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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

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IMPORTANCE Extended-release naltrexone (XR-NTX) is a promising alternative treatment of opioid addiction but has never been compared with opioid agonist treatment for effects on symptoms of anxiety, depression, and insomnia.

OBJECTIVE To investigate whether XR-NTX unmasks or reinforces current comorbid symptoms of anxiety, depression, or insomnia compared with opioid agonist treatment.

DESIGN, SETTING, AND PARTICIPANTS In this prospective randomized clinical trial, 159 men and women aged 18 to 60 years with opioid dependence were randomized to 12 weeks of treatment with either XR-NTX or combined buprenorphine-naloxone (BP-NLX) followed by a 9-month, open-label treatment study with participant choice of 1 of these 2 drugs. The study was conducted at outpatient addiction clinics in 5 urban hospitals in Norway, with the clinical trial performed from November 1, 2012, to October 23, 2015, and the follow-up study completed on July 23, 2016. All analyses were conducted using an intention-to-treat sample.

INTERVENTIONS Extended-release naltrexone hydrochloride, 380 mg, administered as an injection every 4 weeks or flexible doses (4-24 mg; target dosage 16 mg/d) of daily oral combined BP-NLX.

MAIN OUTCOMES AND MEASURES Every 4 weeks, symptoms of anxiety and depression were assessed using the 25-item Hopkins Symptom Checklist, and symptoms of insomnia were assessed using the Insomnia Severity Index.

RESULTS In total, 159 participants were randomized to treatment with either XR-NTX (n = 80) or BP-NLX (n = 79), and 105 participants (66.0%) completed the trial. The treatment groups showed similar distributions of age (mean [SD], 36.4 [8.8] vs 35.7 [8.5] years), sex (61 [76.3%] women and 54 [68.4%] men), and duration of heroin use (mean [SD], 6.9 [5.8] vs 6.7 [5.2] years). For the clinical trial period, no overall differences were detected between treatment groups for anxiety (effect size [95% CI], −0.14 [−0.47 to 0.19]) or depression (effect size [95% CI], −0.12 [−0.45 to 0.21]) scores, but the insomnia score was significantly lower in the XR-NTX group (effect size [95% CI], −0.32 [−0.61 to −0.02]; $P = .008$). In the follow-up period, no overall differences could be detected in the effect size [95% CI] of scores for anxiety (0.04 [−0.34 to 0.42]), depression (−0.04 [−0.42 to 0.33]), or insomnia (0.04 [−0.33 to 0.42]) between participants continuing with and participants switching to XR-NTX. No significant sex differences between the 2 treatment groups were detected.

CONCLUSIONS AND RELEVANCE Comorbid symptoms of anxiety, depression, or insomnia in abstinence-motivated persons with opioid dependence should not prevent switching from treatment with an opioid agonist to treatment with XR-NTX.

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Supplemental content

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Persons dependent on opioids fulfilling the criteria for having substance use disorder have an increased prevalence of lifetime psychiatric disorders compared with that in the general population,[1-3] and these disorders are often in combination with insomnia.[4,5] Grant et al[6] reported that 20% of all persons in the US general population with a current substance use disorder had at least 1 current independent mood disorder and at least 1 current independent anxiety disorder. Epidemiologic studies also report a lifetime history of substance use disorder among approximately 24% to 43% of individuals with anxiety disorders.[7]

Both anxiety and depression negatively contribute to the course and treatment outcome in opioid use disorder.[8,9] Agonist treatment with methadone or buprenorphine or residential treatments 3have shown positive effects on coexisting anxiety and depressive symptoms. However, the data have been inconsistent[8-10] for the type of substance used, frequency of intake, and poly-drug use.[11-15]

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

Extended-release naltrexone hydrochloride (XR-NTX) is a promising treatment of opioid dependence,[18-21] but until now, no study has focused on changes in anxiety, depression, or insomnia after starting such treatment compared with these changes in persons treated with an opioid agonist. Naltrexone inhibits the action of heroin and other opioid agonists by competitively blocking the mu, delta, and kappa opioid receptors and lacks abuse potential or any risk of diversion. Naltrexone also provides a prolonged period of abstinence from opioids with a high level of protection from relapse and overdose.

