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# Characteristics of opioid-dependent patients choosing antagonist treatment with extended-release naltrexone compared with patients in opioid maintenance treatment in Norway

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*Summary*

**Background:** Opioid dependency is a risk factor for several negative life events and conditions. The opioid receptor inhibitor extended-release naltrexone (XR-NTX) is safe and effective in reducing illicit substance use. Here, we report results of a naturalistic, multicentre, open-label trial of XR-NTX for 24 weeks, with an optional 28-week treatment extension (NaltRec study). **Aims**: The study aims were to compare sociodemographic and clinical variables between patients choosing XR-NTX (n=162) and those in opioid agonist treatment (OAT) (n= 155), and to compare these variables in the XR-NTX group between patients who were (n= 103) and were not (n= 59) in OAT before study inclusion. **Methods:** To measure objective-related factors, we used a structured interview at inclusion. **Results:** The XR-NTX group had fewer women, was younger and reported poorer living and social conditions than the OAT group. Both groups had serious health conditions. Across groups, 40% percent reported lifetime suicide attempts, and 60% reported abusive experiences, with 47% women and 17% men reporting sexual abuse. Age at onset of polydrug use was 20 years. Patients preferring XR-NTX to OAT reported poorer social conditions compared with those choosing OAT. **Conclusions:** Women and patients who are not stabilized before enrolment need specific attention to tailored supportive measures during treatment with extended-release naltrexone.

*Key Words:* Extended-release naltrexone; health; opioid agonist treatment; opioid antagonist treatment; opioid dependence; traumatic experiences; substance use

## 1. Introduction

Opioid dependence (OD) is a risk factor for overdose deaths **[1, 11]**, poor health and living conditions, and lack of social support **[39]**. Common mental health problems are depression, anxiety, and personality disorders **[32, 44]**, and somatic health problems are frequent, often related to complications from injecting drugs **[4, 7, 18, 33, 38]**. A further common health burden is previous exposure to relational traumas such as domestic violence and sexual abuse, and development of post-traumatic stress disorder. These exposures may represent a challenge during treatment of illicit opioid use and other illicit substance dependency disorders **[36, 40, 48]**.

Opioid agonist treatment (OAT) reduces the risk of overdose deaths, use of illicit substances, deteriorating health, and poor living conditions among persons with opioid dependence (PWOD) **[4, 7, 33, 38]**. Social support has been highlighted as pivotal to OAT **[39]**. Although OAT and non-opioid treatment options are widely imple-

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mented internationally, patients find it difficult to maintain continued abstinence **[14, 19, 20, 37, 45]**. Thus, an urgent question is how to best support and optimise the recovery process in PWOD.

During the past decade, treatment with an opioid antagonist has become increasingly common, particularly in the form of injectable extended release formulations. Extended-release naltrexone hydrochloride injectable suspension (Vivitrol®) (XR-NTX) is by far the most commonly used opioid antagonist. It is considered safe and equally effective to OAT medication in reducing the use of illicit substances among PWOD **[27-29, 42, 46]**.

While OAT maintains the opioid dependence, XR-NTX blocks the effects of opioids. Thus, the two treatment options are offering PWOD very different pharmacological approaches to handle the problem. A preponderance of the research on XR-NTX has been carried out in the USA and Russia **[6, 9, 10, 12, 25, 26, 30, 31]**. However, these studies may not necessarily be representative for a naturalistic opioid-dependent population in other nations given the substantial differences in availability of treatment and the health and welfare systems. In Russia, XR-NTX is available, while OAT is prohibited **[7]**. The choice of XR-NTX treatment in Russia may thus be the sole pharmacologically supported alternative to abstinence. In the United States, OAT programs are widely available, but patient selection depends on individual state policies or health programs.

Opioid-dependent individuals enrolled in Norwegian regional OAT programs is estimated to be above 70% **[15]**. Hence, choosing XR-NTX over OAT (in the Norwegian study) is more likely to reflect personal preference for XR-NTX than in Russia or the United States. While a recent study found that baseline preference for XR-NTX treatment influenced treatment adherence and longer term opioid use **[16]**, more knowledge is needed regarding possible differences between these groups, and to illuminate why some PWOD choose XR-NTX treatment over OAT when both options are available free of charge. Knowing relevant characteristics could contribute to better recognition of individual preferences and treatment goals and how they can affect the course and outcome of XR-NTX treatment. An overall description of health burden and possible differences between subgroups could provide useful information for treatment providers about the spread in needs and treatment concerns of PWOD in general and specific to the subgroups of patients choosing XR-NTX. Further, such knowledge is considered valuable in regards to the importance of individually adapted medication and social support, a cornerstone in optimising recovery processes for this group of patients.

In the present naturalistic Norwegian study (NaltRec study), we recruited adult PWOD regardless of age, sex, and current treatment status. Participants could choose induction to XR-NTX treatment or to initiate or continue OAT. Patients initiating or continuing OAT were invited to the study as a control group.

**Aims:** The study aims were 1) to compare sociodemographic and clinical baseline variables between patients choosing XR-NTX and patients preferring OAT, and 2) in the XR-NTX-group, to compare the same variables between patients who were (prior OAT) and were not in OAT (non-OAT) prior to study inclusion.

