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Naltrexone-Facilitated Buprenorphine Discontinuation: A Feasibility Trial ☆

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ABSTRACT

Rationale: Buprenorphine is an effective and popular treatment for opioid dependence. It remains unclear, however, when or how to transition stable buprenorphine-maintained individuals to complete abstinence. This trial investigates the feasibility of using naltrexone to facilitate buprenorphine discontinuation in stable individuals who had tolerated a taper to 2 mg or less but were unable to terminate entirely due to withdrawal-related distress.
Methods: The sample consisted of 6 buprenorphine-maintained individuals in sustained full remission, and who had tolerated a taper but were unable to discontinue altogether. A rapid induction procedure was performed, which included supervised buprenorphine discontinuation, oral naltrexone titration with a starting dose of 6.25 mg, and administration of long-acting injectable naltrexone. Participants were followed weekly for 5 weeks after the injection, with telephone follow-up occurring at 6 months.
Results: The rapid induction procedure was well tolerated. There was no observed or reported clinical worsening over the course of study participation. Notably, no participants experienced an increase in Subjective Opioid Withdrawal Scale (SOWS) scores after the first oral dose of NTX as compared to day 1 (24 hours after last dose of buprenorphine); instead, SOWS scores decreased between days 1 and 7 ($p = 0.043$). All participants were able to discontinue buprenorphine and to remain opioid free during the trial and at follow-up.
Conclusions: This preliminary trial represented for all participants the first successful attempt at buprenorphine discontinuation. Further research is needed to better understand if naltrexone is effective at facilitating buprenorphine discontinuation, as well as the feasibility of a sequential approach (buprenorphine stabilization to naltrexone) for opioid use disorders.

1. Introduction

Maintenance treatment with buprenorphine (often in combination with naloxone, as Suboxone®, to preclude inappropriate use) is an effective and increasingly popular approach to opioid dependence, with retention rates found to be as high as 50% at 6 months (Mattick, Kimber, Breen, & Davoli, 2008). Buprenorphine is a partial μ-opioid agonist and k-antagonist that works to ameliorate withdrawal phenomena and opioid craving, as well as attenuate the effects of co-administered opioids (Comer, Walker, & Collins, 2005; Lange, Fudala, Dax, et al., 1990; Orman & Keating, 2009). As with methadone, however, there is limited information about when or how buprenorphine can be safely discontinued once individuals achieve sustained full remission. Another possible complication is that withdrawal phenomena or distress may preclude discontinuation in individuals who might otherwise be ready to stop maintenance treatment. These issues may lead patients to be disinterested in initiating agonist maintenance for fear of indefinite treatment, or to remain in maintenance treatment for the sole reason of not incurring withdrawal-related distress. (See Table 1.)

An important question is therefore how to safely transition stable buprenorphine-maintained individuals to complete abstinence when the process is complicated by discontinuation-related distress. As with other opioids, buprenorphine-related withdrawal largely implicates cessation of μ-opioid agonism. Unlike most other cases of opioid withdrawal, however, the distress may also stem from loss of antagonism at k-opioid receptors. According to animal studies, k-opioid agonism produces aversive effects, such as dysphoria, and can also increase the likelihood of relapse to drug use through stress-mediated mechanisms (Bruchas, Land, & Chavkin, 2010; Wee & Koob, 2010). Thus, a plausible hypothesis is that some of the discomfort observed during discontinuation might be due to the attenuation or loss of the k-opioid antagonism afforded by buprenorphine, as well as to rebound k-opioid activation.

Naltrexone represents a promising candidate for extending k blockade, as well as for more generally addressing the risk of lapse to opioid use. Naltrexone and its active metabolite 6-β-naltrexol are competitive antagonists at the μ and k receptors, and to a lesser extent at the δ receptor (DeHaven-Hudkins, Brostrom, Allen, et al., 1990). Particularly in the injectable long-acting depot formulation (XR-NTX), naltrexone is an effective way to reduce the risk of relapse by robustly blocking opioid effects (Brooks, Comer, Sullivan, et al., 2010; Hulse, Morris, Arnold-Reed, et al., 2009; Krupitsky, Nunes, Ling, et al., 2011; Krupitsky, Zvartau, Blokhina, et al., 2012), as well as to potentially ameliorate distress via

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Table 1
Baseline demographic and morbidity characteristics.

Age, years (SD)	39.60 (14.28)
White	83% ($n = 5$)
Hispanic	17% ($n = 1$)
Male	67% ($n = 4$)
Single	33% ($n = 2$)
Married	50% ($n = 3$)
Divorced	17% ($n = 1$)
Employed	83% ($n = 5$)
Education, years (SD)	17.80 (1.64)
Comorbid ADHD	33% ($n = 2$)
Comorbid depression	67% ($n = 4$)
Baseline Suboxone, mg (SD)	0.75 (0.71)
Baseline HAMD (SD)	6.20 (4.76)
Baseline SOWS	20.60 (10.29)

k antagonism. Further, naltrexone may serve to reduce craving and normalize opioid receptor density (Krupitsky et al., 2011,2012; Lesscher, Bailey, Burbach, et al., 2003).