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

Key Points

Question Does treatment with injectable extended-release naltrexone unmask or reinforce symptoms of anxiety, depression, or insomnia compared with daily sublingual treatment with combined buprenorphine-naloxone among adults who have opioid dependence but have recently undergone detoxification?

Findings In this randomized clinical trial of 159 men and women with opioid dependence, both drug treatments were equally effective in reducing symptoms of anxiety and depression, but symptoms of insomnia were significantly further reduced by the extended-release naltrexone treatment. All symptoms were further improved by longer-term extended release naltrexone treatment.

Meaning Comorbid symptoms of anxiety, depression, or insomnia in abstinence-motivated adults with opioid dependence should not prevent switching from opioid agonist to extended-release naltrexone treatment.

Methods

This study consisted of a 12-week randomized clinical trial allocating patients by using a permuted block algorithm provided by an external authority to treatment with either intramuscular injection of XR-NTX in the gluteal region every fourth week or with daily, sublingual BP-NLX. This portion of the study was followed by a 36-week, open-label follow-up study in which participants chose to receive 1 of the 2 drugs. The primary end points were changes in anxiety, depression, and insomnia scores in the randomized clinical trial portion of the study and during longer-term treatment. Participants were assessed every 4 weeks from baseline to week 48 for anxiety and depression symptoms using the 25-item Hopkins Symptom Checklist (HSCL-25) and for insomnia using the Insomnia Severity Index. The study was performed according to protocol version 3C dated June 12, 2012, at all participating sites (trial protocol in Supplement 1) and was approved by the Regional Committee for Medical and Health Research Ethics South East Norway, the Norwegian Medicines Agency, and the boards of research ethics at the participating hospitals.[20] Written informed consent was provided by all participants.

The HSCL-25 is a screening instrument developed for the assessment of change in anxiety and depressive symptoms in the course of clinical treatment.[22-24] It has robust validity and reliability and can distinguish between low and high levels of neurotic deviations.[25,26] The questions are graded from 1 (not at all) to 4 (extremely). The patient version of the Insomnia Severity Index is a 7-element self-report questionnaire developed to assess insomnia in the previous 4 weeks, and this instrument has shown robust psychometric properties.[16,27] The Insomnia Severity Index measures the latency of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, daytime functioning affected by sleep difficulties, sleep problems apparent to others, and anguish caused by sleep difficulties. The scoring is on a 5-point rating scale, with 0 indicating no problem and 4 indicating a severe problem.

Participants and Setting

Patients were recruited between November 1, 2012, and July 10, 2015, from outpatient clinics and detoxification units at 5 urban addiction clinics in Norway. Eligible participants were men and women aged 18 to 60 years who had opioid dependence as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition). Criteria for exclusion were other drug or alcohol dependencies and serious somatic or psychiatric psychotic illness that would, according to hospital records and our clinical judgment, interfere with study

participation. Women of childbearing age could not be pregnant or lactating and agreed to use contraceptive methods. Study personnel (Z.-H.L., K.K.S., A.O., and K.S.-H.) screened patients for psychiatric disorders using the Mini-International Neuropsychiatric Interview, version 6.0,[28] and a physician examined patients for serious somatic disease. Eligible patients were referred to a detoxification unit following screening. Participants were not paid or compensated for taking part in the study with the exception of reimbursement for travel expenses. Race/ethnicity was defined by the participants and was assessed to show whether the study participants followed the ethnical distribution of the general population.

