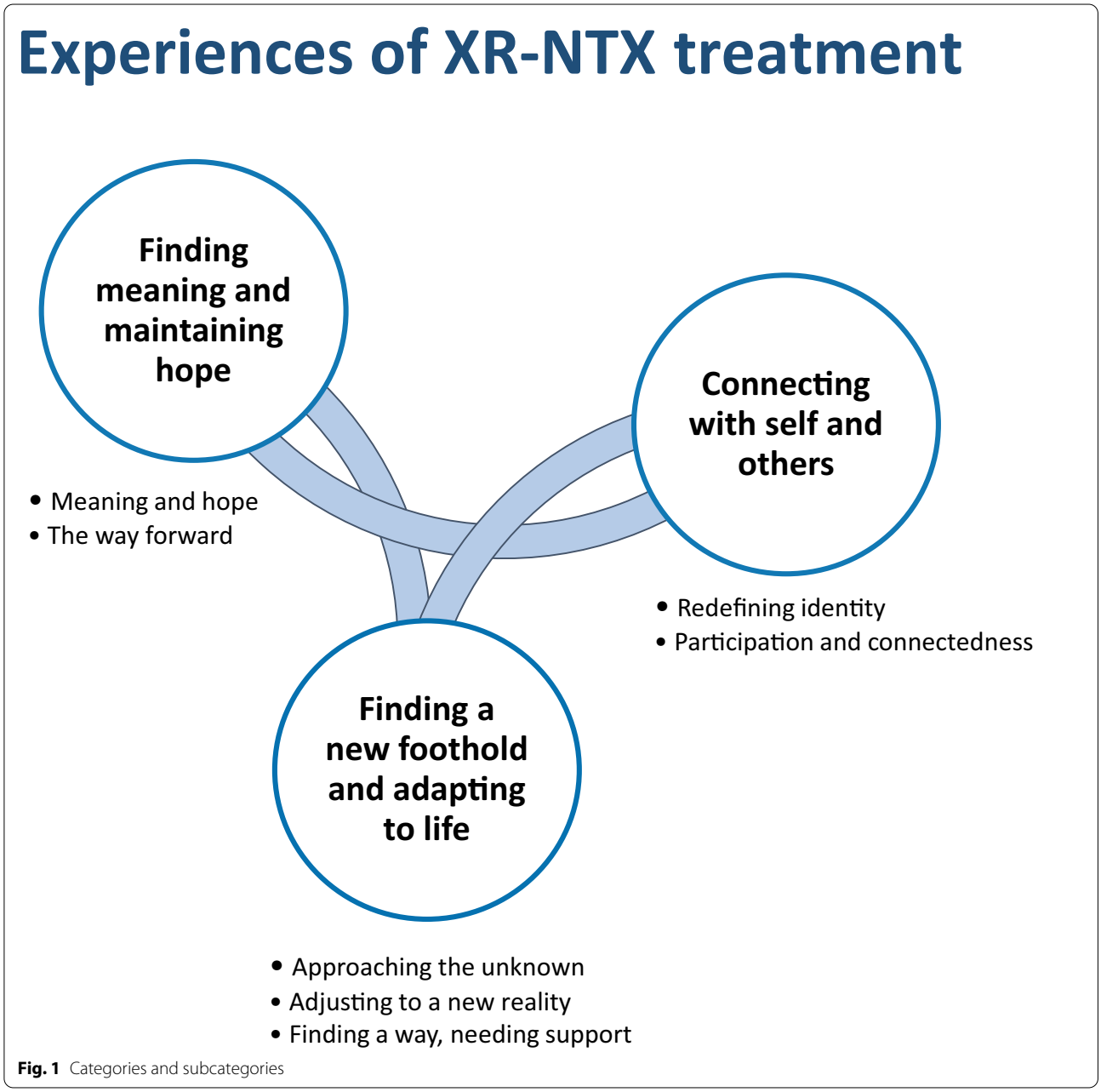

Fig. 1 Categories and subcategories

be a valid description of all participants' experience. The themes describe the process and experiences of treatment with XR-NTX, but are not necessarily chronological, as they may assert themselves repeatedly and at different points during the treatment process. Except for the subtheme of "Approaching the unknown", which is clearly connected to the initiation of treatment, the other themes and sub themes, e.g. the "adaptation" to a new life, or the maintaining of hope, represent aspects or issues that take place throughout treatment, and not only in either the initiation, maintenance or post-treatment phase. When participants discussed their experiences with XR-NTX it became clear that the process is not straight-forward, and that different benefits, challenges and needs might vary throughout treatment.

Finding a new foothold and adapting to life

Even though XR-NTX was chosen voluntarily, being in treatment could be tough. Participants described having to find alternative ways to deal with challenges, which some found difficult, whereas others appreciated not being able to use opioids as a coping strategy and having

to "*…resolve things like everyone else, (…) instead of escaping*" (Daniel, age 24, 9 injections).

Approaching the unknown

XR-NTX is not an established treatment in Norway, and participants starting XR-NTX described entering a somewhat unfamiliar landscape. Nonetheless, the motivator of being free of opioids and/or the OTP system was strong, and the possibility of not experiencing opioid cravings was welcome.

Almost all participants experienced adverse effects around the detoxification and induction on XR-NTX, albeit to varying degrees in both duration and intensity. For some, symptoms such as pain or sleep disturbances persisted, but overall, participants described improvements in physical health after the initial phase.

The start-up was emotionally hard, but also positive because it involved an appreciation of a newfound emotional clearness. Moreover, being able to react "normally," such as feeling empathy, happiness, and even sadness, was appreciated. Some of the participants, however, struggled with overwhelming emotions and found their new situation to be unmanageable. The strength of these emotions could be shocking; one participant reported that "*All the emotions suddenly hit me like a train.*" (Tina, age 26, 4 injections).

After these initial challenges, quitting opioids involved positive changes, e.g., in physical- and cognitive functioning or a general sense of improved mental health, including feeling stable and more in touch with one's emotions. Yet, although most participants experienced improved psychological functioning, some described struggles to deal with mental challenges or underlying issues that reappeared. One participant explained that he had experienced traumatic events and reported having *"so many thoughts in my head I'm unable to suppress, without [opioids]…"* (Roger, age 36, 6 injections).

Adjusting to a new reality.

"*Even though you start naltrexone you are not finished, the road continues.*" (Jon, age 44, 5 injections).

The commencement of XR-NTX treatment did not indicate a problem-free life. Adjusting to an existence without opioids could be encouraging, but no longer having the safety of the OTP system could be challenging. On the one hand, "being blocked" could be wholly unproblematic and mean diminished craving; as opioids "would not work anyway," participants felt they no longer had to use any energy thinking about them. On the other hand, XR-NTX could feel like a prison. For some participants, opioids—especially heroin—had been an escape from reality, and XR-NTX represented losing this.

> *"Seventy to eighty percent [of the time] I have felt safe (…), that no matter how things are in the future, you can't use heroin, you're blocked, you just have to deal with it (…). At other times (…), I feel imprisoned, like what the hell am I supposed to do?!" (Gunhild, age 35, 6 injections)*

Some participants reported trying heroin, mainly to see if XR-NTX really blocked its action and experienced that it did. Several described hearing of ways to break the blockade, and although one participant described succeeding in this, most did not welcome this information as it could induce cravings.

Participants described generally using fewer non-opioid substances after inclusion in the NaltRec study. Some participants reported using no substances, and some described a limited non-opioid use that was typically less problematic than their previous opioid use had been. A few participants however, found being without opioids to be unmanageable; feeling desperate for the opioid effect, resulting in serious and harmful non-opioid use. As Gunhild explained, she had previously identified as a "*heroin* addict", not a "*drug* addict", and the use of other (unfamiliar) drugs was a complete surprise.

> *"It hadn't crossed my mind that I would do it. And maybe that was naïve of me. Because I know I like to escape from myself. Yeah, I thought maybe I would get drunk from time to time or something like that."*

However, suddenly again "struggling with myself", Gunhild, who was well acquainted with fluctuating, long-term psychological difficulties, found it unbearable to manage without anything (i.e. opioids) dulling the emotional pain, thus lapsing into a serious and harmful use of non-opioids.

Finding a way, needing support

Finding a way to manage an opioid-free life was significant. Participants voiced the need for something more than "just the injections", such as support or some activity.

> *"If I didn't have a job, and got naltrexone, then it wouldn't matter, if I just sat at home and watched TV. Because half of what I did when I didn't have a job, to make time go by, was to use drugs." (Daniel, age 24, 9 injections)*

Still, not expecting too much too fast was emphasized; just getting used to being sober could be enough.

> *"Most think, "I'm sober now, [I must get a job]." Then you're starting too high up on the ladder, right, and then you're bound to fall." (Thomas, age 42, 9 injections)*

Although some clearly wanted to manage on their own, participants generally saw the value of some kind of support from external services, which many already had. The first months, in particular, were underlined as a period where extra support was needed.

> *"I needed [help], to understand how I was supposed to cope without looking for something that could dull everything. (…) There should be more follow-up, especially in the first two months. I really think so, because I felt so very alone." (Karl, age 54, 8 injections)*

The discontinuation of opioids could also highlight the need for additional help, and the handling of underlying mental issues was emphasized as important, as these could stand in the way of fully utilizing the potential of the XR-NTX-treatment and of further recovery. In addition to various services, some also voiced a wish for peer support groups with other patients receiving XR-NTX. Several participants found the monthly visits of the NalTRec study useful as an opportunity to reflect on the previous month.

The feeling of support from friends and family—having someone to reach out to if things got difficult—was important. However, having made the decision to quit opioids also involved expectations of continuing to "do good," which was described as a possible barrier to actually utilizing the potential support system.

> *"Mum doesn't know I use amphetamine now (…). It's hell not being able to tell mum I'm struggling." (Roger, age 36, 6 injections)*

Participants generally did not want to involve family in the treatment, not wanting to overtax relatives or feeling that it was nobody's business but their own. However, for some, support from family had "always" been in place, and choosing to start naltrexone was thus a way of "giving back;" showing that a step forward had been taken.

Some participants described that what health services could offer was not what was needed, and proposed the value of peer-support from other patients who had experience with XR-NTX.

> *"[I wanted to] establish a group for those of us using naltrexone, (…) so we can meet and have a coffee and discuss things. NA [narcotics anonymous] says something about it; share strength, hope and experience. Because if you don't, you are horribly alone with your problems." (Harald, age 50, 7 injections)*

Connecting with self and others

"[Heroin] takes a piece of your soul, a piece of your identity." (Roger, age 36, 6 injections).

An important aspect of XR-NTX treatment was that it offered the opportunity to be "normal"; leaving stigma behind, participating in society, and reclaiming the self.

Redefining identity

Quitting opioids allowed for the rediscovery of oneself, which could be both liberating and unpredictable.

> *"What has surprised me most after starting up is that I have found myself again, got to know myself, but at the same time it's been quite an insecure process." (Jon, age 44, 5 injections)*

The need for opioids had previously overshadowed everything, and as Jon explained, having used opioids for a long time could mean uncertainty about one's present identity: "*Who am I today*?" Some expressed feelings of having changed, in preferences or interests, or lost parts of themselves they previously valued. Still, most felt they were moving towards who they wanted to be. No longer being dependent of opioids, and belonging to "the normal group" contributed to a sense of dignity as it also meant escaping the stigma of being an "OTP patient" or "drug addict", a distrusted outsider. Feeling useful and being able to take responsibility meant growing as a person. The accomplishment of quitting opioids or the OTP further contributed to a sense of pride and increased self-esteem.

Participation and connectedness

Belonging and being able to participate in society was considered important. However, functioning in the world with little or no experience of operating in a "normal society" was also challenging. Still, several participants described suddenly feeling like part of something when they had a job, had more time and energy to participate, or experienced strengthened relationships; *"I've always had my family. Before, I was just there, now I am* with *them."* (Anders, age 34, 10 injections).

An increase in social needs could be challenging, as it could involve going out more, and disregarding the previous structure in their life. Nevertheless it could also be beneficial, signifying freedom from an almost compulsive routine and the freedom to participate in social events, and society.

"Before I couldn't… Or, I probably could have if I planned it, but then it had to be part of that plan." (Kevin, age 26, 7 injections)

Finding meaning and maintaining hope

"*It has changed my life; it's a whole new world.*" (Kevin, age 26, 7 injections).

Although the exact reasons for starting treatment and future goals varied, hope for a better life was shared. Dissatisfaction with the regulations of the OTP or the medication itself was common and combined with the desire for an opioid-free life was a strong motivator for attempting XR-NTX.

Meaning and hope

Many participants described having felt there was little hope, and not feeling free as long as they were using opioids. Being on XR-NTX offered a new perspective; it allowed for a future for the first time in a while. XR-NTX could also be the endpoint in a long process, providing the means to finalize the hope and ambition of a "normal life."

The positive changes taking place during treatment seemed to fuel hope and contribute to optimism about the future. Although various difficulties could make hope waiver, it was not lost, and the decision to continue treatment seemed strong. Many participants felt they led a more meaningful life.

"Yes, there is meaning to life. There are many things I want to do now, that I had stopped more or less, like fishing, being outdoors, and getting in shape. Everything feels more meaningful." (Tor, age 43, 7 injections)

However, maintaining hope could prove difficult if things did not turn out as imagined. Having previously seen XR-NTX as a miracle, expectations turned into broken hopes when reality turned out differently.

"Maybe I should just give up and accept that I'm an addict, and that's what I'll be for the rest of my life." (Tina, age 26, 4 injections)

The way forward

The time limitation of XR-NTX treatment felt frightening for some, as the trial was limited to one year, and there was no possibility of continuing treatment after the end of the trial. Although achievements had been made, for some, thinking about "being back on my own" created uncertainty about the risk of relapsing to opioids and further destroying what had been achieved. Others felt that the distance from opioids, attained during treatment, was vital. Although they initially had feared relapse and the end of the treatment, having dealt with life without opioids for nearly a year, they felt these were no longer of concern. Yet, even though much had been accomplished, there was sometimes still a sense of uncertainty about the future, with participants not being sure if the progress would continue once nothing was "holding them back".

"It remains to be seen when I'm actually done, after the 13 injections. That's another task to overcome, right?" (Marius, age 26, 4 injections)

There were also some worries about not being able to achieve abstinence from all substances during treatment, which gave rise to distressing thoughts:

"What will happen if I'm still caught up in drugs and relapse to heroin? What will happen to me then? Is it back to the OTP, and Subutex, and all that? I don't want that. (...) If that happens, I might as well shoot myself, because I don't want to go back." (Roger, age 36, 6 injections)

For patients struggling with a harmful use of substances, the question of whether a return to heroin would be less harmful than the use of various other substances was raised. However, beyond this, participants in the present study did not voice any doubt as to whether or not to continue XR-NTX during the trial.

Discussion

To our knowledge, this is the first study exploring in-depth the experiences of people with opioid dependence successfully inducted and choosing to stay in treatment with XR-NTX over time. This qualitative study offers five major findings. First, the induction to treatment held considerable challenges for patients. This was mainly related to the difficulty of handling the emerging emotions when discontinuing opioids. Second, XR-NTX was experienced as an effective treatment, signifying freedom from both illegal opioids and from the "OPT system", and involving substantial benefits for patients, such as improved health, or the opportunity to participate in society. Third, for a few patients, extensive use of non-opioid illegal substances could indicate considerable challenges dealing with opioid blockade and be a substantial barrier to continued XR-NTX treatment and further recovery. Fourth, mental health problems could also be a considerable barrier to the treatment process, patients not being able to use opioids for symptom relief. Fifth, our results underscore the need for individualized and tailored support and follow-up during XR-NTX treatment.

