ORIGINAL ARTICLE

Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence

A Randomized, Placebo-Controlled Trial

Sandra D. Comer, PhD; Maria A. Sullivan, MD, PhD; Elmer Yu, MD; Jami L. Rothenberg, PhD; Herbert D. Kleber, MD; Kyle Kampman, MD; Charles Dackis, MD; Charles P. O'Brien, MD

Context: Oral naltrexone can completely antagonize the effects produced by opioid agonists. However, poor 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 and Setting: Randomized, double-blind, placebo-controlled, 8-week trial conducted at 2 medical centers.

Participants: Sixty heroin-dependent adults.

Interventions: Participants were stratified by sex and years of heroin use (≥5 vs <5) and then were randomized to receive placebo or 192 or 384 mg of depot naltrexone. Doses were administered at the beginning of weeks 1 and 5. All participants received twice-weekly relapse prevention therapy, provided observed urine samples, and completed other assessments at each visit.

Main Outcome Measures: Retention in treatment and percentage of opioid-negative urine samples.

Results: Retention in treatment was dose related, with 39%, 60%, and 68% of patients in the placebo, 192 mg of naltrexone, and 384 mg of naltrexone groups, respectively, remaining in treatment at the end of 2 months. Time to dropout had a significant main effect of dose, with mean time to dropout of 27, 36, and 48 days for the placebo, 192 mg of naltrexone, and 384 mg of naltrexone groups, respectively. The percentage of urine samples negative for opioids, methadone, cocaine, benzodiazepines, and amphetamine varied significantly as a function of dose. When the data were recalculated without the assumption that missing urine samples were positive, a main effect of group was not found for any drugs tested except cocaine, where the percentage of cocaine-negative urine samples was lower in the placebo group. Adverse events were minimal and generally mild. This formulation of naltrexone was well tolerated and produced a robust, dose-related increase in treatment retention.

Conclusion: These data provide new evidence of the feasibility, efficacy, and tolerability of long-lasting antagonist treatments for opioid dependence.

Arch Gen Psychiatry. 2006;63:210-218

Author Affiliations: Division on Substance Abuse, New York State Psychiatric Institute, and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York (Drs Comer, Sullivan, Rothenberg, and Kleber); and Department of Psychiatry, University of Pennsylvania, and Department of Behavior Health, Philadelphia Veterans Affairs Medical Center, Philadelphia (Drs Yu, Kampman, Dackis, and O'Brien).

HEROIN ABUSE AND, MORE recently, prescription opioid abuse are significant and growing public health problems in the United States, as measured by a variety of indicators.[1-4] Treatment strategies for opioid dependence commonly include agonist maintenance therapies, such as methadone hydrochloride, buprenorphine hydrochloride, and buprenorphine–naloxone hydrochloride. Although 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 hydrochloride is approved by the Food and Drug Administration for the treatment of opioid and alcohol dependence. It acts as a competitive antagonist at opioid receptors and is highly effective in preventing and reversing the effects produced by μ opioid agonists. Despite the strong theoretical potential of naltrexone for treating opioid dependence, clinical experience with this drug 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[15] demonstrated that an injectable depot formulation of naltrexone was safe, well tolerated, and effective in reducing the subjective, cognitive, and physiologic effects of intravenously delivered heroin for 3 to 5 weeks, depending on dose. The present study examines the safety and efficacy of depot naltrexone in a clinical setting for patients seeking treatment for opioid dependence.

METHODS

STUDY PARTICIPANTS

Participants were heroin-dependent (as defined by the *DSM-IV*) men and women aged 18 to 59 years who were voluntarily seeking treatment for their dependence. The target enrollment was 60 patients, stratified by sex and years of heroin use ($\geq$5 vs $<$5). Participants were randomized in blocks of 6 into 1 of 3 parallel cohorts. Patients were in good health based on medical history, physical examination findings, vital sign measurements, and 12-lead electrocardiographic evidence, and laboratory test results were within the appropriate reference ranges (hematology, blood chemistry, and 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 as having major *DSM-IV* Axis I psychiatric disorders (eg, mood disorder with functional impairment or schizophrenia) that might have interfered with study participation; considered to have a significant risk of suicide or had made 1 or more suicide attempts in the past year; had acute hepatitis or liver damage as evidenced by aspartate aminotransferase or alanine aminotransferase levels greater than 3 times the upper end of the laboratory reference 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 of the participants using a multistep 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.

STUDY DESIGN

The study was designed as a multicenter, 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 to ensure that they were willing and able to tolerate the effects of depot naltrexone. Patients were then randomized to receive placebo or 192 or 384 mg of depot naltrexone (Depotrex; BIOTEK, Inc, Woburn, Mass). Four weeks later, patients received a second dose of the study medication. The same dose was administered on both occasions.

After 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 (AEs) 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 the samples were subsequently analyzed by Northwest Toxicologies Inc (Salt Lake City, Utah). Blood samples for liver function tests and for analysis of naltrexone and 6-β-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 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 of naltrexone base. This formulation per vial was designed to release approximately 5 mg of naltrexone per day. The placebo formulation contained the equivalent weight in polymer microspheres. Injections were administered subcutaneously to the buttocks (one 2.4-mL injection per buttock) using an 18-gauge needle. All of the participants received 2 injections to maintain the dose masking. For the placebo dose, participants received 2 placebo injections; for the low dose, participants received 1 placebo and 1 naltrexone injection (192 mg of naltrexone base); and for the high dose, participants received 2 naltrexone injections (384 mg of naltrexone base).