After taking part in individually adapted detoxification programs, patients were randomly assigned to start treatment with either individually dosed BP-NLX (4 mg BP-NLX tablet contains 4 mg buprenorphine hydrochloride and 1 mg naloxone hydrochloride; 24 mg BP-NLX tablet contains 24 mg buprenorphine hydrochloride and 6 mg naloxone hydrochloride), 4 to 24 mg/d (target dosage, 16 mg/d), or XR-NTX, 380 mg, every fourth week for 12 weeks. All per-protocol participants were invited to enter a 36-week follow-up study conducted from October 23, 2015, to July 23, 2016, either continuing their randomized treatment or switching to their preferred medication. Participants who dropped out of the randomization phase could be reincluded in the follow-up study after completing another detoxification program. The procedure and selection of participants are described elsewhere.[20,29]

Dropouts were defined as not attending the assessment examination within 3 days of the scheduled date, terminating the study medicine, or refusing to receive an injection.

Statistical Analysis

The primary analyses assessed the differences between the scores of the 2 treatment groups for the trends of 3 outcome measures—anxiety, depression, and insomnia—by estimating a linear mixed model with fixed effects for group, nonlinear time, and the interaction between group and time for each measure.

Three exploratory analyses were conducted. Associations between anxiety and depression scores and substance abuse (heroin, other opiates, benzodiazepines or sedatives, amphetamine, and cannabis) were assessed by linear mixed models with fixed effects for nonlinear time and substance use. Next, main analyses stratified by sex were conducted by including additional fixed effects for sex and a 3-way interaction between group, sex, and time as well as all lower-order interactions into a linear mixed model. Associations between insomnia score and anxiety or depression scores were examined by the same linear mixed models as in the main analysis with additional fixed effects for anxiety or depression scores; 3-way interactions between time, group, and score; and all lower-order interactions.

All linear mixed models included random intercepts for participants and an additional fixed effect for the period (randomized clinical trial or follow-up), followed by interactions between period and relevant variables. An autoregressive covariance structure was used. The cluster effect on the site level was negligible and thus not included in the models. All analyses were conducted on the intention-to-treat sample using SAS, version 9.4. (SAS Institute Inc). A 2-sided $P < .05$ was considered statistically significant.

Results

Among the 232 participants assessed for eligibility, 165 were included in the study, and 159 were randomized to treatment with either XR-NTX (80 participants) or BP-NLX (79 participants). The reasons for exclusion or not being randomized after inclusion were refusal to participate (51 [69.9%]), not meeting inclusion criteria (9 [12.3%]), failed detoxification (6 [8.2%]), and other reasons (7 [9.6%]). At week 12, 105 participants (66.0%) had completed the randomized part of the study. No significant difference in treatment retention between the groups could be detected. Most participants (117 of 122) preferred XR-NTX when entering the follow-up study after week 12. These data were therefore based on XR-NTX participants only, that is, those who continued with XR-NTX and those who switched from BP-NLX to XR-NTX. At week 16, 8 participants dropped out or failed detoxification, leaving 109 participants in the follow-up study. In each group, 29 participants completed the study (ie, total of 58 participants; 10 women and 48 men) (**Figure 1**). Four participants tested positive for HIV, and 86 participants (54.1%) had positive hepatitis C tests. The mean daily dose of BP-NLX was 11.2 mg (range, 6.0-24.0 mg). Participant characteristics are given in **Table 1**.

The participants receiving XR-NTX and BP-NLX showed similar age distribution (mean [SD], 36.4 [8.8] vs 35.7 [8.5] years), sex distribution (men, 61 [76%] vs 54 [68%]; women, 19 [24%] vs 25 [32%]), duration of heroin use (mean [SD], 6.9 [5.8] vs 6.7 [5.2] years), race/ethnicity (white, 72 [90.0%] vs 70 [88.6%]), and other social characteristics corresponding to data from the national registry of opioid-dependent substance users in Norway. Descriptive statistics for both treatment groups are given in **Table 2**. The mean (SD) age of participants who continued receiving XR-NTX in the follow-up study was 36.0 (8.3) years and that of participants who switched from receiving BP-NLX to receiving XR-NTX in the follow-up was 35.4 (9.7) years.