Our findings are in line with qualitative studies showing that patients consider XR-NTX a relapse-preventing option reducing cravings [48, 49], as well as previous studies concluding that XR-NTX is an effective and feasible treatment for OUD [2–4]. Whether patients struggled greatly with the opioid antagonism, or experienced it as unproblematic, XR-NTX was still overall perceived as life-changing, and the desire to continue was strong. This was mainly connected to escaping what was described as detrimental aspects of the OTP system, as well as leaving dependence behind and no longer having the compulsion to take opioids at the cost of other pleasures or interests. However, the findings also highlight that XR-NTX treatment did not have the desired outcomes for all, and in many cases required additional professional, social and/or familial support. The study answers some of the questions regarding the psychological aspects of opioid receptor blockade, and sheds light on possible hindrances and facilitators for staying in treatment over time. These factors have been identified as important areas for investigation by patients and organizations for people with SUD [1].

Interestingly, few, if any, *external* barriers to treatment retention and heroin abstinence were mentioned by participants, such as economic insecurity or social factors. This is contrary to previous findings [48], and may at least in part be attributable to the Norwegian welfare society, securing inhabitants a minimum standard of living, including free health care and social services. Participants were recruited from a naturalistic outpatient treatment setting, and were highly motivated for XR-NTX. As mentioned, the majority of our participants were previously in OTPs, which is widely accessible at no cost in Norway [7]. Thus the interest to start XR-NTX likely signifies a specific motivation for the antagonist effect of XR-NTX and further recovery, rather than economical motivations or desperation due to having no other alternatives.

Tailored support

In line with a biopsychosocial model of addiction [59], our findings illustrate that OUD is a complex, multifaceted phenomenon, necessitating a diverse and individualized treatment approach. People struggling with OUD need concurrent focus on a wide range of domains, e.g. in medical, psychological, emotional, relational, motivational, occupational, and social issues. Both our findings and those of previous studies [44, 46, 47, 60] emphasize the need for something "in addition" to the monthly blockade of opioid receptors.

One size does however not fit all, illustrated by the variability in participants' experiences and diverse needs for support during treatment. While some participants were undeniably in need of increased enforcement, others clearly desired the autonomy XR-NTX offered, preferring no service involvement. Regardless, the induction and early weeks of treatment will probably be a period where enforced support will be beneficial for most patients. It is also important to note that for some patients, measures beyond basic support will initially be excessive, as merely adjusting to an opioid-free everyday life poses sufficient challenges to overcome.

For many participants clearing up and experiencing the outside world and inside emotional states more intensely felt liberating, yet this freedom could also come at a cost, in the form of increased emotional vulnerability and an increased need for additional support. The various areas requiring strengthened efforts ranged widely, which needs to be taken into consideration when planning XR-NTX treatment course. While some participants expressed a need for health services, such as mental health treatment or addiction and motivational counselling, others just wanted to have something to do, a job, someone to chat with, or to give or receive support from peers with experience of XR-NTX treatment. Interestingly, patients were hesitant to involve family or friends in the treatment, and although their support was valued, the importance of reinforcement from health- or social services was emphasized. Not surprisingly, our results emphasize that additional measures are more important than ever. Although XR-NTX addresses the physiological basis of addiction, the sole blocking of opioids is insufficient alone.

Use of opioids and other illicit substances

Consistent with other studies of XR-NTX, participants overall reported a reduced use of illicit opioids [3, 4, 40]. Still, also in line with other studies [48, 61, 62], some participants described instances of opioid use, mainly to "test the blockade." Contrary to previous findings [62], repeated challenges to the blockade did not seem to be a warning sign for risk of relapse to polydrug use and crime. Rather, testing the blockade seemed to have minor impacts on functioning, and did not drive thoughts of discontinuation, which is in line with previous qualitative findings [48].

Our participants also described an overall reduction in non-opioid substance use, however, a few reported an increase. Many patients with OUD have polysubstance-use disorders [63, 64]. There are indications that frequent substance use is common in OTPs [65, 66], and that agonist treatment, although associated with lowered opioid use, to a lesser degree is associated with lowered polydrug use [25]. However, studies have also shown that substance use, both opioid and non-opioid, appears to

decrease over time in agonist treatment [67]. The picture is likely similar for XR-NTX; when comparing XR-NTX to buprenorphine in a clinical trial over 12 weeks, no overall change in the use of most substances was found [2]. This qualitative study provides some elaboration and additional nuances on non-opioid use during XR-NTX treatment, capturing details in individual experiences.

Some patients, when unable to handle life without opioids and desperate for an escape, may turn to "anything" (i.e. other substances) if there is no prospect of an opioid effect. For our participants, an extensive use of non-opioid substances carried the likelihood of harmful effects on health and functioning and could raise the question whether continued XR-NTX treatment would be sustainable over time if unable to get this use under control. Even though XR-NTX meant avoiding the detrimental effects of opioid dependence, the effects of increased non-opioid use carried disadvantages which could be as great as, or even greater than when previously using opioids. In addition, further recovery and the building of a new life seemed difficult with such a use. Interestingly, participants still preferred to continue XR-NTX treatment, which likely points to the strength of the hopes tied to XR-NTX treatment.

A pronounced desperation for an escape and the turning to other substances will likely be a warning sign that for the patient opioid antagonism is very challenging to handle, and that additional measures are needed to continue to benefit from continued treatment. Non-opioid use is an important outcome measure of XR-NTX treatment, and clinicians should remember that XR-NTX treatment does not automatically mean overall abstinence. An extensive use of non-opioids will in many cases complicate further recovery and raises the question of how to achieve "freedom from opioids" without the cost of introducing or increasing use of harmful substitute drugs.

Experience of opioid blockade

For many, the struggle of "not being able to escape into opioids," an unnerving prospect initially, was not an issue after having passed the early phases of treatment. This might in part be a form of defense mechanism, making it psychologically easier to write off and accept not using opioids when there is no conceivable possibility of intoxication by opioids, which in turn in itself might diminish craving. In addition, the majority of our participants, having previously been in OTPs had probably not used the opioid agonist medication as a means of escape. Thus XR-NTX, instead of feeling like an obstacle to escape, felt mainly as a safety net, guarding against relapse. Others, however, struggled visibly. This may to some extent be understood from a developmental-learning perspective, which also underlines the importance of support when learning and implementing new habits [68]. "Quitting drugs" involves not only breaking old habits, but also learning new, such as the regulation of emotions without the use of opioids. This might prove difficult for some, whereas for others, the ensured abstinence from opioids over time might enforce the learning of new habits and further abstinence.

Based on our findings, mental health difficulties are of importance for how well opioid blockade is handled, coinciding with findings that addressing mental problems in patients with OUD likely enhances the odds of a stable recovery [15]. Comorbid psychiatric disorders are common among people with SUD [69, 70], and contribute negatively to the course and treatment of OUD [71]. Furthermore, previous physical or sexual abuse and comorbid mental disorders are associated with the persistence of opioid use [16], and higher scores of anxiety and depression seem to be concurrent with increased difficulty reducing illicit substance use [42, 72]. However, this association needs further investigation, as not all participants with mental health difficulties found being blocked difficult. In addition, symptoms of anxiety, depression, and insomnia have been shown to be improved by XR-NTX-treatment [42]. Still, for some, lack of adequate psychological treatment and support systems, both before and after starting XR-NTX treatment, might complicate the course of treatment.

How being blocked was experienced did however not seem to be wholly explained by factors like the amount of support offered or received, or the individual's mental health, and was not constant, but could vary within the same person, from "ok" to "like a prison." Likely, differences in social or psychological factors, like personality traits or coping skills are at play, as well as varying life conditions or circumstances. This again highlights the complexity of opioid dependence and the challenges people with OUD face, underscoring the need for diverse approaches and varied professional expertise to help meet these challenges. Still, a more systematic exploration of both external and internal factors associated with how being blocked is experienced and tolerated, and the connection with e.g. treatment outcome and success is needed to conclude further.

Treatment length

XR-NTX-treatment is not intended to be lifelong and there is no recommended standard treatment-length [73]. The limitation of treatment to one year in this study might imply a positive expectation that the person with OUD will be able to manage independently after this period, strengthening agency and self-belief. On the other hand, some patients might need extended time in

treatment [44], and our findings indicate that treatment length should be tailored to individual needs, rather than restricted to predetermined time periods. The commencement of treatment that is time-restricted might prove difficult for those who experience unsatisfying progress during the treatment course.

For many, opioid abstinence sustained by XR-NTX enabled a new, more meaningful life. This might be particularly important as SUDs impair many aspects of a person's life, and might especially restrict the ability to experience meaning in life. Finding meaning is important to recovery in general [74], and has been associated with longer periods of abstinence from substance use [75]. Developing a meaningful life and finding a purpose in life is an important part of recovery from addiction [75–77]. Also, despite the serious, detrimental effects of non-opioid substance use, or the struggle to deal with emotional issues, the positive, life-changing effects of XR-NTX as well as the desire to continue treatment was strong. This was connected to the blocking of opioid effect and the resulting indifference to using them, constituting at least one less problem to handle, whether one had few or many other problems.

As XR-NTX offers a unique opportunity to avoid the effects of opioids over time, we suggest that it is what is achieved during treatment in terms of rehabilitation and recovery, rather than treatment duration or opioid abstinence in itself that is significant. Specifically, it seemed that the positive changes taking place during treatment were of more importance for participants than the abstinence from opioids per se, even though abstinence enabled these advances. This is in line with findings [78] showing that people with OUD are motivated by improvements beyond abstinence, such as better relationships, health, and meaningful everyday lives. These goals seemed, at least in part, to have been met for our participants through XR-NTX treatment.

Strengths and limitations

This study's explorative design offers important in-depth insights into XR-NTX as a treatment option for OUD. Participants were recruited from an open-label naturalistic treatment study, ensuring real-world relevance. Although this qualitative study included a limited sample, the material was rich in content, and presents detailed variations in experience. Both participants highly satisfied, as well as those disappointed with XR-NTX treatment participated, and gave voice to the nuances of the experience of treatment. Although our sample has a gender imbalance, this imbalance is in line with that of the overall study and that of treatment seeking persons with OUD in Europe, and we did not seek to address or explore gender differences explicitly.

Participants were interviewed at different times during the 12-month treatment period, which might influence what was emphasized or recalled. However, the themes presented were independent of the point in time at which the participants were interviewed. Still, the present study does not examine whether participants chose to stay in treatment beyond the time of the interview. Thus we do not know if some of the challenges mentioned were overcome, or if they better represent the narratives of patients choosing to discontinue treatment [51]. In addition, participants were interviewed only once. Multiple interviews with the same people throughout the course of treatment would perhaps have allowed for a better longitudinal examination, as well as captured treatment trajectories and the possible discontinuation among participants. At the same time, the single interviews allowed for an in-depth exploration of several individuals, at different times during the treatment period, and gave insight into the experiences of patients currently in treatment, in line with the study aim.

Participants might have been particularly motivated for the new treatment approach that XR-NTX represents in Norway, or have had a particular dissatisfaction with agonist treatment. Caution should be taken regarding the generalizability of our findings; nevertheless, they are transferable to similar settings, as a detailed description of the study's context has been given, and patients freely choosing XR-NTX will likely share the same motivation. A detailed description of the research process has been given, ensuring transparency. It is also worth emphasizing that retaining patients in XR-NTX treatment over time can involve considerable challenges [9]. The patients in our sample had stayed in treatment for at least 12 weeks, many of them considerably longer. Thus this study offers a unique and interesting perspective on XR-NTX treatment over a longer period of time, and offers insights into the benefits and challenges of treatment over time.

Conclusions

XR-NTX treatment, although potentially life-changing, can also involve serious challenges for patients. This means individuals receiving XR-NTX treatment will need additional services and support, especially in the beginning of treatment, but also when it comes to difficulties handling emerging thoughts, feelings and experiences when blocked from the effects of opioids. A strengthening of health- and social services, and emotional support whether from such services or from the patient's network seems essential. Further, the monitoring of and assistance with arising emotional difficulties, as well as the possible subsequent harmful use of non-opioids is vital to help

patients cope, and stay in treatment over time. Nevertheless, patients need for help will vary between people, at different times and with varying circumstances, which highlights the importance of seeing XR-NTX as part of a comprehensive, individualized treatment approach.

Abbreviations

MOUD: Medication for opioid use disorder; NOMA: Norwegian medicine agency; OPTs: Opioid (agonist) treatment programs; OUD: Opioid use disorders; SUD: Substance use disorders; XR-NTX: Extended-release naltrexone.

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Author contributions

CASRAI CRediT Taxonomy: authors' contribution(s) to the submitted manuscript are attributed as below. AM, Data curation-Lead, Formal analysis-Lead, Methodology-Supporting, Writing-original draft-Lead, Writing-review & editing-Lead, IHB, Formal analysis-Supporting, Validation-Equal, Writing-original draft-Supporting, Writing-review & editing-Equal, BW, Conceptualization-Equal, Formal analysis-Supporting, Funding acquisition-Equal, Methodology-Lead, Project administration-Supporting, Supervision-Lead, Validation-Equal, Writing-original draft-Supporting, Writing-review & editing-Equal, KS, Project administration-Supporting, Writing-review & editing-Supporting, LT, Conceptualization-Equal, Funding acquisition-Equal, Project administration-Lead, Writing-review & editing-Supporting, BR, Writing-review & editing-Supporting, BB, Formal analysis-Supporting, Supervision-Supporting, Validation-Equal, Writing-original draft-Supporting, Writing-review & editing-Equal. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the possibility of compromising individual privacy and anonymity, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for the NaltRec trial, including the present study, was granted by the Norwegian Regional Ethical Committees for Medical and Health Research Ethics (REK) committee South East A (# 2018/132), by the personal data protection representative for each of the sites, and by the Norwegian Medicine Agency (NOMA), EudraCT Code 2017-004706-18. The trial is registered on Clinicaltrials.gov # NCT03647774. It was first registered on Aug 28, 2018, before first participant inclusion on Sep 21, 2018 [1]. All participants gave written, informed consent for their participation.

Consent for publication

All participants gave general written, informed consent for publication, in the consent form of the main NaltRec study. All characteristics, including participants' names have been anonymized, and the participants have been given fictitious names in the text.

Competing interests

None.

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'Not at all what I had expected': Discontinuing treatment with extended-release naltrexone (XR-NTX): A qualitative study

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ABSTRACT

Background: Extended-release naltrexone (XR-NTX), an opioid antagonist, has demonstrated equal treatment outcomes, in terms of safety, opioid use, and retention, to the recommended OMT medication buprenorphine. However, premature discontinuation of XR-NTX treatment is still common and poorly understood. Research on patient experiences of XR-NTX treatment is limited. We sought to explore participants' experiences with discontinuation of treatment with XR-NTX, particularly motivation for XR-NTX, experiences of initiation and treatment, and rationale for leaving treatment.

Methods: We conducted qualitative, semi-structured interviews with participants from a clinical trial of XR-NTX. The study participants ($N = 13$) included seven women and six men with opioid dependence, who had received a minimum of one and maximum of four injections of XR-NTX. The study team analyzed transcribed interviews, employing thematic analysis with a critical realist approach.

