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Opioid use and dropout in patients receiving oral naltrexone with or without single administration of injection naltrexone

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ABSTRACT

Background: Adherence to oral naltrexone has been poor and can be improved somewhat with behavioral therapy. We compared behavioral naltrexone therapy (BNT) to compliance enhancement (CE) and tested efficacy of single-dose injection naltrexone (XR-NTX; 384 mg) with behavioral therapies at further improving adherence to oral naltrexone.
Methods: A 24-week, randomized, placebo-controlled trial ($n = 125$) compared four treatment conditions following inpatient detoxification and oral naltrexone induction: (1) BNT + XR-NTX; (2) BNT + placebo injection; (3) CE + XR-NTX; and (4) CE + placebo injection. All participants were maintained on oral naltrexone throughout the trial. Primary outcome was retention in treatment.
Results: Of 89 randomized participants, 78.7% (70/89) completed 4 weeks, 58.2% (54/89) completed 8 weeks, 47.2% (42/89) completed 12 weeks, and 25.8% (23/89) completed 24 weeks. A Cox proportional hazards regression modeled time to dropout as a function of treatment condition, baseline opioid dependence severity (bags per day of heroin use), and their interaction. Interaction of conditions by baseline severity was significant ($X^2_3 = 9.19$, $p = 0.027$). For low-severity patients (≤6 bags/day), retention was highest in the BNT – XR-NTX group (60% at 6 months), as hypothesized. For high-severity (>6 bags/day) patients, BNT – XR-NTX did not perform as well, due to high early attrition.
Conclusion: For low-severity heroin users, single-dose XR-NTX improved long-term treatment retention when combined with behavioral therapy. In higher-severity opioid-dependent patients, XR-NTX was less helpful, perhaps because, combined with oral naltrexone, it produced higher blood levels and more withdrawal discomfort. When cost considerations recommend oral naltrexone following XR-NTX, the latter should be phased in slowly.

1. Introduction

Opioid dependence represents a serious public health problem affecting a growing number of individuals in the United States. It is estimated that there are 1 million heroin addicts in need of treatment and nearly 2 million untreated prescription opioid addicts in the U.S. (NSDUH, 2011). Agonist maintenance with methadone or buprenorphine is not available or acceptable to many patients, and not all patients respond well to agonists. Naltrexone, a mu-opioid antagonist, acts by a different mechanism and offers an alternative approach to agonist treatment. Naltrexone blocks the effects of opioids, while producing no agonist effects itself, and thus may be helpful to patients who are not suitable for agonist maintenance or have already failed trials of agonist treatment. However, the effectiveness of naltrexone in pill form had been limited by poor adherence and was rarely utilized in practice (Johansson et al., 2006). Prior studies suggested the effectiveness of contingency management, and involvement of significant others at improving adherence to oral naltrexone (Preston et al., 1999; Carroll et al., 2001a,b). Long-acting injectable or implantable formulations of naltrexone, by circumventing the need for daily pill adherence, also improved effectiveness (Comer et al., 2006; Hulse et al., 2005; Krupitsky et al., 2011).

In prior Stage I trials conducted to improve adherence with oral naltrexone for opioid dependence, we developed and tested

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behavioral naltrexone therapy (BNT), a manual-based therapy integrating elements of network therapy, community reinforcement approach, relapse prevention therapy and motivational interviewing (Rothenberg et al., 2002; Nunes et al., 2006; Sullivan et al., 2006). BNT was developed to address four potential limitations of naltrexone maintenance: (1) difficulty transitioning from opiates to naltrexone; (2) poor adherence; (3) possible dysphoric effects; and (4) inadequate psychotherapeutic context. The aims in this early Stage II trial were (1) to test the efficacy of BNT compared to a standard therapy (compliance enhancement, a control condition simulating outpatient pharmacotherapy management) for the treatment of opioid dependence; and (2) to test the efficacy of a single dose of a long-acting injectable formulation of naltrexone (XR-NTX; Depotrex, BIOTEK) in reducing early attrition on oral naltrexone and improving long-term outcome of behavioral naltrexone therapy (BNT). In previous trials, we had observed high rates of attrition in the first 4 weeks after inpatient detoxification (Nunes et al., 2006; Sullivan et al., 2006; Rothenberg et al., 2002). By including a single administration of XR-NTX as a condition in the present trial, we hoped to provide a treatment condition in which patients could remain abstinent long enough to engage in therapy and benefit from the elements of BNT. We hypothesized that the combination of BNT and XR-NTX would perform best, resulting in the highest rates of retention among the four treatment groups.