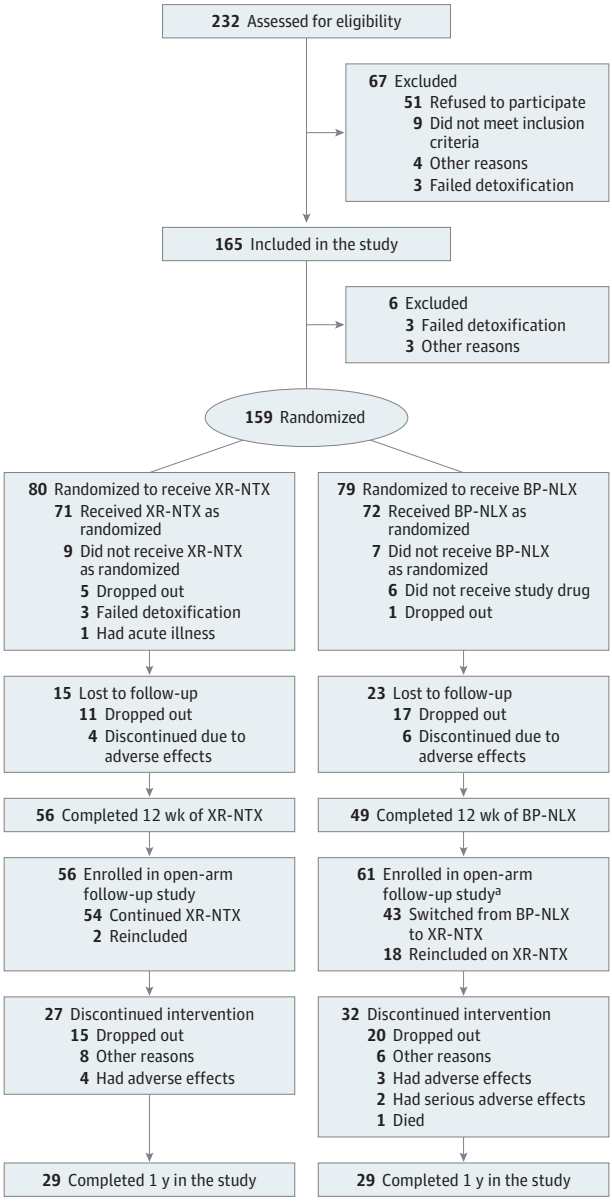
At baseline, the mean (SD) scores were 18.6 (6.8) for anxiety, 31.1 (10.3) for depression, and 12.9 (8.1) for insomnia. The scores were moderately to highly intercorrelated: anxiety and depression, 0.73; anxiety and insomnia, 0.58, and depression and insomnia, 0.56.

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

Randomized Clinical Trial Period

We were unable to detect any overall differences between the XR-NTX and BP-NLX treatment groups in the trends for the anxiety and depression scores, but the insomnia score was significantly lower in the XR-NTX treatment group (−0.32; −0.55

Figure 1. CONSORT Flowchart



[a] An additional 5 patients continued combined buprenorphine-naloxone (BP-NLX) treatment in the follow-up period but were not included in the analysis. XR-NTX indicates extended-release naltrexone hydrochloride.

to −0.08; P = .008) (**Figure 2**). This difference would remain significant after adjustment for multiple testing. The estimated effect sizes were small, and the 95% CIs were relatively narrow for scores of anxiety (−0.14; 95% CI, −0.47 to 0.19), depression (−0.12; 95% CI, −0.45 to 0.21), and insomnia (−0.32; 95% CI, −0.61 to −0.02).

