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Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial

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ABSTRACT

Background: Injectable extended-release naltrexone (XR-NTX), approved to prevent relapse to opioid dependence, requires initial abstinence. This multisite outpatient clinical trial examined the efficacy and safety of low-dose oral naltrexone (NTX), combined with a brief buprenorphine (BUP) taper and standing ancillary medications, for detoxification and induction onto XR-NTX.

Methods: Patients (N = 378) were randomized, stratified by primary short-acting opioid-of-use, to one of three regimens: NTX + BUP; NTX + placebo BUP (PBO-B); placebo NTX (PBO-N) + PBO-B. Patients received 7 days of ascending NTX or placebo, concurrent with a 3-day BUP or placebo taper, and ancillary medications in an outpatient setting. Daily psychoeducational counseling was provided. On Day 8, patients passing a naloxone challenge received XR-NTX.

Results: Rates of transition to XR-NTX were comparable across groups: NTX/BUP (46.0%) vs. NTX/PBO-B (40.5%) vs. PBO-N/PBO-B (46.0%). Thus, the study did not meet its primary endpoint. Adverse events, reported by 32.5% of all patients, were mild to moderate in severity and consistent with opioid withdrawal. A first, second, and third XR-NTX injection was received by 44.4%, 29.9%, and 22.5% of patients, respectively. Compared with the PBO-N/PBO-B group, the NTX/BUP group demonstrated higher opioid abstinence during the transition and lower post-XR-NTX subjective opioid withdrawal scores.

Conclusions: A 7-day detoxification protocol with NTX alone or NTX + BUP provided similar rates of induction to XR-NTX as placebo. For those inducted onto XR-NTX, management of opioid withdrawal symptoms prior to induction was achieved in a structured outpatient setting using a well-tolerated, fixed-dose ancillary medication regimen common to all three groups.

1. Introduction

Substance use disorders involving prescription pain relievers and heroin (opioid use disorder, OUD) affect 1.6 million and 0.6 million Americans over the age of 18, respectively (Substance Abuse and Mental Health Services Administration SAMHSA, 2016). A major challenge with the rate of substance use disorders is the rapid increase in deaths from drug overdose; in 2015, drug overdose was the leading cause of accidental death in the United States, accounting for over 52,000 deaths, with 63% involving an opioid (Rudd et al., 2016b), with the number threatening to climb (Rudd et al., 2016a).

The rising costs and limited availability of inpatient treatment as well as patient preference are leading to an increasing number of providers initiating treatment in an outpatient setting (Mitchell et al., 2013). A traditional approach to treatment of OUD involving detoxification followed by an outpatient treatment without pharmacotherapy has been shown to have low completion rates and high rates of relapse (> 60%) (Day et al., 2005; Weiss et al., 2011) and is not recommended (American Society of Addiction Medicine, 2015). Therefore, to help address this epidemic of opioid use disorder, there is a need to expand

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available pharmacotherapy approaches that can be initiated in an outpatient setting. Patients seeking treatment in the office-based treatment setting can be offered methadone, an opioid receptor agonist; buprenorphine (BUP), an opioid receptor partial agonist; or extended-release naltrexone (XR-NTX), an opioid receptor antagonist.

XR-NTX was approved by the U.S. Food and Drug Administration (FDA) in 2010 for the prevention of relapse to opioid dependence following detoxification, in conjunction with psychosocial counseling. XR-NTX has been associated with increased treatment retention, decreased relapse, and decreased cravings for opioids in outpatient and in short- and long-term inpatient settings (Herbeck et al., 2016; Krupitsky et al., 2011; Mannelli et al., 2014; Nunes et al., 2018). XR-NTX can only be started in individuals who are not physiologically dependent on opioids, to minimize the risk of precipitated withdrawal. It is therefore advised that patients abstain from opioids for 7–10 days prior to receiving XR-NTX; however, this represents a substantial clinical challenge, particularly in the outpatient setting. As a result, many patients relapse before they are able to initiate treatment with XR-NTX. After induction, rates of treatment retention and prevention of relapse are similar for patients treated with either BUP or XR-NTX (Lee et al., 2017; Tanum et al., 2017), but the induction process is more challenging with XR-NTX. Lee et al. (2017) reported that 72% (n = 204/283) of patients were inducted onto XR-NTX vs. 94% (n = 270/287) inducted onto BUP-naloxone (odds ratio [OR], 0.16; 95% confidence interval [CI], 0.09–0.28; $p < 0.0001$). Nearly all who failed induction in this study experienced early relapse.

Various opioid agonist/antagonist-based regimens have been proposed to transition patients from opioid agonists onto XR-NTX while minimizing the severity of opioid withdrawal symptoms (Sigmon et al., 2012). A component of several proposed regimens is the use of increasing doses of oral naltrexone (NTX) in combination with non-opioid medications targeting specific symptoms of opioid withdrawal to shorten the transition from physiological dependence on opioids to XR-NTX treatment (Collins et al., 2005; Comer et al., 2006; O'Connor et al., 1995; Sullivan et al., 2006a,b; ; Umbricht et al., 1999; Vining et al., 1988). A more recent strategy combines a brief BUP taper with initiation of low, ascending doses of oral NTX prior to a first XR-NTX injection (Mannelli et al., 2014). This combination was designed to reduce physiological dependence by providing intermediary treatment with a partial agonist while concurrently introducing a gradual opioid blockade through increasing doses of oral NTX. Smaller controlled trials have demonstrated successful transition onto XR-NTX using a regimen that includes BUP and low-dose NTX administered sequentially or in combination (Bisaga et al., 2015; Mannelli et al., 2014; Sullivan et al., 2017), along with adjunctive medications targeting residual opioid withdrawal symptoms. These research developments highlight the potential clinical utility of such a combination strategy to safely and comfortably transition patients using opioids on to antagonist treatment in an outpatient setting. Many clinical trials have also employed ancillary medications (Sigmon et al., 2012) in an effort to ameliorate symptoms of opioid withdrawal, but their utility has not previously been examined independently from oral NTX and BUP.

