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Predictors of Continued Use of Extended-Released Naltrexone (XR-NTX) for Opioid-Dependence: An Analysis of Heroin and Non-Heroin Opioid Users in Los Angeles County☆

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ABSTRACT

Extended-release naltrexone (XR-NTX) is associated with an increased number of opioid-free days, improved adherence rates in substance use disorder treatment programs, and reduced cravings and drug-seeking behaviors. There is little evidence on the predictive associations between baseline characteristics of opioid-dependent patients and XR-NTX utilization. Some studies have demonstrated better pharmacotherapy adherence and/or retention rates among non-heroin opioid users compared to heroin users. This study examines predictive associations between characteristics of patients and XR-NTX utilization, as well as participants' urge to use opiates. Our findings suggest that XR-NTX may contribute to decreases in urges to use among both heroin and non-heroin opioid users. Non-heroin opioid users and heroin users were retained in XR-NTX treatment for comparable periods of time. However, those who identified as homeless, injected opioids (regardless of opioid-type), or were diagnosed with a mental illness were less likely to be retained in treatment with XR-NTX.

1. Introduction

Extended-release naltrexone (XR-NTX) is approved for use in the treatment of opioid use disorders. It is a long-acting (30-day duration of action) injectable form of naltrexone that has a higher treatment adherence rate than oral tablet naltrexone (Center for Substance Abuse Treatment (CSAT), 2005; Comer et al., 2006; Krupitsky, Zvartau, & Woody, 2010; Krupitsky et al., 2013; Sullivan et al., 2013). When used by opioid users in combination with psychosocial treatment, XR-NTX is associated with an increased number of opioid-free days, improved adherence rates for those in substance use disorder (SUD) treatment programs, and reduced cravings and drug-seeking behaviors (Krupitsky et al., 2013; Sullivan et al., 2013). Further, patients who use XR-NTX also have shown higher abstinence rates at discharge compared to those using buprenorphine or oral naltrexone (Crits-Christoph, Lundy, Stringer, Gallop, & Gastfriend, 2015).

Although few studies have compared XR-NTX and oral naltrexone, several have found promising XR-NTX retention rates (Bryson, McConnell, Korthuis, & McCarty, 2011). A randomized, double-blind, placebo-controlled trial found that between 60% and 68% of individuals obtained a second dose of XR-NTX (Comer et al., 2006). Similarly a randomized controlled trial in Russia found that 58% of patients took at least six doses of XR-NTX (Krupitsky et al., 2011). Further, a case study of 16 adolescent opioid users found that a majority (12 of 16) of patients returned for a second dose of XR-NTX (Fishman, Winstanley, Curran, Garrett, & Subramaniam, 2010). Though promising, these findings should be interpreted with caution, given the small sample sizes and/or research setting of the studies, which limit their generalizability (e.g., there are no alternative pharmacotherapies for opioid dependency in Russia).

Little is known about predictive associations between baseline characteristics of opiate-using patients and XR-NTX utilization. One recent study examined XR-NTX response as it related to 25 different clinical and demographic variables, and found no significant interactions (Nunes et al., 2015) However, predictive associations between utilization and adherence with other SUD medications have been identified. For instance, Rubio et al. (2005) found that oral naltrexone was beneficial in the treatment of alcohol use disorders if patients had an onset of alcohol abuse before the age of 25, a family history of alcohol use disorder, or a history of substance use disorder. Among opiate users treated with methadone maintenance therapy, significant baseline predictors

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of adherence and outcomes, include the type and route of substance used (injection drug, heroin, and/or alcohol use) and housing status (Fischer, Cruz, Patra, & Rehm, 2008). Among non-heroin opioid users, baseline characteristics such as sociodemographics (age, lifetime major depressive disorder) and history of substance use (having only used opioids orally or through sublingual administration, and receiving no prior opioid dependence treatment) predicted reduced opioid use during a 12-week buprenorphine intervention (Dreifuss et al., 2013). Among youth and young adult opioid users, predictors of buprenorphine dose levels have included sociodemographic characteristics (gender, race, age, and education), specific substances (alcohol, cannabis, cocaine, and/or nicotine use), and other clinical characteristics (pain and withdrawal severity; Chakrabarti, Woody, Griffin, Subramaniam, & Weiss, 2010).

The Los Angeles (LA) County Department of Public Health, Substance Abuse Prevention and Control (SAPC), in collaboration with UCLA Integrated Substance Abuse Programs (UCLA ISAP), developed a demonstration project to increase access to XR-NTX within the county. The rationale for the demonstration project was to provide medication-assisted treatment (MAT) to persons with alcohol use disorders, and after FDA approval in 2010, to those with opioid use disorders. To facilitate the utilization of XR-NTX, SAPC purchased supplies of the medication, established a distribution system to make it accessible, and conducted MAT informational sessions to educate providers about XR-NTX and its potential use in treatment. Additionally, SAPC funded an evaluation of the program carried out by UCLA ISAP. The demonstration project determined that it was feasible to expand the use of XR-NTX throughout the county and that patients would utilize multiple doses of XR-NTX (Cousins et al., 2015).

