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Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial

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Abstract

Context—Naltrexone is a medication available in oral form that can completely block the effects produced by opioid agonists, such as heroin. However, poor medication compliance with naltrexone has been a major obstacle to the effective treatment of opioid dependence.

Objective—To evaluate the safety and efficacy of a sustained-release depot formulation of naltrexone in treating opioid dependence.

Design, Setting, and Participants—Randomized, double-blind, placebo-controlled, 8-week multi-center trial of male and female heroin-dependent patients who participated in the study between September 2000 and November 2003. Participants were stratified by years of heroin use (≥5, <4.9) and gender, and then randomized to receive one of three doses: placebo, 192 mg, or 384 mg depot naltrexone. Doses were administered at the beginning of Week 1 and then again four weeks later at the beginning of Week 5. All participants received twice-weekly relapse prevention therapy, provided observed urine samples, and completed other assessments at each visit.

Main Outcome Measures—Primary outcome measures were retention in treatment and percentage of opioid-negative urine samples.

Results—A total of 60 patients were randomized at two centers. Retention in treatment was dose related with 39%, 60%, and 68% of the patients in the placebo, naltrexone 192 mg, and naltrexone 384 mg groups, respectively, remaining in treatment at the end of the two-month treatment period. Analysis of the time to dropout revealed a significant main effect of dose with mean time to dropout of 27, 36, and 48 days, respectively, for the placebo, naltrexone 192 mg, and naltrexone 384 mg groups. The percentage of urine samples negative for opioids varied significantly as a function of dose, as did the percentage of urine samples negative for methadone, cocaine, benzodiazepines, and amphetamine. The percentage of urine samples negative for cannabinoids was not significantly different across groups. When the data were recalculated without the

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assumption that missing urine samples were positive, however, a main effect of group was not found for any of the drugs tested with the exception of cocaine, where the percentage of cocaine-negative urines was lower in the placebo group. Adverse events were minimal and generally mild in severity. This sustained-release formulation of naltrexone was well tolerated and produced a robust and dose-related increase in treatment retention.

Conclusion—The present data provide exciting new evidence for the feasibility, efficacy, and tolerability of long-lasting antagonist treatments for opioid dependence.

Introduction

Heroin abuse and, more recently, prescription opioid abuse are significant and growing public health problems in the U.S., as measured by a variety of indicators[1–4]. Treatment strategies for opioid dependence commonly include agonist maintenance therapies, such as methadone, buprenorphine, and the buprenorphine/naloxone combination. While all of these medications are effective in reducing illicit opioid use[5–8], problems associated with their use such as social resistance to the idea of "replacing one drug of abuse with another," difficulties in tapering patients off the medication due to long-lasting withdrawal effects, and illicit diversion of the maintenance medications make the search for alternative forms of pharmacotherapy important.

Orally delivered naltrexone is approved by the Food and Drug Administration for the treatment of both opioid and alcohol dependence. It acts as a competitive antagonist at opioid receptors and is highly effective in both preventing and reversing the effects produced by mu opioid agonists. Despite its strong theoretical potential for treating opioid dependence, clinical experience with naltrexone has been disappointing because of high dropout rates during treatment and poor compliance with medication ingestion[9–12]. The development of sustained-release depot formulations of naltrexone has renewed interest in this medication for treating opioid dependence. Depot naltrexone has also been used recently in the treatment of alcohol dependence[13–14]. A recent inpatient study conducted in our laboratory demonstrated that an injectable depot formulation of naltrexone was safe, well tolerated, and effective in reducing the subjective, cognitive, and physiological effects of intravenously delivered heroin for 3–5 weeks, depending on dose[15]. The present study was designed to examine the safety and efficacy of depot naltrexone in a clinical setting for patients who were seeking treatment for opioid dependence.

Methods

Study Participants

Participants were heroin dependent men and women (18–59 years of age), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), who were voluntarily seeking treatment for their dependence. The target enrollment was 60 patients, stratified by years of heroin use (≥5, <4.9) and gender. Participants were randomized in blocks of 6 into one of three parallel cohorts. Patients were in good health based on medical history, physical examination, vital signs measurements, and 12-lead electrocardiogram, and laboratory tests within appropriate normal ranges (hematology, blood chemistry, urinalysis).

