The Effectiveness of Buprenorphine-Naloxone on Opioid Use Disorder

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Abstract

Opioid use disorder (OUD) is a disorder characterized by extreme opioid misuse which causes issues within all aspects of life. To treat OUD, buprenorphine-naloxone (BNX) is used as a partial opioid agonist paired with naloxone to discourage injection. This medication is often prescribed as a sublingual medication for participants to self-administer. This paper investigates the effectiveness of BNX on treating OUD by examining various empirical studies concerning BNX. The studies suggest BNX has a moderate to strong effectiveness on treating OUD compared to other available treatments. Future directions primarily consist of addressing the common limitation of low retention rates in treatment through a variety of means. Assessment of BNX on OUD is necessary as the opioid crisis present in North America continues to grow.

Keywords: Opioid use disorder, buprenorphine-naloxone, opioid replacement therapy

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Opioid use disorder (OUD) is a substance-related disorder that affects over 16 million people globally (Chang et al., 2018). OUD is characterized by using opioids more or longer than intended, unsuccessful attempts to cease or control use, cravings, continued use despite issues presenting in professional and personal settings, or dangers to oneself (American Psychiatric Association, 2022). Increased tolerance to opioids as well as withdrawal symptoms when ceasing use are additional markers of OUD. Individuals who are addicted to opioids have a mortality rate up to 20 times greater than the general population, prompting the necessity for an effective treatment (Barlow et al., 2021). Treatment for OUD often includes opioid replacement therapy, involving introducing the user to another opioid that is less addictive than heroin or prescription opioids (Dydyk et al., 2022). Sublingual buprenorphine is one of the most popular replacement opioids for treating OUD and is often combined with naloxone to discourage injection (National Academies of Sciences, Engineering, and Medicine, 2019). Buprenorphine-naloxone (BNX) is usually prescribed for self-administration. Research into treatment for OUD often involves comparing two or more treatments to determine effectiveness. I will focus on the methodology and results pertaining to BNX treatments, mentioning other treatments only if necessary for context. This paper will examine the effectiveness of BNX as a treatment for OUD.

Jutras-Aswad et al. (2022) examines the effectiveness of take-home BNX as an opioid agonist therapy (OAT) in reducing opioid use in prescription-type opioid users with OUD. This study uses a pragmatic, open-label, randomized control trial where the interest is if BNX is non-inferior to supervised methadone (MET) as an OAT. At the beginning of the study, participants with prescription-type OUD met with a study physician to receive treatment medication and to discuss the treatment plan, induction procedure, and to supervise the first dose. Participants were

required to provide urine samples, update information on file, and conduct routine tests throughout the study and take-home doses were given to clinically stable patients at self-administer. Variable “opioid use” was measured through opioid-free (negative) drug screens, while missing urine drug screens were considered positive. Variable “retention in treatment” was defined as having both an active prescription and a positive urine drug screen result for their assigned treatment at week 24. Later in the study, there were alternative definitions for retention: (1) having an active OAT prescription at week 24, and (2) having both an active prescription and a positive urine drug screen for any OAT at week 24. Variable “quality of life” was analyzed at baseline and every 4 weeks using EuroQol-5D, which provides a visual analogue scale for participants to rate their health from 0-100 (EuroQol Research Foundation, 2021). Researchers analyzed 138 in the BNX treatment group (Jutras-Aswad et al., 2022). From the BNX group, 22.5% of participants switched to another OAT, 73.8% of participants received take-home doses, and the mean percentage of negative urine drug screens was 24.0%. Non-inferiority between the treatments was demonstrated through a mean difference of 5.6% in negative urine drug screens. Both treatment groups had comparable numbers of collected urine drug screens. For retention, participants in the BNX group had lower odds of continuing than the MET treatment regardless of the definition for retention. However, retention in any OAT did not statistically significantly differ between treatment groups. The above findings may suggest BNX is easier to transition from than MET. This quality is an advantage for BNX patients who want to switch or are otherwise required to. The accessibility of OATs through Canadian health care coverage and availability of more potent illicit opioids are noted as possible factors for lower retention and more positive urine drug screens. Quality of life significantly improved throughout the study, with BNX showing an increase from mean 57.0 to 72.2 and a faster increase at the beginning of