DATA ANALYSIS

Analyses of the efficacy measures were conducted on the intention-to-treat population. Primary dependent measures were the average number of weeks in treatment and the percentage of urine toxicology samples negative for opioids during the 8 weeks of treatment. The number of negative samples collected in the 8-week treatment period was used to calculate the percentage 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 percentage of negative urine results between each naltrexone group and the placebo group and the difference between the 2 naltrexone groups were analyzed using a 2-way analysis of variance (ANOVA) model, including the treatment and medical center factors. The 3 pairwise comparisons and the 95% confidence intervals for the differences between treatments were performed using the Tukey method, controlling for the experiment-wise error rate at $\alpha = .05$. Residuals of the ANOVA were analyzed to determine whether the normality assumption was violated. The Levene 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 medical centers was examined using the ANOVA model with the added treatment $\times$ center interaction term should there be no signs of violation of the assumptions of ANOVA. Consistency of the evaluation across age, race, and sex for the primary efficacy measure was evaluated using either the ANOVA or the analysis of covariance model.

Secondary dependent measures included time to dropout; percentages of urine samples negative for cocaine, benzodiazepines, cannabinoids, amphetamine, and methadone; heroin crav-

ing scores; Clinical Global Impressions scale scores for severity of opiate and cocaine use rated by clinicians (CGIC) and patients (CGIS); and Hamilton Depression Rating Scale (HAM-D) total scores. The distributions of time to dropout in the 3 treatment groups were compared to determine the 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. The Kaplan-Meier 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 using an 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 visits after baseline were analyzed using the model for repeated measures to assess the significance of the treatment × time interaction and the treatment effect. The severity of opiate and cocaine use was rated on the CGIS and the CGIC using an 8-point scale, with 1 being no abnormality; 7, extreme abnormality; and 8, not assessed. Patients with no assessment were not included in the analysis. The treatment effects on the CGIS and the CGIC for opiates and cocaine were analyzed using an ANOVA model. If the distribution of the CGIS and CGIC scores concentrated on a few rating scores, then the data were analyzed using the Cochran-Mantel-Haenszel method, stratified by medical center. The total score on the HAM-D was analyzed using an ANOVA model.

Safety of the treatment was evaluated based on reports of AEs, vital signs, liver function test results, clinical laboratory test results, and electrocardiographic findings. Only the treatment-emergent AEs were analyzed. Treatment-emergent AEs were defined as AEs that occurred after the first administration of study medication or previously occurring AEs that worsened after the start of study medication. The incidence of treatment-emergent AEs was summarized by treatment, body system, and severity. The incidence of treatment-emergent AEs that were considered to be possibly, probably, or definitely related to the study medication was summarized similarly. The AEs that resulted in study discontinuation were tabulated by treatment group and listed individually. The overall incidence of treatment-emergent AEs in each naltrexone group was compared with that of the placebo group using the Fisher 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 (Dexter, Mich), which conducted periodic audits during and after the study on all case report forms and corresponding source documents for each participant. Monitoring by Biopharmaceutical Research Consultants Inc ensured 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 met the inclusion and exclusion criteria, and ensured that all essential documentation required by Good Clinical Practice guidelines was appropriately filed.

RESULTS

DEMOGRAPHICS

Sixty patients were randomized at 2 medical centers. Patients were aged 18 to 59 years, and 77% were men. The white and black races were similarly represented at 37% and 35%, respectively, and were the majority. The distributions of sex, age, and race were not significantly different in the 3 groups (**Table 1**). Lifetime drug use was 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 in the following subsections.

PLASMA LEVELS OF STUDY MEDICATION

Plasma levels of naltrexone (**Figure 1**A) and 6-β-naltrexol (Figure 1B) are shown as a function of study week and treatment group. After the administration of 192 mg of depot naltrexone, mean naltrexone plasma levels ranged from 0.4 to 1.9 ng/mL. After the administration of 384 mg of depot naltrexone, mean naltrexone plasma levels ranged from 1.3 to 3.2 ng/mL. Across the 8-week study, plasma naltrexone levels tended to be fairly constant, with perhaps a slight decline during the fourth week after drug administration. Plasma levels of 6-β-naltrexol, the primary pharmacologically active metabolite of naltrexone, tended to be higher than naltrexone levels and more variable across time and between participants.

RETENTION IN TREATMENT AND TIME TO DROPOUT

The percentage of patients retained in treatment is presented as a function of study week and treatment group (**Figure 2**). During the first visit, all the randomized participants were present. By week 8 (visit 16), 7 (39%) of 18 patients in the placebo group, 12 (60%) of 20 in the 192 mg of naltrexone group, and 15 (68%) of 22 in the 384 mg of naltrexone group remained in treatment. The distribution of time from randomization to dropout or completion in the 3 treatment groups was compared to determine the significance of the difference in retention among groups (**Table 2**). The mean number of days to dropout was lowest in the placebo group (27 days; 3.8 weeks), followed by the 192 mg of naltrexone group (36 days; 5.1 weeks), and the 384 mg of naltrexone group (48 days; 6.8 weeks). The main effect of group was significant at $P=.002$. Pairwise comparisons between groups revealed a significant difference in days to dropout between the placebo and 384 mg of naltrexone groups ($P<.001$) and between the 2 active dose groups ($P=.046$).