Because no difference was detected between the treatment groups for anxiety and depression scores, the associations between the anxiety and depression scores and illicit substance abuse scores were assessed for all participants together. The anxiety score was not related to the use of heroin. The mean anxiety scores increased significantly for

Table 1. Demographic and Baseline Clinical Characteristics of Participants Randomized to Treatment With Extended-Release Naltrexone or Buprenorphine-Naloxone

Characteristic	No. (%) of Participants	
	Extended-Release Naltrexone (n = 80)	Buprenorphine-Naloxone (n = 79)
Age, mean (SD), y	36.4 (8.8)	35.7 (8.5)
Sex		
Male	61 (76)	54 (68)
Female	19 (24)	25 (32)
White race/ethnicity	72 (90)	70 (89)
Intravenous injection users	72 (90)	64 (81)
HIV positive	2 (2)	2 (2)
Hepatitis C seropositive	44 (55)	42 (53)
Duration of substance use, mean (SD), y		
Heavy opioid use	8.9 (7.8)	9.6 (10.5)
Heroin	6.9 (5.8)	6.7 (5.2)
Other illicit opioids	2.4 (5.1)	3.2 (7.0)

1 day's extra use of other opiates (0.17; 95% CI, 0.27-0.11; P = .002), amphetamine (0.08; 95% CI, 0.02-0.14; P = .01), benzodiazepine (0.10; 95% CI, 0.06-0.14; P < .001), or cannabis (0.05; 95% CI, 0.01-0.10; P = .02). The mean depression scores were significantly higher for 1 extra day's use of heroin (0.14; 95% CI, 0.06-0.21; P < .001), other opiates (0.27; 95% CI, 0.10-0.45; P = .002), benzodiazepine (0.17; 95% CI, 0.10-0.23; P < .001), amphetamine (0.20; 95% CI, 0.09-0.30; P < .001), and cannabis (0.15; 95% CI, 0.07-0.22; P = .001). When adjusted for substance use, the trends in anxiety and depression scores remained unchanged.

The study did not detect any overall sex differences in the trends of the anxiety, depression, or insomnia scores between the 2 treatment groups. Although increases in anxiety and depression scores were significantly associated with higher insomnia scores (anxiety mean, 0.55; 95% CI, 0.42-0.68; depression mean, 0.36; 95% CI, 0.28-0.45; P < .001), no difference was found between treatment groups. We found only weak correlations between craving for opioids and anxiety, depression, and insomnia scores. In addition, among participants who completed the study, we did not find any significant differences between treatment groups for anxiety or depressions scores but found a small overall difference between the groups for insomnia scores (0.02; 95% CI, −0.56 to −0.06; P = .02).

Follow-up Study Period

No overall differences in anxiety, depression, or insomnia scores were detected between participants continuing with XR-NTX after the randomized clinical trial and participants switching from BP-NLX to XR-NTX after week 12 (Figure 2). The estimated effect sizes were 0.04 (95% CI, −0.34 to 0.42) for anxiety, −0.04 (95% CI, −0.42 to 0.33) for depression, and 0.04 (95% CI, −0.33 to 0.42) for insomnia scores.

When assessing all participants as 1 treatment group, higher mean anxiety scores were significantly associated with 1 day's

Table 2. Descriptive Statistics for Anxiety, Depression, and Insomnia Scores of Participants by Treatment Group and Time

