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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*

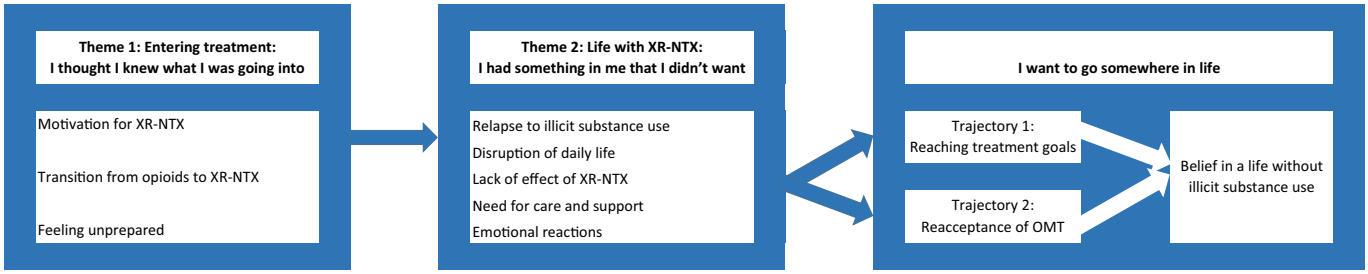

Fig. 1. Overview of themes.

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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