## 2. Methods

This naturalistic, multicentre, open-label trial of XR-NTX **[51]** lasted 24 weeks, with an optional 28-week treatment extension. Participants taking part in the treatment study received 380 mg XR-NTX intramuscularly (Vivitrol®) every fourth week during the study period. All participants and controls were recruited from outpatient clinics and detoxification units at five urban addiction clinics in Norway. In the XR-NTX group, some participants were in OAT before study inclusion, and some were not. In the control group, all patients were in OAT prior to inclusion.

### *2.1. Inclusion and exclusion criteria*

Eligible participants and controls were opioid-dependent (per DSM-IV criteria) men and women ages 18-65 years. Exclusion criteria were pregnancy, lactation, acute alcoholism, and severe somatic or psychiatric illness interfering with study participation, such as decompensated hepatic cirrhosis, renal failure, HIV with related symptoms, current or recurrent affective disorders with suicidal behaviour, or psychotic disorders. Females of childbearing age were required to use contraceptive methods if receiving study medication. Members of study staff performed screening for psychiatric disorders, and a physician screened for severe somatic disease in the XR-NTX participant group. Participants receiving study treatment were referred to a detoxification unit before induction to XR-NTX. The study design is described in detail elsewhere **[51]**.

### *2.2. Assessments*

All participants and controls participated in a structured interview at study inclusion. The European version of the Addiction Severity Index (EuropASI) was used to assess demographics, substance use, physical and mental health, work, education, crimi-

**Table 1.** Sociodemographics of the study participants (N = 317) with data presented as n (%) or mean (± standard deviation) (NaltRec study)

| Background information | XR-NTX [1] group (n = 162) | Control group [2] (n = 155) | p |
|---|---|---|---|
| Age, mean | 37.8 (±9.7) | 43.9 (±10.1) | <0.001 |
| Female sex | 39 (24) | 53 (34) | 0.047 |
| Marital status (n = 314) | | | 0.095 |
| Married | 6 (4) | 11 (7) | |
| Divorced/widowed/separated | 24 (15) | 33 (22) | |
| Single | 131 (81) | 109 (71) | |
| Years of education | 11.9 (±2.5) | 11.5 (±2.6) | 0.147 |
| Income, main source (n = 316) | | | 0.765 |
| Work | 24 (15) | 24 (16) | |
| Social welfare | 129 (80) | 125 (81) | |
| Criminal activity | 6 (4) | 3 (2) | |
| Other | 2 (1) | 3 (2) | |
| Children (n = 314) | | | |
| Having own children | 74 (46) | 85 (56) | 0.089 |
| Daily caring responsibility for children | 12 (8) | 16 (11) | 0.350 |
| Housing previous 3 years (n = 314) | | | 0.007 |
| Living with own family/ partner/children | 37 (23) | 50 (33) | |
| Living with parents, other family members or friends | 19 (12) | 5 (3) | |
| Living alone | 94 (58) | 93 (61) | |
| Unstable housing situation | 11 (7) | 5 (3) | |

[1] = patients receiving extended-release naltrexone
[2] = patients included in opioid agonist treatment

nal activity, and social functioning **[24]**. In addition, we included a questionnaire screening for impulsivity, hyperactivity and inattention symptomatology (IHI), the Adult ADHD Self-Report Scale 18-item version (ASRS-18) v1.1 **[23]**. The 18 questions were dichotomised according to Kessler et al.'s description, and a positive score ≥9 was considered as a clinically significant symptom level. For a complete list of assessments, see Weimand et al. **[51]**.

### 2.3. Ethics

The study was funded by the Research Council of Norway, the South-Eastern Norway Regional Health Trust, and the participating hospitals and approved by the South-East Regional Ethical Board for Medical Research Ethics (#2018 /132), the Norwegian Medicines Agency, and the Boards of Research Ethics at every participating hospital.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, which are consistent with the International Conference on Harmonization guidelines for Good Clinical Practice **[13]** and with national regulatory requirements. Registration of participant data was done in accordance with the General Data Protection Regulation and the National Personal Data Protection regulations. All participants and controls gave written informed consent before study start. To ensure an adequate follow-up and availability of agonist therapy in case of early discontinuation, all participants were enrolled or continued in an OAT program at inclusion. Co-researchers from user organizations took part in the development of the study. The study is registered at clinicaltrials.gov (identifier NCT01717963).

### 2.4. Statistical analyses

Descriptive statistics were used to describe the study sample. Normally distributed continuous variables are reported as mean ± (standard deviation). Continuous variables that were not normally distributed are reported as median and range. Between-group differences were examined using Pearson's chi-square for categorical variables and Student's t-test or the Mann–Whitney U test for continuous variables. Significance level was set to $p < 0.05$. All analyses were performed using SPSS, version 27 **[8]**.