URINE DRUG TOXICOLOGY

The mean percentage of urine samples negative for opioids across the study was lowest for the placebo group (25.3%) and highest for the 384 mg of naltrexone group (61.9%) (**Table 3** and **Figure 3**). The main effect of group was significant ($P=.03$). Pairwise comparisons between groups revealed a significant difference between the placebo and the 192 mg of naltrexone groups ($P=.04$) and between the placebo and the 384 mg of naltrexone groups ($P<.001$). However, when the data were recalculated without the assumption that missing visits and missing samples were positive, the mean percentage of urine samples negative for opioids increased to 74.2% in the placebo group, 73.5% in the 192 mg of naltrexone

Table 1. Demographic Characteristics of the 60 Study Participants

	Placebo Group (n = 18)	192 mg of Naltrexone Group (n = 20)	384 mg of Naltrexone Group (n = 22)	Total (N = 60)	*P* Value*
Sex, No. (%)					
M	12 (67)	15 (75)	19 (86)	**46** (77)	.38
F	6 (33)	5 (25)	3 (14)	**14** (24)	
Race, No. (%)					
White	7 (39)	7 (35)	8 (36)	**22** (37)	.34
Black	7 (39)	5 (25)	9 (41)	**21** (35)	
Hispanic	3 (17)	5 (25)	3 (14)	**11** (18)	
Asian	0	0	2 (9)	**2** (3)	
Other	1 (6)	3 (15)	0	**4** (7)	
Age, y					
18-30, No. (%)	3 (17)	4 (20)	4 (18)	**11** (18)	.85
31-59, No. (%)	15 (83)	16 (80)	18 (82)	**49** (82)	
Mean (SD)	40 (11)	42 (10)	41 (11)	41 (10)	
Range	20-59	26-59	19-56	19-59	
Heroin use, mean (SD)					
Lifetime, y	15.1 (11.8)	15.7 (12.0)	10.7 (9.8)	13.7 (11.1)	.39
Past month, d	29.3 (2.6)	28.7 (4.6)	24.4 (2.4)	29.2 (3.2)	.90
Methadone use, mean (SD)					
Lifetime, y	1.5 (3.3)	1.1 (1.2)	3.0 (6.2)	1.9 (4.3)	.26
Past month, d	0.9 (1.8)	0.1 (0.4)	0.2 (0.5)	0.4 (1.1)	.14
Other opioid use, mean (SD)					
Lifetime, y	0.0 (0.1)	0.8 (2.6)	1.9 (7.8)	1.0 (5.0)	.56
Past month, d	0.1 (0.3)	0.3 (1.0)	0.4 (1.2)	0.3 (1.0)	.63
Barbiturate use, mean (SD)					
Lifetime, y	0.0	0.0	0.1 (0.2)	0.0 (0.1)	.16
Past month, d	0.0	0.0	0.0	0.0	NA
Other sedative use, mean (SD)					
Lifetime, y	0.1 (0.5)	0.3 (0.9)	0.3 (1.0)	0.3 (0.8)	.94
Past month, d	0.2 (0.8)	1.4 (3.8)	0.5 (1.3)	0.7 (2.3)	.30
Cocaine use, mean (SD)					
Lifetime, y	4.4 (5.5)	4.8 (8.6)	3.6 (6.6)	4.2 (6.9)	.80
Past month, d	3.1 (5.7)	2.1 (4.5)	1.3 (2.4)	2.1 (4.3)	.54
Alcohol use, mean (SD)					
Lifetime, y	2.0 (4.1)	0.3 (1.0)	2.3 (6.0)	1.6 (4.4)	.77
Past month, d	0.1 (0.3)	0.0	0.0 (0.0)	0.0 (0.1)	>.99
Cannabis use, mean (SD)					
Lifetime, y	5.5 (8.9)	9.2 (13.2)	9.8 (11.3)	8.3 (11.2)	.51
Past month, d	3.5 (8.1)	4.1 (8.8)	2.4 (5.8)	3.3 (7.5)	.78

**P* values for comparisons of the distributions of sex and race among treatment groups are based on the Cochran-Mantel-Haenszel (general association) test stratified by medical center. *P* values for comparisons of the distributions of age and drug use among treatment groups are based on a 2-way analysis of variance model containing the effect of treatment and medical center.

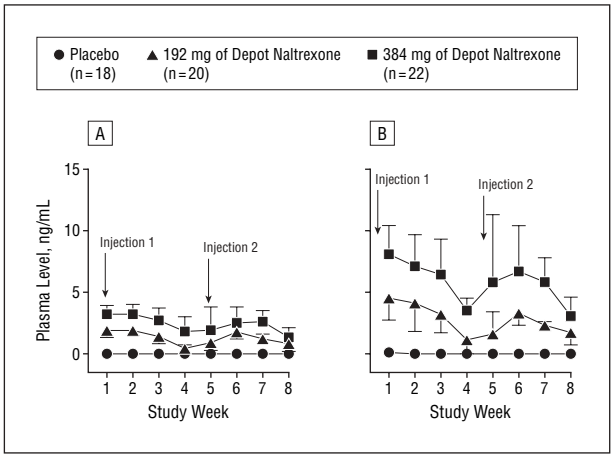

Figure 1. Plasma levels of naltrexone (A) and 6-β-naltrexol (B) by study week and treatment group. Error bars represent standard deviation.

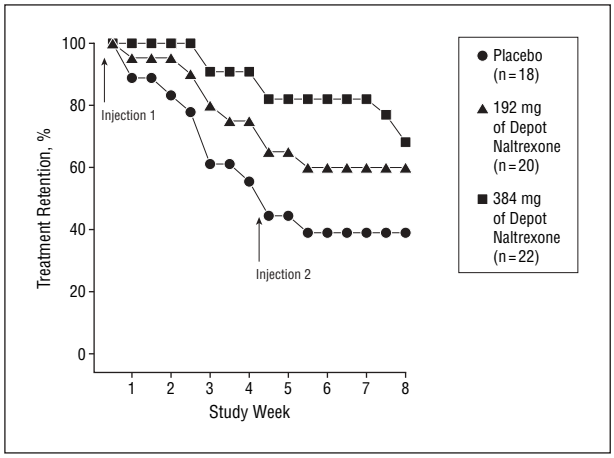

Figure 2. Retention in treatment by study week and treatment group.