	No. of Participants		Mean (SD) Score					
			Anxiety Subscale		Depression Subscale		Total Insomnia	
Treatment Week	BP-NLX	XR-NTX	BP-NLX	XR-NTX	BP-NLX	XR-NTX	BP-NLX	XR-NTX
0	79	80	18.2 (6.7)	19.0 (6.9)	31.6 (10.3)	30.6 (10.2)	12.9 (8.0)	13.4 (8.2)
4	71	69	16.4 (5.4)	18.2 (6.8)	27.5 (9.5)	28.7 (10.1)	13.4 (7.8)	12.3 (7.3)
8	57	56	16.8 (6.8)	16.3 (5.7)	27.7 (8.9)	25.5 (9.7)	11.3 (7.5)	9.8 (7.6)
12	49	56	16.3 (5.4)	16.1 (5.6)	28.4 (8.5)	26.0 (9.3)	12.8 (7.4)	9.2 (7.3)
			Switched to XR-NTX	Continued XR-NTX	Switched to XR-NTX	Continued XR-NTX	Switched to XR-NTX	Continued XR-NTX
12	61	56	18.2 (6.6)	16.1 (5.7)	30.5 (9.6)	25.9 (9.4)	13.7 (7.8)	9.1 (7.5)
16	59	50	18.1 (7.4)	15.3 (5.0)	28.3 (10.0)	25.9 (9.0)	13.2 (8.7)	9.2 (7.2)
20	50	45	16.6 (7.1)	15.3 (5.4)	26.1 (9.8)	24.7 (9.9)	11.8 (8.4)	7.9 (7.1)
24	44	44	16.0 (6.9)	15.6 (6.0)	25.0 (9.7)	24.8 (8.6)	9.4 (7.6)	7.1 (6.5)
28	41	38	15.8 (7.2)	14.4 (5.1)	26.0 (11.1)	23.9 (9.2)	10.4 (8.3)	7.6 (7.0)
32	37	33	15.5 (7.4)	15.2 (5.9)	25.1 (10.4)	24.5 (9.2)	8.7 (7.6)	7.4 (7.4)
36	33	35	16.7 (7.1)	16.1 (6.0)	27.8 (10.8)	26.2 (10.3)	11.0 (8.3)	9.1 (7.9)
40	31	30	15.5 (6.5)	13.3 (4.3)	26.2 (10.7)	22.8 (7.1)	9.5 (8.5)	7.5 (7.0)
44	28	32	15.5 (7.1)	14.1 (4.7)	26.6 (9.6)	23.0 (7.8)	10.6 (9.1)	8.0 (7.4)
48	29	29	16.2 (7.8)	13.7 (5.6)	25.6 (10.7)	21.5 (6.4)	9.6 (8.0)	6.6 (6.1)

Abbreviations: BP-NLX, combined buprenorphine-naloxone; XR-NTX, extended-release naltrexone.

extra use of heroin (0.11; 95% CI, 0.02-0.20; $P = .01$), benzodiazepine (0.13; 95% CI, 0.09-0.17; $P < .001$), amphetamine (0.16; 95% CI, 0.10-0.22; $P < .001$), and cannabis (0.06; 95% CI, 0.02-0.11; $P = .004$), and mean higher depression scores were significantly associated with 1 day's extra use of heroin (0.25; 95% CI, 0.11-0.40; $P = .001$), benzodiazepine (0.25; 95% CI, 0.18-0.32; $P < .001$), amphetamine (0.30; 95% CI, 0.20-0.39; $P < .001$), and cannabis (0.13; 95% CI, 0.06-0.20; $P < .001$). We found no association between the use of other opioids and depression or anxiety scores.

Increases in the anxiety and depression scores were significantly associated with higher insomnia scores (mean, 0.65; 95% CI, 0.41-0.84 and mean, 0.43; 0.30-0.57, respectively; $P < .001$) in the follow-up period, with no differences detected between treatment groups. Our analyses did not show any overall sex differences in the trends for anxiety, depression, or insomnia scores between the 2 groups of participants.