Findings: The research team identified three themes, and we present them as a chronological narrative: theme 1: Entering treatment – *I thought I knew what I was going into*; theme 2: Life with XR-NTX – *I had something in me that I didn't want;* and theme 3: Leaving treatment – *I want to go somewhere in life*. Patients' unfulfilled expectations of how XR-NTX would lead to a better life were central to decisions about discontinuation, including unexpected physical, emotional, or mental reactions as well as a lack of expected effects, notably some described an opioid effect from buprenorphine. A few participants ended treatment because they had reached their treatment goal, but most expressed disappointment about not achieving this goal. Some also expressed renewed acceptance of OMT. The participants' motivation for abstinence from illegal substances generally remained.

Conclusion: Our findings emphasize that a dynamic understanding of discontinuation of treatment is necessary to achieve a long-term approach to recovery: the field should understand discontinuation as a feature of typical treatment trajectories, and discontinuation can be followed by re-initiation of treatment.

1. Introduction

Opioid dependence has comprehensive and harmful consequences for the individual, their families, and society (EMCDDA, 2020; McLellan et al., 2000; World Drug Report 2020, 2020). Opioid maintenance treatment (OMT), with agonist methadone or partial agonist buprenorphine, is currently the treatment modality recommended by the World Health Organization (WHO, 2009), and research has shown OMT to

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reduce illicit opioid use and prevent relapse, as well as reduce morbidity and mortality (Mattick et al., 2014; Sordo et al., 2017; Wakeman et al., 2020). Non-pharmacological abstinence-oriented treatment approaches are alternatives to OMT, but research has found such treatments not to be effective for sustaining abstinence, and they are associated with a high number of overdoses after discharge (Mattick et al., 2009, 2014). Many people with opioid dependence express a desire for lasting abstinence (Laudet, 2007; McKeganey et al., 2004; McKeganey et al., 2006). For some, such abstinence includes ending the use of opioid agonist medications prescribed through OMT (Zaaijer et al., 2016).

Antagonist treatment with extended-release naltrexone (XR-NTX) is a promising treatment approach for opioid dependence, which combines the safety and efficacy of OMT with a treatment goal of avoiding all use of opioid agonists, including medications prescribed through OMT. The opioid antagonist naltrexone blocks the reinforcing and physiological effects of opioid agonists (Bigelow et al., 2012), and the extended-release injection Vivitrol® (hereafter XR-NTX) provides antagonist action for four weeks, and was approved for treatment of opioid dependence in the United States in 2010.

Previous trials have shown that XR-NTX is effective in preventing relapse to and reducing use of illicit opioids. Two randomized controlled trials in the United States found that days of opioid use for patients receiving XR-NTX decreased similarly to treatment as usual (TAU) (Korthuis et al., 2017), that opioid relapse was significantly lower (38% vs 88%), and that more urine samples were negative for opioids (59% vs 29%) among patients receiving XR-NTX compared to TAU (Lee et al., 2015). When compared with treatment referral controls, patients with opioid dependence in the U.S. criminal justice system who received XR-NTX showed significantly longer time to relapse (10.5 vs 5 weeks), lower rate of relapse (43% vs. 64%), and more negative urine samples (74% vs. 56%) (Lee et al., 2016). A Russian study (Krupitsky et al., 2011) investigated the efficacy of XR-NTX versus placebo over a 6-month period in a randomized, double-blind design. XR-NTX demonstrated a statistically significant advantage over placebo on negative opioid urine samples. After one year, approximately half of the XR-NTX participants were abstinent from opioids during the study (Krupitsky et al., 2013). The two most recently conducted RCTs compared XR-NTX with the recommended OMT medication buprenorphine, demonstrating that XR-NTX showed similar efficacy to buprenorphine in reducing opioid use, once initiated (Lee et al., 2018; Tanum et al., 2017). A recently published follow-up to Tanum et al. showed that risk of relapse was significantly lower in the XR-NTX group compared with the BP-NLX group (Opheim et al., 2021).

However, a systematic review of the published literature on XR-NTX (Jarvis, Holtyn, et al., 2018b) pointed out that premature discontinuation of treatment with XR-NTX is common, with retention rates ranging from 15% to 74% in prospective studies, and that less than 10% adhered to XR-NTX after 6 months in retrospective studies of medical records. A recent review identified that retention rates in OMT are equally variable, ranging from 20.0% to 83.8% (Klimas et al., 2021). Nevertheless, Jarvis, Holthyn et al. (2018b) concluded that the high proportion of patients discontinuing treatment limits the clinical utility of XR-NTX.

Research on patients' experiences of discontinuation of XR-NTX treatment is limited. Velasquez et al. (2019) assessed the perceptions of participants recently released from NYC jails, who received treatment with XR-NTX, opioid agonist treatment, or no treatment at all. Although seen as a useful post-release intervention by many, the authors found that those who discontinued XR-NTX treatment described the decision as intentional, often driven by a desire to resume opioid use. Randall-Kosich et al. (2020) compared reasons for starting and stopping methadone, buprenorphine, and naltrexone treatment in another U.S. qualitative study. Notably, the authors found that some participants ended XR-NTX treatment because they were unable to pay for the medication, but they also identified wanting to "stop dependence on a medication" (p. 48) as a reason for discontinuation across the three medications.

Understanding discontinuation of treatment is important to support recovery, as retention in OUD treatment is one of the factors most consistently associated with favorable outcomes (Bart, 2012). Conversely, research has shown early discontinuation of OMT to be associated with increased risk of relapse and mortality (Clausen et al., 2008; Cousins et al., 2011; Kornor & Waal, 2005; Krawczyk et al., 2020; Williams et al., 2020). Due to its detrimental consequences, discontinuation of OUD treatment has been extensively studied. Research points to certain patient demographic factors as associated with discontinuation, such as younger age, polysubstance use, and substance-related criminal offences during treatment (Bukten et al., 2014; Iovine et al., 2020; Krawczyk et al., 2021). However, a systematic review of discontinuation from SUD treatment suggested that treatment process factors might be more significant, such as motivation, alliance, and satisfaction with treatment (Brorson et al., 2013).

To our knowledge, the current qualitative study is the first study performed outside of the United States to explore patients' experiences of intentionally discontinuing treatment with XR-NTX. The Norwegian health care system differs from the U.S. system in that, for instance, OMT or other treatment is provided free of charge to all citizens with opioid dependence. The aim of this study was to better understand the experiences among patients that led to early discontinuation of treatment with XR-NTX, in a setting where OMT is freely available. Specifically, we explored participants' motivation for XR-NTX, experience of initiation and treatment, and rationale for leaving treatment.

2. Methods

The current qualitative study is a substudy nested within "Long acting naltrexone for opioid addiction: the importance of mental, physical and societal factors for sustained abstinence and recovery" (NaltRec), a naturalistic, multicenter, open-label trial of treatment with extended-release naltrexone hydrochloride injectable suspension (Vivitrol®). Weimand et al. (2021) describes NaltRec in detail. Briefly, the study included 162 men or women, age 18–65 years, with a diagnosis of opioid dependence. All participants were voluntarily seeking treatment for opioid dependence, and expressed a goal of ending illicit opioid use, or ending opioid agonist medication prescribed through OMT. The study recruited participants through OMT counselors or municipality health care workers, by study personnel at the detoxification units, or through newspaper articles.

The overall study period was 24 weeks with an optional 28-week prolongation of treatment. Upon inclusion in NaltRec (hereafter referred to as the parent study), all participants went through complete detoxification from illicit opioids and/or opioid agonist medications. The participants were referred to an in-patient detoxification unit at one of the participating hospitals, where detoxification was completed in accordance with current Norwegian national guidelines (The Norwegian Directorate of Health, 2016) and in line with international standards (Gowing et al., 2017). After the required minimum days without any opioids, the participants received their first injection of XR-NTX, administered by study personnel. After initiation, participants received an XR-NTX injection and underwent multiple assessments every 4 weeks. The study team conducted the parent study at five urban (population > 40.000) addiction clinics in Norway. Treatment with XR-NTX was not generally available in Norway when the study team conducted the study.

2.1. The qualitative substudy

This article is part of a qualitative substudy nested within the parent study, NaltRec. The Norwegian naltrexone research group that is behind the parent study previously compared treatment with XR-NTX and buprenorphine-naloxone in a multi-center randomized controlled trial (RCT) (Kunøe et al., 2016; Tanum et al., 2017). In the RCT, study participants, as well as the user organizations, emphasized the importance

of investigating in more detail the factors that contributed to treatment outcomes. This feedback was included in the base of the parent study, and contributed heavily to the development of the qualitative substudy, and more specifically to the development of the interview guide. The qualitative substudy consisted of interviews with 32 participants, of whom 19 chose to continue treatment for at least 12 weeks. The remaining 13 participants chose to discontinue treatment before 12 weeks, and constituted the sample for the current article. Study staff interviewed both samples using the same interview guide.

2.1.1. Recruitment and participants

Members of the qualitative research team approached participants who had given written consent to an in-depth interview upon inclusion in the parent study, and who met the following inclusion criteria: to have received at least one injection, and have decided to discontinue treatment within twelve weeks after inclusion in the parent study. The research group sought equal distribution of gender among the five sites, but this was not possible due to difficulties with recruitment.

The research team attempted to recruit a total of 32 patients meeting the inclusion criteria, of whom 19 either were impossible to reach, or unable to participate in the qualitative interview. Thirteen patients accepted and the study team interviewed them—seven women and six men. The participants' age ranged from 18 to 63 (mean 38). All participants were white, and identified their ethnicity as Norwegian. The participants came from four of the five hospitals participating in the parent study. All the participants had previous experiences of opioid detoxification prior to participating in the parent study. Nine participants were in OMT when they entered the parent study, and an additional two had previous experience with OMT. The participants had received from one to four injections with XR-NTX: seven received one, two received two, one received three, and three received four injections before they decided to discontinue treatment.

2.2. Data collection

The qualitative research group developed a semi-structured interview guide with input from representatives of the Norwegian user groups RIO—a Norwegian users' organization in the field of alcohol and drugs, and proLAR Nett—an OMT user group. The research team based the interview guide on feedback from participants in the research group's previous RCT, and used it to explore the experiences of treatment with XR-NTX for all participants, both those who chose to remain in treatment and those who chose to discontinue treatment. The interview guide contained open-ended questions under the main topics "motivation for treatment with XR-NTX" ("Why did you want treatment with XR-NTX?"), "experience of being blocked from using opioids" ("How did you experience being prevented from receiving effects from opioids?"), "barriers and facilitators to treatment with XR-NTX" ("What made it easier or more difficult to be in treatment with XR-NTX?"), "mental and physical health" ("How does opioid abstinence influence your mental and physical health"), "care and support" ("What kind of health care and support did you receive/need?"), and "quality of life and recovery" ("How has XR-NTX contributed to your recovery/quality of life?"). Each topic consisted of three to six "core questions", which were supported by prompts to encourage detail or elaboration where needed. Each interview addressed the same questions or themes, but the order could vary, depending on the participants' responses and reflections. At the end of each interview, the participants could share their thoughts on any additional subject they found relevant.

The study interviewed participants after they had explicitly decided to leave XR-NTX treatment. Due to difficulties in establishing contact with some of the participants, study staff conducted interviews from a few weeks to several months after their decision about discontinuation. The interviews lasted approximately 60 min. IHB, BW, BR, and other study staff trained in qualitative interviewing conducted the interviews. In sum, the group who conducted qualitative interviews consisted of study personnel, user representatives, and other researchers not involved in participant follow-up in the parent study. Study personnel who were involved in recruitment or follow-up of the participant in question in the parent study did not conduct the participant's qualitative interview. IHB, AM, and LT were involved in participant follow-up in the parent study, but only IHB conducted interviews with any participants in the current article. Each interview took place in a suitable, sheltered place at the individual site, to safeguard anonymity. The interviews were audio recorded, and transcribed verbatim by study staff who had previously signed a confidentiality form. Study staff stored the transcriptions at a secure server at the sponsor hospital. No names are used in quotes in the current article.

2.3. Analysis

The core author group (IHB, AM, BB and BW) who conducted the analysis consists of health professionals from psychology, mental health nursing, and social work, all of whom had extensive experience with substance use problems: either from a professional (clinical or research) point of view, and/or from personal experiences with substance use problems in the family. These personal and professional factors were regularly discussed throughout the research process, where the researchers constantly posed questions regarding our understandings and interpretations of data.

The analysis employed a critical realist approach informed by Maxwell (2012) and Bhaskar (2009). Briefly, the critical realist approach entails a realist ontology combined with a relativist epistemology, accompanied by an emancipatory focus inspired by Bhaskar (2009). This approach enabled addressing structures "which determine, constrain and oppress" (Houston, 2001, p. 846) the participants in their lives.

Maxwell emphasizes the potential for qualitative analysis in combining categorizing (coding) and connecting (narrative) strategies, looking for both similarities and contiguities (Maxwell, 2012, pp. 118–123). The analysis for the current article proceeded in three stages: categorizing, summarizing and integrating.

The initial, categorizing phase employed an inductive approach. The experiences of treatment with XR-NTX is a comparatively unexplored area, especially in the sociodemographic context of the current study. Thus, the team deemed pre-creating themes for a deductive analysis too restrictive. Moreover, an inductive approach better enabled maneuvering the authors' preconceptions. Several of the authors were involved with patient follow-up in the parent study, and had undoubtedly established a personal understanding of the topics explored in the interviews. All transcripts were read several times by the first author (IHB), and at least once by AM and BW. Interviews were coded and analyzed using NVIVO 12 software (QSR International Pty Ltd, 2020) by the first author (IHB). The initial stages of analysis consisted of detailed coding of the data, creating new codes each time a section of text did not correspond to an existing code. AM, BW, and BB read the codes in relation to the interview transcripts, and discussed them with IHB. IHB grouped the initial extensive number of codes into code groups, or subthemes, and developed them further into preliminary themes, with inputs from AM and BW.

After the initial, categorizing part of the analysis, it was evident to the team that a dimension that was central to the understanding of the participants' experiences was lost during the coding process. As the participants talked about their experiences with XR-NTX and explained why they decided to discontinue the treatment, they created a narrative and a context for their decisions. Thus, in the summarizing next step of the analysis, IHB created narrative summaries for each participant, providing a context for the preliminary themes. AM read these narratives in relation to the transcripts.

The qualitative research group then made cross-references between the narrative summaries and the preliminary themes. On some occasions, the team rearranged subthemes, as content was moved to another

subtheme, or changes made to the names of codes or subthemes. Finally, the team scrutinized subthemes and re-organized them until agreement was reached, and data were organized into three main themes. The themes are presented as a chronological narrative, chosen to highlight how the participants' increasing experience with XR-NTX led to their decisions about discontinuation.

2.4. Ethics

The Regional Committees for Medical and Health Research Ethics, committee South East A approved the NaltRec study protocol in which the current study is included as a substudy (# 2018/132). Furthermore, the NaltRec study was approved by the Norwegian Medicine Agency (NOMA), EudraCT Number 2017–004706-18, and personal data protection representative of each of the participating hospitals. The trial is registered on Clinicaltrials.gov # NCT03647774, first registered: Aug 28, 2018, before the first participant was included on Sep 21, 2018 (Weimand et al., 2021).