**Table 2.** Health problems, n (%) or median (range)

| | XR-NTX [1] group (n = 162) | Control group [2] (n = 155) | p |
|---|---|---|---|
| Somatic health | | | |
| Positive hepatitis, lifetime (n = 313) | 87 (55) | 104 (67) | 0.029 |
| Other chronic somatic illness (n = 316) | 60 (37) | 81 (52) | 0.007 |
| Poor dental health (n = 315) | 66 (41) | 79 (51) | 0.084 |
| Hospitalisations due to somatic illness, including overdoses | 4 (0-102) | 5 (0-120) | 0.101 |
| Mental health | | | |
| Depression (n = 313) | 132 (82) | 122 (80) | 0.697 |
| Anxiety (n = 313) | 142 (88) | 124 (82) | 0.101 |
| Any suicidal attempts - lifetime (n = 313) | 65 (40) | 59 (39) | 0.778 |
| ASRS above clinical cut-off (n = 305) | 65 (41) | 61 (41) | 0.970 |
| Hospitalisations due to mental illness | 0 (0-15) | 0 (0-130) | 0.625 |

[1] = patients receiving extended-release naltrexone
[2] = patients included in opioid agonist treatment
P value obtained by cross-table analysis and chi-square for categorical variables and Mann–Whitney U-test for continuous variables.

## 3. Results

### 3.1. Sociodemographic variables

We enrolled 162 XR-NTX participants and 155 OAT patients as a control group (**Table 1**). The overall mean age was 40.8 (±10.4) years. Compared with the control group, the XR-NTX group was on average ~6 years younger ($p < 0.001$) and had a lower proportion of women (24% vs. 34%, $p = 0.047$). Regarding housing, a higher proportion of XR-NTX patients had an unstable and less satisfactory housing situation. Compared with the OAT group, a smaller proportion of the XR-NTX group lived with a partner and a higher proportion lived with other family or friends. In both groups, 80% had social welfare as their main source of income. All controls were already in an OAT program at inclusion, whereas 36% of the XR-NTX participants had not received any treatment with opioid agonists. For other sociodemographic variables, we found no significant differences between the groups (**Table 1**).

### 3.2. Health problems

The OAT participants more often reported lifetime hepatitis infections (55% vs 67%, $p = 0.029$) and other chronic somatic diseases (37% vs 52%, $p = 0.007$) (**Table 2**). Regarding mental health, more than 80% of all participants (both groups) reported periods with serious depression and/or anxiety during their lifetime, and 40% reported one or more previous suicide attempts. However, the two groups did not differ significantly for lifetime mental health problems (depression, anxiety, suicide attempts), number of previous hospitalisations for mental or physical health problems, or level of impulsivity, hyperactivity and inattention symptomatology. In both groups, 41% scored above the cut-off on the Adult ADHD Self-Report Scale (**Table 2**).

### 3.3. Exposure to violence and abuse

Overall, 59% of patients reported being victims of emotional abuse, 42% had been victims of physical abuse, and 59% reported any type of abuse from

**Table 3.** Proportion of participants who reported lifetime exposure to violence and abuse, n (%)

| | XR-NTX [1] group (n = 162) | Control group [2] (n = 155) | p |
|---|---|---|---|
| Emotional abuse from someone closely related (n = 314) | 91 (57) | 93 (61) | 0.443 |
| Physical abuse from someone closely related (n = 314) | 63 (39) | 68 (44) | 0.340 |
| Sexual abuse from someone closely related (n = 314) | 34 (21) | 46 (30) | 0.069 |
| Any abuse from others than closely related (n = 312) | 95 (58) | 90 (59) | 0.868 |

[1] = patients receiving extended-release naltrexone
[2] = patients included in opioid agonist treatment
P value obtained by cross-table and chi square analysis.

**Table 4.** Substance use–related variables; data are mean (± standard deviation), median (range), or n (%)

| | | XR-NTX group [1] | Control group [2] | P[a] |
|---|---|---|---|---|
| Alcohol | Age at onset (n = 162) | 19.1 (±7.2) | 18.4 (±6.2) | 0.515 |
| | Years of use (n = 162) | 6.6 (±6.3) | 8.4 (±8.0) | 0.113 |
| | Any use last 28 days (n = 264) | 26 (17) | 18 (16) | 0.781 |
| Cannabis | Age at onset (n = 253) | 16.2 (±4.0) | 17.4 (±6.1) | 0.069 |
| | Years of use (n = 253) | 14.0 (±9.8) | 18.4 (±12.1) | 0.002 |
| | Any use last 28 days (n = 309) | 68 (43) | 50 (34) | 0.106 |
| Benzodiazepines | Age at onset (n = 221) | 22.7 (±8.4) | 22.7 (±8.9) | 0.945 |
| | Years of use (n = 221) | 9.1 (±8.2) | 13.5 (±11.5) | 0.001 |
| | Any use last 28 days | 94 (60) | 58 (39) | <0.001 |
| Stimulants [a] | Age at onset (n = 240) | 20.7 (±5.9) | 20.3 (±6.4) | 0.292 |
| | Years of use (n = 240) | 8.1 (±6.9) | 12.8 (±11) | <0.001 |
| | Any use last 28 days (n = 308) | 58 (37) | 26 (17) | <0.001 |
| Opioids [b] | Age at onset (n = 296) | 24.5 (±7.2) | 22.0 (±6.6) | <0.001 |
| | Years of use (n = 296) | 7.8 (±6.5) | 12.7 (±10.8) | <0.001 |
| | Any use last 28 days (n = 312) | 76 (48) | 28 (18) | <0.001 |
| Polydrug use | Age at onset (n = 266) | 20.4 (±7.0) | 19.6 (±6.0) | 0.371 |
| | Years of use (n = 266) | 13.3 (±8.7) | 16.1 (±11.6) | 0.028 |
| | Any use last 28 days [d] (n = 285) | 89 (59) | 30 (22) | <0.001 |
| Injection use | Age of first injection (n = 296) | 22.2 (±6.9) | 20.8 (±6.7) | 0.080 |
| | Years of use [c] (n = 296) | 11.0 (±8.5) | 15.1 (±10.8) | <0.001 |
| | Any injections last 28 days (n = 295) | 65 (44) | 22 (15) | <0.001 |
| OAT medication (MET/BUP) [e] | Age at onset (n = 295) | 30.2 (±8.0) | 30.2 (±8.8) | 0.977 |
| | Years of use (n = 295) | 7.3 (±5.6) | 8.8 (±7.1) | 0.070 |
| Overdoses | Any overdoses, lifetime (n = 311) | 123 (78) | 114 (74) | 0.371 |
| | Number of overdoses, lifetime | 3 (0–100) | 4 (0–120) | 0.086 |