In an effort to establish a standardized and well-tolerated outpatient regimen for clinicians seeking to transition patients with OUD to antagonist therapy, we conducted a phase 3, double-blind, randomized trial in patients seeking treatment for heroin or prescription OUD to determine the efficacy, safety, and tolerability of oral NTX used in conjunction with BUP prior to the first dose of XR-NTX. All three treatment arms included fixed doses of adjunctive medications to address withdrawal symptoms. Prior clinical research has explored the use of these medications in varying combinations and doses, given the absence of clinical guidelines for non-agonist strategies to treat opioid withdrawal. An important second goal of this study was to develop a regimen of ancillary medications that could be tested for safety and efficacy to support outpatient management of opioid withdrawal.

2. Methods

2.1. Study design

This phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy, safety, and tolerability of a procedure involving 7 days of low and ascending doses of oral NTX or placebo used in conjunction with 3 days of tapered sublingual BUP or placebo and fixed doses of ancillary medications for adults with OUD transitioning to a first dose of XR-NTX on Day 8/8a. The study compared three regimens: oral naltrexone (NTX) + buprenorphine (BUP); oral NTX + placebo BUP (PBO-B); and placebo NTX (PBO-N) + PBO-B. The procedure lasted 7 days and was conducted daily in an outpatient clinic, followed by a naloxone challenge and a first dose of XR-NTX.

The study was conducted at 19 sites in the United States between August 2015 and January 2017, in accordance with the Declaration of Helsinki, 1964, and Good Clinical Practice principles (International Conference on Harmonization, 1997). The protocol, amendments, and informed consent were approved by a qualified institutional review board for each site, and all patients completed written informed consent prior to study participation. This study was registered at ClinicalTrials.gov: NCT02537574.

2.2. Patient populations

Patients 18–60 years of age voluntarily seeking opioid withdrawal and transition to antagonist treatment with XR-NTX were eligible if they: (1) had the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (American Psychiatric Association, 2013) diagnosis of moderate or severe OUD confirmed by the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1997); (2) reported consistently using opioids for at least 3 months; (3) had a positive urine test result for opioids at screening; and (4) demonstrated at least mild withdrawal symptoms (Clinical Opiate Withdrawal Scale [COWS] ≥ 6) (Tompkins et al., 2009; Wesson and Ling, 2003) on Day 1.

Key exclusion criteria included a positive drug test result for BUP or methadone; use of BUP or methadone within 7 or 14 days prior to randomization, respectively; use of XR-NTX within 90 days prior to screening; history of seizures; diagnosis of schizoaffective disorder or bipolar disorder; unstable major depressive disorder; physiological dependence on any psychoactive substance requiring medical intervention for detoxification (except opioids, caffeine, or tobacco); history of more than three unsuccessful inpatient or medically assisted outpatient opioid detoxifications; or history of accidental drug overdose in the past 3 years.

2.3. Study endpoints

2.3.1. Primary endpoint

The primary efficacy endpoint was the proportion of patients who received and tolerated an XR-NTX injection, as demonstrated by mild (COWS score ≤ 12 or Subjective Opiate Withdrawal Scale [SOWS] (Handelsman et al., 1987) score ≤ 10) opioid withdrawal symptoms 1 h following XR-NTX administration. We hypothesized that the addition of low-dose NTX, with or without BUP, would improve the success rate of initiating treatment with XR-NTX. Assuming the proportion of patients who receive and tolerate an XR-NTX injection is 60% in the NTX/BUP group, 50% in the NTX/PBO-B group, and 30% in the PBO-N/PBO-B group, a sample size of 110 patients per group was planned to provide at least 85% power to detect a statistically significant difference between NTX/BUP and PBO-N/PBO-B and between NTX/PBO-B and PBO-N/PBO-B groups at an overall 2-sided significance level of 0.05.

2.3.2. Secondary endpoints

The secondary efficacy endpoints included the mean score for “desire for opioids” (visual analog scale [VAS]); tolerability of the

procedure as defined as the number of days with peak COWS score ≤12; mean peak COWS score; and area under the curve COWS score prior to the XR-NTX injection.

2.4. Study procedures

2.4.1. Randomization

Patients were randomly assigned on Day 1 in a 1:1:1 ratio to one of three transition regimens: (1) oral NTX + sublingual BUP (NTX/BUP); (2) oral NTX + placebo sublingual BUP (NTX/PBO-B); or (3) placebo oral NTX + placebo sublingual BUP (PBO-N/PBO-B). Randomization of patients was stratified based on the primary opioid of use at baseline (heroin vs. prescription opioids), and enrollment was monitored throughout the study to ensure at least 35% primary prescription opioid users in the total randomized sample.