3. Findings

The findings are presented as a chronological narrative, as illustrated in Fig. 1: theme 1: Entering treatment – *I thought I knew what I was going into*, theme 2: Life with XR-NTX – *I had something in me that I didn't want*, and theme 3: Leaving treatment – *I want to go somewhere in life*. The main themes are illustrated by quotes by participants. The sub-themes connected to 1) *entering treatment* and 2) *life with XR-NTX* describe experiences that are common across all participants, while decisions about ending treatment with XR-NTX in theme 3 are based on two distinct trajectories or treatment outcomes: *reaching treatment goals* and *reacceptance of OMT*. A concluding subtheme, *belief in a life without illicit substance use*, encapsulates the participants' visions of the future.

3.1. Theme 1: entering treatment: I thought I knew what I was going into

The first theme describes participants' experiences of starting treatment with XR-NTX. This includes the following subthemes: *motivation for XR-NTX*, *transition from opioids to XR-NTX*, and *feeling unprepared*.

3.1.1. Motivation for XR-NTX

All participants started treatment with XR-NTX with a goal of ending illicit opioid use, or ending opioid agonist medications prescribed through OMT. Participants highlighted both the promised protection from opioid effects and the freedom of XR-NTX. Many remembered being intrigued by a medication that would remove cravings for opioids. Although interested, some participants also remembered being apprehensive about an unknown medication.

Leaving, or avoiding, OMT was part of all the participants' descriptions of their motivation for XR-NTX, often stated more explicitly than stopping the use of illicit opioids. Some participants recounted several years' stabilization in OMT without any illicit substance use, and presented XR-NTX as a step forward in their recovery process. A few implied that their wish to leave OMT was partly due to an understanding that it was expected by those around them. Many were not satisfied with OMT, some because they experienced undesirable physical, mental, or social side effects of the medication. Participants also described complying with control measures within the OMT program as challenging.

> [I don't] want to be in OMT. I don't want to be addicted to anything (…) I want to be able to go where I want to without having to ask [OMT] first. I [am] fucking tired of being in (…) «the kindergarten».

Participants described treatment with XR-NTX as a final opportunity to achieve treatment goals: *"I have realized that I am too weak to resist opiates and I have tried everything else. So I felt that [XR-NTX] was a kind of last resort in a way, a last lifeline."* Many presented leaving behind all substances, both illicit and prescribed, as their ultimate goal, and this view was often connected with hopes of a better life: *"I saw a way of becoming clean. I saw a way of getting a new life."*

3.1.2. Transition from opioids to XR-NTX

All participants described extensive treatment experiences, and had been through opioid detoxification (detox) at least once prior to entering XR-NTX treatment. Although the prospect was unpleasant, most participants described feeling a certain degree of confidence about their ability to complete detox and start XR-NTX. Physical and mental discomfort was a prominent part of most participants' accounts of transition from opioids to XR-NTX, ranging from gastrointestinal problems to suicidal thoughts. Participants consistently described mental distress as more difficult to handle than the physical discomfort.

> To me, it was like sitting on a train and hitting a rock wall in 360 km/h. (…). If you imagine one of those snow globes, when you turn it upside down, there's a full storm in there. I didn't know what I was thinking at times, it was just a full storm.

However, some participants were surprised by how manageable detox had been: *"It's almost a bit strange, that when you have a goal in mind, it's a lot easier."*

Some described difficulties discerning opioid withdrawal from adverse effects of the first injection. Others emphasized an increase in discomfort after their first injection. These reactions were transient for some, while others experienced prolonged periods of distress. Some described how starting XR-NTX had led to an increase in symptoms of preexisting conditions like ADHD or PTSD. Many participants experienced insomnia, which some said they expected, while others described as distressing. Some also expressed how insufficient sleep was associated with increased symptoms of mental disorders.

3.1.3. Feeling unprepared

Several participants described feeling rushed into treatment with XR-NTX. Particularly, participants stressed how their opioid tapering had been too fast, and some questioned if this had contributed to adverse reactions following the first injection. Participants mentioned uncertainty about the terms of participation as contributing to the feeling of being rushed *"I was afraid of losing my place in the project, that someone*

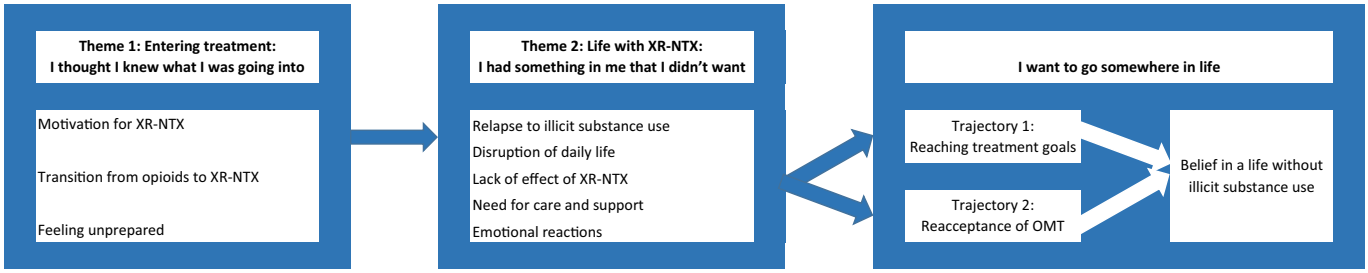

Fig. 1. Overview of themes.

would come and take it from me and that I had to rush the tapering". Some also expressed misgivings about whether their induction to XR-NTX had been conducted per protocol:

> I'm a bit surprised that it only took three days. Because when I read the [medical information] about the injection, it says a minimum of 7-10 days. So I find it damn annoying that you're thinking that you're going to block us from overdose risk, and then you don't give a shit about how we're reacting to it. (…) Yeah, there should have been more information, that it actually won't be fine. Because it wasn't. Because I think, maybe, that if there was a longer period of time [before the injection], it would have been more successful.

Moreover, participants said they had not been prepared for the severity of prolonged withdrawal symptoms, and the challenges of the initial period without opioids: *"I was shocked when I tapered from one milligram to zero. It was like my brain just said «you've got to have something, you've got to have something.» And I wasn't prepared for that."* A few participants were more explicit, and called for specific interventions tailored to XR-NTX. They highlighted the importance of addressing reasons for substance use prior to quitting OMT, exemplified by trauma-oriented treatment, and suggested a more specific screening process to determine whether XR-NTX would fit potential patients' background and treatment goals.

For some, especially those who had experienced serious post injection reactions or side effects, these unexpected experiences had resulted in a feeling of being misinformed. Some also emphasized that information must be understandable and relatable, in a situation that for many was described as chaotic and rushed: *"What kind of information do we get, really? Maybe you get a pamphlet beforehand, but who really reads that pamphlet thoroughly?"* Moreover, several participants implied that they trusted information from peers more than that of health care professionals. *"Those who had tried it earlier, they said «no, no, you can't think of doing that». But I didn't listen to that, but of course, when they're saying things like that, it sticks, somewhere."* Some participants also emphasized that they had heard only the "stories with a happy ending", prior to participation. *"It can't be just one poster boy for the whole thing. It has to be a few more. (…), we should get to know a little about how people do in the long run."*

3.2. Theme 2: life with XR-NTX: I had something in me that I didn't want

The second theme consists of participants' descriptions of life with XR-NTX, including the subthemes: *relapse to illicit substance use; disruption of daily life, lack of effect of XR-NTX; need for care and support;* and *emotional reactions*.

3.2.1. Relapse to illicit substance use

For some participants, the physical and mental distress of starting XR-NTX led to severe reactions, culminating in relapse to illicit substance use. Participants who experienced relapses described it as a shock once again to see themselves as a "junkie".

> I'm 48 years old and I went over to [meeting place], laid down on the ground and let someone shoot me up in my neck [with amphetamines]. I haven't done anything like that since I was in my early twenties, that's just something I don't do. It says something about how sick I was, how desperate, I was totally hysterical.

XR-NTX affected the participants' lives post-transition in different ways. Some who had previously achieved stable lives when in OMT described the relapse to illicit substance use following transition to XR-NTX as particularly dramatic. Participants emphasized both feelings of shame and the practical consequences of relapse.

> I haven't relapsed in 14 years and it was a real downer to sit there with the needle in my arm in the living room and [smoke hash] and so on (…) I called people, got a babysitter (…) and organized everything so I wasn't high when I was with [the children]. Thank God for that. But I could have lost custody. I could have died. There are so many things that could have gone wrong.

3.2.2. Disruption of daily life

Prolonged withdrawal reactions, side effects and the state of being "clean" could also disrupt participants' customary activities in a way that seemed to deprive their existence of its usual meaning. Some participants described how mental and physical health problems from the transition period continued to cause major challenges that prevented them from keeping up activities that gave meaning and joy to their lives.

> Everything was exhausting, even going to the store (…) And then there was the mental side of it, the feeling that I couldn't function right (…) To me, when I'm just sitting there without being able to do anything, and feeling all helpless, I get really desperate.

Some participants described their lives prior to XR-NTX as centered on substance use. When abandoning their day-to-day substance-related routine, some described an existence without its usual structure and meaning:

> It was all very clear and simple kind of… (…) I've been used to my routines, [rolling joints], or whatever (…) But then I had to change that as well, now I was supposed to sit there all clean and watch television and be able to be at peace with myself.

Even though the two participants' situations differed, with one unable to be physically active because of side effects, and the other unable to "find peace" without their usual activities, both are examples of how XR-NTX disrupted participants' lives.

3.2.3. Lack of effect of XR-NTX

Most participants were indifferent or dismissive about the pharmacological effects of XR-NTX. "*I asked [study nurse] if it [XR-NTX] wasn't supposed to suppress anything. That's what I associate with it taking away cravings. That something in my head is suppressed. Because naltrexone does not take away any cravings, apparently."* Others had not been as troubled by opioid cravings during tapering and detoxification prior to XR-NTX and thus felt no improvement. Some even described more cravings after their first injection: "*Before I started with naltrexone I hadn't really thought that much about [opioids], but when I had got [XR-NTX] it felt like everything was all about that. I couldn't think about or focus on anything else."*

A few participants reported that they had tried opioids while on XR-NTX, typically to "test the blockade". Those who tried this described that XR-NTX did block the effect of opioids such as heroin, morphine, and OxyContin, but a few participants described how XR-NTX had not effectively blocked the effect when they tried buprenorphine. According to some participants, stories of buprenorphine's effect despite XR-NTX were circulating within the substance use community. Participants who experienced effects of buprenorphine expressed that the very premise for using XR-NTX was gone. *"Yeah, I tried it [buprenorphine]. I just had to try it after two weeks, but that was actually what made me drop out, because I got full effect."*

3.2.4. Need for healthcare and support

The participants expressed varying needs for health care and support. Some were satisfied with the help they received at the detoxification unit, and had wanted to stay longer, but had been discharged earlier than they expected. However, many participants chose to leave the detox unit immediately after they received their first injection, despite being advised to stay for at least one night. Some stated that they did not receive the help they needed at the detox unit, citing encounters with staff and other patients, lack of tailored withdrawal treatment, and simply "hating being there" as reasons. Some expressed that they had wanted to stay at a facility more suited to their needs.

A few participants described receiving important support from their family, but the majority of participants expressed an unwillingness to involve family. Some participants missed necessary outpatient care or support at home:

> I think the follow-up from NaltRec was fucking terrible. When a person says that he's more or less planned a suicide, it would have been normal, as I see [it] (…), to call after a few days and ask, "how are you doing now".

Another participant said she had felt unable to benefit from the support she was offered: "*[I] had no need to talk to people actually, I just wanted (…) to be left alone (…) and get well again.*" However, most participants emphasized that treatment with XR-NTX would not be effective without supplementary treatment. One participant called for psychotherapy tailored to the effects of being blocked from opioids by XR-NTX:

> I can imagine that others had the same thought as me, that WOW, these are great changes happening, and if it then had been possible to follow up with some conversations (…) where naltrexone and how you were doing in relation to that were topics, then maybe that had been an advantage. That it could have been possible to prevent dropout.

3.2.5. Emotional reactions

Most of the participants presented reflections on how previous use of illicit opioids or opioid agonist medications had affected their emotions. Participants who came from long-term OMT typically described how they had failed to realize to what extent the opioid agonist medications had blunted their emotions. *"[I]did [not] know that [I] was as sedated as I was. Because everything has in a way always been going on autopilot for 14 years."* Or as another participant said: *"At least I'm glad now. Because earlier... I never cried... I just felt totally flat. So it's so good to, like, get my feelings back again. (…) Yeah, for better or worse."* Participants also described re-emerging feelings as overwhelming.

> You get some kind of filter [when using opioid agonist medications] and it's a long time since I've been in opiate withdrawal (…) Being triggered like that, I get panic attacks, I get really scared, I get destructive and I want it to go away. (…) I think I linked it all to that injection. I felt that, ugh, I had something in me that I didn't want.

For most participants, life with XR-NTX was not what they anticipated, entailing unexpected physical and emotional reactions as well as unfulfilled hopes and expectations. *Re*-emerging feelings, relapse to illicit substance use, and prolonged periods of discomfort were some effects of starting XR-NTX that were described as unexpected by participants, and for some, as threats to the meaning of their existence. *"I've been very frustrated and very angry. Very sad actually (…). These months have been hard. So… And not at all what I had expected. I had imagined that this would be fairly easy."*

Participants described a lack of information, or receiving unrealistic information as contributing to their emotional reactions because this information (or lack thereof) shaped their expectations. Participants described the intensity of their hopes about the potential of XR-NTX as a central component in their disappointment.

> *I was so motivated to get [XR-NTX] and like, I was looking forward to it, finally my life is about to begin. And then I got that disappointment when I came home. So it felt like my entire world was crumbling.* (…) *I've tried everything now, and even this isn't working, like (…) am I going to become a heroin addict or am I going to die, or what is going to happen? (…) It's the shittiest thing I've ever been through, it's the worst month of my entire life.*

3.3. Theme 3: leaving treatment: I want to go somewhere in life

The last theme describes the participants' experiences of leaving XR-NTX treatment. We can divide these experiences into two distinct "treatment outcomes" or trajectories: *reaching treatment goals* and *reacceptance of OMT*. Although many participants were disappointed about the unfulfilled expectations they had for XR-NTX, the majority ended their treatment with XR-NTX with *belief in a life without illicit substance use*.

3.3.1. Trajectory 1: reaching treatment goals

The participants' self-defined successful treatment outcomes were more heterogeneous than the study's definitions. For instance, some participants who discontinued treatment according to the study criteria did not define the outcome of their treatment with XR-NTX as a failure. On the contrary, they described ceasing treatment after only a few injections because they had reached their goal of ending all use of illicit opioids or opioid agonist medications, and regarded XR-NTX as unnecessary to maintain this state. Some described treatment with XR-NTX as a useful step in their overall, independent plan to leave OMT. Participants described how achieving their goal was significant to how they viewed themselves.

> It's a sense of freedom. I feel stronger and I feel like I can deal with things that I hadn't thought I could deal with. It's a sense of achievement to go off [OMT]. And to like it, and be content every day and feel that you are stronger mentally, yeah in every way (…) Of course, I've got my social issues [problems], but I've had that on OMT, too. But actually, I think it's easier to look people in the eye, to have contact with people and talk. I feel like I'm more [myself] now than I have been for many, many years.