Patients were excluded from the study if they were dependent on methadone or on drugs other than heroin, nicotine, or caffeine (based on DSM-IV criteria), pregnant or lactating, unwilling to use a satisfactory method of birth control, currently diagnosed with major DSM-IV Axis I psychopathology (e.g., mood disorder with functional impairment, schizophrenia) that might have interfered with study participation, considered to have a significant risk of suicide or had made one or more attempts in the past year, had acute hepatitis or liver damage as evidenced by SGOT or SGPT greater than three times the upper end of the laboratory normal range, had a history of allergy, adverse reaction or sensitivity to the study medication, regularly used psychoactive drugs including anxiolytics and antidepressants, currently received any other investigational drug, or had any medical condition that might have interfered with study participation or significantly increased the medical risks of study participation. Participants were recruited through advertising in local newspapers and through word-of-mouth. Written informed consent was obtained from all participants through a multi-step process in which study procedures were explained by several staff members. This study was approved by the Institutional Review Boards of the New York State Psychiatric Institute and the University of Pennsylvania, Philadelphia.

Study Design

The study was designed as a multi-center randomized, double-blind, placebo-controlled, parallel-group, 8-week clinical trial. Patients received an initial inpatient detoxification, followed by oral naltrexone for 3 consecutive days in order to ensure that they were willing and able to tolerate the effects of depot naltrexone. Patients were then randomized to receive placebo, 192 mg, or 384 mg depot naltrexone (Depotrex®, Biotek Inc., Woburn, MA). Four weeks later, patients received a second dose of the study medication. The same dose was administered on both occasions.

Following each dose administration, patients attended the clinic twice per week to receive manualized relapse prevention therapy and to complete various questionnaires designed to assess drug craving, opioid withdrawal symptoms, and global functioning. At each visit, potential adverse events were assessed and patients provided urine samples for analysis of opioids, cocaine, benzodiazepines, cannabinoids, methadone, and amphetamine. Urine sample collections were observed by research staff and subsequently analyzed by Northwest Toxicologies, Inc. (Salt Lake City, UT). Blood samples for liver function tests and for analysis of naltrexone and 6-beta-naltrexol levels were collected weekly. Depression was assessed twice monthly and patients met with a psychiatrist at least once per month. At the last study visit, hematology and blood chemistry profiles, liver function tests, urinalyses, electrocardiograms, and physical examinations were performed.

Depot Naltrexone

A long-lasting, injectable formulation of naltrexone (Depotrex® was manufactured by BIOTEK, Inc. (Woburn, MA) and provided by the National Institute on Drug Abuse (Rockville, MD). Naltrexone microcapsules and placebo microspheres were packaged in sterile single-dose vials. After reconstituting in suspending medium, 2.4 ml of the suspension was injected. Each single-dose vial of the active formulation contained drug equivalent to 192 mg naltrexone base. This formulation per vial was designed to release

approximately 5 mg naltrexone per day. The placebo formulation contained the equivalent weight in polymer microspheres. Injections were administered subcutaneously into the buttocks (one 2.4 ml injection per buttock), using an 18 gauge needle. All participants received two injections to maintain the dosing blind. For the placebo dose, participants received two placebo injections, for the low dose, participants received one placebo and one naltrexone injection (192 mg naltrexone base), and for the high dose, participants received two naltrexone injections (394 mg naltrexone base).

Data Analysis

Analyses of the efficacy measures were conducted on the intent-to-treat population. Primary dependent measures were average number of weeks in treatment and the percentage of negative urine toxicology samples for opioids during the 8-week treatment period. The number of negative samples taken in the 8-week treatment period was used to calculate the percent for each patient. The denominator was the maximum number of possible samples for a completed patient, with the assumption that the missing visits and missing test results were positive[16]. The data were also recalculated without those assumptions. The difference in the percent of negative urine results between each naltrexone group and the placebo and the difference between the two naltrexone groups was analyzed with a two-way analysis of variance model (ANOVA) including the treatment and center factors. The three pairwise comparisons and the 95% confidence intervals for the differences between treatments were performed using Tukey's method, controlling for the experiment-wise error rate at 0.05. Residuals of the ANOVA were analyzed to verify whether the normality assumption was violated. Levene's test was used to determine whether the assumption of homogeneity of variance was violated. If either assumption was violated, then the rank transformation or nonparametric procedure was applied instead. Consistency of the evaluation between the centers was examined with the ANOVA model with the added treatment-by-center interaction term, should there be no signs of violation of the assumptions of ANOVA. Consistency of the evaluation across age, race, and gender for the primary efficacy measure was evaluated with the ANOVA or ANCOVA model.