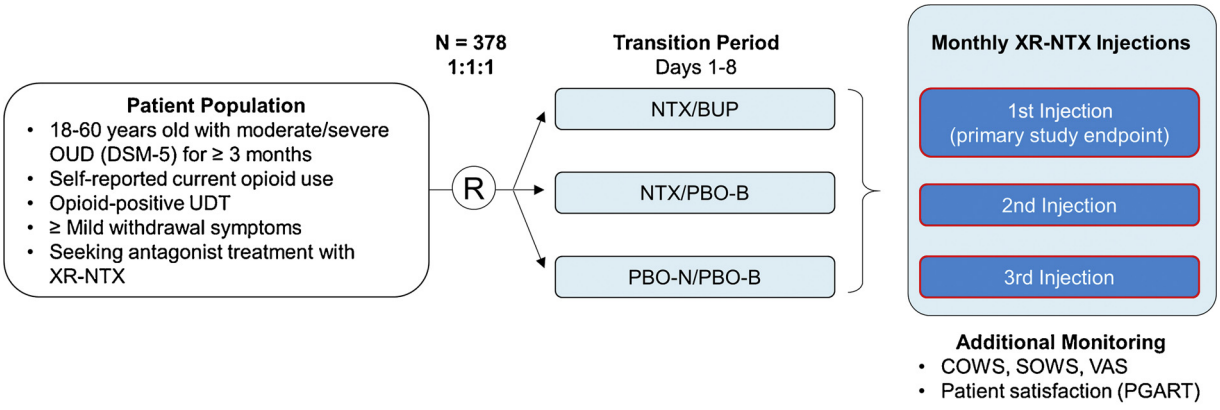
2.4.2. Detoxification and transition protocol

Patients were instructed to discontinue all opioids for at least 12 h prior to randomization, confirmed by self-report and a COWS score of ≥6

Patients attended the outpatient clinic daily during the transition period (Days 1–7) (see Supplemental Table 1 for timing of all procedures). During each visit, withdrawal (COWS, SOWS) and craving (VAS) scores were assessed, followed by the administration of ascending doses of oral NTX/placebo, with each daily dose administered as two doses separated by 1 h (see Fig. 1). The outpatient setting at each study site afforded a period of extended daily observation to permit close monitoring for opioid withdrawal symptoms. Tolerability of NTX was assessed (COWS and SOWS) at approximately 30, 60, 90, and 120 min following the first daily dose of NTX or PBO-N. Patients who tolerated the first dose (defined as ≤2 point increase in total COWS score at 60 min from the pre-dose score) received a second dose of oral NTX or PBO-N. If withdrawal symptoms increased by COWS score of 3 or more, patients were re-evaluated at 90 and 120 min and, if withdrawal symptoms had stabilized (≤2 points increase in COWS score from pre-dose) by 120 min, patients received the second dose of NTX or PBO-N. Patients whose withdrawal symptoms did not sufficiently abate within 120 min of the first dose of oral NTX or PBO-N did not receive the second dose of NTX or PBO-N but still received BUP or PBO-B on BUP dosing days. BUP or PBO-B was administered on Days 1–3, immediately after the second dose of NTX or PBO-N or 120 min after the first NTX or PBO-N dose. Craving (VAS) and mental status (i.e., Months of the Year Backward and modified Mini-Mental State Examination (Folstein et al., 1975)) were evaluated following the final COWS/SOWS assessment. To mitigate evening withdrawal symptoms, patients were dispensed 2 mg BUP or PBO-B to take at home on Day 1 only, to use if needed.

On Day 8, patients with a COWS score of ≤4 were given a 2-part naloxone challenge (0.4 mg followed by 0.8 mg; intramuscular injection). Those with a negative naloxone challenge (defined as a ≤4 COWS score increase across the 2-part challenge) received an XR-NTX injection on the same day. Those with a positive naloxone challenge repeated Day 8 procedures and returned for a repeat naloxone challenge the next day (Day 8a). Patients who failed the second naloxone challenge on Day 8a were discontinued from the study and offered treatment referrals.

Ancillary medications (clonidine 0.1 mg three times daily [TID], trazodone 100 mg at bedtime, and clonazepam 0.5 mg TID) were initiated on Day -1 to manage withdrawal symptoms and were administered daily in the clinic and dispensed daily for home use as needed during the transition week and for up to 3 days after the first XR-NTX injection. Patients were instructed to return to the clinic any unused ancillary medications at the next clinic visit. Patients were assessed daily for substance use, vital signs, withdrawal symptoms, and opioid craving. All patients received daily psychoeducational counseling throughout the transition period, focusing on medication adherence



	1st dose NTX or PBO-N	2nd dose NTX or PBO-N	BUP or PBO-B
Day 1	0.25 mg	0.25 mg	2 mg + 2 mg 2 mg[a]
Day 2	0.25 mg	0.25 mg	2 mg
Day 3	0.5 mg	0.5 mg	2 mg
Day 4	1.5 mg	1.5 mg	
Day 5	3 mg	3 mg	
Day 6	7.5 mg	7.5 mg	
Day 7	15 mg	15 mg	
Day 8/8a	Naloxone challenge		

Fig. 1. Study design.

[a]Optional 2 mg buprenorphine at home

Abbreviations: BUP, buprenorphine; COWS, Clinical Opiate Withdrawal Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th edition; OUD, opioid use disorder; PBO-B, placebo for buprenorphine; PBO-N, placebo for oral naltrexone; PGART, Patient Global Assessment of Response to Therapy; NTX, oral naltrexone; R, randomization; SOWS, Subjective Opiate Withdrawal Scale; VAS, visual analog scale for cravings; XR-NTX, extended-release naltrexone.

monitoring and management of common withdrawal symptoms.