3.3.2. Trajectory 2: reacceptance of OMT

Although the participants mentioned above expressed confidence about the prospects of a life without OMT or illicit opioid use, most of the participants had experienced reactions during treatment with XR-NTX, which made them reevaluate their immediate goal of leaving or avoiding OMT. At the time of the interview, most participants had reentered, or planned to enter OMT. "*I [chose] to go back to OMT, even if it felt like going to Canossa."* Participants described not having succeeded in their goal of leaving OMT as a disappointment at first. However, many participants described the mental or physical effects of life without opioid agonist medications as more challenging than they had expected, and that they *needed* the medication. *"[I] was walking like a Scrooge McDuck, in circles, making a circle in my living room, and my cat would not have anything to do with me until I got Subutex again and became normal."*

Although many expressed disappointment and frustration over not achieving their goal of abstinence from illicit opioids or of leaving OMT, the majority of the participants' images of the future when discontinuing treatment were not characterized by despair. Rather, participants expressed a refocused awareness of what they valued about their lives, which for many also consisted of a renewed acceptance of OMT.

> The project [made] me realize that for me, I don't think I will ever live without OMT. (…) You always hear so much negative about OMT, you know? But for me, it's the opposite now. That… No. I don't think I'll ever quit OMT medications. Ever.

3.3.3. Belief in a life without illicit substance use

Regardless of whether the participants left XR-NTX treatment satisfied, having achieved their treatment goal, or whether they left to return to OMT, all participants expressed an enduring belief in life without illicit substance use, at some point in the future. For some, this meant a hope that OMT would help them to reach this goal, as a permanent solution. Others described their present use of OMT as a period of

stabilization after their distressing experience with XR-NTX. These participants presented persistent plans about leaving OMT later. Some described how their experiences with XR-NTX had made them more prepared for when they eventually would end their use of opioid agonist medications. Participants mentioned positive experiences from their time without opioids as important motivation.

One participant expressed that the experience with XR-NTX had made him accept that it was okay to need help to deal with his problems: *"In a way, it's been made clearer to me how difficult it can be. (…) So, some kind of acknowledgement that it's like, it's okay to receive help."*

Another participant had a severe adverse reaction after his first injection and decided to end treatment before he received his second. However, he also expressed that this distressing experience had been a wakeup call for him. Afterward, he had been better able to focus on his goals, and what he needed to do to achieve them.

> I don't want to use drugs, it's like, I've been using drugs every day for 17 years, and I am 32 so it's kind of, I want to go somewhere in life. I don't want to die, I've got my whole life ahead of me.

4. Discussion

The current qualitative study sought to explore participants' experience of discontinuation of treatment with XR-NTX. The participants' accounts of their time in XR-NTX treatment were characterized by their descriptions of unfulfilled expectations for the medication, and broken hopes of how treatment with XR-NTX would lead to a better life. Most participants decided to leave treatment because they did not believe that XR-NTX had promoted their ultimate goal of recovery, or that life had been improved in any meaningful way. In the following sections, we dsicuss participants' unfulfilled expectations of XR-NTX in light of dominant understandings of retention as the ultimate treatment outcome.

4.1. Unfulfilled expectations, broken hopes and dreams

Participants expressed their motivation for XR-NTX as a drive for abstinence from substances, including, but not limited to, illicit opioids and prescribed opioid agonist medications. Overall, participants emphasized being completely substance-free as a prerequisite for a better life. The participants' motivation for discontinuing OMT, initiating treatment with XR-NTX, and eventually complete abstinence reflects a strive for belonging and contributing to society. These motivations can also be a challenge to the dominant professional understanding of how best to treat the problems they are facing, as discussed by Neale et al. (2013). Most participants were determined that XR-NTX would be the endpoint of all opioid use, prescribed or illicit. Similar to Gauthier et al.'s (2021) findings, several participants stated that they had "tried everything" prior to XR- NTX, and presented their decision of starting treatment as monumental. The study context itself may have shaped the participants' experiences of the high stakes involved, including the happy ending stories of the life-changing effects of XR-NTX circulating in Norwegian media at the time of the study (e.g. Fosse, 2014; Hovden, 2019; Øfsti, 2019; Vebenstad & Garden, 2017), as well as the general unavailability of XR-NTX in Norway outside of this clinical trial.

Participants sometimes described the challenging and uncomfortable process of detoxification and initiation as more feasible because of the participants' strong belief in the potential of XR-NTX to resolve challenges they had previously encountered when striving for abstinence. This conceptualization of XR-NTX may also have contributed to disproportionate expectations of how XR-NTX in itself could transform their lives. Similar to the participants in Bardwell et al. (2020), the participants in this study expressed expectations for non-medical treatment outcomes of XR-NTX. Other studies of OMT patients' experiences point out that expectations of OMT seem connected to satisfaction with treatment, and high expectations may set patients up for dissatisfaction (Steiro et al., 2020). Strong motivation and belief in the potential of XR-NTX as a last resort or even a "miracle cure" might have overshadowed possible disadvantages they heard about prior to transition. This is similar to what has been called therapeutic misconception or misestimation, that is, a patient's underestimation of risk and overestimation of benefit from participating in clinical trials (Fisher et al., 2008; Horng & Grady, 2003). Rather than attributing this to participants' lack of understanding, both inadequate information from study investigators and unaddressed expectations can be important explanations of such misestimations. Indeed, participants' demands for improved information highlight the necessity of a more dynamic information process, as suggested by Kinnersley et al. (2007), especially when people are in vulnerable and stressed positions. Participants' emphasis on information from peers being more understandable and trustworthy than that of health care professionals is also worth noting (Bassuk et al., 2016).

Not surprisingly, transition from opioids to XR-NTX seemed to be more successful when tailored to the participants' individual needs, including flexibility during opioid tapering (Henry et al., 2019), preadmission preparation (Hogan et al., 2018), and satisfactory conditions at the detoxification unit (Gauthier et al., 2021; Simon et al., 2020). Our findings resonate with research suggesting the need for comprehensive services in SUD treatment (Lachapelle et al., 2020), highlighting the lack of personalized treatment and unavailability of treatment and support services (Fleury et al., 2016), and supplement research suggesting that inpatient treatment is preferred when initiating XR-NTX (Nunes et al., 2018; Sigmon et al., 2012; Sullivan et al., 2017). Several participants described experiences of unsatisfactory health care and support services *prior to* participation in the parent study. Choosing to participate, despite the apprehension some expressed toward XR-NTX, might be understood as a last hope for help that would contribute to a better life (Jackson et al., 2003). However, many participants described not receiving adequate psychosocial support, which previous research has suggested can be a reason for discontinuation of treatment with XR-NTX (Solli et al., 2020). Studies have found that a supportive relationship with a therapist can predict significantly longer retention in outpatient treatment, often regardless of treatment type (Elliott et al., 2018; Hatcher & Barends, 1996; Jinks, 1999; Kasarabada et al., 2002; McLellan et al., 1988; Najavits et al., 2000; Redko et al., 2007). Moreover, research has suggestive supportive relationships, characterized by mutual trust and respect, to be integral for "rebuilding hopes for the future" (Sælør et al., 2015; Vanderplasschen et al., 2015; Veseth et al., 2019). Not receiving necessary support during the transition from opioid use to XR-NTX sustained abstinence might have meant yet another unfulfilled expectation, in addition to its possible influence on reaching treatment goals.

4.2. Unblocked effects and pharmacological considerations

Some participants experienced that XR-NTX neither removed opioid cravings nor blocked the effect of buprenorphine. Participants perceived both issues as deal-breakers, but not surprisingly, they described feeling the effect of buprenorphine as particularly disappointing. Participants typically described illicit opioid use while on XR-NTX as "testing the blockade", and patients in previous studies have also reported doing this (Fishman, 2008; Jarvis, DeFulio, et al., 2018a; Kruptisky et al., 2007; Kunøe et al., 2010; Velasquez et al., 2019). Studies have previously reported subjective effects of opioids, but consensus seems to be that the "high" is not as great (as high) as it was before initiation to NTX (Jarvis, DeFulio, et al., 2018a; Kunøe et al., 2010). In the current study, participants were adamant that the buprenorphine effect they experienced was similar to, or even more intense than, before XR-NTX. Few, if any, clinical trials of XR-NTX have dealt with this issue. However, pharmacological explanations of the phenomenon exist, though perhaps are not well known. To commit to recognizing and understanding participants'

experiences, we briefly explore some of these explanations.

Early NTX efficacy trials used full agonist opioids with lower affinity, such as heroin or morphine, to test the blocking effect (Bigelow et al., 2012; Brewer, 2002; Comer et al., 2002; Tennant et al., 1984; Verebey et al., 1976). Unlike full agonist opioids, buprenorphine is a partial agonist to the mu receptor and an antagonist to kappa and delta receptors, with high affinity to all (Lewis, 1985). The high mu receptor affinity of buprenorphine may suggest that NTX and BUP can coexist in mu opioid competitive binding (Gerra et al., 2006; Mello et al., 1993), implying that participants may in fact have experienced a euphoric, mu-receptor effect of buprenorphine. Another explanation suggests a synergic effect of NTX and BUP. Research has suggested that the kappa opioid receptor system has a role in mood disorders (Banks, 2020; Chavkin & Koob, 2016; Crowley & Kash, 2015; Tejeda & Bonci, 2019; Wee & Koob, 2010). Studies have proposed that prolonged opioid use, and thus continued exposure to mu agonists, can result in kappa receptor system overdrive (Banks, 2020; Chavkin & Koob, 2016). This overdrive may lead to dysphoric mood states, which may be part of a prolonged abstinence reaction, symptoms which may be further increased by naltrexone mu opioid receptor blockade (Rothman, 1992; Rothman et al., 1991). Participants who tested the blockade with buprenorphine may have achieved an effect where buprenorphine reinforced NTX' weak kappa and delta antagonism, producing an anti-depressant effect (Ehrich et al., 2015; Fava et al., 2020; Karp et al., 2014; McCann, 2008), which research has suggested affects dysphoric mood and opioid-seeking behavior associated with prolonged opioid withdrawal (Gerra et al., 2006; Rothman et al., 2000).

Any effect experienced, whether as the result of ineffectual mu receptor blockade, kappa-antagonist mood regulating effect, or a combination, might have been interpreted as a "drug effect", particularly in combination with other substance-associated cues, such as injection (McBride et al., 2001). Moreover, more participants than those who reported having tested it, described the *possibility* of an effect of buprenorphine as common knowledge. This may have induced an expectancy effect (Brown, 1993; Leventhal & Schmitz, 2006), increasing the subjective experience of any pharmacological effect of buprenorphine. For the participants in the current study, the vital point is that they did experience an opioid effect, which they had wanted to avoid. This eliminated their very premise for treatment with XR-NTX. An inescapable question is whether patients should be informed about this possibility prior to XR-NTX treatment.

4.3. Should discontinuation of treatment be considered a failure?

In contrast to findings by Velasquez et al. (2019), none of the participants in the current study said that they decided to discontinue treatment with XR-NTX to return to illicit opioid use. However, our findings are similar to other findings from these authors and others, in that a few participants decided to leave treatment with XR-NTX because they had reached their goal of leaving OMT, and thus achieving abstinence from all opioids, illicit or prescribed (Randall-Kosich et al., 2020; Velasquez et al., 2019). Themes identified as important during and immediately after transition did not seem to indicate whether the participants reached their goal. For instance, reoccurring memories of traumatic experiences, which intuitively might seem to be a plausible rationale for leaving antagonist treatment, was never explicitly stated as such. What does seem to be important is whether the participants were able to lead fulfilling lives after the transition period. Other studies suggest that abstinence achieved during short periods of treatment with XR-NTX seem to wane after treatment discontinuation (Lee et al., 2016; Ngo et al., 2011; Williams et al., 2017). However, experiences of satisfactorily reaching opioid abstinence after a few injections are in line with previous and current clinical observations of the phenomenon, and provide nuance to the understanding of early discontinuation of treatment as indicative of failed treatment (Dennis et al., 2020; Walker, 2009). It also supplements earlier findings from Solli et al. (2020), who suggested that some XR-NTX patients might need longer than a year to reach their treatment goal. Findings from the current study suggest that for some, personal treatment goals may be achieved earlier than the framework of a clinical trial allows.

However, for most of the participants, deciding to leave treatment with XR-NTX also meant abandoning visions of a life without any use of prescribed or illicit opioids, by reentering OMT. Discontinuing or avoiding use of prescribed, opioid agonist medications in OMT was a central component in all the participants' motivations for XR-NTX, often stated more explicitly than stopping the use of illicit opioids. Indeed, the participants' reasons for wanting XR-NTX resembled other patients' reasons for leaving OMT (Randall-Kosich et al., 2020), notably to end physical opioid dependence and because of experiences of stigma. In many ways, OMT manifests the ambiguity and duality of the expectations to which the participants may be subjected, and perhaps have internalized. Professional knowledge supports OMT as the most effective and feasible treatment option for opioid dependence (WHO, 2009). With the chronic and relapsing characteristics of opioid dependence (Leshner, 1997), research has suggested that providers may even recommend OMT to be life-long (Mattick et al., 2014; Vogel et al., 2017; WHO, 2009). However, participants who had been in OMT prior to XR-NTX treatment described how they faced stigma and ignorance from the wider society, similar to a recent systematic review of qualitative studies of OMT patient experiences (Steiro et al., 2020). A public perception might indeed be that people with opioid dependence need to leave OMT eventually, for the treatment to be judged successful, or recovery to be considered complete (Randall-Kosich et al., 2020; Tofighi et al., 2020). The association between motivation for XR-NTX and stigma regarding OMT was also discussed by Gauthier et al. (2021), who suggested improving patient education to mitigate the impact of stigma. Strengthening efforts to educate wider society regarding opioid use and the complexity of treatment and recovery might be another way of preventing stigma from influencing patients' treatment decisions. For example, calling attention to the life stories of people with SUD may reduce stigmatizing public attitudes (Sumnall et al., 2020).

This study's overall findings support an emerging notion in both research and clinical work that the dominant understanding of successful treatment outcomes is rigid, unrealistic, and potentially harmful. Discontinuing treatment is typically understood as a poor outcome (WHO, 2009), although in a real-life setting such events are features of typical treatment trajectories, and are often followed by subsequent re-initiation to treatment (Fishman et al., 2020). Opioid dependence is most effectively treated as a chronic disorder: relapses are frequent and successive treatment episodes may be necessary to achieve treatment goals (Hser et al., 2015; Laudet, 2007). Although perceived as a "failure" by participants and in the framework of a clinical trial, such phenomenon are more in line with what might be expected in a real-world setting (Fishman et al., 2020).

4.4. Methodological considerations

The parent study was open-label, and conducted in as naturalistic a manner as possible, thus creating a research setting more in accordance with a real-world setting than a typical clinical trial. Although small, the sample in the current study is diverse, recruited from four geographically and demographically different sites. Moreover, we interviewed as many women as men, in contrast to the low proportion of women in the parent study as well as in OMT in Norway (Lobmaier et al., 2021) and among treatment-seeking persons with OUD in Europe (EMCDDA, 2020). Women in OUD treatment face different challenges than men, including mental health burden, exposure to traumatic experiences, and stigma (Huhn & Dunn, 2020). The relatively high proportion of women in the current study allowed for us to explore such issues, but we did not address gender differences explicitly.