Secondary dependent measures included the following: time to dropout, percentages of negative urine samples for cocaine, benzodiazepines, cannabinoids, amphetamine, and methadone, heroin craving scores, clinical global impression scale scores for severity of opiate and cocaine use rated by clinicians (CGIC) and patients (CGIS), and Hamilton Depression Index (HAM-D) total scores. The distributions of time to dropout in the three treatment groups were compared to determine significance of the difference in retention between treatments. The number of days from randomization to dropout or completion of the study was summarized by treatment. Kaplan-Meier's method was used to estimate the distribution of the time to dropout, where completion of the study was handled as censored observations. The distribution of the time to dropout in each pair of treatment groups was compared using the log-rank test. The percentages of negative urine toxicology outcomes were examined with an analysis of variance (ANOVA) model. How much or how little the patient felt that he or she wanted and needed heroin since the last visit was rated on a visual analog scale. The craving scores at the post-baseline visits were analyzed with the model for repeated measures to assess significance of the treatment by time interaction and the

treatment effect. The severity of opiate and cocaine use was rated on the CGIS and CGIC using an 8-point scale with 1 being no pathology, 7 extreme pathology and 8 not assessed. Patients with no assessment were not included for analysis. The treatment effects on CGIS and CGIC for opiates and cocaine were analyzed with an ANOVA model. If the distribution of CGIS and CGIC concentrated on a few rating scores, then the data were analyzed with the Cochran-Mantel-Haenszel method, stratified by center. The total score of the HAM-D was analyzed with an ANOVA model.

Safety of the treatment was evaluated based on reports of adverse events (AE's), vital signs, liver function tests, clinical lab tests and electrocardiograms. Only the treatment-emergent adverse events were analyzed. Treatment-emergent adverse events were defined as adverse events that occurred after start of study medication or previously occurring adverse events that worsened after start of study medication. The incidence of treatment-emergent adverse events was summarized by treatment, body system and severity. The incidence of the treatment-emergent adverse events that were considered possibly, probably or definitely related to the study medication was summarized similarly. Adverse events that resulted in discontinuation were tabulated by treatment group and listed individually. The overall incidence of treatment-emergent adverse events in each naltrexone group was compared with that of the placebo group using the Fisher's exact test.

Clinical monitoring was performed under the direction of the National Institute on Drug Abuse. The primary clinical monitoring was performed by Biopharmaceutical Research Consultants, Inc. (BRCI, Dexter, MI). BRCI conducted periodic audits during and after the study on all case report forms and corresponding source documents for each participant. The BRCI monitors assured that submitted data were accurate and in agreement with source documentation, verified that investigational agents were properly stored and accounted for, verified that patients' consent for study participation had been properly obtained and documented, confirmed that research participants entered into the study met inclusion and exclusion criteria, and assured that all essential documentation required by good clinical practices guidelines were appropriately filed.

Results

Demographics A total of 60 patients were randomized at 2 centers. Patients were between 19 and 59 years old, 77% of whom were male. The White and Black races were equivalent at 37% and 35%, respectively, and were the majority. The distributions of gender, age, and race were not significantly different in the three groups (Table 1). Lifetime drug use was quite similar across all groups, as was drug use in the past 30 days (Table 1). There were no significant differences between study sites for any of the demographic measures or for any of the dependent measures described below.

Plasma levels of study medication Plasma levels of naltrexone (Figure 1, left panel) and 6-beta-naltrexol (Figure 1, right panel) are shown as a function of study week and treatment group. After administration of 192 mg depot naltrexone, average naltrexone plasma levels ranged between 0.4 and 1.9 ng/ml. After administration of 384 mg depot naltrexone, average naltrexone plasma levels ranged between 1.3 and 3.2 ng/ml. Across the 8-week study,

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