Table 2. Summary of Time to Dropout by Treatment Group

	Placebo Group (n = 18)	192 mg of Naltrexone Group (n = 20)	384 mg of Naltrexone Group (n = 22)	*P* Value	Pairwise Comparisons*	
					Treatment†	*P* Value
Time from randomization to dropout/completion, d						
Mean (SD)	27 (19)	36 (20)	48 (13)	.002		
Range	2-65	1-60	16-59		192 vs 0	.13
					384 vs 0	<.001
					384 vs 192	.046

*P values for pairwise comparisons among treatment groups were based on the Kaplan-Meier method, where completion of the study was handled as censored observation. *P* values for paired comparisons were based on the log-rank test.
†0 indicates placebo group; 192, 192 mg of naltrexone group; and 384, 384 mg of naltrexone group.

Table 3. Analysis of Negative Opioid Urine Samples by Treatment Group

	Placebo Group (n = 18)	192 mg of Naltrexone Group (n = 20)	384 mg of Naltrexone Group (n = 22)	Pooled SD	*P* Value	Pairwise Comparisons*		
						Treatment†	*P* Value	95% Confidence Interval
Negative opioid urine samples when missing samples were considered positive, %‡								
Mean (SD)	25.3 (17.2)	47.1 (38.2)	61.9 (28.7)	30.4	.03			
Range	0-64.7	0-100	0-100			192 vs 0	.04	(–1.9 to 45.5)
						384 vs 0	<.001	(13.2 to 60.1)
						384 vs 192	.17	(–7.6 to 37.3)
Recalculation: negative opioid urine samples when missing samples were not considered positive %								
Mean (SD)	74.2 (33.4)	73.5 (33.2)	79.4 (28.9)	32.5	.85			
Range	0-100	0-100	0-100			192 vs 0	.95	(–25.9 to 24.6)
						384 vs 0	.61	(–19.8 to 30.2)
						384 vs 192	.55	(–18.0 to 29.8)
Missing urine samples, %								
Mean (SD)	64.4 (21.7)	42.7 (32.4)	29.4 (21.5)	25.6	.02			
Range	11.8-88.2	0-88.2	0-82.4			192 vs 0	.03	(–42.3 to –1.0)
						384 vs 0	<.001	(–55.2 to –14.7)
						384 vs 192	.13	(–32.9 to 6.3)

*P values for pairwise comparisons among treatment groups were based on a 2-way analysis of variance model containing the effect of treatment, medical center, and the medical center × treatment interaction. The pairwise comparisons and the 95% confidence intervals were performed using the Tukey method.
†0 Indicates placebo group; 192, 192 mg of naltrexone group; and 384, 384 mg of naltrexone group.
‡The percentage was calculated for each participant using a denominator of 17 (2 samples per week for 8 weeks plus an additional sample collected when the second dose of depot naltrexone was administered). This denominator was used when the data were calculated with the assumption that missing urine samples were positive.

group, and 79.4% in the 384 mg of naltrexone group, and there were no significant differences among groups.

Similar trends in the average percentage of negative urine samples as a function of group were obtained for cocaine ($P = .003$), benzodiazepines ($P = .02$), amphetamine ($P = .03$), and methadone ($P = .05$) when the missing values were calculated as positive for the drug of interest (Figure 3). The difference among the 3 groups for cannabinoids was not significant ($P = .08$). The percentage of missing urine samples was inversely related to the percentage of negative urine samples, with the highest percentage of missing urine samples for the placebo group (64.4%), followed by the 192 mg of naltrexone group (42.7%) and the 384 mg of naltrexone group (29.4%) (Table 3).

Across time, the percentage of urine samples negative for cocaine was significantly lower in the placebo group than in the 192 mg of naltrexone group at week 1 (visit 2) (30.0% vs 90.9%; $P = .003$), week 2 (visit 4) (62.5% vs 93.8%; $P = .04$), week 5 (visit 10) (33.3% vs 100%; $P = .03$), and week 7 (visit 14) (0% vs 100%; $P = .01$). The percentage of urine samples negative for cocaine was significantly lower in the placebo group than in the 384 mg of naltrexone group at week 1 (visit 2) (30.0% vs 88.9%; $P = .002$), week 3 (visit 6) (71.4% vs 100%; $P = .04$), and week 7 (visit 14) (0% vs 84.6%; $P = .04$). The percentages of urine samples negative for benzodiazepines and methadone were significantly lower in the placebo group than in the 384 mg of naltrexone group at week 7 (visit 13) (66.7% vs 100%; $P = .02$ for both drugs). There were no significant differ-

ences in the percentages of negative urine samples among groups for cannabinoids or amphetamine.

When the data were recalculated without the assumption that missing values were positive, there were no statistically significant differences between groups for any of the drugs. For cocaine, the average percentage of negative urine samples was lower, but not significantly so, in the placebo group (65.7%) compared with the 192 mg of naltrexone (86.0%) and 384 mg of naltrexone (83.9%) groups. The mean percentage of urine samples negative for cannabinoids ranged from 60.7% to 63.5% across the 3 groups, and the mean percentage of negative urine samples ranged from 87.8% to 100% for benzodiazepines, amphetamine, and methadone.