[1] = patients receiving extended-release naltrexone
[2] = patients included in opioid agonist treatment
Note: Substance classes are presented in ascending order by age at onset. P value obtained from Student's t-test or Mann–Whitney U test for continuous variables and chi-square for categorical variables. MET = methadone; BUP = buprenorphine.
"Any use" and "years of use" refer to high-frequency use, as defined by EuropASI. For alcohol, high-frequency use was the consumption of 5 or more standard drinks at least 3 times weekly, or binge drinking on 2 consecutive days to a level that affected daily functioning. For drug use, only frequency was needed: 3 times weekly or 2 consecutive days.
[a] Amphetamine and/or cocaine
[b] Heroin and/or other opioids
[c] Years of injection use as defined by EuropASI is at least one injection per year.
[d] Any use last 28 days before enrolment in the study is not relevant for OAT medication because most patients were on prescribed OAT medication.

someone other than close relatives (**Table 3**). Exposure to sexual abuse was reported by 21% in the XR-NTX group and 30% in the control group. The groups did not differ significantly (**Table 3**), but men and women differed considerably. Among women, 47% had experienced sexual abuse, compared with 17% of the men ($\chi^2 = 32.0$, $p < 0.001$) (not shown).

### *3.4. History of substance use*

The XR-NTX participants had a 2.5-year later onset of opioid use ($p < 0.001$). Most patients reported a history of using illicit substances other than opioids. The mean age of onset of polydrug use was ~20 years for both groups, with 84% (266 of 317) reporting at least one year of high-frequency polydrug use (**Table 4**). The groups did not differ significantly for time of onset of high-frequency use of cannabis, benzodiazepines, and stimulants or years of high-frequency use of cannabis, benzodiazepines, stimu-

lants, opioids, and injection use (**Table 4**). Injection use started for both groups in their early twenties. Regarding current substance use in the last 28 days before study enrolment, a larger proportion of the XR-NTX group reported use of benzodiazepines, stimulants, and opioids, as well as injection use. Almost 80% overall had previous overdoses during the lifetime, with no differences between groups.

### *3.5. Differences in XR-NTX participants between patients who were and were not in OAT before the study*

Within the XR-NTX group, the prior-OAT subgroup (n = 103) differed significantly in several variables from the non-OAT subgroup (n = 59), as elaborated below.

#### *3.5.1. Sociodemographic variables*

Compared with the prior-OAT subgroup, the non-OAT subgroup was 3 years younger (35.8 years vs 38.9 years; p = 0.05), fewer had children (34% vs. 53%, p = 0.019), and fewer had caring responsibility for their children (2% vs. 11%, p = 0.034). The non-OAT group also had on average one more year of education (12.5 vs 11.5 years, p = 0.016).

#### *3.5.2. Health variables and childhood trauma*

Regarding somatic health, compared with the prior-OAT subgroup, a smaller proportion of the non-OAT subgroup reported hepatitis during the lifetime (41% vs 63%, p = 0.008). The two subgroups did not differ for mental health variables, but a lower proportion of the non-OAT study participants reported physical (27% vs. 46%, p = 0.018) and emotional maltreatment (46% vs. 63%, p = 0.036) from close relatives, indicating a slightly less dysfunctional family environment during childhood.

#### *3.5.3. Substance use variables*

For substance use variables, the two subgroups did not differ significantly in those related to historical substance use, but the non-OAT subgroup had more severe substance use in the last 28 days before study enrolment: median 5 vs 0 days with injection use ($p < 0.001$), median 15 vs 0 days with opioid use ($p < 0.001$), and median 1 vs 0 days with stimulant use ($p < 0.001$).

