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Healthcare utilization in adults with opioid dependence receiving extended release naltrexone compared to treatment as usual

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ABSTRACT

Background: Opioid use disorders have reached epidemic proportions, with overdose now the leading cause of accidental death in the United States. Extended release naltrexone (XR-NTX) has emerged as a medication treatment that reduces opioid use and craving. However, the effect of XR-NTX therapy on acute healthcare utilization, including emergency department visits and inpatient hospitalizations, remains uncertain. The objective of the current study is to evaluate hospital-based healthcare resource utilization in adults involved in the criminal justice system with a history of opioid use disorder randomized to XR-NTX therapy compared with treatment as usual (TAU) during a 6-month treatment phase and 12 months post-treatment follow up.
Methods: This retrospective exploratory analysis uses data collected in a published randomized trial. Comparisons of the number of emergency department visits and hospital admissions (for drug detox, psychiatric care and other medical reasons) were performed using chi square tests for any admission and negative binomial models for number of admissions.
Results: Of the 308 participants randomized, 96% had utilization data (76% complete 6 months, 67% complete follow up). No significant differences were seen in overall healthcare utilization (IRR = 0.88, 95%CI 0.63–1.23, $p = 0.45$), or substance use-related drug detox hospitalizations (IRR = 0.83, 95%CI 0.32–2.16, $p = 0.71$). Despite having more participants report chronic medical problems at baseline (43% vs. 32%, $p = 0.05$), those receiving XR-NTX generally experienced equivalent or lower rates of healthcare utilization compared to TAU. The XR-NTX group had significantly lower medical/surgical related hospital admissions (IRR = 0.55, 95%CI 0.30–1.00, $p = 0.05$) during the course of the entire study.
Conclusions: XR-NTX did not significantly increase rates of healthcare utilization compared to TAU. Provider concerns regarding healthcare utilization should not preclude the consideration of XR-NTX as therapy for opioid use disorders.

1. Introduction

Opioid use disorders (OUDs) have reached epidemic proportions, with overdose now the leading cause of accidental death in the US·(Center for Disease Control and Prevention et al., 2015). Traditional medical treatments for OUDs include agonist pharmacotherapies, such as methadone and buprenorphine, which reduce opioid use and improve treatment retention (Mattick, Breen, Kimber, & Davoli, 2014). However, social stigma, daily dosing, and limited access to prescribers have constrained the effectiveness of these medications for the growing population of patients with OUDs (Awgu, Magura, & Rosenblum, 2010; Friedmann et al., 2012).

Extended release depot naltrexone (XR-NTX) has emerged as a therapeutic alternative to traditional agonist therapies for OUDs. Formulated as a non-scheduled opioid antagonist administered as a once monthly intramuscular injection, XR-NTX has demonstrated increased abstinence from opioids as well as decreased cravings compared with placebo in observational and randomized controlled trials (Comer et al., 2006; Gordon et al., 2015; Krupitsky et al., 2011; Lee et al., 2016).

Abbreviations: XR-NTX, extended release depot naltrexone; TAU, treatment as usual; OUD, opioid use disorders.

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While XR-NTX therapy has demonstrated benefits treating OUD's, the relationship of XR-NTX therapy on healthcare utilization remains unclear. Researchers have theorized XR-NTX may increase rates of overdose when patients attempt to overcome antagonist effects or after completion of therapy due to decreased tolerance (Hulse et al., 2005; Wolfe et al., 2011). Furthermore, opioid antagonism may make painful medical conditions more difficult to manage, resulting in increased healthcare utilization. In contrast, retrospective medical claims data (Baser, Chalk, Fiellin, & Gastfriend, 2011) have demonstrated lower inpatient hospital utilization rates of XR-NTX therapy compared with placebo and agonist pharmacotherapies.

However, medical claims research occurred prior to FDA approval of XR-NTX for opioid use disorders, resulting in possible prescribing bias; patients who received XR-NTX therapy may have been selected because they were less likely to overdose, relapse or utilize healthcare resources. The current study examines healthcare utilization of participants on XR-NTX therapy in a randomized-controlled trial (Lee et al., 2016). We hypothesize, consistent with prior literature, that opioid-addicted patients randomized to XR-NTX therapy will demonstrate decreased rates of healthcare utilization.

2. Materials and methods

This is an exploratory analysis of a randomized trial evaluating a XR-NTX treatment protocol compared with a treatment as usual (TAU) protocol in an adult criminal justice population with a history of opioid use disorder.