After the first XR-NTX injection on Day 8/8a, patients returned to the clinic for seven follow-up visits on Days 9, 15, 22, 29, 36, 64, and 92. The second and third XR-NTX injections were administered on Days 36 and 64 during the follow-up period.

2.4.3. Statistics

The safety population included all randomized patients who received at least one dose of a study drug (i.e., BUP, NTX, PBO-B, or PBO-N). The full analysis set (FAS) was to include all patients in the safety population. Values are mean ± standard error except where indicated. The primary efficacy endpoint was analyzed for the FAS population using the logistic regression model. The logistic regression model included transition group assignment and randomization stratification of prior drug use (heroin vs. prescription opioids) as factors. No additional baseline variable was included as a covariate in this model. Statistical testing for the primary efficacy endpoint was carried out using the Hochberg testing procedure for the following comparisons: NTX/BUP vs. PBO-N/PBO-B, and NTX/PBO-B vs. PBO-N/PBO-B. SAS version 9.4 software (SAS Institute Inc., Cary, NC) was used for statistical analyses.

3. Results

3.1. Study population

The safety population contained 378 patients and the FAS contained 374 patients

(see Fig. 2). Four duplicate patients who were enrolled for a second time were excluded from the FAS. Approximately 34% of patients were female; 73.8% and 20.1% of patients were white and black/African American, respectively (see Table 1). At baseline, the overall median craving VAS score was 80.0, the overall median COWS score was 9.0, and the overall median SOWS score was 28.0. Prior to study entry, 136 (36%) patients primarily used prescription opioids and 242 (64%) used heroin.

3.2. Patient retention

The proportion of patients who completed the 7-day detoxification regimen was similar for the NTX/BUP (54.8%, n = 69), NTX/PBO-B (43.7%, n = 55), and PBO-N/PBO-B (61.9%, n = 78) groups.

3.3. Primary outcome: XR-NTX induction

The proportion of patients who received and tolerated an injection of XR-NTX on Day 8/8a was comparable in all three treatment groups: 46.0% (n = 57) in the NTX/BUP group, 40.5% (n = 51) in the NTX/PBO-B group, and 46.0% (n = 57) in the PBO-N/PBO-B group (see Table 2). Thus, the study did not meet its primary endpoint.

3.4. Secondary outcomes

All procedures used were generally well tolerated, with only mild-level COWS scores across all treatment days. The mean daily peak COWS score decreased from Day 1 (9.0 ± 0.22) to Day 8/8a (4.7 ± 0.21; $p < 0.001$), and continued to decline after the first XR-NTX injection, reaching 1.1 ± 0.2 by Day 36 and 0.5 ± 0.1 by Day 92 (see Fig. 3**A**). SOWS scores across all groups showed a similar pattern of decline from Day 1 (24.0 ± 0.73) to Day 8/8a (8.6 ± 0.54), but with more variability throughout the transition period (see Fig. 3**B**). SOWS scores after the first XR-NTX injection were significantly lower for the NTX/BUP group compared with the other two transition groups at Day

