

Anxiety, Depression, and Insomnia Among Adults with Opioid Dependence Treated with Extended Release Naltrexone vs. Buprenorphine-Naloxone

BACKGROUND:

- Persons who are opioid dependent have an increased prevalence of lifetime psychiatric disorders, such as anxiety and depression, compared to the general population
- Depression and anxiety, as well as insomnia, can impact a person's treatment outcomes for their substance abuse disorder

OBJECTIVE:

- To determine if extended-release naltrexone (XR-NTX) unveils or benefits persons with opioid dependence who have anxiety, depression, or insomnia compared to opioid agonist treatment

METHODS:

- **Study Design:** 12-week prospective, randomized clinical trial that used a permuted block algorithm to assign patients to treatment with either intramuscular injection of XR-MTX in the gluteal region every fourth week or daily sublingual tablet of buprenorphine-naloxone (BP-NLX), followed by a 9-month, open-label trial where patients were given the opportunity to choose either one of these two medications
- Conducted in the outpatient addiction clinics of 5 urban hospitals in Norway
- **Inclusion Criteria:** Men and women aged 18 to 60 years who had opioid dependence as defined by the *Diagnostic and Statistics Manual of Mental Disorders (Fourth Edition)*
- **Exclusion Criteria:** Other drug or alcohol dependencies, serious somatic or psychiatric psychotic illnesses that would interfere with study participation, women of childbearing age who are pregnant or lactating
- 159 patients were enrolled within the randomized portion of the study
 - 80 patients received XR-NTX treatment: 380 mg every fourth week for 12 weeks
 - 79 patients received BP-NLX treatment: 4 to 24 mg/d (individually dosed) for 12 weeks (target dose: 16 mg/d)
- 120 patients were enrolled within the open-label portion of the study
- **Primary outcome measures:**
 - Assess the difference between the scores of the 2 treatment groups for the 3 outcome measures (anxiety, depression, and insomnia) during the randomized short-term treatment and the follow-up longer-term treatment
 - 25-item Hopkins Symptom Checklist (HSCL-25) was used to assess the symptoms of anxiety and depression, while the Insomnia Severity Index were used to measure the symptoms of insomnia
- Power was not mentioned in the study
- Data handling method was intent-to-treat

RESULTS

- 105 patients completed the randomized portion of the study (56 completed 12 weeks of XR-NTX, 49 completed 12 weeks of BP-NLX)
- 58 patients had completed the study (29 in each treatment group)
- **Primary outcome measures:**
 - No overall difference between the two randomized treatment groups relating to the anxiety and depression scores; however, the insomnia scores were significantly lower in the XR-NTX treatment group (-0.32; -0.55 to -0.08, P=0.008) compared to the BP-NLX treatment group

- No overall difference between patients continuing XR-NTX after the randomized clinical trial or switching to XR-NTX from BP-NLX after week 12
- **Authors stated conclusion:**
 - Since similar improvements occurred in both the XR-NTX and BP-NLX groups in anxiety, depression, and insomnia scores, XR-NTX should also be an initial treatment of choice for patients who are opioid dependent with these symptoms

STRENGTHS

- Approximately number of participants in both treatment groups

LIMITATIONS

- Since symptoms of depression and anxiety were assessed with the 25-item Hopkins Symptom Checklist (HSCL-25) and Insomnia Severity Index, which are self-report questionnaires, patients could have different interpretations of the questions and rating scales
- Did not conduct drug testing using urine samples in the follow-up period
- Specific adverse drug events patients had experienced were not listed
- Power was not stated in the study: was the sample size appropriate?
- Lack of diversity in the study population: majority of patients were white and male: difficult to extrapolate results
- Increase frequency for assessing symptoms of depression, anxiety, and insomnia
- Patient population was not classified as having significant anxiety, depression, and insomnia
- The study excluded patients with other drug or alcohol dependencies; however, an exploratory analysis was conducted to see if there was an association between anxiety, depression, and substance abuse (heroin, other opiates benzodiazepines or sedatives, amphetamines, and cannabis)
- After the randomized control portion of the trial, majority of patients (117 of 122) wanted the XR-NTX treatment in the follow up study period, but was not explained why in the study

CONCLUSIONS

- Since the study concluded that XR-NTX should be used as a starting treatment for patients addicted to opioids due to similar improvements seen, XR-NTX could potentially be useful as alternative treatment to the combination product in actual practice. However, patient preference and cost would probably be the deciding factors in what medication would be chosen.
 - Each vial of XR-NTX costs \$1,570.80 compared to each BP-NLX sublingual tablet, which cost ranges from \$10.00-\$20.00
 - Patient would have to go to clinic to receive XR-NTX injection compared to a community pharmacy to receive BP-NLX
 - Do patients want to get an injection every month?
 - Adherence was not measured in the study
- Future research:
 - Given the small sample size, another trial with more patients (who are more diverse) should be conducted to increase the study's power and identify if there is statistical significance in the outcome measures

Reference: Latif Z., Benth JS., Solli K, Opheim A. Kunoe N., Krajci P., Sharma-Haase K., et al. 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.* 2019;76(2):127-134.