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Naltrexone treatment for opioid dependence: Does its effectiveness depend on testing the blockade?

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ABSTRACT

Background: FDA approval of long-acting injectable naltrexone (Vivitrol) for opioid dependence highlights the relevance of understanding mechanisms of antagonist treatment. Principles of learning suggest an antagonist works through extinguishing drug-seeking behavior, as episodes of drug use ("testing the blockade") fail to produce reinforcement.

We hypothesized that opiate use would moderate the effect of naltrexone, specifically, that opiate-positive urines precede dropout in the placebo group, but not in the active-medication groups.

Methods: An 8-week, double-blind, placebo-controlled trial ($N = 57$), compared the efficacy of low (192 mg) and high (384 mg) doses of a long-acting injectable naltrexone (Depotrex) with placebo (Comer et al., 2006). A Cox proportional hazard model was fit, modeling time-to-dropout as a function of treatment assignment and urine toxicology during treatment.

Results: Interaction of opiate urines with treatment group was significant. Opiate-positive urines predicted dropout on placebo and low-dose, but less so on high-dose naltrexone, where positive urines were more likely followed by sustained abstinence. Among patients with no opiate-positive urines, retention was higher in both low- and high-dose naltrexone conditions, compared to placebo.

Conclusions: Findings confirm that injection naltrexone produces extinction of drug-seeking behavior after episodes of opiate use. Adequate dosage appears important, as low-dose naltrexone resembled the placebo group; opiate positive urines were likely to be followed by dropout from treatment. The observation of high treatment retention among naltrexone-treated patients who do not test the blockade, suggests naltrexone may also exert direct effects on opiate-taking behavior that do not depend on extinction, perhaps by attenuating craving or normalizing dysregulated hedonic or neuroendocrine systems.

1. Introduction

The opioid receptor antagonist naltrexone has been available in pill form since the 1980s for treatment of opiate dependence, but was largely ineffective due to poor adherence to daily pill regimen. The advent of long-acting injections (Comer et al., 2006) and implants (Hulse et al., 2009) of naltrexone circumvents the problem of adherence to daily pill taking, and has shown considerable promise as a treatment. A monthly intramuscular injection of naltrexone (trade name Vivitrol) has received FDA approval for treatment of opioid dependence, based on a pivotal 6-month placebo controlled trial, which showed that over 50% of opioid-dependent patients randomized to Vivitrol were retained in treatment and predominantly abstinent for the full 6 months (Krupitsky et al., 2011).

The advent of long-acting formulations of naltrexone makes it possible to address questions about the mechanism of action of antagonist treatment. The immediate pharmacological effect of naltrexone is potent blockade of the subjective and reinforcing effects of even substantial doses of opiates (Comer et al., 2002; Sullivan et al., 2006). Principles of learning implicated in the mechanisms of addiction suggest an antagonist would reduce opiate use through extinction, as episodes of drug use ("testing the blockade") fail to produce reinforcement or other unconditioned responses. Clinical experience suggests some opiate-dependent patients treated with naltrexone do test the blockade repeatedly before establishing sustained abstinence. However, others seem to remain abstinent throughout, never testing the blockade, or report using opiates only once, suggesting the extinction of opiate use after one trial (typical report: "I tried heroin once, and nothing happened, so I

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realized I was wasting my money"). This raises questions regarding the mechanism of antagonist treatment for opiate dependence: (1) Does the effectiveness of antagonist treatment depend upon episodes of blocked use and consequent extinction? (2) Do some patients stop using opiates because of a placebo or expectancy effect – the expectation of blockade? Or, (3) Does naltrexone exert a direct effect on opiate use reduction that does not depend on extinction over episodes of use, by blocking the effect of conditioned cues or influencing the neural mechanisms of craving and relapse?

A previously completed double-blind, placebo-controlled trial, which demonstrated the efficacy of a long-acting injectable formulation of naltrexone (Comer et al., 2006), affords an opportunity to address these questions. Because patients and staff were blind to treatment condition, effects of expectancy should have occurred equally in the placebo and active medication groups. Urine was collected twice per week during the 8-week trial and tested for opiates. To examine the role of blocked use on the clinical effect of naltrexone, we employed data from this trial, using information on the presence/absence of one or more opiate-positive urine test results, treatment assignment (placebo, vs. low-dose naltrexone, vs. high-dose naltrexone), and retention in treatment. Primary outcome was retention in treatment since treatment dropout is most commonly associated with relapse to opiate use, and naltrexone was found to have a dose-dependent effect on treatment retention (Comer et al., 2006).

This analysis examines whether the treatment arms followed different patterns of survival for those who tested the opiate blockade compared to those who did not test. We considered the possibility of a dose-dependent therapeutic effect of naltrexone through a mechanism that is independent of its block of the opioid receptors. In the absence of any information as to whether, and to what degree, they could feel opiate effects during the study, non-testing participants who drop out and eventually relapse must be presumed to be influenced by other factors such as withdrawal or craving. If the naltrexone 'non-testing' groups had higher survival probabilities than the placebo 'non-testing' group, this outcome supports the possibility that naltrexone exerts a beneficial effect that does not rely on receptor blockade. We hypothesized that opiate use (positive urines) during treatment would moderate the favorable effect of naltrexone, a use-by-treatment interaction. Specifically, we expected that episodes of opiate use would precede dropout in the placebo group, but not in the high-dose naltrexone group, with the low-dose group showing an intermediate outcome.