## 4. Discussion

For the total sample (XR-NTX and control group) our descriptive data showed a comprehensive health burden in both the somatic and psychological areas. We found differences between the treatment groups, and also between non OAT XR-NTX users and those switching from OAT to XR-NTX. This burden was especially pronounced for mental health, with more than 8 out of 10 reporting serious depressive episodes during their lifetime and as many as 4 out of 10 reporting a suicide attempt. Although these numbers seem high, they are in line with previous findings among OAT patients and emphasize the general extensive treatment needs of this population. For example, a recent study of OAT patients found a similar proportion (41%) who had attempted suicide during their lifetime **[47]**. Although a substance use disorder can negatively influence poor mental health **[21]**, we note that a very high proportion of the total sample reported traumatic events, e.g., sexual abuse, compared with findings in general population studies. This proportion was especially pronounced among the female participants. In a large Norwegian mother-and-child cohort study **[43]** (n > 50,000), about 11% had experienced sexual abuse, compared with almost half of the women in our study. Such traumatic experiences may be underlying causes of the mental health burden seen in the present study participants **[5]**. Treatment guidelines recommend that treatment of substance use disorders should take a trauma-informed approach **[17]** and that traumatic experiences should be assessed and addressed during treatment to avoid discontinuation and to enhance the likelihood of treatment success **[2, 36]**.

In addition to the above mentioned vulnerability factors, there is an inherit risk involved with the severity of the substance use per se. The participants had a very long history of severe substance use, with both groups having begun injection use in their early twenties, and a large majority reporting previous overdoses (>80%). It is well-known that the somatic health burden is high among PWOD, partly because of the substance use and partly because of high-risk health behaviour, such as injection use **[34]**. The inclusion criteria for the study was an OD diagnosis, but many participants overall were clearly polydrug users, as evidenced by their past and current use of several substances before study inclusion. Previous studies have suggested that polydrug use compromises the effects of treatment of opioid use disorder **[50]**. Adding to the overall picture of vulnerability in both groups is the fact that about 6 out of 10 were living alone and 8 out of 10 had social welfare as their main income.

Regarding whether the choice of XR-NTX over OAT reflected less or worse severity or more extensive treatment needs, the picture is somewhat difficult to interpret. The XR-NTX group had fewer years of high-frequency substance use, but this finding was likely the result of the age difference between groups, as the XR-NTX group was considerably younger. The age difference may not imply that younger PWOD are more attracted to XR-NTX treatment per se, and could trace to selection biases

or confounders we did not measure, such as dissatisfaction with OAT. However, a previous Norwegian study of XR-NTX also found a lower age among XR-NTX participants (36 years) compared with the general OAT population in Norway (43 years) **[46, 49]**. Age has previously not been associated with treatment dissatisfaction **[35]**. Yet, it may still be that younger individuals are more dissatisfied with the treatment regimens involved in OAT, e.g., the regulations typically involved in this treatment, and that they would then be more prone to seek alternatives when these are available. Nonetheless, the lower age in the XR-NTX group may be seen as a negative prognostic factor, as younger age has been posed to be a risk factor for discontinuing SUD treatment **[3]**. The control group reported somewhat worse somatic health, but this finding may also reflect the higher age in this group. The XR-NTX group did not seem to have a higher psychological severity burden, as there were no significant group differences for the mental health variables. A previous report based on the same study population suggested that those seeking XR-NTX treatment had a higher impulsivity, hyperactivity and inattention symptomatology compared with findings in other OAT studies **[22]**. However, the direct control in the present study contradicts this conclusion: We found a similar proportion among patients treated with opioid agonists, i.e., 41% in both groups.

A main concern in the findings is the high prevalence of polydrug use, with more than 80% of the total sample reporting at least one year of high frequency polydrug use. Co-occurring substance use and polydrug use were more pronounced in the XR-NTX group, and a larger proportion of this group reported current use in the last month prior to study enrolment. In addition, a higher proportion of the XR-NTX group reported current injection use. Thus, the XR-NTX group seemed to be less stabilized than the control group. This finding was partly explained by a subset of the XR-NTX group: the one third who were not stabilized in OAT before inclusion. This "non-OAT" group reported even more severe current substance use with more injection use, more opioid use, and more stimulant use than the "prior-OAT" XR-NTX participants. This finding is important and confirms similar results from a previous Norwegian XR-NTX study **[41]**. In the latter, 40% of participants were not stabilized in OAT prior to study inclusion, and they reported more severe ongoing addiction-related problems compared with participants who were stabilized in OAT prior to inclusion **[41]**. NTX is approved as a medication for treating opioid and alcohol dependence only and not targeted at other substances. As a preventive measure, patients included in the XR-NTX treatment in the present study had to have undergone a proper detoxification and were required to be enrolled in the local OAT program and to ensure follow-up by OAT clinicians. Future clinical routines may need to introduce a more cautious inclusion strategy to XR-NTX treatment to ensure that patients are stabilized if they are to be considered eligible for this type of treatment. Alternatively, stabilizing measures must be used during treatment to meet the needs of those who are not ufficiently stabilized in OAT. When the outcome data of this study are available, the findings should be viewed in the context of the less stabilized XR-NTX participants, and later discussions can address whether the inclusion criteria in the present study may have been too broad.