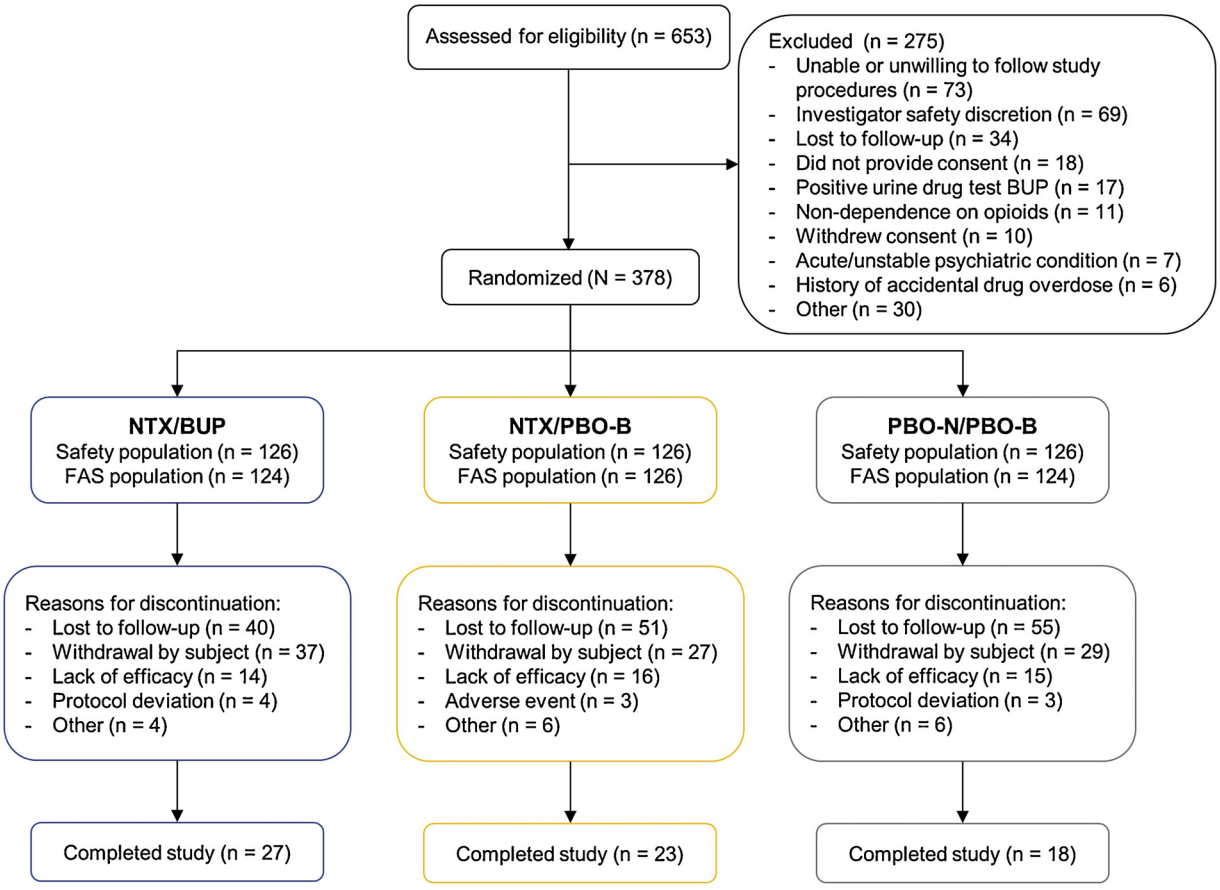


Fig. 2. CONSORT diagram of patients in a study of strategies to transition patients from opioid use disorder to treatment with extended-release naltrexone.

Table 1
Baseline patient demographics.

	NTX/BUP (n = 126)	NTX/PBO-B (n = 126)	PBO-N/PBO-B (n = 126)	Total (N = 378)
Median age, years (range)	39.5 (20–60)	35.0 (21–60)	34.0 (19–59)	36.0 (19–60)
Sex, n (%)				
Male	86 (68.3)	79 (62.7)	84 (66.7)	249 (65.9)
Female	40 (31.7)	47 (37.3)	42 (33.3)	129 (34.1)
Race, n (%)				
White	95 (75.4)	91 (72.2)	93 (73.8)	279 (73.8)
Black or African American	27 (21.4)	25 (19.8)	24 (19.0)	76 (20.1)
Other	4 (3.2)	10 (8)	9 (7.1)	23 (6.1)
Median weight, kg (range)	77.2 (43.8–136.1)	76.5 (45.3–136.4)	77.5 (40.8–136.5)	77.1 (40.8–136.5)
Median MMSE total score (range)	30.0 (25–30)	30.0 (25–30)	30.0 (26–30)	30.0 (25–30)
Median VAS score (range)	80.0 (0–100)	80.0 (3–100)	75.0 (0–100)	80.0 (0–100)
Median COWS score (range)	9.5 (2–23)	9.0 (5–24)	9.0 (6–18)	9.0 (2–24)
Median SOWS score (range)	28.0 (2–64)	29.0 (3–62)	28.0 (1–64)	28.0 (1–64)
Primary opioid used, n (%)				
Heroin	82 (65.1)	80 (63.5)	80 (63.5)	242 (64.0)
Prescription opioids	44 (34.9)	46 (36.5)	46 (36.5)	136 (36.0)
Median lifetime duration of opioid use for primary opioid used, years (range)[a]				
Heroin	5.0 (1.0–42.0)	4.5 (1.0–35.0)	5.0 (0.0–37.0)	5.0 (0.0–42.0)
Prescription opioids[b]	6.0 (1.0–30.0)	7.0 (1.0–40.0)	5.5 (1.0–38.0)	6.0 (1.0–40.0)
Median duration of opioid use in past 30 days for primary opioid used, days (range)[a]				
Heroin	30.0 (10.0–30.0)	30.0 (3.0–30.0)	30.0 (3.0–30.0)	30.0 (3.0–30.0)
Prescription opioids[b]	30.0 (15.0–30.0)	30.0 (17.0–30.0)	30.0 (10.0–30.0)	30.0 (10.0–30.0)
Number of prior treatments for substance abuse (range)	1 (0–15)	1 (0–12)	1 (0–8)	1 (0–15)

Abbreviations: BUP, buprenorphine; COWS, Clinical Opiate Withdrawal Scale; MMSE, Mini-Mental State Examination; NTX, oral naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for oral naltrexone; SOWS, Subjective Opiate Withdrawal Scale; VAS, visual analog scale.

[a] Data are from the Addiction Severity Index (ASI) interview.

[b] Prescription opioids were coded in the ASI as "other opiates/analgesics".

Table 2
Primary and secondary outcomes.

	NTX/BUP (n = 124)	NTX/PBO-B (n = 126)	PBO-N/PBO-B (n = 124)
Received naloxone challenge, %	53.2	42.9	59.5
Received XR-NTX, %	46.8	40.5	46.8
Received and tolerated XR-NTX[a]			
N (%)	57 (46.0)	51 (40.5)	57 (46.0)
p value[b]	0.940	0.383	

Abbreviations: BUP, buprenorphine; NTX, oral naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for oral naltrexone; XR-NTX, extended-release naltrexone.

[a] Demonstrated by mild (COWS ≤12 or SOWS ≤10) opioid withdrawal symptoms following XR-NTX administration.

[b] PBO-N/PBO-B used as reference group in logistic regression that also included randomization stratification by prior drug use (heroin vs prescription opioids) as variables.

