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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