Methodological considerations: As this multicentre study recruited patients from five larger OAT centres, the participants are likely representative for PWOD in Norwegian OAT programs. We report drug use solely based on self-report, which we consider to be reliable because analyses have shown good agreement with urine samples (compliance in 98% of cases concerning testing of opioid use). We recommend further studies in this field to explore a variety of outcomes between two treatment options such as XR-NTX and OAT. We note that XR-NTX is still not available as a standard treatment option in the present setting. Although the groups differed in several characteristics and the XR-NTX group had a predominance of male participants, we believe that the study may provide information that will be useful when clinical routines are to be developed. Such baseline findings also may help to explain treatment outcomes.

## 5. Conclusions

Conclusively, patients choosing XR-NTX over OAT have similar, severe challenges in health, trauma, and suicidal behaviour. Women and patients who are not stabilized before enrolment need specific attention to tailored supportive measures during treatment. Likewise, more knowledge is needed from longitudinal, trajectory analyses to tailor supportive measures to achieve the desired treatment outcome.

## References

1. Baldacchino A., Tolomeo S., Khan F., Humphris G., Carra G. (2016): Acute Risk Factors in Fatal Opioid Overdoses as a Result of Hypoxia and Cardiotoxicity. A Systematic Review and Critical Appraisal. *Heroin Addict Relat Clin Probl.* 18(4): 33-42.
2. Bergly T. H., Sømhovd M. J. (2021): Improvements of Substance Use Disorder Treatment and the Impact of Traumatic Experiences. *J Subst Use*: 1-5.
3. Brorson H. H., Ajo Arnevik E., Rand-Hendriksen K., Duckert F. (2013): Drop-out from

Addiction Treatment: A Systematic Review of Risk Factors. *Clin Psychol Rev.* 33(8): 1010-1024.
4. Clausen T., Waal H., Thoresen M., Gossop M. (2009): Mortality among Opiate Users: Opioid Maintenance Therapy, Age and Causes of Death. *Addiction.* 104(8): 1356-1362.
5. Coles J., Lee A., Taft A., Mazza D., Loxton D. (2015): Childhood Sexual Abuse and Its Association with Adult Physical and Mental Health: Results from a National Cohort of Young Australian Women. *J Interpers Violence.* 30(11): 1929-1944.
6. Comer S. D., Sullivan M. A., Yu E., Rothenberg J. L., Kleber H. D., Kampman K., Dackis C., O'Brien C. P. (2006): Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence: A Randomized, Placebo-Controlled Trial. *Arch Gen Psychiatry.* 63(2): 210-218.
7. Connery H. S. (2015): Medication-Assisted Treatment of Opioid Use Disorder: Review of the Evidence and Future Directions. *Harv Rev Psychiatry.* 23(2): 63-75.
8. Corp. I. (2020): . Ibm Spss Statistics for Windows, Version 27.0. . IBM Corp, Armonk, NY.
9. Cousins S. J., Denering L., Crèvecoeur-MacPhail D., Viernes J., Sugita W., Barger J., Kim T., Weimann S., Rawson R. A. (2016): A Demonstration Project Implementing Extended-Release Naltrexone in Los Angeles County. *Subst Abuse.* 37(1): 54-62.
10. Crits-Christoph P., Markell H. M., Gibbons M. B. C., Gallop R., Lundy C., Stringer M., Gastfriend D. R. (2016): A Naturalistic Evaluation of Extended-Release Naltrexone in Clinical Practice in Missouri. *J Subst Abuse Treat.* 70: 50-57.
11. Crowley D., Van Hout M. C. (2017): Effectiveness of Pharmacotherapies in Increasing Treatment Retention and Reducing Opioid Overdose Death in Individuals Recently Released from Prison: A Systematic Review. *Heroin Addict Relat Clin Probl.* 19(2): 25-42.
12. DeFulio A., Everly J. J., Leoutsakos J.-M. S., Umbricht A., Fingerhood M., Bigelow G. E., Silverman K. (2012): Employment-Based Reinforcement of Adherence to an FDA Approved Extended Release Formulation of Naltrexone in Opioid-Dependent Adults: A Randomized Controlled Trial. *Drug Alcohol Depend.* 120(1-3): 48-54.