9 (NTX/PBO-B, p = 0.010; PBO-N/PBO-N, p = 0.010) and Day 15 (NTX/PBO-B, p = 0.009; PBO-N/PBO-N, p = 0.014).

Mean daily VAS craving scores generally decreased in all three groups throughout the transition period (see Fig. 3**C**), and continued to decline after XR-NTX induction. No significant differences were observed in the mean VAS scores during the transition period among the three transition groups.

Patients in the NTX/BUP group were significantly more likely to remain abstinent during the 7-day transition period than patients in the PBO-N/PBO-B group (OR, 1.54; 95% CI, 1.31–1.80). The NTX/PBO-B group was also more likely to remain abstinent during the transition period than the PBO-N/PBO-B group (OR, 1.44; 95% CI, 1.22–1.69). Among all patients who passed a naloxone challenge and were successfully inducted onto XR-NTX on Day 8/8a, 57.3% (n = 51/89) of patients had an opioid-positive urine drug test result on the day of induction (13.6% [n = 51/374] of the intention-to-treat sample).

3.5. Primary opioid used at baseline

In *post hoc* analyses, a greater proportion of prescription opioid users (56.3%, n = 76/135) vs. heroin users (37.2%, n = 89/239) received and tolerated the first XR-NTX injection (OR, 2.17; relative risk, 1.51; p < 0.001). Modeling time to study withdrawal as a function of opioid type indicated that heroin users had an 81% (HR 1.81; p < 0.01) higher risk of discontinuation during the 7-day transition period than prescription opioid users.

3.6. Safety

No overdoses or deaths occurred during the study. Among those who completed the transition period (Days 1–7), the numbers of adverse events (AEs) were similar among transition groups and were reported by 34.9% of the NTX/BUP group (n = 126), 24.6% of the NTX/PBO-B group (n = 126), and 38.1% of the PBO-N/PBO-B group (n = 126; see Table 3). Most AEs were consistent with symptoms of opioid withdrawal. Four (1.1%) AEs led to study discontinuation. These included two cases of nausea and one each of opioid withdrawal and anxiety. Serious AEs (SAEs) occurred in five patients, including one that occurred during the transition period and was deemed to be study drug-related. Acute confusion occurred in one patient following administration of clonidine, clonazepam, and NTX 0.25 mg, which resolved during the study visit and was associated with pre-existing bilateral hearing loss, a risk factor for the development of confusion (Fong et al., 2009). The four other SAEs included panic attack, alcohol use, somnolence, and dehydration.

4. Discussion

This double-blind, randomized controlled, phase 3 trial was designed to evaluate the relative efficacy, safety, and tolerability of low-