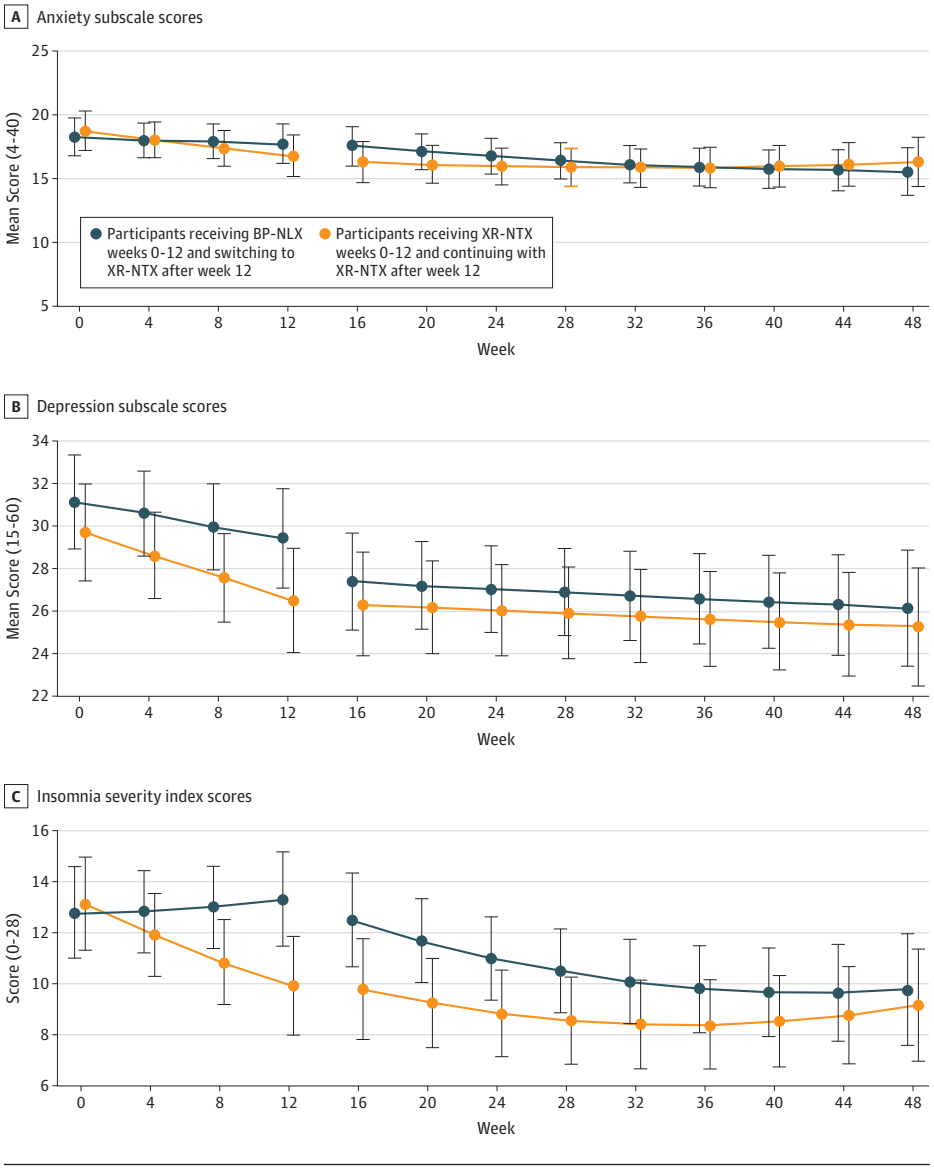
Discussion

To our knowledge, this is the first study comparing the effects of the administration of XR-NTX injections with those of daily oral BP-NLX treatment on the comorbid symptoms of anxiety and depression as assessed by the HSCL-25 subscale scores and insomnia as assessed by the Insomnia Severity Index score. The levels of anxiety and of depression were positively correlated with the use of illicit substances in both study periods and were also positively associated with the degree of insomnia. On the basis of our findings, we postulate that opioid agonist treatment with BP-NLX has no advantage over XR-NTX on the comorbid symptoms of anxiety, depression, or insomnia in abstinence-motivated adults with opioid dependence.

Previous reports have discussed anhedonia, depression, and reduced pleasure after starting treatment with either XR-NTX or oral naltrexone in participants with or without substance use disorders.[30-33] However, our findings are consistent with a study by Krupitsky et al[32] that reported gradual improvements in anxiety, depression, anhedonia, and insomnia with time in participants treated with either oral NTX or XR-NTX implants. Both Zaaijer et al[34] and Mysels et al[35] reported a significant improvement in depressive symptoms with NTX treatment, but Mysels et al[35] found no improvement in anxiety symptoms and a transient worsening of late insomnia. A study by Dean et al[36] showed improvement in depressive symptoms only and a worsening of anxiety symptoms with oral NTX.