13. Dixon J. R. (1999): The International Conference on Harmonization Good Clinical Practice Guideline. *Qual Assur.* 6(2): 65-74.
14. Eastwood B., Strang J., Marsden J. (2017): Effectiveness of Treatment for Opioid Use Disorder: A National, Five-Year, Prospective, Observational Study in England. *Drug Alcohol Depend.* 176: 139-147.
15. EMCDDA (2021): Elimination Barometer on Viral Hepatitis among People Who Inject Drugs in Europe
16. Gaulen Z., Brenna I. H., Fadnes L. T., Šaltytė Benth J., Solli K. K., Kunoe N., Opheim A., Tanum L. (2022): The Predictive Value of Degree of Preference for Extended-Release Naltrexone for Treatment Adherence, Opioid Use, and Relapse. *Eur Addict Res.* 28(1): 56-67.
17. Health U. D. o., Services H. (2014): SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach.
18. Heidebrecht F., Macleod M. B., Dawkins L. (2022): Exploration of the Physical Health of Dual Users of Heroin and Crack in Methadone Treatment Who Inject or Have Previously Injected Drugs. *Heroin Addict Relat Clin Probl.* 24(1): 5-19.
19. Hjern A., Arat A., Vinnerljung B. (2014): Att Växa Upp Med Förälder Som Har Missbruksproblem Eller Psykisk Sjukdom-Hur Ser Livet Ut I Vuxen Ålder. *Nka Linnéuniversitetet Chess, Barn som anhöriga.* 4.
20. Hser Y.-I., Evans E., Grella C., Ling W., Anglin D. (2015): Long-Term Course of Opioid Addiction. *Harv Rev Psychiatry.* 23(2): 76-89.
21. Jill RachBeisel, M.D. ,, Jack Scott, Sc.D. , and, Lisa Dixon, M.D., M.P.H. (1999): Co-Occurring Severe Mental Illness and Substance Use Disorders: A Review of Recent Research. *Psychiatr Serv.* 50(11): 1427-1434.
22. Karlsson A. T., Vederhus J.-K., Clausen T., Weimand B., Solli K. K., Tanum L. (2021): Levels of Impulsivity, Hyperactivity, and Inattention and the Association with Mental Health and Substance Use Severity in Opioid-Dependent Patients Seeking Treatment with Extended-Release Naltrexone. *J Clin Med.* 10(19): 4558.
23. Kessler R. C., Adler L., Ames M., Demler O., Faraone S., Hiripi E., Howes M. J., Jin R., Secnik K., Spencer T. (2005): The World Health Organization Adult Adhd Self-Report Scale (ASRS): A Short Screening Scale for Use in the General Population. *Psychol Med.* 35(2): 245-256.
24. Kokkevi A., Hartgers C. (1995): Europasi: European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence. *Eur Addict Res.* 1(4): 208-210.
25. Krupitsky E., Nunes E. V., Ling W., Illeperuma A., Gastfriend D. R., Silverman B. L. (2011): Injectable Extended-Release Naltrexone for Opioid Dependence: A Double-Blind, Placebo-Controlled, Multicentre Randomised Trial. *Lancet.* 377(9776): 1506-1513.
26. Krupitsky E., Zvartau E., Blokhina E., Verbitskaya E., Wahlgren V., Tsoy-Podosenin M., Bushara N., Burakov A., Masalov D., Romanova T. (2016): Anhedonia, Depression, Anxiety, and Craving in Opiate Dependent Patients Stabilized on Oral Naltrexone or an Extended Release Naltrexone Implant. *Am J Drug Alcohol Abuse.* 42(5): 614-620.
27. Latif Z.-E. (2019): Long-Term Effectiveness, Psychiatric Distress, and Chronic Pain in Opioid-Dependent Individuals Receiving Treatment with Extended-Release Naltrexone.
28. Latif Z.-e.-H., Benth J. Š., Solli K. K., Opheim A., Kunoe N., Krajci P., Sharma-Haase K., Tanum L. (2019): Anxiety, Depression, and Insomnia among Adults with Opioid Dependence Treated with Extended-Release Naltrexone Vs Buprenorphine-Naloxone: A Randomized Clinical Trial and Follow-up Study. *JAMA psychiatry.* 76(2): 127-134.
29. Latif Z. e. H., Solli K. K., Opheim A., Kunoe N., Benth J. Š., Krajci P., Sharma-Haase K., Tanum L. (2019): No Increased Pain among Opioid-Dependent Individuals Treated with Extended-Release Naltrexone or Buprenorphine-Naloxone: A 3-Month Randomized Study and 9-Month Open-