Briefly, the original study was a 5 site, open label, unblended effectiveness trial, randomizing adults with a history of opioid use disorder and criminal justice system involvement into a 6 month XR-NTX treatment protocol or a TAU protocol. The XR-NTX protocol received an initial injection of 380 mg depot naltrexone then subsequent injections every 4 weeks during the 6-month treatment phase. Follow up visits occurred every 2 weeks during the treatment phase and at weeks 27, 52 and 78 post treatment. The TAU protocol included counseling and referral to community resources, including methadone and buprenorphine treatment programs. Participants completed surveys evaluating drug use, criminal activity, and healthcare utilization at each follow up. All patients received medical and opioid counseling at scheduled follow-ups. A data and safety monitoring board logged all adverse events, including hospitalizations, XR-NTX study drug complications, and death (Lee et al., 2016).

2.1. Participant selection

Participants involved in the original study were included for analysis. Participants who provided no healthcare utilization or follow up survey information were excluded.

2.2. Survey data

De-identified data from two study surveys were utilized in analyses. The Addiction Severity Index collected at the start of the study contained basic demographic data, including number of hospitalizations and prior chronic medical problems.

The Non-Study Medical and Other Services survey (NSS) was collected at the start of the study, at 4-week intervals until week 25 (0, 5, 9, 13, 17, 25), then at week 27, 52 and 78 as follow up. Data from the NSS survey included the following patient self-reported outcomes: number of emergency department (ED) visits, number of hospitalizations for detoxification, psychiatric stabilization, other medical reasons.

2.3. Adverse event data

Adverse event (AE) data, which included any events from very mild to severe, and serious adverse event (SAE) data, which documented deaths and serious or life threatening events requiring hospitalization, were collected by site investigators and used to verify patient self-reported hospitalization extracted from the NSS survey. AE and SAE data included dates of hospitalization, diagnoses, and a brief description of the reason for hospitalization.

2.4. Data management

Survey and adverse event data were transcribed into a combined spreadsheet for analysis by author DW. Data collected from the NSS provided, for each study and follow-up visit attended, the number of self-reported hospitalizations (for detox, psych or other reasons) and ED visits since the participant's last study visit. By cross-referencing this information with the AE and SAE data we were able to gain additional information regarding the exact dates and nature of approximately 40% of these events (NSS data showed 151 participants reporting a total of 377 hospitalizations or ED visits, 149 events were documented as an AE or SAE). This additional information was especially helpful in categorizing reasons for ED visits and non-detox and non-psych hospitalizations.

Authors WS and PF, blinded to assigned treatment groups, independently coded all hospital diagnoses into two categories. The first category included general diagnostic groups (medical/surgical, psychiatric, drug related, other/missing). The second category included diagnoses coded into substance abuse related medical conditions (SAMC). SAMC (Mertens, Lu, Parthasarathy, Moore, & Weisner, 2003) are diagnoses related to drug and alcohol abuse and were defined as the following:

> "*depression*, *injury and poisonings/overdoses*, *anxiety and nervous disorders*, *hypertension*, *asthma*, *psychoses*, *acid-peptic disorders*, *ischemic heart disease*, *pneumonia*, *chronic obstructive pulmonary disease*, *cirrhosis*, *hepatitis C*, *diseases of the pancreas*, *alcoholic gastritis*, *toxic effects of alcohol* (*ethyl and unspecified*), *alcoholic neuropathy*, *alcoholic cardiomyopathy*, *excess blood alcohol level*, *and perinatal alcohol and drug dependence*"
>
> [(Weisner, Mertens, Parthasarathy, Moore, & Lu, 2001)]

Coding differences were resolved first by author consensus then independently coded by a third medical provider (NR) blinded to study design and coding.

2.5. Outcomes

The primary outcome was healthcare utilization among participants randomized to XR-NTX compared to TAU. Healthcare utilization was defined as frequency of ED visits and hospital admissions during the entire 78-week treatment and post treatment phases of study.

Secondary outcomes included comparisons of healthcare utilization stratified by study phase (treatment and post treatment phase), utilization type (detox, psych, other hospitalization, ED visit), and SAMC (yes/no).

2.6. Analysis

Descriptive statistics were used to summarize baseline demographic data. Evaluation of the primary outcome was carried out in two ways: chi square tests of dichotomous variables indicating each participant's healthcare utilization status and negative binomial models comparing the total count of ED visits and hospital admissions, as well as days admitted to the hospital. To account for varying lengths of follow up time per participant, a log weeks offset was used. Clinically relevant covariates, including participant age, number of prior hospitalizations and chronic medical problems, were included as covariates in adjusted models. Data was analyzed using SAS v.9.4 statistical software package.

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