The participants in the current study can be characterized as a self-selected sample, by pursuing a novel and "unknown" treatment,

despite the comparatively unrestricted availability of OMT and other treatment approaches in Norway. This may involve more dissatisfaction with OMT, a stronger drive for abstinence, and showing a higher interest in treatment alternatives to OMT (Sharma Haase et al., 2016; Solli et al., 2019). Self-selection might have been a further issue in the current study, where those who chose to participate might have been those who were reconciled with the result of their "failed" XR-NTX treatment. Others, with more distressing treatment outcomes, such as a return to illicit substance use, might have been those unwilling to participate, or impossible to reach.

The study interviewed participants at different time points relative to their last injection, which might have influenced the participants' recall of the events, as well as their view of treatment with XR-NTX. However, the study team identified the themes presented in this article independent of the point of time that the study interviewed participants. It is also worth emphasizing that the participants in the current study were those who chose to discontinue treatment earlier than the parent study's predefined treatment period. Thus, their experiences with XR-NTX can be expected to differ from those who chose to stay in treatment.

4.5. Conclusion

Although the participants presented ending all opioid use as a significant part of their recovery, we found that blocking the effect of opioids only solved part of their problems. The participants' accounts of transitioning from opioid use to XR-NTX were characterized by unmet needs and unfulfilled expectations regarding XR-NTX and the accompanying health and support services. Their rationale for ending XR-NTX centered on experiences of XR-NTX not promoting their own goal of recovery. Our findings emphasize that a dynamic understanding of discontinuation of treatment is necessary to achieve a long-term approach to recovery, which recognizes discontinuation as a feature of typical treatment trajectories and often followed by re-initiation to treatment.

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CRediT authorship contribution statement

Ida Halvorsen Brenna: Investigation, Writing – original draft, Formal analysis. **Anne Marciuch:** Formal analysis, Writing – review & editing. **Bente Birkeland:** Formal analysis, Writing – review & editing. **Marius Veseth:** Supervision, Writing – review & editing. **Bente Røstad:** Investigation, Writing – review & editing. **Else-Marie Løberg:** Supervision, Writing – review & editing. **Kristin Klemmetsby Solli:** Conceptualization, Writing – review & editing, Project administration. **Lars Tanum:** Conceptualization, Supervision, Writing – review & editing, Funding acquisition, Project administration. **Bente Weimand:** Conceptualization, Methodology, Supervision, Writing – review & editing, Project administration.

Declaration of competing interest

None.

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III

Personal recovery among people with opioid use disorder during treatment with extended-release naltrexone

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Declarations

Ethics approval and consent to participate

Ethical approval for the NaltRec trial, including the present study, was granted by the Norwegian Regional Ethical Committees for Medical and Health Research Ethics (REK) committee South East A (# 2018/132), by the personal data protection representative for each of the sites, and by the Norwegian Medicine Agency (NOMA), EudraCT Code 2017-004706-18. The trial is registered at Clinicaltrials.gov # NCT03647774. It was first registered on Aug 28, 2018, before first participant inclusion on Sep 21, 2018 (Weimand, Solli, Reichelt, & Tanum, 2021). All participants gave written, informed consent for their participation.

Consent for publication

All participants gave general written, informed consent for publication.

Availability of data and material

The data used in this study are based on a still ongoing study that will be finalized in 2025. According to current Norwegian regulations and practice, the data will then be anonymized and deposited in a publicly available data repository (e.g., The Norwegian Centre for Research Data).

Competing interests

None

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Abstract

Background and aims: Recovery from substance use disorders (SUD) has traditionally been equated with abstinence. "Personal recovery" however emphasizes recovery as a unique and personal process, supported by changes in connectedness, hope, identity, meaning and empowerment. This study aimed to examine personal recovery in people receiving extended-release naltrexone (XR-NTX); specifically investigate changes in personal recovery during treatment, identify groups of participants following distinct trajectories of recovery, and characteristics predicting group-belonging.

Methods: Overall change in recovery (Questionnaire about the Process of Recovery, QPR) score was assessed by linear mixed model in a subsample of 135 people with opioid use disorder (OUD) participating in a 24+28 week trial of XR-NTX. Growth mixture model was used to identify potential groups of people following distinct trajectories of personal recovery.

Results: Overall, there was a significant change in QPR score during treatment. Four groups with distinct recovery trajectories were identified; "initially low– increase" (G1), "initially average– no change" (G2), "initially high– no change" (G3) and "initially high– increase" (G4). The groups were different with regards to level of psychological distress, social support, and the use of benzodiazepines. In addition, previous participation in opioid agonist treatment programs, current pain, life satisfaction, employment, heroin craving and previous use of heroin also differed between groups.

Conclusions: Personal recovery among people receiving XR-NTX follows different trajectories, and various factors are associated with personal recovery. Particular attention regarding psychological distress, social support and heroin use among patients commencing XR-NTX treatment is important to facilitate successful recovery trajectories.

Word count: 4069

Key words: personal recovery, QPR, extended-release naltrexone, XR-NTX, opioid use disorder, opioids

1 Background

Recovery is a key concept in mental health and addiction services. In the field of substance use disorders (SUDs), the concept was traditionally synonymous with abstinence, for some (e.g. 12-step movements) meaning total abstinence from all substances. Nevertheless, it is now widely agreed that recovery can be supported by appropriate medications (Strang, 2012), and that abstinence, although important, is not the only prerequisite for recovery (A. B. Laudet & White, 2010). While an increased control over the intake of substances might be necessary (yet not sufficient) (A. T. McLellan, McKay, Forman, Cacciola, & Kemp, 2005) or even pivotal (Kelly & Bergman, 2021; A. B. Laudet, 2007; McKeganey, Morris, Neale, & Robertson, 2004) for further long term improvements, other factors, such as health and wellness (SAMHSA, 2012), relationships (Price-Robertson, Obradovic, & Morgan, 2017) and improved quality of life (J. Neale, Nettleton, & Pickering, 2011) have been increasingly recognized as important for recovery.

Still, the notion of recovery from SUDs has been unclear, and remains somewhat ambiguous, despite increased interest in the concept. While there has been a progression towards including psychosocial outcomes and their association with long-term abstinence, the WHO still heavily emphasizes the abstinence aspect, defining recovery as "maintenance of abstinence from alcohol and/or other drug use by any means" (World Health Organization, 1994). Although multiple other definitions, stressing recovery as a process towards improvements in various life areas, exist, there is a tendency for researchers to sometimes implicitly define recovery in terms of substance use or abstinence, almost 15 years after Laudet's (A. B. Laudet, 2007; A.B. Laudet, 2008) call for emphasis on other factors and greater clarity of the term. This lack of consensus may also have contributed to the emphasis of abstinence in recovery (Joanne Neale et al., 2014).

Opioid use disorder (OUD) is a serious, long-lasting condition with detrimental consequences for the individual and society as a whole. While the recommended treatment for OUD (WHO, 2009) is opioid agonist treatment (OAT), an alternative is the opioid antagonist extended-release naltrexone (XR-NTX)(American Society of Addiction Medicine, 2020). XR-NTX has shown good treatment outcomes when compared to OAT, such as a reduction in relapse rates, illicit drug use and depression or anxiety symptoms (Latif et al., 2018; Lee et al., 2018; Tanum et al., 2017). Treatment with XR-NTX involves blocking the effects of opioids, thus preventing the experience of pleasure or intoxication, which reduces reinforcement of further use, and supports abstinence. As individuals are blocked from the effects of opioids, they can focus on aspects of recovery other than getting the use of opioids under control.

In the mental health field, the concept of *personal recovery*, has gained wide acknowledgment as an alternative to the traditional focus on clinical recovery. The personal recovery concept is founded in service users' experiences, and highlights the dynamic and multidimensional process of recovery as a unique, personal journey towards living a satisfying life, even with the limitations of the disorder (Anthony, 1993). Five core processes of personal recovery have been identified: Connectedness, Hope and optimism, Identity, Meaning and Empowerment, constituting the CHIME framework (Leamy, Bird, Le Boutillier, Williams, & Slade, 2011). Studies examining addiction recovery, highlight recovery as a personal, ongoing process (A. B. Laudet, 2007; A.B. Laudet, 2008; J. Neale et al., 2015), emphasizing factors in line with the CHIME framework, such as support and relationships, identity and empowerment (David Best, Irving, Collinson, Andersson, & Edwards, 2017; D. Best & Laudet, 2010; Brekke, Ness, & Lien, 2020; A. B. Laudet, 2007).

Few studies have examined personal recovery among people with SUD, or in the context of SUD and mental health problems, and most studies are qualitative. One such study examining personal

recovery among members of Narcotics anonymous (Dekkers, Vos, & Vanderplasschen, 2020), found connectedness to be a crucial recovery-supportive element. When examined in the context of people with both SUD and mental health challenges (dual diagnosis; DD), recovery has been emphasized as a relational process (Brekke et al., 2020).

As the comorbidity between mental health problems and SUDs is high (Regier et al., 1990), the investigation of personal recovery in SUD settings should also be relevant. The concept has been examined in the context of people with DD, and personal recovery has been suggested as the bridging principle between mental health care and substance abuse treatment (Davidson & White, 2007). Several studies have examined how people with DD experience recovery, and a review from 2017 (De Ruysscher, Vandevelde, Vanderplasschen, De Maeyer, & Vanheule, 2017) showed the themes people with DD see as important for their personal recovery in large overlap with the themes identified in the CHIME framework.

OUD is a heterogeneous disorder (Carroll, 2021), and it can be expected that potential changes seen in recovery may not be representative for subgroups of patients. Previous studies have shown there are different subgroups of patients in treatment when it comes to opioid use patterns over time, both patients in OAT (Eastwood, Strang, & Marsden, 2017; Hser et al., 2017) and patients on XR-NTX (Ruglass et al., 2019). Identifying how individuals' recovery process develops over time while receiving XR-NTX, as well as characteristics associated with different patterns might be important to achieve a better understanding of recovery among people with OUD receiving XR-NTX, and possibly informing timing or type of intervention efforts.

The main aim of this exploratory study was to examine the process of personal recovery among opioid dependent people receiving treatment with XR-NTX. Specifically we sought to explore 1) possible changes in personal recovery during the course of treatment; 2) whether there are groups of patients following distinct trajectories of personal recovery, and 3) if baseline characteristics could predict belonging to such groups with different QPR trajectories.

2. Materials and methods

2.1 Design

The present study is part of the Norwegian open-label, multi-center NaltRec study ("Long acting naltrexone for opioid addiction: the importance of mental, physical, and societal factors for sustained abstinence and recovery"). For further details on NaltRec, see Weimand et al. (Weimand et al., 2021)

After complete detoxification from all opioids, an injectable suspension of 380 mg XR-NTX (Vivitrol®) was administered every 4 weeks, for 24+28 weeks.

2.2 Setting and participants

The study was performed at five urban addiction clinics in Norway, in a naturalistic outpatient setting. Men and women, aged 18-65 years, with a diagnosis of opioid dependence according to DSM-IV criteria (Black & Grant, 2013) were recruited from addiction clinics, detoxification wards or community health services. Participants had to be enrolled in an OAT program to ensure access to OAT if needed after ending participation. Treatment with XR-NTX was not available outside of the clinical trial.

Participants with severe psychiatric or somatic illness that could interfere with study participation, as well as pregnant or breastfeeding women, and people with a primary alcohol dependence were excluded.

2.3 Measures

2.3.1 Personal recovery

Personal recovery was measured using the 15-item version of the *Questionnaire about the Process of Recovery* (QPR) (Law, Neil, Dunn, & Morrison, 2014; S. T. Neil et al., 2009; Williams et al., 2015). QPR is one of the most widely used measures of personal recovery, has a strong evidence base and is related to the CHIME framework (Shanks et al., 2013). The items are rated on a 5-point scale from 0="disagree strongly" to 4="agree strongly". The total sum score ranges from 0 to 60, with higher scores indicating higher degrees of personal recovery. Internal consistency, with a Cronbach's alpha of 0.93, test re-test reliability and convergent validity has been found to be high (Law et al., 2014). In this study, QPR was measured at baseline, 12, 24, 40 and 52 weeks.

2.3.2 Covariates

Covariates included in this study were measured at baseline.

Demographic variables were measured using the Europ-ASI (Kokkevi & Hartgers, 1995; A.T. McLellan et al., 1992). Number of close relationships was calculated based on a positive response in any of the 6 categories in questions H14-19, giving a maximum score of 6 if the respondent has close relationships in all categories.

Previous experiences of **traumatic events**, as well as a PTSD diagnosis was assessed using the MINI interview (Sheehan et al., 1998).

Substance use of alcohol, heroin, methadone or buprenorphine, other opioids, benzodiazepines , cocaine, amphetamines, cannabis and multiple substances, was measured using the Europ-ASI (Kokkevi & Hartgers, 1995). Use last 6 months was measured on a 5-point scale where 0="no use", 1="sometimes but no more than 2-3 times a month", 2="1-3 times a week", 3="used daily, or almost daily", 9="never used". The scores were categorized into: no use (0+9), occasional use (1), frequent use (2+3). Historical severity of substance use was assessed as years of regular use (Carise).

Craving was measured using an 11-point scale where participants were asked to indicate how often they had thought about "getting high on heroin" the last month, from 0="not at all" to 10="constantly/very much" (Kunøe et al., 2016).

Current experience of pain was measured using the single-item numeric pain rating scale (Hawker, Mian, Kendzerska, & French, 2011),(Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011), an 11-point scale where 0="no pain" and 10="worst pain imaginable".

Mental distress was measured using the 25-item Hopkin's Symptom Checklist (H-SCL-25) (Strand, Dalgard, Tambs, & Rognerud, 2003) employing a 4-point scale ranging from 1="not at all" to 4="extremely."

Life satisfaction was measured using the Temporal Satisfaction with Life Scale (TSWLS) (Pavot, Diener, & Suh, 1998). Items are scored on a 7-point scale ranging from "strongly agree" to "strongly disagree".

Social support was measured using the Interpersonal Support Evaluation List (ISEL-12) (Cohen & Hoberman, 1983; Cohen, Mermelstein, Kamarck, & Hoberman, 1985). Items are scored on a 4-point scale ranging from 0="definitely false" to 3="definitely true."

2.4 Statistical analysis

Baseline characteristics are presented as means and standard deviations (SDs) or frequencies and percentages.

Overall change in QPR score in the entire sample was assessed by linear mixed model with random intercepts and fixed effects for time coded as dummy. As to exploratory approach, growth mixture model was estimated to identify possible unobserved groups of participants following distinct QPR trajectories (Nagin & Nagin, 2005). The approach attempts to identify homogeneous groups of participants based on individual profiles by applying a set of statistical criteria. The criteria used were Bayes Information Criterion, reasonable group sizes, high average within-group probabilities, and non-overlapping 95% confidence intervals (CIs) for the trajectories in the identified groups. The groups were further compared by ANOVA for continuous and χ^2-test for categorical baseline characteristics and substance use variables. Pairwise-comparisons were performed in post-hoc analyses. Due to relatively small group size, sensitivity analyses employing non-parametric tests were performed.

Cases receiving at least one XR-NTX injection but missing a QPR score at baseline were excluded. Missing values on single items lead to a missing overall score. Due to the exploratory nature of the study no adjustment for multiple testing was implemented. All analyses were conducted in STATA v16. All tests were two-sided and results with p-values below 0.05 were considered statistically significant.