HEROIN CRAVING

At baseline, heroin craving was high for all 3 groups: mean ratings of "wanting heroin" and "needing heroin" ranged from 54 to 64 mm on a 100-mm scale. After receiving the study medication, the lowest heroin craving scores were reported by the 192 mg of naltrexone group for most visits (range, 1-28 mm). No statistically significant differences were found for ratings of wanting heroin among the treatment groups during the study ($P=.22$). However, patients who received active depot naltrexone reported needing heroin less than those who received placebo ($P=.002$). The pairwise comparisons for ratings of "needing heroin" showed that there were significant differences between the placebo and 192 mg of naltrexone groups ($P<.001$) and between the placebo and 384 mg of naltrexone groups ($P<.001$) but insignificant differences between the 192 and 384 mg of naltrexone groups ($P=.20$).

CLINICAL GLOBAL IMPRESSIONS SCALE AND HAM-D TOTAL SCORE

There was no obvious pattern of difference or statistical significance between the mean CGIC and CGIS scores across visits among the 3 treatment groups. Throughout the study, depression scores did not significantly differ across the 3 treatment groups. At baseline, mean HAM-D total scores for the placebo and 192 and 384 mg of naltrexone groups were 14.8 (n=17), 14.6 (n=19), and 13.3 (n=20), respectively. By week 8 (visit 16), mean HAM-D total scores for the placebo and 192 and 384 mg of naltrexone groups were 4.0 (n=2), 6.7 (n=9), and 3.1 (n=14), respectively.

ADVERSE EVENTS

Overall AEs

In the placebo group (n=18), 9 patients (50%) experienced an AE, 4 (22%) experienced a treatment-related AE, and 1 (6%) discontinued study participation because of an AE. In the 192 mg of naltrexone group (n=20), 13 patients (65%) experienced an AE, 8 (40%) experienced a treatment-related AE, and 2 (10%) discontinued because of an AE. In the 384 mg of naltrexone group (n=22), 15 patients (68%) experienced an AE, 3 (14%) experienced a treatment-related AE, and none discontinued because of an AE. There were no significant differences among treatment groups in the number of AEs, treatment-related AEs, or discontinuations due to AEs.

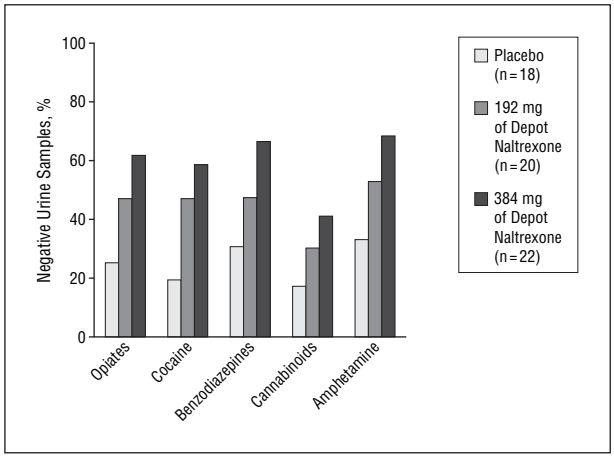

Figure 3. Percentage of urine samples negative for various drugs of interest. Missing urine samples were considered positive.

Treatment-Related AEs

The most common treatment-related AEs were "general disorders and administration site conditions" (eg, fatigue, injection site induration, and injection site pain), where 2 AEs (11.1%) were reported in the placebo group, 6 (30.0%) were reported in the 192 mg of naltrexone group, and 3 (13.6%) were reported in the 384 mg of naltrexone group. Five patients who were discontinued from the study included 1 in the placebo group who experienced an injection site induration and 4 in the 192 mg of naltrexone group who experienced injection site redness, mass, and induration (n=1); a headache (n=1); and increases in liver function test results (n=2) (see the following subsection). All of the injection site reactions were rated as moderate in severity and resolved spontaneously within 2 to 3 weeks.

Treatment-Emergent AEs

Two serious AEs occurred during the study. One 50-year-old patient developed diabetes mellitus after receiving the second dose of 384 mg of naltrexone. The relationship to the study medication was noted as being "unlikely." Three months after the end of study participation, a patient who received 192 mg of naltrexone made a suicide attempt, which was deemed unrelated to the study.

Liver function test (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase) values were within twice the upper limit of the reference range throughout the study, except for 1 participant who was discontinued before administration of the second set of injections owing to elevated γ-glutamyltransferase values (aspartate aminotransferase and alanine aminotransferase values were only mildly elevated). This patient was being treated for hepatitis C by his primary care physician, and it was believed that the most conservative medical approach would be to discontinue him from the study. A second patient demonstrated 4- to 7-fold increases in alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase values over the values before nal-

trexone use, accompanied by other symptoms, including jaundice, dark-colored urine, and light-colored stools, within 1 week after the administration of 192 mg of depot naltrexone. This patient, who was hepatitis negative during screening, subsequently had a positive test result for hepatitis C, and it was determined that the acute increases in liver function test values most likely occurred as a result of this new infection.

COMMENT

Although sustained-release preparations of naltrexone have been investigated since the 1970s,[17-23] problems with biocompatibility have prevented their widespread use. The present study represents the first prospective, randomized, placebo-controlled clinical trial of a sustained-release formulation of naltrexone for the treatment of opioid dependence. The data demonstrate that this 30-day injectable form of naltrexone is safe and effective in retaining heroin-dependent patients in treatment. The fact that the percentage of urine samples negative for opioids was high (75%-80%) regardless of the depot naltrexone dose used suggests that patients who attend clinic visits are more likely to abstain from using opioids and other drugs of abuse, except possibly cocaine and cannabinoids. By increasing treatment retention, depot naltrexone treatment will allow patients greater contact with appropriate supportive counseling to reduce drug use and ease the transition to a life without heroin.