the trial than MET. Low retention is the primary limitation of this study, which may have been influenced by the pragmatic design. However, the design also allows for greater generalizability as the participants reflect real-world populations. Although the researchers only intended to assess non-inferiority, the results suggest superiority of BNX over MET in treating OUD. Hser et al. (2012) compares long-term outcomes among participants randomized to BNX and MET. 1080 total participants were randomized into either BNX or MET (630 in BNX and 450 in MET). Researchers conducted interviews at the beginning of the study to collect toxicological samples necessary for establishing a baseline. Both treatment groups had similar baseline measures. Researchers conducted follow-up interviews 2-8 years after randomization, 73.7% BNX participants were interviewed. Variable "treatment participation" was collected using the timeline follow-back (TLFB) instrument between randomization and the follow-up interview. Researchers examined current opioid use as well as opioid use during the follow-up period. Current opioid use was determined through self-reported days of use in the 30 days prior to the follow-up interview or a positive opioid urine test, while use during the follow-up period was measured by self-reported days of opioid use per month. The TLFB helped participants complete reports on use by providing tools for memory cues such as a calendar (Scobell & Scobell, 1992). For treatment participation, BNX participants had fewer days of treatment than those in MET (111 versus 149) and BNX participants spent fewer months in any treatment after the initial treatment (Hser et al., 2012). Only 53.7% of those randomized to BNX were in any treatment at follow-up, compared to 63.1% of MET participants. However, participants originally randomized to BNX were more likely to go into BNX treatment during the follow-up period, suggesting a positive response to the medication. Current opioid use at the end of the study was found to be higher (42.8% positive urine drug screens; 5.8 days of use in the last 30) in the BNX

group than the MET group. During the follow-up period both treatments had a drop in opioid use immediately after induction, which then steadily increased again after 6 months, reaching a peak around 10-12 months then averaging out afterwards. Both treatments were successful at reducing opioid use compared to no treatment. MET produces a stronger physiological dependence than BNX which may contribute to lower treatment participation rate in the BNX group. This finding supports the suggestion in Jutras-Aswad et al. (2022) that BNX treatment may be easier to transition from than MET. Researchers noted BNX has notable benefits as a treatment, as it is available more widely and can be offered in more casual settings than other treatments (Hser et al., 2012). Limitations of this study primarily concerns treatment participation and generalizability. Treatment was only provided for 6 months through MET maintenance sites, which may have contributed to low participation. Additionally, post-trial BNX treatment varied dramatically due to differences in availability and administration policies. Generally, the study concluded with the researchers finding success in opioid maintenance treatment when participants were successfully retained in treatment, regardless of BNX or MET.

In Lee et al. (2018), potential differences between extended-release naltrexone (XR-NTX) and BNX are examined for relapse to regular opioid use (time to relapse). 570 participants with OUD from acute inpatient detoxification programs were randomly assigned to open-label treatment, with 287 participants in the BNX treatment. The detoxification procedure, length of stay, and timing of randomization varied with some being randomized early during the detoxification period and the rest being randomized late after completing detoxification. Sublingual film BNX treatment was given to self-administer after randomization over the course of 20 weeks and was ceased following a relapse event or at the end of 24 weeks. Participants met with a physician to check on medication adherence, side effects, and abstinence to non-study