2.5 Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics Southeast Norway, the Norwegian Medicines Agency, and the boards of research ethics at the participating hospitals, and conducted in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2013). Patient data was handled according to the General Data Protection Regulation (GDPR), and National Personal Data protection regulations. The study is registered at clinicaltrials.gov (NCT01717963).

3 Results

3.1 Participant characteristics

The overall NaltRec study included 162 persons, of whom 138 received at least one injection of XR-NTX. The sample for the present study consisted of the 135 participants who received at least one injection, and in addition filled out the QPR at baseline. The sociodemographic variables of the sample are presented in table 1.

<Table 1 >

3.2 QPR score over time

During the course of treatment, the mean QPR score for the group as a whole increased by 7 points.. According to linear mixed model, there was a significant increase in QPR score from baseline to week 24, 40 and 52 - but not to week 12 (Table 2 and figure 1). No other changes in QPR score were significant.

<Table 2 and Figure 1 >

3.3 Personal recovery trajectories

A growth mixture model identified four distinct groups of participants following distinct QPR trajectories, coined the "initially low– increase" (G1), "initially average– no change" (G2), "initially high– no change" (G3) and "initially high– increase" (G4) (table 3, figure 2).

High average within-group probabilities indicated that the groups were homogenous, which is also confirmed by essentially non-overlapping 95% CIs for the trajectories in each group. The baseline values of QPR were significantly different between groups, according to non-overlapping 95% CIs at baseline. Even though the two "improvement" groups were small, they were quite distinct and exhibited a significant linear change.

<Table 3 and Figure 2 >

G2 and G3 constituted the majority of participants (35.6 % and 48.1%, respectively), and showed no significant change in score over the course of treatment.

G1 had the lowest starting point, with initial QPR scores almost half of those of G2. However, G1 exhibited a significant change in score during the course of treatment, ending up with a QPR score higher than G2, and closer to that of G3 at 52 weeks.

G4 had the highest starting point, about 30 points higher than G1, and still exhibited a significant increase in score.

3.4 Covariates associated with change in QPR

Table 4 and Table 5 present comparison of groups with respect to baseline characteristics and substance use variables, respectively. Sensitivity analysis showed no major deviations from reported results.

<Table 4 and 5 >

No significant differences between groups were found for age or gender, or sociodemographic variables. However, the groups differed significantly regarding OAT status at the time of study enrolment; in G1 41.7% were in OAT, whereas this number was 90% in G4.

Post hoc tests (table 6) showed G1 differed significantly from all other groups with respect to all variables where the overall significant difference between groups was found, except for the variable "working last 4 weeks."

<Table 6 >

G1 showed significantly higher scores on overall mental distress and lower perceived social support than the other groups, and experienced higher pain and lower life satisfaction than G3 and G4. This was also the case for the craving variable.

In G2 the social support as well as the mental distress scores were significantly higher than in both G3 and G4. There were however no differences in how participants or the interviewer rated their need for help with psychological/emotional problems, or regarding experience of traumatic events or PTSD diagnosis. Also G2 was significantly less likely to be working in the last 4 weeks than G3 or G4.

For the substance use variables, years of regular use did not differ between groups for any substance. No differences between groups were found on use of alcohol, other opioids, cocaine, amphetamines or cannabis. For heroin, use during the last 6 months, but use the last 4 weeks,

differed between groups. For benzodiazepines, G4 had a significantly lower use than the other groups, both during the last 4 weeks and 6 months

4.0 Discussion

The identification of differential trajectories for personal recovery adds understanding to the recovery process during the course of XR-NTX treatment, highlighting different subgroups of patients which may benefit differently from XR-NTX in terms of personal recovery. In the following, we will shortly discuss the change in QPR score in the course of treatment, then focus mainly on the groups of patients following distinct QPR trajectories and associated characteristics.

4.1: Personal recovery during the course of treatment

There was an overall increase in personal recovery from baseline to 24, 40 and 52 weeks. This may not be surprising, given previous findings of people receiving XR-NTX showing higher life satisfaction (Gaulen, Šaltytė Benth, Fadnes, Brenna, & Tanum, 2021), which is closely related to personal recovery. In line with viewing recovery as a process, the change was not significant from baseline to 12 weeks, supporting the notion that the process requires time.

While a concern might be the QPR is not previously used in SUD settings, the processes important in personal recovery (Connectedness, Hope, Identity, Meaning and Empowerment) are easily seen as universal, nonspecific processes important for any recovery. Our findings add a preliminary support to the use of the QPR in SUD populations, provided further examination of the concept and validation of the measure.

4.2: Trajectories of personal recovery

The identification of four groups of patients following distinct recovery trajectories provides an increased understanding of personal recovery among patients receiving XR-NTX in this Norwegian study. Most patients (i.e. the two “no-change groups”, constituting almost 84%) reported little change in QPR score. This might not be surprising, considering SUD-recovery can be a yearlong process (Dennis, Foss, & Scott, 2007; Hser, 2007; A.B. Laudet, 2008). In addition, it is suggested the QPR should not only be used to give a total recovery score, but also to facilitate engagement and individual goalsetting (S. Neil et al., 2007). Thus it would possibly be more meaningful for some patients to look at subdomains of recovery related to individual goals, instead of the total QPR score.

The two “improvement” groups (G1 and G4), although small, represent notable patterns of recovery. Firstly, G4 with considerably high QPR scores at baseline, both relative to the other groups and to previous findings (Dehmahdi et al., 2021; Williams et al., 2015), experienced a significant increase in QPR during the course of treatment. This is in contrast with the notion of ceiling effects (Garin, 2014), where one would expect patients scoring initially high to experience limited increase. Possibly this group of patients is especially “high-functioning”, and already in the process of recovery, a hypothesis strengthened by the higher OAT participation, and the lower burden of pain and psychological distress, compared to the other groups. XR-NTX treatment may thus have propelled their recovery process, in line with qualitative findings that many patients seeking XR-NTX treatment do so to advance their recovery by exiting OAT (Brenna et al., 2021; Marciuch et al., 2022).

Secondly, the initially low scoring G1 seems to represent a group of patients with likely much to gain by commencing XR-NTX treatment, as they surpassed G2 in QPR score, and also had the largest increase in score during the course of treatment. Nevertheless, they are also a group of patients experiencing considerable burden, and clinicians should be aware of the serious struggle these

patients face when entering treatment. Factors differentiating between trajectories further underline the importance of "something" in addition to «just the injection» in personal recovery among people receiving XR-NTX.

4.3 Characteristics associated with recovery trajectories

Several pre-treatment characteristics were associated with QPR trajectory, and thus significant for personal recovery in people receiving XR-NTX. Demographic characteristics did however not vary by group, underlining personal recovery as a universal process, not tied to differences in age, gender or education. Nevertheless, individual factors, such as pattern of previous heroin use, psychological distress or social support did impact recovery trajectory. This is in line with findings of social support (Dunne, Perich, & Meade, 2019), or severity of mental problems (Resnick, Rosenheck, & Lehman, 2004) as important covariates of personal recovery.

The initially low scoring G1 was more likely to not be in OAT, experience higher psychological distress, more pain, lower life satisfaction and social support, and exhibit more heroin and benzodiazepine use, implying a lower functioning in this group. Although we do not know how the associated characteristics developed over the course of treatment, pain and psychological distress have not been found to rise during XR-NTX treatment (Latif et al., 2018; Latif et al., 2019), while life satisfaction likely increases (Gaulen et al., 2021).

In SUD recovery, substance use, and its discontinuation, has been considered important, and in this study, heroin use in the last 6 months emerged as a factor distinguishing between groups. However, heroin use last 4 weeks did not differ significantly, and neither did any substance use, other than of benzodiazepines and multiple substances. The lack of difference in use of heroin in the last month might however be due to participants overall having made the decision to enter XR-NTX treatment, and thus reducing their use to a similar level.

Regarding psychological distress, except for G4, participants had H-SCL scores above the cut-off for clinically significant distress. However we found no differences between groups on previous experiences of traumatic events or PTSD diagnosis, which may be surprising given that previous experiences of trauma or abuse are associated with OUD (Mills, Teesson, Ross, & Peters, 2006), and persistent opioid use (Hser, Evans, Grella, Ling, & Anglin, 2015). Co-occurring mental disorders are common among people with SUD (Regier et al., 1990) and contribute negatively to the course and treatment of OUD (Rounsaville, Weissman, Crits-Christoph, Wilber, & Kleber, 1982), while addressing mental problems likely enhances long-term abstinence (Hser et al., 2015). Mental distress has been associated with higher levels of impulsivity, hyperactivity and inattention among patients seeking treatment with XR-NTX, and is highlighted as important to focus on when considering treatment options for OUD (Karlsson et al., 2021). Although our analysis does not allow for a longitudinal examination of associated factors, one hypothesis is that the increase in personal recovery seen in G1 could be connected to a decrease in mental distress. This would be in line with the findings of reduced mental symptoms during XR-NTX-treatment (Latif et al., 2018), as well as qualitative findings that mental health difficulties are of importance for how well the opioid blockade in XR-NTX treatment is handled (Marciuch et al., 2022).

Social support is related to the concept of connectedness, and has been shown to be important in SUD recovery (Dekkers et al., 2020; Hser, 2007). In the present study, social support at baseline differed significantly between groups of high vs. low baseline QPR; G1 and G2 with the lower baseline QPR score differed from G3 and G4, but not from each other. Thus a lower social support score at baseline would mean a lower baseline QPR score (G1/G2), regardless of whether an increase in QPR score was experienced later in treatment (G1/G4) or not (G2/G3). Nevertheless, all groups

were above the midpoint on the ISEL, indicating positive views of the social support available. Interestingly, no other social or relational variables such as number of close relationships differed significantly between groups.

On a final note, we do not know if treatment increased mental wellbeing, social support, or some other factor, thereby increasing QPR score. However, the factors found to predict QPR trajectory are nevertheless relevant to recognize and observe when patients commence XR-NTX treatment.

4.4 Strengths and Limitations

The current study had several strengths; including a relatively large sample size, as well as the exploration of personal recovery in a sample where this concept has not been previously studied. The study is naturalistic, which strengthens the clinical relevance, further it offers a longitudinal exploration of the process of personal recovery. However, there were also several limitations.

Two of the identified groups were rather small, possibly meaning too low power to detect certain differences between groups. The exploration of personal recovery in people receiving XR-NTX could also have benefited further from comparisons with a control group from the general OUD population, or people in OAT.

Further, the baseline characteristics were possibly influenced by the patients' current situation, e.g. withdrawal or excitement to soon start a new treatment. Patients seeking XR-NTX treatment are perhaps more recovery-focused, as well as have a high preference for XR-NTX, as this is a novel treatment in Norway.

The study offers assessment of associations between baseline characteristics and QPR score and subsequent trajectory, not allowing for comparisons between groups on different factors over the course of treatment. The chosen cross-sectional examination of relevant covariates means we do not know how the associated characteristics developed during treatment, and how this corresponds to the process of recovery. In addition, although characteristics were chosen from a wide area of factors, we did not measure all potential factors that may have differentiated between trajectories.

5. Conclusions

People with OUD in XR-NTX treatment experienced an increase in personal recovery. Especially patients with an initially poor outset in terms of psychological distress, social support and heroin use might have much to gain by commencing NTX in terms of recovery, as well as those already in an active recovery process. Clinical awareness of these factors is important to facilitate successful recovery trajectories.

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Tables and figures

Table 1. Baseline characteristics, N=135

Characteristic	Statistic
Gender, female, n (%)	30 (22.2)
Age, mean (SD)	37.6 (9.4)
In OAT before enrolment in study, Yes, n (%)	81 (60.0)
No. of XR-NTX injections received, mean (SD)	9.6 (5.2)
Years of completed education, mean (SD)	12.0 (2.4)
Working last 4 weeks, n (%)	30 (22.2)
Common housing arrangement past 3 years, n (%)	
Alone	80 (59.3)
With family or friends	47 (34.8)
In prison/institution	4 (3.0)
No stable living situation	4 (3.0)
Spends most of free/leisure time with…, n (%)	
Family or friends without problematic substance use	65 (48.1)
Family or friends with problematic substance use	18 (13.3)
Alone	52 (38.5)
Years of regular heroin use, mean (SD)*	6.3 (6.1)
Years of regular use of methadone/buprenorphine , mean (SD)	5.3 (5.0)
Years of regular benzodiazepine use , mean (SD)	6.3 (7.6)
No. of days used last 4 weeks, mean (SD)	
Heroin	6.8 (10.2)
Methadone/buprenorphine	16.8 (12.4)
Benzodiazepines	10.0 (11.6)
Exposure to traumatic event, n (%)**	111 (84.1)
Fills MINI-criteria for PTSD, n (%)**	20 (15.2)

*2 missing, **3 missing

Table 2. *Results of linear mixed model* (RC=regression coefficient, CI=confidence interval)

	RC (95% CI)	*p-value*
Baseline – ref.	0	
Week 12	1.64 (-0.26; 3.55)	*0.091*
Week 24	2.07 (0.05; 4.10)	***0.045***
Week 40	3.72 (1.46; 5.98)	***0.001***
Week 52	4.48 (1.85; 7.11)	***0.001***

Figure 1. QPR score over time

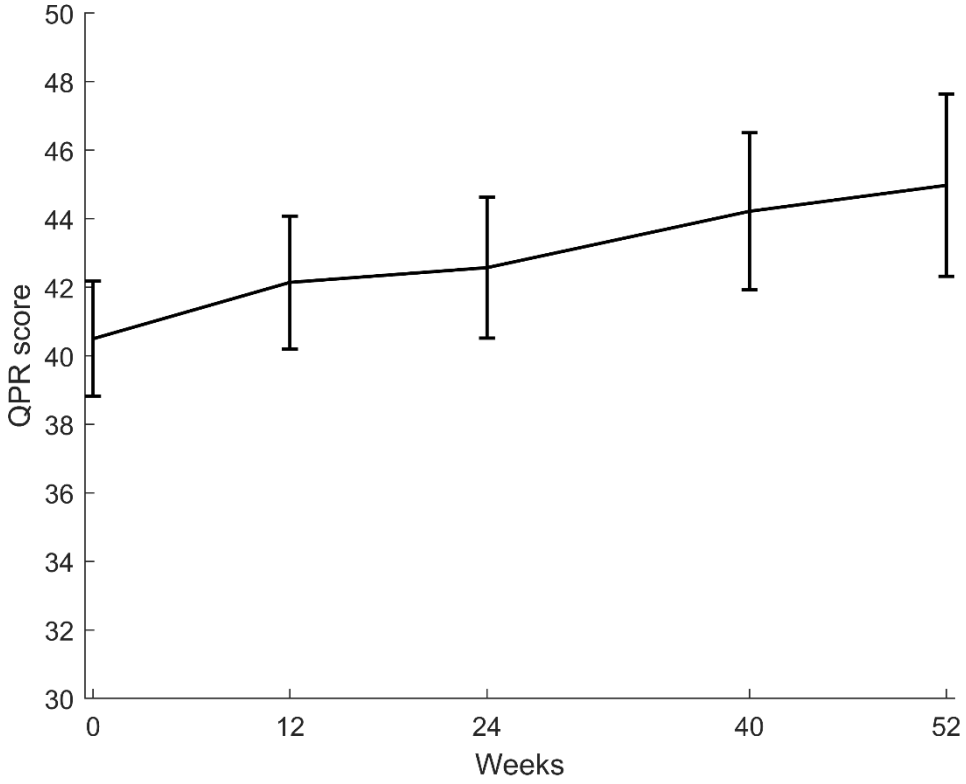

Table 3 Results of growth mixture model (RC=regression coefficient)