The mean±SD peak naltrexone plasma levels measured approximately 1 week after the administration of 192 and 384 mg of depot naltrexone were 1.9±0.6 and 3.2±0.7 ng/mL, respectively, which were consistent with the levels reported in a previous study[15] of the same formulation of depot naltrexone. For comparison, a single oral dose of 50 mg of naltrexone produces mean peak naltrexone plasma concentrations of approximately 9 ng/mL 1 hour after drug administration.[24] The mean half-life of naltrexone was 3.6 hours, with large individual variability in values, which is common with drugs subject to extensive first-pass metabolism.[24] In general, many investigators agree that doses that maintain naltrexone plasma levels of approximately 2 ng/mL are sufficient for antagonizing the effects of high doses of opioid agonists.

One potential concern with a long-lasting antagonist is that patients will attempt to override the blockade by using large amounts of heroin, thereby placing themselves at increased risk for overdose, especially during the period when naltrexone blood levels are decreasing. This concern is particularly relevant given the literature in laboratory animals demonstrating an up-regulation in mu opioid receptors after discontinuation of long-term treatment with opioid antagonists.[25-33] In healthy human participants, however, a study of morphine sensitivity before and after naltrexone treatment did not show any evidence of mu receptor up-regulation in the respiratory control system, the most likely site of opioid overdose lethality.[34] There have also been reports[35,36] of increased opioid overdose in patients after discontinuation of oral naltrexone maintenance compared with discontinuation of agonist replacement therapies. The more appropriate comparison, however, would be between discontinuation of naltrexone and discontinuation of long-term abstinence because in both cases the former heroin user has remained free of opioids and thus there is significant loss of tolerance and greater risk of overdose. In the present study, several participants used heroin after receiving the depot injections, but there was no evidence that attempts to override the blockade were successful, and no accidental or intentional opioid overdoses occurred. In fact, a previous study[37] demonstrated that the incidence of opioid overdoses dramatically decreased in "high-risk" adolescents treated with an implantable form of naltrexone. Another study by the same research group,[38] using a larger sample size, also showed that the incidence of opioid overdose decreased after administration of a naltrexone implant, even beyond the period of expected effectiveness of the implant. It is possible that the gradual dissipation of naltrexone from these sustained-release formulations protected these patients from experiencing opioid overdose.

Another potential concern regarding use of a sustained-release formulation of naltrexone is that the use of nonopioid drugs may increase. This phenomenon apparently did not occur in the present study because other drug use remained relatively low throughout the study. These data are consistent with other studies[39,40] demonstrating that other drug use declines when patients stop using heroin. However, one study[38] concluded that sedative and perhaps other drug "overdoses" may increase after administration of a naltrexone implant. Several of the sedative overdoses occurred soon after implant administration, suggesting that the presence of residual opioid withdrawal symptoms may have prompted the use of benzodiazepines. Because patients who met the criteria for current dependence on other drugs of abuse were excluded from the present study, it is difficult to conclude confidently that other drug use does not increase after treatment with sustained-release naltrexone. Future studies with a more heterogeneous drug-abusing population should carefully assess potential changes in the amounts and patterns of other drug use.

Potential AEs that may be unique to sustained-release formulations of naltrexone include the possibility that patients will attempt to remove the medication and tissue reactions around the site of drug administration. In the present study, none of the participants attempted to remove the medication. This particular risk is lower for injectable depot formulations of naltrexone because patients are informed beforehand that it is impossible to remove the medication once it is administered. With implantable formulations of naltrexone, some reports, although rare, exist of patients attempting to remove the medication. Regarding tissue reactions around the site of injections, the formulation of depot naltrexone used in the present study was well tolerated. In the 2 patients dropped from the study because of injection site reactions, the severity was considered to be moderate, and both reactions resolved spontaneously over time.

Impairment in liver function is a common concern with naltrexone therapy because early studies[41] suggested that high doses of naltrexone may produce hepatotoxicity. However, several subsequent studies,[42-45] including those

conducted in alcoholic individuals and in patients with severe liver disease, generally have not shown clinically significant changes in liver function after treatment with naltrexone. Except for a patient who was diagnosed as having new-onset hepatitis C after depot naltrexone administration, clinically significant elevations in liver enzyme levels did not occur in the present study, and neither did they occur in a previous study[15] with the same formulation of depot naltrexone. The hepatitis resolved uneventfully in the patient who received 192 mg of depot naltrexone just before being diagnosed as having hepatitis C. A similar case was reported in a patient who received a naltrexone implant.[46] These results are particularly reassuring given the high prevalence of hepatitis C among injecting heroin users.[47]

In summary, the present results demonstrate that this injectable, sustained-release formulation of naltrexone is safe, well tolerated, and effective in retaining patients in treatment. An increase in treatment retention is particularly important because it will allow clinicians sufficient time to engage patients in psychotherapy so that they can learn to make other psychological and social adjustments that support a life without opioids. Medication noncompliance has been cited as a major problem with oral naltrexone therapy, making firm conclusions regarding the efficacy of naltrexone in the treatment of opioid dependence difficult.[48] One reason for high treatment dropout is that discontinuation of naltrexone ingestion has no negative physical consequences, as opposed to discontinuation of agonist maintenance therapies, which results in the emergence of opioid withdrawal symptoms. For most opioid abusers, the decision of whether to take a medication that produces no psychoactive effects or to "get high" is a difficult one. The availability of sustained-release formulations of naltrexone holds the promise of allowing patients to circumvent their ambivalence to taking the medication and to focus instead on other issues relevant to sustaining abstinence.