opioids. Visits with research staff occurred through weeks 0-24, 28, and 36 to gather information about medical, drug, and treatment history, demographics, and to obtain blood and urine samples for testing at baseline. Participants filled out weekly self-reports on opioid and other substance use and had routine urine drug screens. Variable “time to a relapse event” was defined as using non-study opioids any time 20 days after randomization. Observation of relapse events started on day 21 as recently detoxified participants were likely to have positive urine samples from detoxification medication for 2-3 weeks after randomization. Variable “frequency of non-study opioid use” was measured with the aid of the TLFB measure and verified with weekly urine samples. 270 BNX participants were successfully inducted to the treatment, and 194 participants completed the follow-up at week 28. More participants in the BNX treatment were successfully inducted than in the XR-NTX treatment and completed a median of 14 weeks of treatment. Though, when participants successfully started medication, XR-NTX and BNX were found to be similarly effective. The BNX group also had a lower proportion of relapse events (57%) than the XR-NTX group (65%). Regardless of treatment, relapse risk was higher in the early randomization groups than in the late randomization groups. One difference revealed in this trial is that BNX, unlike XR-NTX, does not require full detoxification before induction. A major challenge for this study was treatment retention, which may have been influenced by recruitment occurring in detoxification programs, though this is consistent with retention difficulties seen in Jutras-Aswad et al. (2022). While BNX demonstrated better overall results than XR-NTX due to induction failures in the latter, both treatments were shown to be equally effective once treatment was successfully started (Lee et al., 2018).

Dunlop et al. (2017) examines the effectiveness of take-home self-administered weekly BNX in comparison to a waitlist control condition for patients with heroin dependence. The

sample included 50 individuals with current heroin dependence disorder who had used heroin for at least 20 of the last 28 days. Participants were randomized 1:1 to either the waitlist control group or the BNX group; the trial was open-label. The BNX group was supervised for induction on day 1 and given medication self-administer on day 2. Participants would meet weekly for 12 weeks to assess progress and side effects, as well as receive the next weeks' take-home medication. Those in the waitlist condition did not have any appointments during the 12-week period. Variable "heroin use" was self-reported using the Opiate Treatment Index (OTI) and confirmed by urine toxicology collected weekly. The OTI also measured the variable "other substance use." Variables were measured at weeks 4, 8, and 12. Those in the BNX treatment reported a decrease in heroin use and other opioids at each measurement point. Over the 12-week study period, self-reported heroin use was 19.02 days less per 28 days in the BNX group compared to the waitlist group. This was supported by a stable reduction in positive drug screens in the BNX treatment over the study period. The small sample size is a limitation of this study, as it may affect the generalizability of the results; however, the smaller sample size may have contributed to a higher retention rate, which has been a reoccurring issue in the previous studies examined earlier. Although this study only focused on heroin dependent individuals, the decreased usage of other opioids after BNX treatment supports the previously mentioned studies that examine individuals' general or prescription-type OUD. The researchers conclude that in comparison with those in the waitlist condition, participants with heroin dependence treated with BNX had significant decreases in heroin use.

Jutras-Aswad et al. (2022) suggest future research should involve developing strategies to improve treatment outcomes that specifically target retention. This may include psychosocial methods and better adapted models of care. Hser et al. (2015) is also interested in future research

to improve retention, though this study takes a different approach than Jutras-Aswad et al. (2022) by suggesting examining factors at the patient and contextual level that lead to medication discontinuation. By addressing some of these factors, such as a lack of medication knowledge, use of other substances, and involuntary medication discontinuation due to strict clinical requirements or incarceration, patients may continue treatment for longer times which may improve treatment outcomes overall. Similar to the previous two studies, Lee et al. (2018) is interested in examining the individual-level clinical and genetic factors on treatment effects, which will likely look at factors similar to Hser et al. (2015). Dunlop et al. (2017) suggests further research into reduced clinical contact time, which may overall contribute to increased retention rates which was a challenge in each trial other than Dunlop et al.

This paper investigates the effectiveness of BNX on OUD by examining four empirical studies that utilize BNX to treat OUD. Jutras-Aswad et al. (2022) found that take-home BNX was superior to supervised MET. Hser et al. (2017) noted the benefits of BNX treatment but did not conclude if it was better than MET, instead stating that retention in any treatment is best. Lee et al. (2018) also found that BNX was overall better than XR-NTX due to less induction failures in the former. Dunlop et al. (2017) found significant reduces in heroin use after BNX treatment as well as a reduction in other opioid use. Overall, the findings of the above four studies suggest that BNX is moderately to strongly effective for treating OUD.

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