Parameter	G1 (N=12, 8.9%)		G2 (N=48, 35.6%)		G3 (N=65, 48.1%)		G4 (N=10, 7.4%)	
	RC (SE)	*p-value*	RC (SE)	*p-value*	RC (SE)	*p-value*	RC (SE)	*p-value*
Intercept	20.64 (2.50)	***<0.001***	36.57 (1.36)	***<0.001***	45.58 (1.39)	***<0.001***	50.76 (2.12)	***<0.001***
Linear	0.44 (0.11)	***<0.001***	0.06 (0.04)	*0.171*	0.03 (0.04)	*0.407*	0.21 (0.08)	***0.007***
Av.prob.*	0.88		0.80		0.75		0.90	

*Average within-group probability

Figure 2 Results of growth mixture model (should include color)

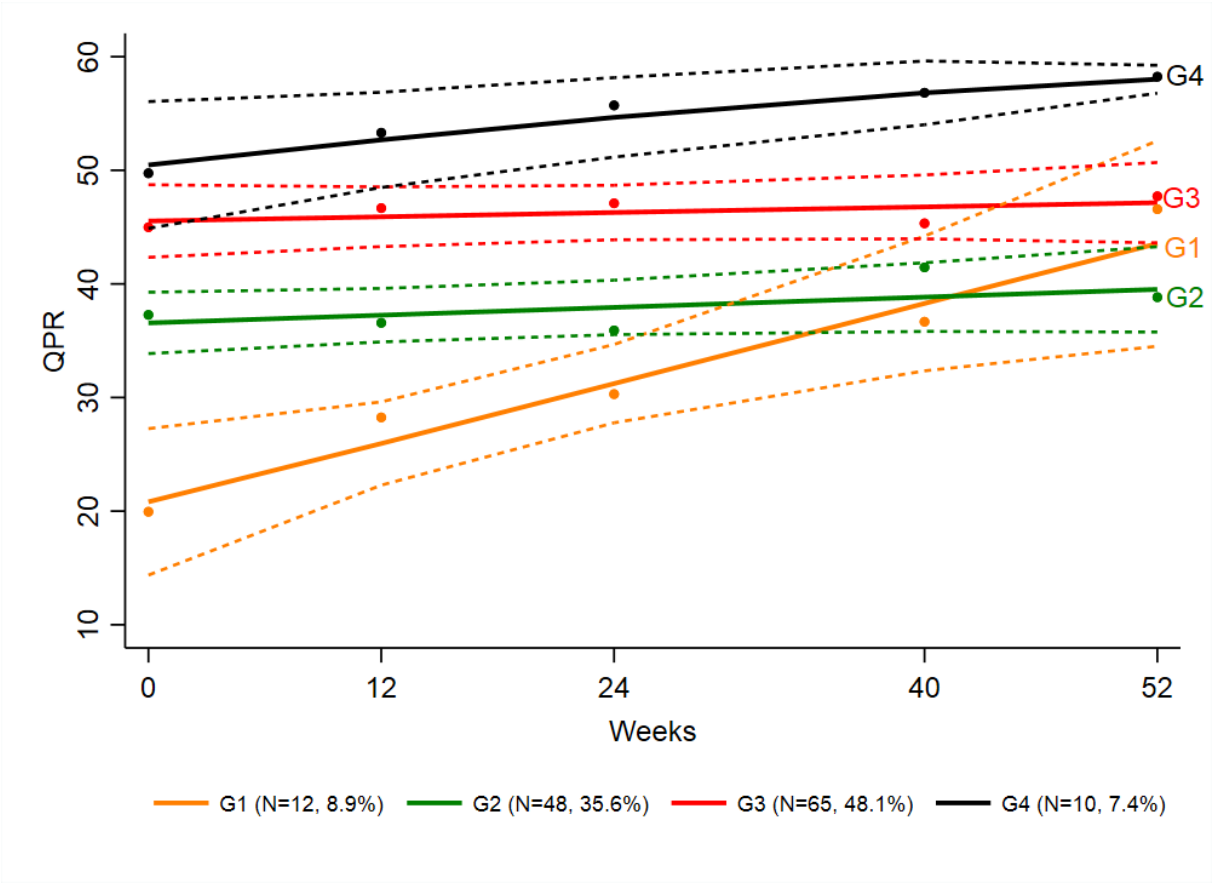

Table 4 Descriptive statistics within groups (N=135), presented as mean (SD) or *N(%) [italic]*

Variable	G1 (n=12)	G2 (n=48)	G3 (n=65)	G4 (n=10)	*p-value*
Age	37.8 (9.4)	36.6 (9.6)	38.2 (8.9)	38.7 (11.9)	*0.828*[1]
Gender, women	*4 (33.3)*	*12 (25.0)*	*14 (21.5)*	*0*	*0.267*[2]
In OAT prior to study participation	5 (41.7)	24 (50.0)	43 (66.2)	9 (90.0)	***0.037***[2]
Total injections with XR-NTX received	8.1 (5.2)	9.7 (5.3)	9.3 (5.1)	12.9 (4.4)	*0.151*[1]
Satisfaction with life					
Life Satisfaction (TSWLS)	6.6 (2.2)	11.9 (6.2)	14.5 (8.0)	16.4 (11.5)	***0.003***[1]
Health related variables					
Psychological distress (SCL-25)	2.6 (0.5)	2.1 (0.6)	1.8 (0.5)	1.5 (0.4)	***<0.001***[1]
Exposed to traumatic event	*12 (100)*	*40 (83.3)*	*49 (79.0)*	*10 (100)*	*0.147*[2]
Fills MINI-criteria for PTSD	*3 (25.0)*	*8 (16.7)*	*8 (12.9)*	*1 (10.0)*	*0.696*[2]
Current pain	4.7 (3.1)	3.0 (2.6)	2.5 (2.6)	1.4 (2.1)	***0.014***[1]
Social/familial variables					
Social support (ISEL)	30.9 (7.3)	32.1 (6.8)	37.9 (6.7)	38.6 (5.6)	***<0.001***[1]
Close relationships	3.4 (1.6)	3.8 (1.4)	3.7 (1.3)	4.1 (1.4)	*0.713*[1]
Civil status, n (%)					
Married	*0*	*1 (2.1)*	*5 (7.7)*	*0*	*0.277*[3]
Separated	*0*	*0*	*3 (4.6)*	*0*	
Divorced	*2 (16.7)*	*5 (10.4)*	*5 (7.7)*	*3 (30.0)*	
Never Married	*10 (83.3)*	*42 (87.5)*	*52 (80.0)*	*7 (70.0)*	
Education/work variables					

Occupation last 3 years					
Not working	8 (66.7)	35 (72.9)	37 (56.9)	7 (70.0)	*0.352*[2]
Any form of occupational activity	4 (33.3)	13 (27.1)	28 (43.1)	3 (30.0)	
Working last 4 weeks, yes	*1 (8.3)*	*5 (10.4)*	*20 (30.8)*	*4 (40.0)*	***0.020***[2]
Years of education	11 (1.7)	11.7 (2.0)	12.5 (2.8)	11.6 (1.8)	*0.126*[1]
Living arrangement and leisure time					
Living situation, last 3 years					
With family/friends	*3 (25.0)*	*17 (35.4)*	*25 (38.5)*	*2 (20.0)*	*0.601*[3]
Other (alone, prison or institution)	*9 (75.0)*	*31 (64.6)*	*40 (61.5)*	*8 (80.0)*	
Living with someone…					
without problematic substance use	*8 (66.7)*	*32 (66.7)*	*47 (72.3)*	*6 (60.0)*	*0.718*[2]
with problematic substance use	*1 (8.3)*	*1 (2.1)*	*5 (7.7)*	*1 (10.0)*	
Lives alone	*3 (25.0)*	*15 (31.3)*	*13 (20.0)*	*3 (30.0)*	
Spends most of leisure time with..					
Family, w/o problematic subst. use	*1 (8.3)*	*16 (33.3)*	*22 (33.8)*	*1 (10.0)*	*0.219*[2]
Family, w/ problematic subst. use	*0*	*1 (2.1)*	*2 (3.1)*	*0*	
Friends w/o problematic subst. use	*1 (8.3)*	*8 (16.7)*	*12 (18.5)*	*4 (40.0)*	
Friends w/ problematic subst. use	*4 (33.3)*	*4 (8.3)*	*5 (7.7)*	*2 (20.0)*	
Mostly alone	*6 (50.0)*	*19 (39.6)*	*24 (36.9)*	*3 (30.0)*	
Satisfaction with leisure time					
No	*7 (58.3)*	*21 (43.8)*	*28 (43.1)*	*4 (40.0)*	*0.235*[2]
Indifferent	*3 (25.0)*	*7 (14.6)*	*5 (7.7)*	*0*	
Yes	*2 (16.7)*	*20 (41.7)*	*32 (49.2)*	*6 (60.0)*	

[1] ANOVA, [2] χ^2-test

Table 5 Substance use variables, presented as mean (SD) or *N(%) [Italic]*

Variable	G1 (n=12)	G2 (n=48)	G3 (n=65)	G4 (n=10)	*p-value*
Craving for heroin	7.2 (3.4)	4.6 (3.8)	3.4 (3.9)	2.7 (3.2)	***0.008***[1]
Alcohol, use last 6 mos.					
No use	*9 (75.0)*	*33 (68.8)*	*48 (73.8)*	*8 (80.0)*	*0.829*[2]
Occasional use	*3 (25.0)*	*11 (22.9)*	*11 (16.9)*	*2 (20.0)*	
Frequent use	*0*	*4 (8.3)*	*6 (9.2)*	*0*	
Alcohol days of use, last 4 weeks	0 (0)	1.0 (3.6)	0.9 (2.9)	0 (0)	*0.588*[1]
Heroin, use last 6 mos.					
No use	*1 (8.3)*	*20 (41.7)*	*32 (49.2)*	*8 (80.0)*	***0.036***[2]
Occasional use	*4 (33.3)*	*10 (20.8)*	*8 (12.3)*	*1 (10.0)*	
Frequent use	*7 (58.3)*	*18 (37.5)*	*25 (38.5)*	*1 (10.0)*	
Heroin days of use	9.3 (10.9)	7.7 (10.7)	6.2 (10.0)	2.9 (8.8)	*0.442*[1]
Methadone/buprenorphine use last 6 mos.					
No use	*0*	*6 (12.5)*	*11 (16.9)*	*3 (30.0)*	*0.170*[2]
Occasional use	*4 (33.3)*	*8 (16.7)*	*7 (10.8)*	*0*	
Frequent use	*8 (66.7)*	*34 (70.8)*	*47 (72.3)*	*7 (70.0)*	
MET/BUP days of use last 4 weeks	16.3 (11.0)	14.2 (13.1)	18.3 (12.0)	20.1 (12.8)	*0.285*[1]
Other opioids (OO), use last 6 mos.					
No use	*7 (58.3)*	*34 (70.8)*	*53 (81.5)*	*10 (100)*	*0.117*[2]
Occasional use	*4 (33.3)*	*7 (14.6)*	*9 (13.8)*	*0*	
Frequent use	*1 (8.3)*	*7 (14.6)*	*3 (4.6)*	*0*	
OO days of use last 4 weeks	3.4 (8.3)	2.4 (7.5)	1.2 (4.8)	0 (0)	*0.427*[1]
Benzodiazepines (BZD) use last 6 mos.					
No use	*0*	*9 (18.8)*	*20 (30.8)*	*8 (80.0)*	***0.001***[2]
Occasional use	*4 (33.3)*	*14 (29.2)*	*20 (30.8)*	*1 (10.0)*	
Frequent use	*8 (66.7)*	*25 (52.1)*	*25 (38.5)*	*1 (10.0)*	
BZD days of use last 4 weeks	18.2 (11.8)	12.5 (12.3)	7.6 (10.1)	2.9 (8.8)	***0.001***[1]
Cocaine use last 6 mos.					
No use	*11 (91.7)*	*35 (72.9)*	*49 (75.4)*	*9 (90.0)*	*0.126*[2]
Occasional use	*1 (8.3)*	*9 (18.8)*	*16 (24.6)*	*1 (10.0)*	
Frequent use	*0*	*4 (8.3)*	*0*	*0*	
Cocaine use days last 4 weeks	0 (0)	0.6 (2.2)	0.2 (0.5)	0 (0)	*0.332*[1]
Amphetamines, use last 6 mos.					
No use	*4 (33.3)*	*29 (60.4)*	*38 (58.5)*	*7 (70.0)*	*0.341*[2]
Occasional use	*7 (58.3)*	*11 (22.9)*	*18 (27.7)*	*2 (20.0)*	
Frequent use	*1 (8.3)*	*8 (16.7)*	*9 (13.8)*	*1 (10.0)*	
Amphetamines days of use last 4 weeks	3.3 (8.0)	2.7 (7.0)	0.7 (4.7)	1.4 (4.1)	*0.737*[1]
Cannabis, use last 6 mos.					
No use	*5 (41.7)*	*19 (39.6)*	*31 (47.7)*	*7 (70.0)*	*0.050*[2]
Occasional use	*5 (41.7)*	*6 (12.5)*	*15 (23.1)*	*0*	
Frequent use	*2 (16.7)*	*23 (47.9)*	*19 (29.2)*	*3 (30.0)*	
Cannabis days of use last 4 weeks	3.1 (7.9)	9.5 (12.2)	5.8 (10.1)	3.4 (5.8)	*0.104*[1]
Multiple substances last 6 mos.					
No use	*2 (16.7)*	*13 (27.1)*	*25 (38.5)*	*8 (80.0)*	***0.010***[2]
Occasional use	*2 (16.7)*	*6 (12.5)*	*15 (23.1)*	*0*	
Frequent use	*8 (66.7)*	*29 (60.4)*	*25 (38.5)*	*2 (20.0)*	
Multiple substances last 4 weeks	14.8 (13.9)	12.8 (12.7)	7.2 (9.8)	4.5 (9.7)	***0.012***[1]

[1] ANOVA, [2] χ^2-test

Table 6 Results of post-hoc analyses. Pairwise comparisons between groups.

Numbers are p-values (only significant differences presented)

Variable	G1 vs G2	G1 vs G3	G1 vs G4	G2 vs G3	G2 vs G4	G3 vs G4
In OAT prior to study participation			*0.019*		*0.020*	
Psychological distress (SCL-25)	*0.006*	*<0.001*	*<0.001*	*0.003*	*0.002*	
Social support (ISEL)		*0.002*	*0.013*	*<0.001*	*0.006*	
Current pain		*0.006*	*0.011*			
Working last 4 weeks				*0.010*	*0.019*	
Life Satisfaction (TSWLS)	*0.005*	*0.001*	*0.009*			
Craving for heroin	*0.040*	*0.003*	*0.005*			
Heroin, use last 6 mos, n (%)		*0.020*	*0.003*			
BZD use last 6 mos			*<0.001*		*<0.001*	*0.011*
BZD days of use last 4 weeks		*0.002*	*0.003*	*0.022*	*0.023*	
Multiple substances last 6 mos			*0.011*		*0.006*	*0.038*
Multiple substances last 4 weeks			*0.023*	*0.010*		