Submitted for Publication: February 16, 2005; final revision received July 25, 2005; accepted August 18, 2005.
Correspondence: Sandra D. Comer, PhD, New York State Psychiatric Institute and College of Physicians and Surgeons of Columbia University, 1051 Riverside Dr, Unit 120, New York, NY 10032 (sdc10@columbia.edu).
Funding/Support: This research was supported by center grants P50 DA09236 and P60 DA05186 from the National Institute on Drug Abuse (NIDA) (Bethesda, Md) and the VA/NIDA Interagency Agreement at Philadelphia VA Medical Center. Biopharmaceutical Research Consultants Inc received funding for data management and statistical support under contract N01DA-1-8817, and the University of Utah and Northwest Toxicologies Inc received funding for bioanalytical support under contract N01DA-3-8829 from NIDA.
Previous Presentation: This study was presented in part at the annual meeting of the College on Problems of Drug Dependence; June 15, 2004; San Juan, Puerto Rico.
Acknowledgment: We thank Pamela Parris, Meredith Kelly, Sarah Dubner, and Andre Roche for their assistance with data collection; Randi Adelman, RN, and Gary Pagliaro, RN, for their medical assistance; Edward Nunes, MD, and Kenneth Carpenter, PhD, for reviewing an early draft of the manuscript; and Elie Nuwayser, PhD, and James Kerrigan, MS, of BIOTEK, Inc, for providing instructions on the proper methods of preparing, administering, and storing Depotrex, as well as their ongoing advice during the study. Finally, we thank C. Nora Chiang, PhD, and Richard L. Hawks, PhD, for their scientific advice throughout the study.

REFERENCES

1. Office of Applied Studies. *Emergency Department Trends From the Drug Abuse Warning Network, Preliminary Estimates January-June 2001 With Revised Estimates 1994 to 2000*. Rockville, Md: Substance Abuse and Mental Health Services Administration; 2002. DAWN series D-20; DHHS publication SMA 02-3634.
2. Office of Applied Studies. *Results From the 2001 National Household Survey on Drug Abuse: Volume I: Summary of National Findings*. Rockville, Md: Substance Abuse and Mental Health Services Administration; 2002. NHSDA series H-17; DHHS publication SMA 02-3758.
3. Office of Applied Studies. *Results From the 2001 National Household Survey on Drug Abuse: Volume II: Technical Appendices and Selected Data Tables*. Rockville, Md: Substance Abuse and Mental Health Services Administration; 2002. NHSDA series H-18; DHHS publication SMA 02-3759.
4. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend*. 2003;69:215-232.
5. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther*. 1988;247:47-53.
6. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*. 1992;267:2750-2755.
7. Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry*. 1996;53:401-407.
8. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry*. 1994; 151:1025-1030.
9. Azatian A, Papiasvilli A, Joseph A. A study of the use of clonidine and naltrexone in the treatment of opioid addiction in the former USSR. *J Addict Dis*. 1994; 13:35-52.
10. Callahan EJ, Rawson RA, McCleave B, Arias R, Glazer M, Liberman RP. The treatment of heroin addiction: naltrexone alone and with behavior therapy. *Int J Addict*. 1980;15:795-807.
11. Kosten TR, Kleber HD. Strategies to improve compliance with narcotic antagonists. *Am J Drug Alcohol Abuse*. 1984;10:249-266.
12. Capone T, Brahen L, Condren R, Kordal N, Melchionda R, Peterson M. Retention and outcome in a narcotic antagonist treatment program. *J Clin Psychol*. 1986; 42:825-833.
13. Kranzler HR, Wesson DR, Billot L. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. *Alcohol Clin Exp Res*. 2004;28:1051-1059.
14. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA*. 2005; 293:1617-1625.
15. Comer SD, Collins ED, Kleber HD, Nuwayser ES, Kerrigan JH, Fischman MW. Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology (Berl)*. 2002;159:351-360.
16. Lachin JM. Worst-rank score analysis with informatively missing observations in clinical trials. *Control Clin Trials*. 1999;20:408-422.
17. Abrahams RA, Ronel SH. Biocompatible implants for the sustained zero-order release of narcotic antagonists. *J Biomed Mater Res*. 1975;9:355-366.
18. Alim TN, Tai B, Chiang CN, Green T, Rosse RB, Lindquist T, Deutsch SI. Tolerability study of a depot form of naltrexone substance abusers. In: Harris LS, ed. *Problems of Drug Dependence 1994*. Vol 2. Washington, DC: National Institute on Drug Abuse; 1995:253. NIDA research monograph 153; NIH publication 95-3883.
19. Chiang CN, Hollister LE, Gillespie HK, Foltz RL. Clinical evaluation of a naltrexone sustained-release preparation. *Drug Alcohol Depend*. 1985;16:1-8.
20. Chiang CN, Kishimoto A, Barnett G, Hollister LE. Implantable narcotic antagonists: a possible new treatment for narcotic addiction. *Psychopharmacol Bull*. 1985;21:672-675.
21. Harrigan SE, Downs DA. Pharmacological evaluation of narcotic antagonist de-