2. Methods

2.1. Participants

Details of the methods and sample have been reported previously (Comer et al., 2006). Briefly, participants were 57 men and women (age 18–59 years) meeting DSM-IV criteria for heroin dependence and seeking treatment at one of two university medical centers. Recruitment was through word-of-mouth and advertising in local newspapers. To be eligible, patients were required to be in good general health, based on psychiatric and medical history, physical examination, routine laboratory tests, and electrocardiogram. 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 that could interfere with study participation (e.g., mood disorder with functional impairment, schizophrenia), significant risk of suicide, or regular use of psychotropic medications. Acute or severe hepatitis was exclusionary, but patients with moderate liver enzyme elevations (SGOT or SGPT less than three times the upper end of the normal range) were eligible. The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute and the University of Pennsylvania, and all participants gave written informed consent.

2.2. Study design

This was a two-site, randomized, double-blind, placebo-controlled 8-week trial. Participants received an inpatient detoxification, followed by 3 days of ascending doses of oral naltrexone to ensure tolerability. Participants were then randomized to receive injections of either placebo, low dose-192 mg or high dose-384 mg of depot naltrexone (Depotrex; BIOTEK, Inc.) and discharged to outpatient treatment. Four weeks later, patients received a second injection. Depotrex is a subcutaneous injection of a suspension of polymer microspheres (Nuwayser et al., 1990), which at the 384 mg dose, produces a pharmacokinetic profile of naltrexone and the active metabolite 6-beta naltrexol (Comer et al., 2002) similar to that of Vivitrol (Dunbar et al., 2006), and produces dose-dependent blockade of the effects of up to 25 mg of intravenous heroin for at least 4 weeks (Comer et al., 2002). Participants were asked to attend the outpatient clinic twice per week during the 8-week outpatient trial. At each visit patients received manual-guided relapse prevention therapy, completed assessments, and provided a urine sample under staff observation, which was tested for opiates as well as other drugs.

2.3. Data analysis

The primary outcome measure for the present analysis is retention in treatment, analyzed as a time-to-event (dropout) variable with survival analysis. Retention is arguably the most clinically meaningful outcome measure for this population, because dropout from treatment is the most common failure mode among outpatients under treatment for opiate dependence; patients who drop out of treatment have most likely relapsed. A Cox proportional hazard model was fit, modeling biweekly visits retained in treatment as a function of treatment assignment (placebo, low dose-192 mg naltrexone, high dose-384 mg naltrexone), the presence of one or more positive urine toxicology results during treatment as a dichotomous covariate, and the interaction of treatment and urine toxicology. To assess the overall interaction, the type 3 test with 2 degrees of freedom was employed at the significance level of 0.05. Once the overall interaction was found significant, subgroup analysis was conducted at the significance level of 0.05. Proportional hazards assumption was assessed and validated in the final model. PROC PHREG in SAS was used to conduct these analyses (SAS Institute, 2012).

While we originally (Comer et al., 2006) reported an N of 60 participants, three (3/60) randomized participants did not provide any urine data and were excluded from this analysis. In addition, one participant with consistently opiate-positive urines in the last visits of the study was counted as completing Visit 16 because we measured treatment retention regardless of urine result. These differences account for the fact that retention figures reported here are slightly higher than those reported in the original paper (Comer et al., 2006).

3. Results

3.1. Participants

Of the sample randomized ($N = 57$), 77% were men, 37% were Caucasian, 35% were African–American, and 18% were Hispanic. The mean age was 41 (s.d. 11) years. The mean number of years of heroin use in this sample was 13.9 (s.d. 11.3). The distributions of sex, age, race and measures of lifetime and past 30-day drug use were not significantly different among the three treatment conditions.

3.2. Naltrexone, during-treatment opiate use, and retention in treatment

Fig. 1A–C displays the raw data for the relationships between during-treatment opiate use and retention in treatment in the placebo (Fig. 1A), low dose naltrexone-192 mg (Fig. 1B), and high dose naltrexone-384 mg (Fig. 1C) conditions. Each row in the figures represents the data for a patient, and the columns represent each of the 16 twice-weekly clinic visits at which urine was collected across the 8-week trial. There was also an initial visit at the time of hospital discharge post-injection (Visit 0) and an extra visit ("2nd") to receive the second depot naltrexone injection, for a total of 17 visits (Visits 1–8 and 9–16). Open circles represent visit dates when the patient attended the clinic and the urine toxicology was negative for opiates, indicating the patient has most likely been abstinent since the previous visit. Closed (darkened) circles represent visit dates when the patient attended the clinic and the urine toxicology was positive for opiates, indicating the patient used opiates in the several days prior to the visit. Empty points in the grid represent visits in which the patient either failed to attend or did not provide a urine sample. The patient-rows are ordered in such a way that patients who gave one or more opiate-positive urines are