Treatment Follow-up Study. *Am J Addict.* 28(2): 77-85.
30. Lee J. D., Friedmann P. D., Kinlock T. W., Nunes E. V., Boney T. Y., Hoskinson Jr R. A., Wilson D., McDonald R., Rotrosen J., Gourevitch M. N. (2016): Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *N Engl J Med.* 374(13): 1232-1242.
31. Lee J. D., Nunes Jr E. V., Novo P., Bachrach K., Bailey G. L., Bhatt S., Farkas S., Fishman M., Gauthier P., Hodgkins C. C. (2018): Comparative Effectiveness of Extended-Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X: Bot): A Multicentre, Open-Label, Randomised Controlled Trial. *Lancet.* 391(10118): 309-318.
32. Lieb M., Wittchen H.-U., Palm U., Apelt S. M., Siegert J., Soyka M. (2010): Psychiatric Comorbidity in Substitution Treatment of Opioid-Dependent Patients in Primary Care: Prevalence and Impact on Clinical Features *Heroin Addict Relat Clin Probl.* 12(4): 5-16.
33. Mattick R. P., Breen C., Kimber J., Davoli M. (2014): Buprenorphine Maintenance Versus Placebo or Methadone Maintenance for Opioid Dependence. *Cochrane Database Syst Rev*(2).
34. Medved D., Clausen T., Bukten A., Bjørnestad R., Muller A. E. (2020): Large and Non-Specific Somatic Disease Burdens among Ageing, Long-Term Opioid Maintenance Treatment Patients. *Subst Abuse: Treat Prev Policy.* 15(1): 87.
35. Muller A. E., Bjørnestad R., Clausen T. (2018): Dissatisfaction with Opioid Maintenance Treatment Partly Explains Reported Side Effects of Medications. *Drug Alcohol Depend.* 187: 22-28.
36. Najavits L. M., Clark H. W., DiClemente C. C., Potenza M. N., Shaffer H. J., Sorensen J. L., Tull M. T., Zweben A., Zweben J. E. (2020): PTSD / Substance Use Disorder Comorbidity: Treatment Options and Public Health Needs. *Curr Treat Options Psychiatry.* 7(4): 544-558.
37. Neale J., Nettleton S., Pickering L. (2013): Does Recovery-Oriented Treatment Prompt Heroin Users Prematurely into Detoxification and Abstinence Programmes? Qualitative Study. *Drug Alcohol Depend.* 127(1-3): 163-169.
38. Nielsen S., Gassowski M., Wenz B., Bannert N., Bock C.-T., Kücherer C., Ross R. S., Bremer V., Marcus U., Zimmermann R. (2016): Concordance between Self-Reported and Measured Hiv and Hepatitis C Virus Infection Status among People Who Inject Drugs in Germany. *Hepatol Med Policy.* 1(1): 1-7.
39. Pettersen H., Landheim A., Skeie I., Biong S., Brodahl M., Oute J., Davidson L. (2019): How Social Relationships Influence Substance Use Disorder Recovery: A Collaborative Narrative Study. *Subst Abuse: Res Treat.* 13: 1178221819833379.
40. Rugani F., Maremmani A. G. I., Rovai L., Mautone S., Perugi G., Pani P. P., Dell'Osso L., Maremmani I. (2011): Life Events (Loss and Traumatic) and Emotional Responses to Them in Heroin-Dependent Patients before and after the Dependence Age of Onset. *Heroin Addict Relat Clin Probl.* 13(3): 17-26.
41. Solli K. K., Kunoe N., Sharma-Haase K., Opheim A., Krajci P., Gaulen Z., Benth J. Š., Tanum L. (2019): Availability of Extended-Release Naltrexone May Increase the Number of Opioid-Dependent Individuals in Treatment: Extension of a Randomized Clinical Trial. *Eur Addict Res.* 25(6): 303-309.
42. Solli K. K., Latif Z. e. H., Opheim A., Krajci P., Sharma- Haase K., Benth J. Š., Tanum L., Kunoe N. (2018): Effectiveness, Safety and Feasibility of Extended-Release Naltrexone for Opioid Dependence: A 9-Month Follow-up to a 3-Month Randomized Trial. *Addiction.* 113(10): 1840-1849.
43. Sørbø M. F., Grimstad H., Bjørngaard J. H., Schei B., Lukasse M. (2013): Prevalence of Sexual, Physical and Emotional Abuse in the Norwegian Mother and Child Cohort Study. *BMC Public Health.* 13(1): 186.
44. Strain E. C. (2002): Assessment and Treatment of Comorbid Psychiatric Disorders in Opioid-Dependent Patients. *Clin J Pain.* 18(4): S14-S27.
45. Strang J., McCambridge J., Best D., Beswick T., Bearn J., Rees S., Gossop M. (2003): Loss of Tolerance and Overdose Mortality after Inpatient Opiate Detoxification: Follow up Study. *Bmj.* 326(7396): 959-960.
46. Tanum L., Solli K. K., Benth J. Š., Opheim A., Sharma-Haase K., Krajci P., Kunøe N. (2017): Effectiveness of Injectable Extended-Release Naltrexone Vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. *JAMA psychiatry.* 74(12): 1197-1205.
47. Vold J. H., Løberg E.-M., Aas C. F., Steier J. A., Johansson K. A., Fadnes L. T. (2022): Prevalence and Correlates of Suicide Attempts in High-Risk Populations: A Cross-Sectional Study among Patients Receiving Opioid Agonist Therapy in Norway. *BMC Psychiatry.* 22(1): 181.
48. Vukadinovic Z. (2013): Psychosis, Trauma, and Opioid Hypoactivity in the Thalamus: A Hypothesis. *Heroin Addict Relat Clin Probl.* 15(3): 35-46.
49. Waal H., Bussesund K., Clausen T., Skeie I., Håseth A., Lillevold P. (2016): The Annual Omt Status Survey for 2015 (in Norwegian Only: Statusrapport 2015-Mot Grensene for Vekst Og Nytte?). *Oslo, University of Oslo, Norwegian Centre for Addiction Research*.
50. Wang L., Min J. E., Krebs E., Evans E., Huang D., Liu L., Hser Y. I., Nosyk B. (2017): Polydrug Use and Its Association with Drug Treatment Outcomes among Primary Heroin, Methamphetamine, and Cocaine Users. *Int J Drug Policy.* 49: 32-40.
51. Weimand B., Solli K. K., Reichelt W. H., Tanum L. (2021): Enablers and Hindrances for Longer-Term Abstinence in Opioid Dependent Individuals Receiving Treatment with Extended-Release Naltrexone: A Norwegian Longitudinal Recovery Trial (Naltrec Study). *Contemp Clin Trials Commun.* 21: 100728.

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### Conflict of interest

The authors declare that they have no competing interests.

### Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval.

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