livery systems in rhesus monkeys. In: Willete RE, Barnett G, eds. *Narcotic Antagonists: Naltrexone Pharmacochemistry and Sustained-Release Preparations*. Washington, DC: National Institute on Drug Abuse; 1981:77-92. NIDA research monograph 28.
22. Heishman SJ, Francis-Wood A, Keenan RM, Chiang CN, Terrill JB, Tai B, Henningfield JE. Safety and pharmacokinetics of a new formulation of naltrexone. In: Harris LS, ed: *Problems of Drug Dependence 1993*. Vol 2. Washington, DC: National Institute on Drug Abuse; 1994. NIDA research monograph 141; NIH publication 94-3749.
23. Martin W, Sandquist VL. A sustained release depot for narcotic antagonists. *Arch Gen Psychiatry*. 1974;30:31-33.
24. Meyer MC, Straughn AB, Lo M-W, Schary WL, Whitney CC. Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. *J Clin Psychiatry*. 1984;45:15-19.
25. Bardo MT, Bhatnagar RK, Gebhart GF. Chronic naltrexone increases opiate binding in brain and produces supersensitivity to morphine in the locus coeruleus of the rat. *Brain Res*. 1983;289:223-234.
26. Bardo MT, Neisewander JL. Chronic naltrexone supersensitizes the reinforcing and locomotor-activating effects of morphine. *Pharmacol Biochem Behav*. 1987; 28:267-273.
27. Paronis CA, Holtzman SG. Increased analgesic potency of mu agonists after continuous naloxone infusion in rats. *J Pharmacol Exp Ther*. 1991;259:582-589.
28. Paronis CA, Holtzman SG. Sensitization and tolerance to the discriminative stimulus effects of mu-opioid agonists. *Psychopharmacology (Berl)*. 1994;114: 601-610.
29. Tempel A, Gardner EL, Zukin RS. Neurochemical and functional correlates of naltrexone-induced opioid receptor up-regulation. *J Pharmacol Exp Ther*. 1985; 232:439-444.
30. Tempel A, Zukin S, Gardner EL. Supersensitivity of brain opiate receptor subtypes after chronic naltrexone treatment. *Life Sci*. 1982;31:1401-1404.
31. Yoburn BC, Inturrisi CE. Modification of the response to opioid and nonopioid drugs by chronic opioid antagonist treatment. *Life Sci*. 1988;42:1689-1696.
32. Young AM, Mattox SR, Doty MD. Increased sensitivity to rate-altering and discriminative stimulus effects of morphine following continuous exposure to naltrexone. *Psychopharmacology (Berl)*. 1991;103:67-73.
33. Unterwald EM, Rubenfeld JM, Imai Y, Wang J-B, Uhl GR, Kreek MJ. Chronic opioid antagonist administration upregulates mu opioid receptor binding without altering mu opioid receptor mRNA levels. *Brain Res Mol Brain Res*. 1995;33: 351-355.
34. Cornish JW, Henson D, Levine S, Volpicelli J, Inturrisi C, Yoburn B, O'Brien CP. Naltrexone maintenance: effect on morphine sensitivity in normal volunteers. *Am J Addict*. 1993;2:34-38.
35. Ritter AJ. Naltrexone in the treatment of heroin dependence: relationship with depression and risk of overdose. *Aust N Z J Psychiatry*. 2002;36:224-228.
36. Digiusto E, Shakeshaft A, Ritter A, O'Brien S, Mattick RP; NEPOD Research Group. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction*. 2004;99:450-460.
37. Hulse GK, Tait RJ. A pilot study to assess the impact of naltrexone implant on accidental opiate overdose in "high risk" adolescent heroin users. *Addict Biol*. 2003;8:337-342.
38. Hulse GK, Tait RJ, Comer SD, Sullivan MA, Jacobs IG, Arnold-Reed D. Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants. *Drug Alcohol Depend*. 2005;79:351-357.
39. Dunteman GH, Condelli WS, Fairbank JA. Predicting cocaine use among methadone patients: analysis of findings from a national study. *Hosp Community Psychiatry*. 1992;43:608-611.
40. Fairbank JA, Dunteman GH, Condelli WS. Do methadone patients substitute other drugs for heroin? predicting substance use at 1-year follow-up. *Am J Drug Alcohol Abuse*. 1993;19:465-474.
41. Malcolm R, O'Neil PM, Sexauer JD, Riddle FE, Currey HS, Counts C. A controlled trial of naltrexone in obese humans. *Int J Obes*. 1985;9:347-353.
42. Brahen LS, Capone TJ, Capone DM. Naltrexone: lack of effect on hepatic enzymes. *J Clin Pharmacol*. 1988;28:64-70.
43. Croop RS, Faulkner EB, Labriola DF. The safety profile of naltrexone in the treatment of alcoholism. *Arch Gen Psychiatry*. 1997;54:1130-1135.
44. Marrazzi MA, Wroblewski JM, Kinzie J, Luby ED. High-dose naltrexone and liver function safety. *Am J Addict*. 1997;6:21-29.
45. Sax DS, Kornetsky C, Kim A. Lack of hepatoxicity with naltrexone treatment. *J Clin Pharmcol*. 1994;34:898-901.
46. Brewer C, Wong JS. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. *Addict Biol*. 2004;9:81-87.
47. Freeman AJ, Zekry A, Whybin LR, Harvey CE, van Beek IA, de Kantzow SL, Rawlinson WD, Boughton CR, Robertson PW, Marinos G, Lloyd AR. Hepatitis C prevalence among Australian injecting drug users in the 1970s and profiles of virus genotypes in the 1970s and 1990s. *Med J Aust*. 2000;172:588-591.
48. Kirchmayer U, Davoli M, Verster AD, Amato L, Ferri M, Perucci CA. A systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence. *Addiction*. 2002;97:1241-1249.