This present study describes a real-world project that examined the outcomes of providing XR-NTX to a large and diverse group of community providers for use with their patients. The study addressed the following research questions: (1) What patient characteristics are associated with XR-NTX adherence among individuals with opioid use disorders? (2) Do heroin and non-heroin opioid users differ in XR-NTX adherence?

2. Methods

2.1. Design and sampling methods

This demonstration trial, described in detail elsewhere (Cousins et al., 2015), involved 171 participants. Three medication hubs were set up across LA County to provide XR-NTX to patients who were referred from SUD treatment centers. These medication hubs were residential SUD treatment centers that had the staffing and facilities to administer and store the medication. Additionally, these SUD treatment agencies had a longstanding partnership with LA County.

All psychosocial SUD treatment centers funded by L.A. County were eligible to provide patients with a link to a XR-NTX medication hub while the patient continued to receive psychosocial treatment. No attempt was made to standardize or measure the psychosocial treatments provided by the referring treatment sites. Out of 431 SUD treatment sites across LA County, 39 referred at least one patient who received XR-NTX.

The current study, which comprises a subsample of the 609 patients who received XR-NTX for alcohol or opioid dependence (Cousins et al., 2015), describes admission and discharge characteristics of 171 patients who obtained XR-NTX for opioid dependence. Additionally, this study describes baseline data (e.g., data prior to the first dose) and adherence data (e.g., data obtained while the patient was on XR-NTX) on 60 opioid patients.

The evaluation was conducted in two phases. During the first phase of the evaluation, (April 2010–December 2011), 111 participants were enrolled into the evaluation. Treatment staff met with participants to assess eligibility. Demographic, dose, and treatment records were available for this current sample. However, at the initial inception of Phase 1, XR-NTX was not approved for opioid use disorders. Therefore the evaluation design for opioid users in Phase 1 was limited to admission and discharge records. In Phase 2 of the project (February 2012–August 2013), 60 participants completed assessments of their urges to use opioids, and these assessments were repeated at follow-up (30 and 60 days after their last dose of XR-NTX). This survey data were gathered by UCLA research assistants who met with participants to collect face-to-face baseline interviews and then conducted weekly telephone follow-up assessments. Interviews were collected in English or Spanish.

All participants who received psychosocial treatment in Los Angeles County SUD treatment centers were eligible for a referral to XR-NTX. Patients who were adequately opioid-free (i.e., who were abstinent for at least 7 days and who passed a urine toxicology test) and met medical eligibility criteria were offered the opportunity to utilize XR-NTX in conjunction with the psychosocial treatment that they were already receiving at their SUD treatment center. All study design and consent procedures were approved by the human subjects committees of the University of California, Los Angeles, and the Los Angeles County Department of Public Health.

2.2. Measures

2.2.1. Number of doses

The total number of XR-NTX injections was derived using records kept by administrative staff that were maintained at each medication hub for billing purposes. These records indicated the date that patients received XR-NTX doses ($N = 171$).

2.2.2. Admission and discharge data

The Los Angeles County Participant Reporting System (LACPRS) is a data collection system that provides admission, discharge, and outcome data for all county-assisted patients. LACPRS is the LA County version of the SAMHSA-mandated Treatment Episode Data Set (TEDS) data collection (Crèvecoeur, Rutkowski, & Rawson, 2007). LACPRS captures data on demographics, primary and secondary drug of choice, age at first use, number of days using drugs/alcohol in month before admission, number of days of injecting drug use, needle use, number of prior treatment episodes, number of times arrested, number of days spent in jail, number of days spent at the emergency room, number of days engaged in illegal activities, HIV testing (*yes/no*), hepatitis C testing (*yes/no*), and housing status (*homeless yes/no*). Data from this system were collected on the entire study sample ($N = 171$).

2.2.3. Urge to use

Participants ($N = 60$) enrolled in the Phase 2 evaluation completed the Urge to Use Scale, which was adapted from the Penn Alcohol Craving Scale (PACS). PACS has been used to determine differences in craving scores following medication-assisted treatment (Flannery, Volpicelli, & Pettinatti, 1999). PACS was adapted by UCLA for opioid users by replacing references to "alcohol" with references to "opioids." The revised scale ("Urge to Use" scale) was tested for face validity and showed high reliability in the current sample of follow-up patients (Cronbach's Alpha = 0.93). The scale contains five questions about cravings concerning frequency, duration, time spent thinking about using, craving severity, difficulty resisting, and overall craving. Each question is rated from 0 to 6, with 6 indicating the highest severity. A cumulative score from 0 to 30 was derived.

2.3. Analyses plan

UCLA conducted a secondary descriptive data analysis (on participant characteristics and the number of doses) based on 171 participants. In addition, UCLA conducted an analysis of 60 participants who enrolled in Phase 2 of the demonstration project regarding participants' urge to use. All analyses were conducted using STATA 13.

To explore relationships between heroin and non-heroin opioid users and the independent variables of interest, bivariate analysis using t-tests for continuous variables and Chi-square tests for binary