The purpose of this open-label trial is to investigate the feasibility and tolerability of naltrexone-facilitated discontinuation of buprenorphine in stable individuals who had previously experienced intolerable discontinuation-related distress. We selected a unique sample of stable individuals who have been maintained on buprenorphine for opioid dependence, who have achieved sustained full remission, and who have tolerated a taper to 2 mg or less of buprenorphine without being able to discontinue altogether.

2. Methods

2.1. Population

Individuals were recruited through advertisements, public outreach, professional referral, and referral from the Columbia Buprenorphine Providers clinic. Participants were initially evaluated by phone, and then in person at the New York State Psychiatric Institute (NYSPI), where they received a psychiatric evaluation, as well as a medical evaluation including physical examination, blood and urine testing, and electrocardiogram. Opioid dependent participants were considered eligible if they had tapered down to 2 mg or less of buprenorphine, had demonstrated an inability to discontinue altogether, and were in sustained full remission from opioid dependence (abstinent from illicit or other prescription opioids for at least a year). Eligible participants were also medically and psychiatrically stable, denied a history of overdose, denied current substance or alcohol abuse or dependence, denied a history of problematic responses to study medications, and denied a history of chronic pain (Table 1).

2.2. Study procedures

Eligible participants were consented into the following protocol, which received approval from the Institutional Review Board at the NYSPI. The protocol involved a brief inpatient stay followed by weekly outpatient visits for 5 weeks.

Participants were asked to take the last dose of buprenorphine on the morning of their admission to the inpatient research unit at NYSPI. 48 hours later they received the first oral dose of naltrexone (6.25 mg), with the dose doubling at each subsequent day (12.5, 25, and 50 mg). If participants were able to tolerate the 50 mg dose, they were provided an intramuscular injection of 380 mg depot long-acting naltrexone (XR-NTX).

Adjuvant medications aimed at managing an array of withdrawal phenomena, such as clonidine, clonazepam, zolpidem, ibuprofen, and loperamide, were available from the first hospital day. Participants who appeared clinically appropriate after receiving the 12.5 mg dose for continuing the naltrexone titration on an outpatient basis were asked to return to clinic at the NYSPI for daily naltrexone dosing and assessments until XR-NTX was administered.

After XR-NTX was administered, participants were asked to return weekly to clinic for 5 weeks for assessments and monitoring, including 12-panel urine toxicology testing. At the end of the monitoring period, participants were referred for further treatment if appropriate. Study staff contacted participants at 6 months for a telephone interview.

Daily assessments during buprenorphine discontinuation and naltrexone induction included Subjective Opioid Withdrawal Scale (SOWS), Spielberger State-Trait Anxiety Test (STAI), Craving Scales, and a risk assessment battery aimed at elucidating behaviors, affects, or thoughts that place an individual at risk for relapse. These assessments, as well as urine toxicology, were also administered weekly for the duration of the 5-week outpatient phase.

2.3. Statistical analyses

Friedman's tests compared pre-naltrexone scores of SOWS, STAI, HAMD, and craving with post-naltrexone scores at various timepoints, including within 1 hour of the first dose of naltrexone, when precipitated withdrawal is most likely to emerge, and again at the end of the induction period. Bonferroni-corrected Wilcoxon's signed ranks tests compared values at the beginning and end of the induction period.

3. Findings

Six participants were enrolled into the study. A majority was white, employed, and highly educated. The mean final buprenorphine dose was 0.75 mg. All participants had been maintained on buprenorphine for at least a year, had achieved sustained full remission from opioid dependence, and had tolerated, without lapse to opioid use, a taper to 2 mg or lower for at least 2 months in an effort to discontinue buprenorphine. All participants had failed medically supervised discontinuation of buprenorphine at least once (e.g., resumed buprenorphine shortly after cessation was attempted, despite the availability of adjuvant medications such as clonidine and clonazepam). One participant had tried to discontinue three times, with one attempt involving hospitalization in a detoxification unit.

Participants tolerated study procedures without significant adverse events. Every participant experienced withdrawal symptoms consistent with opioid discontinuation. Clonazepam and clonidine were used in all participants to manage the emergence of anxiety, agitation, and restlessness for the first 4 days of the procedure. No participants required clonazepam and clonidine following the induction. 2 of 6 participants reported sleep difficulties in the follow-up period for which zolpidem was continued for 2 weeks, and 3 of 6 reported fatigue. These difficulties resolved in all cases by the time that the 6-week trial concluded. There were no dropouts from the study, and all 6 participants remained abstinent from opioids, including buprenorphine, throughout the 5 week outpatient period (by urine toxicology and self-report) and at follow-up (by self-report).

Subjective measures of distress did not worsen at any time-point following the first oral dose of naltrexone, including immediately after administration. Most notably, subjective withdrawal (as assessed by SOWS) did not worsen (Fig. 1); instead, it may have significantly improved from baseline by the conclusion of the naltrexone induction period (18 at day 1 vs. 7 at day 7, median scores, $p = 0.043$). Other measures, including HAMD, STAI, and craving, did not significantly change from baseline over the course of study participation ($p > 0.05$).

4. Discussion

4.1. Main findings

This preliminary trial demonstrates the feasibility of using a rapid oral titration of naltrexone to initiate XR-NTX and facilitate