2. Methods

2.1. Participants

Individuals seeking treatment for opioid dependence at the Substance Treatment and Research Service (STARS) outpatient clinic of Columbia University, in New York City were recruited for this study. Clinical screening included the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (SCID Axis I/P version; First et al., 2002) and a clinical interview assessing substance abuse severity. Medical assessment included history, laboratory tests, electrocardiogram (ECG), a physical examination, and a psychiatric evaluation. Included were men and women 18–60 years old, who met DSM-IV criteria for current opioid dependence and used opioids daily. Participants were required to identify a significant other who was able to attend sessions and monitor compliance. Individuals with major severe affective or psychotic disorder were excluded. Other exclusion criteria included: (1) regular use of methadone (>30 mg per week); (2) history of accidental opioid overdose in the past 3 years (since a prior overdose event likely raises the risk for subsequent overdoses, and a loss of opioid tolerance can increase risk of overdose if oral naltrexone is abruptly discontinued), (3) ongoing treatment with prescription opioids; (4) physiological dependence on alcohol or sedative–hypnotics, and (5) unstable medical disorders which might make participation hazardous.

2.2. Study procedures

General procedures: Following study consent, participants were admitted to an inpatient unit at the New York State Psychiatric Institute for the purpose of detoxification and naltrexone induction. We employed a modification of a buprenorphine-assisted, rapid opioid detoxification and naltrexone induction procedure (Collins et al., 2005). Briefly, participants were stabilized on buprenorphine for 1 day, followed by a washout period of 1–2 days, then received increasing daily doses of naltrexone (12.5 mg, 25 mg, 50 mg, 100 mg) while precipitated withdrawal symptoms were treated with clonidine, clonazepam, and other adjuvant medications. After receiving the 50-mg dose of naltrexone participants were stratified by two levels of baseline heroin use (<6 bags per day vs. 7 or more bags per day), and by two levels of dysphoria (none or minimal as indicated by Ham-D total score less than 12, vs. mild or greater dysphoria with Ham-D >12). During the pilot trial, these variables were found to be independent predictors of dropout (Sullivan et al., 2006). The stratification of low-severity vs. high-severity patients reflects a binary construct of baseline opioid use, in which physiological severity is defined based on the amount of heroin or other opioids that the patient reports taking, on a daily basis, prior to seeking treatment. Heroin amount is quantified as "bags per day," which is the common unit used in illicit sales in the region where our treatment studies are located. Approximate equivalents with respect to prescription opioids the patient was taking (e.g., oxycodone) were calculated. The cut-off point of high severity based on the opioid equivalent of 6 bags of heroin or more per day has been shown to predict worse outcome in prior studies of naltrexone treatment of opioid dependence, and to interact with treatment (Sullivan et al., 2006; Nunes et al., 2006; Carpenter et al., 2009; Brooks et al., 2010).

Participants were then randomized by a research pharmacy to one of four conditions in a two-by-two factorial design: (1) behavioral naltrexone therapy (BNT) plus one dose (384 mg) of XR-NTX; Depotrex, BIOTEK) prior to hospital discharge; (2) BNT plus placebo injection; (3) compliance enhancement, simulating standard treatment with oral naltrexone plus XR-NTX injection; and (4) CE plus placebo injection.

Both participants and study personnel were blind to medication assignment. The BIOTEK product used in this trial was a prototype of injectable naltrexone that did not achieve marketability. However, this injectable naltrexone (Depotrex) demonstrated plasma levels of naltrexone above 1 ng/ml for approximately 4 weeks after administration of 384 mg naltrexone (Comer et al., 2002), which is comparable bioavailability to the current commercial XR-NTX product (Vivitrol, Alkermes; Bigelow et al., 2012). Participants were discharged on Day 8 with small amounts of adjuvant medications that they had been receiving in the hospital (clonidine, trazodone, and zolpidem), and these were tapered off during the first two weeks of outpatient treatment.

Following discharge, all participants received oral naltrexone during the 24-week study. Naltrexone tablets were encapsulated with 25 mg of riboflavin, added by the research pharmacy as a urine marker to assess compliance. All BNT participants received oral naltrexone in the research clinic, under observed ingestion conditions, for the first two weeks in doses of 100 mg on Mondays and Wednesdays and 150 mg on Fridays before transitioning to home-based administration monitored by their significant other or family member. This dosing schedule for oral naltrexone was selected in order to ensure that patients received naltrexone under conditions of observed ingestion during each study visit in Weeks 1–2, and that they received a dose sufficient to provide a 48- to 72-h blockade, lasting until the next study visit. During these initial two weeks of the study, monitored ingestion of oral naltrexone was considered clinically necessary, in order to reduce the risk of relapse and overdose during this period of heightened vulnerability. Liver function tests were obtained every week for 4 weeks and then monthly, and there were no patients demonstrating elevated liver enzymes considered to be naltrexone-related. From Week 1, CE participants received medication to be self-administered at home. Participants were given an emergency supply of naltrexone to take at home in case of a missed visit (Carroll et al., 2001a,b).

Participants were required to attend the clinic three times per week. During each visit, participants gave an observed urine specimen and completed self-report measures of drug use, craving, and mood. Both groups attended twice per week therapy visits, and for the BNT group, the second session was a network session with their monitor.