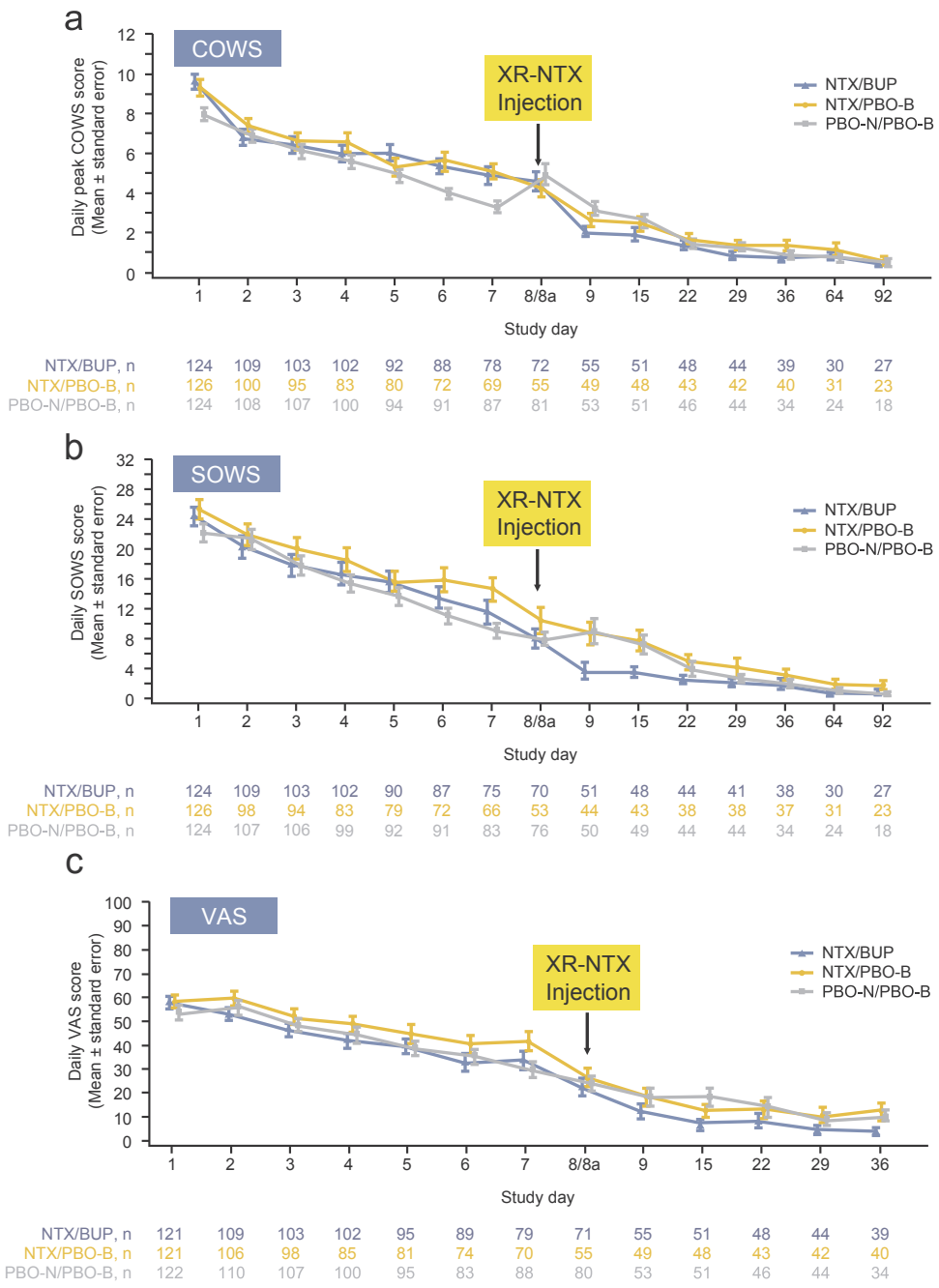


Fig. 3. (a). Daily peak Clinical Opiate Withdrawal Scale scores. (b). Daily mean Subjective Opioid Withdrawal Scale scores. (c). Daily mean visual analog scale craving scores.

dose naltrexone used in conjunction with BUP in adults with OUD, transitioning from physiological opioid dependence to treatment with XR-NTX in a structured outpatient setting. The methods were selected to determine whether oral NTX, or oral NTX in combination with a 3-day BUP taper, increased the rate of successful XR-NTX induction relative to that associated with symptomatic treatment with the ancillary regimen alone.

Similar rates of receiving and tolerating XR-NTX were achieved by patients in all three transition-group regimens (~44%), comparable to rates seen in other studies of inpatient (range, 55–72% (Bisaga et al., 2015; Lee et al., 2017)) and outpatient (range, 33–56% (Sullivan et al., 2017)) XR-NTX induction. The rate found here suggests that the addition of low-dose NTX titration, with or without BUP taper, to an 8-day regimen of ancillary medications does not increase the likelihood that patients will receive the first XR-NTX injection. Further *post hoc* analyses showed that regardless of the transition regimen, prescription opioid users were significantly more likely than heroin users to initiate XR-NTX treatment.

Objective and subjective measures of opioid withdrawal severity were in the mild range, did not differ among the three transition groups, and declined over time during the transition period and following the first XR-NTX injection. Interestingly, subjective ratings of withdrawal were significantly lower in the week following XR-NTX for the NTX/BUP groups as compared with the other two groups. Baseline SOWS and COWS scores were similar to those reported by other studies, strengthening the validity of these tests (Rosenthal et al., 2013; Strain et al., 2011; Tompkins et al., 2013).

The safety and opioid withdrawal data demonstrated that all three tested regimens were well tolerated by patients inducted onto XR-NTX. Most AEs were of mild to moderate severity and consistent with

Table 3
Adverse events.

	NTX/BUP (n = 126)	NTX/PBO-B (n = 126)	PBO-N/PBO-B (n = 126)	Total (N = 378)
Any TEAE, %	34.9	24.6	38.1	32.5
TEAE by severity, %				
Mild	18.3	9.5	11.9	13.2
Moderate	13.5	10.3	19.8	14.6
Severe	3.2	4.8	6.3	4.8
AE leading to discontinuation, %	0.8	1.6	0.8	1.1
Any SADR, %	0	0.8	0	0.3

Abbreviations: AE, adverse event; BUP, buprenorphine; NTX, oral naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for oral naltrexone; TEAE, treatment-emergent adverse event; SADR, serious adverse drug reaction.

symptoms of opioid withdrawal. The fixed-dose ancillary regimen including clonidine, clonazepam, and trazodone and the 8-day duration of the transition period employed in this study permitted safe and effective daily management of opioid withdrawal and XR-NTX induction in an outpatient setting. It is worth noting that most of the treatment sites that took part in this multisite trial had no prior experience conducting outpatient opioid detoxification and XR-NTX induction; therefore, we believe that this protocol can be utilized in community-based treatment programs. Given that rates of successful induction were similar with or without the use of BUP, the proposed protocol may be of particular relevance to practitioners who may not have a U.S. Drug Enforcement Administration waiver to prescribe BUP or do not feel comfortable with opioid-based detoxification. The ability to prescribe ancillary medications to allow patients to comfortably transition to XR-NTX is likely to increase patient access to this form of treatment. The use of ancillary medications has relevance to current efforts to expand access to all types of medication-assisted treatment. In addition, it is important to note that daily on-site monitoring of withdrawal symptoms was integral to each of the regimens employed in this study.

Whereas recent investigations have demonstrated the utility of low ascending doses of oral NTX for assisting induction onto XR-NTX (Bisaga et al., 2014; Bisaga et al., 2015; Mannelli et al., 2014; Sullivan et al., 2017), this is the first double-blind, randomized study that has sought to examine independently the components of these oral NTX-assisted induction regimens, including low-dose oral NTX (with or without a brief BUP taper) and the standing fixed-dose ancillary regimen. The reasons for not showing additional benefit of BUP taper or low-dose NTX may include an extended duration of treatment. An unexpected finding was that the regimen comprising standing ancillary medication alone, when used in a blinded manner, was associated with comparable safety and efficacy to the oral NTX/BUP regimen. While rates of conversion to XR-NTX were equivalent (46.0%) in these two groups, we also found that use of NTX/BUP was associated with: (1) significantly higher rates of abstinence from opioids during the transition period (Days 1–7); and (2) significantly lower SOWS scores in the week following XR-NTX induction. Thus, it is possible that the NTX/BUP regimen offers certain advantages with respect to sustained abstinence and greater post-induction comfort.