Among individuals with opioid dependence who use opioids, anxiety and depressive symptoms are heavily influenced by the use of other substances.[37] A 10-year prospective study by Ravndal et al[10] of patients receiving opioid maintenance treatment found that high and stable scores of anxiety and depression correspond well with substantial difficulty in reducing the abuse of benzodiazepines and cannabis. This outcome is in line with our finding of a higher use of illicit substances in participants reporting more symptoms of anxiety and depression. Although no improvement was observed at any point in time in the study by Ravndal et al,[10] our results showed improvements in anxiety, depression, and insomnia within only a few weeks of beginning either study treatment. Our study also showed reductions in the use of opioids and other illegal substances in both treatment groups. This finding is in accordance with a reduction in illicit opioid use among participants treated with XR-NTX compared with those receiving placebo injections reported in a study by Comer et al,[19] general treatment aftercare,[38] or oral NTX treatment.[39] However, it is difficult to know whether the observed improvements in symptoms of anxiety, depression, and insomnia were

Figure 2. Changes in Anxiety, Depression, and Sleep Scores During the Randomized Clinical Trial Portion of the Study and in the Follow-up Period



The 25-item Hopkins Symptom Checklist mean anxiety subscale (A) and mean depression subscale (B) scores and the Insomnia Severity Index scores (C) among participants randomized to extended-release naltrexone (XR-NTX) or combined buprenorphine-naloxone (BP-NLX) treatment from baseline (week 0) to week 12 and receiving XR-NTX during the follow-up period (from week 16 to week 48) analyzed using a linear mixed model. Values in parentheses on the y-axes indicate minimum and maximum values of each scale; error bars represent 95% CI.

merely a reflection of the reduced use of illicit substances or a positive pharmacological effect of XR-NTX treatment per se.

It is commonly assumed that there is a complex interplay between the use of illicit substances and sleep disturbances, anxiety, and depressive symptoms. A number of studies report that opioid agonists have psychotropic effects on mood, sedation, and anxiety and that BP and BP-NLX are useful in the palliation of such symptoms in individuals with opioid dependence.[40-44] People with depression and opioid dependence have also reported a reduction in symptoms following methadone treatment.[33] This finding is consistent with the results of the present study for the participants receiving BP-NLX, but our results also suggested that this effect could be obtained with an opioid antagonist, such as XR-NTX.

Sleep problems are regarded as a risk factor, a consequence, and a complication of both depression and opioid dependence. Studies have suggested that depression and insomnia may share a common etiology or may simply coexist[17] and that depression and anxiety disorders independently affect sleep among users of illicit substances.[45,46] One study reported improved sleep patterns and insomnia with opioid agonist treatment.[47] We believe that the improvement in anxiety and depressive symptoms and possibly the reduction in substance abuse may have led to this reported improvement in insomnia.[48]

The majority of the participants who dropped out of the randomized clinical trial part of the present study due to side effects were randomized to receive BP-NLX. Most of these patients were initially motivated to receive treatment with

XR-NTX, which may have influenced the dropout rate among patients receiving BP-NLX.

Limitations and Strengths

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

Another limitation is that we did not confirm reported drug use by testing urine samples in the follow-up period. However, analyses performed in the randomized clinical trial part of the study showed a high correlation between the reported use of illicit substances and urine analysis results. Having a current psychiatric disorder was not an exclusion criterion for the present study except for psychotic disorders and other severe psychiatric illnesses that would most likely have made participation in the study difficult. A strength of the study was that an even distribution of participants in the XR-NTX and BP-NLX groups reduced the possibility of bias in observed improvement in both treatment groups.

Conclusions

Because participants receiving treatment with XR-NTX or BP-NLX showed equal improvements in anxiety, depression, and insomnia as assessed by the HSCL-25 and the Insomnia Severity Index, such symptoms should not preclude the choice to leave opioid agonist treatment and to start treatment with XR-NTX. There was a significant relationship between higher HSCL-25 scores and more frequent use of illicit substances.

ARTICLE INFORMATION

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Correction: This article was corrected on February 6, 2019, to fix an error in a 95% CI in the abstract and the Results section.

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