Although patients were instructed to refrain from using opioids during the transition period, many continued to use illicit opioids. However, infrequent use of opioids did not seem to preclude patients from making a successful transition to XR-NTX. Thus, while it is recommended that 7–10 days of opioid abstinence are established prior to the first XR-NTX injection, an isolated use in the context of an outpatient opioid detoxification may not necessitate restarting the induction regimen to receive XR-NTX. A proportion of patients in the PBO-N/PBO-B group were not able to pass the naloxone challenge and receive XR-NTX, which supports the importance of administering the challenge in patients who do not receive oral NTX during detoxification.

Patients who received oral NTX during the transition period were more likely to be abstinent from opioids during this period. Continuing use of opioids during detoxification hampers the chances of passing the naloxone challenge and receiving XR-NTX. Despite this finding, we did not observe higher rates of XR-NTX induction in patients treated with oral NTX. This may be due to the fact that the naloxone challenge took place on Day 8. Additional investigations could assess whether patients who receive NTX are able to pass a naloxone challenge and receive XR-NTX earlier during the detoxification than patients who do not receive NTX.

In this outpatient study, we observed significantly higher rates of successful transition to XR-NTX for prescription opioid users than for heroin users. However, Lee et al. (2017) achieved substantially higher rates (> 70%) of XR-NTX induction for heroin users in an inpatient context. Taken together, these findings suggest that the use of the standing ancillary regimen tested, delivered in an outpatient setting that affords daily monitoring, is a promising strategy for prescription opioid users seeking transition to XR-NTX. By contrast, heroin users may benefit from residential or inpatient detoxification, and heroin-dependent individuals interested in XR-NTX induction should be advised of the higher likelihood of successful induction afforded by inpatient detoxification.

The finding that multiple detoxification and induction regimens are well tolerated and efficacious for transition to XR-NTX in an outpatient setting should increase clinician confidence in this procedure. Moreover, the fact that outpatient induction onto XR-NTX was associated with only mild opioid withdrawal (COWS) and that both objective and subjective measures of withdrawal, together with craving for opioids, declined steadily throughout the transition period should be reassuring to providers and patients concerned that detoxification may be associated with significant discomfort.

4.1. Limitations

Our study had a few potential limitations. The sites participating in the trial were heterogeneous with respect to prior experience in the outpatient management of opioid detoxification, although this likely reflects real-world opioid treatment. The frequency and duration of study visits exceeded those common in outpatient practice. Payments for participation may have encouraged study visits, albeit across all groups. The validity of these data may not be generalizable to real-world patient populations that have acute psychiatric needs or have failed several detoxification attempts, as patients with these characteristics were excluded from this study. Patients with a positive urine drug screen for methadone or BUP at screening were excluded from the study. Finally, the doses of oral NTX used in this study are not FDA approved or commercially available and can only be obtained in non-research settings with pharmacy compounding.

4.2. Conclusion

A 7-day detoxification protocol with NTX alone or NTX with BUP provided similar rates of induction onto XR-NTX as placebo. The use of a fixed-dose standing regimen of ancillary medications was well tolerated and ameliorated withdrawal symptoms during opioid detoxification in patients who were successfully inducted on XR-NTX. Such a regimen of ancillary medications is of immediate clinical relevance, as this approach has the potential to expand access to antagonist therapy by increasing the acceptability of outpatient induction procedures for both patients and practitioners.

Conflict of interest

Adam Bisaga has received honoraria, consultation fees, and travel reimbursement for training, medical editing, and market research from UN Office on Drugs and Crime, Motive Medical Intelligence, Healthcare

Research Consulting Group, GLG Research Group, and Guidepoint Global. Dr Bisaga received compensation from Indivior for an unbranded educational activity. He received medication (extended-release naltrexone) from Alkermes for NIH-funded research studies, is an investigator for a multisite clinical trial funded by Alkermes, and served as an unpaid consultant to Alkermes. Paolo Mannelli received consultation fees from Guidepoint Global and research funding from Orexo and Alkermes, has served on scientific advisory boards for Alkermes, Inc., and is an investigator for a multisite clinical trial funded by Alkermes. D. Andrew Tompkins has received medication from Indivior for NIH-funded studies and is an investigator for a multisite clinical trial funded by Alkermes, Inc. Thomas Kosten has received honoraria from Alkermes, Inc., and is an investigator for a multisite clinical trial funded by Alkermes, Inc. Miao Yu, Narinder Nangia, Christine E. Graham, Sarah C. Akerman, and Bernard Silverman are employees and shareholders of Alkermes, Inc. Maria A. Sullivan is an employee of Alkermes, Inc. and had received medication (extended-release naltrexone) from Alkermes for NIH-funded research studies.

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Contributors

AB, PM, CEG, DAT, TRK, SCA, BLS, MAS contributed to data interpretation and development of the final manuscript. SCA and MAS wrote the first draft of the manuscript. MY and NN did the statistical analyses and generated tables and figures. All authors had access to the data used in this article. All authors approved the final article before submission.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2018.02.023.

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