

RAPID COMMUNICATION

Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study

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This 12-week study examined the bioavailability, tolerability, and potential efficacy of an injectable sustained-release preparation (SRP) of naltrexone (NTX). Twenty alcohol-dependent subjects took NTX 50 mg po daily for 2 weeks, followed by a 2-week, no-medication Washout Period, a 4-week Injection Period, and a 4-week Follow-up Period. Fifteen subjects (75%) received a single subcutaneous injection of 206 mg of sustained-release NTX, and five subjects (25%) received a placebo injection. All subjects also received eight weekly coping skills sessions during the Oral NTX, and the Washout and Injection Periods. **Results:** After injection, NTX plasma concentrations exceeded a mean of 1 ng/ml for 21 days. Adverse effects produced by the SRP of NTX were comparable with those resulting from oral NTX therapy. Compared with placebo, the SRP of NTX significantly reduced the frequency of heavy drinking days during the Injection and Follow-up Periods. **Conclusions:** The results of this preliminary study support the potential clinical utility of the SRP of NTX for treatment of alcohol dependence.

Key Words: Naltrexone, Sustained-Release Preparation, Alcoholism, Alcohol Dependence, Pharmacotherapy.

NALTREXONE (NTX), an opioid antagonist, reduces alcohol consumption in alcohol-dependent patients.^{1,2} Despite these early results, more recent findings indicate that, as in opioid addicts,³ the effectiveness of NTX in alcoholics is limited by problems with compliance. Recent studies by Chick⁴ and Volpicelli et al.⁵ failed to show an overall advantage for NTX. In these studies, the active medication was superior to placebo (PLA) in reducing alcohol consumption only among highly compliant subjects. Although compliance with a variety of medications is often problematic,⁶ the importance of these findings is underscored by the fact that alcoholics show particularly low rates of medication compliance.^{7,8}

One approach to ensuring medication compliance is the

use of a sustained-release preparation (SRP), which may also increase the likelihood of a therapeutic response by yielding a more predictable and constant plasma concentration than oral drug administration.⁹ A parenterally administered SRP may also result in a higher brain concentration of the parent compound by bypassing hepatic metabolism.⁹

Chiang et al.¹⁰ administered a 63-mg, sustained-release NTX bead preparation to three healthy male volunteers. Concentrations of NTX were highest on the first day after subcutaneous administration and then fell to 0.2 to 0.4 ng/ml from day 2 until the end of the experiment (23 to 32 days after implantation). Local irritation occurred in two of the subjects. In a subsequent study, Chiang et al.¹¹ found relatively constant plasma concentrations of NTX (0.30 to 0.46 ng/ml) and 6- β -naltrexol (0.64 to 1.07 ng/ml) for 2 to 4 weeks after implantation, concentrations that partially or completely blocked the effects of intravenous challenges with 15 mg of morphine.

More recently, an SRP of NTX that uses biodegradable, injectable microcapsules was administered to four healthy volunteers with no reported adverse effects.¹² Alim et al.¹³ administered the same microcapsule preparation subcutaneously to 8 cocaine-dependent subjects: 2 received a PLA injection, 3 received 103 mg of NTX, and 3 received 206 mg of NTX. Patients in the NTX and PLA groups reported mild pain during the first few days after injection, with erythema and induration occurring commonly. The present study examined the bioavailability, tolerability, and potential efficacy of this microcapsule SRP of NTX (produced by BIOTEK, Inc., Woburn, MA) in alcohol-dependent subjects.

METHODS

Procedures

Twenty alcohol-dependent subjects participated in this 12-week study. After a minimum of 3 days of abstinence from alcohol, all subjects underwent 2 weeks of treatment with 50 mg/day of oral NTX (Oral NTX Period) to identify those individuals who could not tolerate the medication. Subjects then entered a 2-week, medication-free Washout Period, followed by random assignment to receive one injection of either depot NTX (15 subjects, 75%) or placebo (5 subjects, 25%), which was expected

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Received for publication January 28, 1998; accepted April 6, 1998

This study was supported by the National Institutes of Health Grants AA03510, AA07290, AA00239, and RR06192 (General Clinical Research Center).

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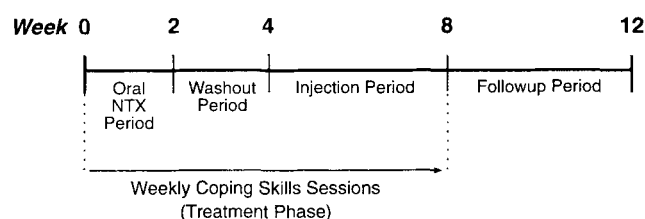


Fig. 1. Timeline of study periods.

to deliver medication for 4 weeks (Injection Period). The first 8 weeks of the study (which included the 2-week Oral NTX Period, the 2-week Washout Period, and the 4-week Injection Period) were designated as the Treatment Phase, because during this time all subjects also received weekly, individual coping skills psychotherapy.^{14,15} After the 8-week Treatment Phase, all subjects underwent two research assessments over a 4-week Follow-up Period. Figure 1 shows a timeline of each subject's participation.

Assessments

The Michigan Alcoholism Screening Test,¹⁶ Addiction Severity Index,¹⁷ and Alcohol Dependence Scale¹⁸ were administered at study entry to evaluate alcoholism severity and alcohol treatment history. The Time-Line Follow-Back Assessment method¹⁹ was used to quantify drinking days, heavy drinking days (≥ 4 drinks in a day for females and ≥ 5 drinks in a day for males), and total alcohol consumption during the 4-week Pretreatment Period and for each period of the 12-week study. γ -Glutamyltranspeptidase (GGTP) levels were obtained at the same intervals to validate reported alcohol consumption.

Three assessments were repeated weekly during the 8-week Treatment Phase: breath alcohol testing, the Systematic Assessment for Treatment Emergent Events²⁰ to monitor adverse events, and the Beck Depression Inventory²¹ to measure recent depressive symptoms.

Subjects

Subjects were recruited through advertisements. All subjects gave written, informed consent to participate. After screening, subjects were evaluated using the Structured Clinical Interview for DSM-IV,²² clinical laboratory tests (CBC, urinalysis, blood chemistries, and, for women, a serum pregnancy test), and a physical examination. Inclusion criteria were age 18 to 60 years, ability to read English, and a current DSM-IV diagnosis of Alcohol Dependence.²³ Exclusion criteria were a current DSM-IV diagnosis of drug dependence (other than nicotine), a lifetime diagnosis of opioid dependence, psychoactive drug use in the preceding month, no stable residence, evidence of a major psychiatric or medical illness, pregnancy, or lack of birth control. As shown in Table 1, there were no significant between-group differences on any demographic or clinical variables. All subjects were Caucasian.

Treatment

Prior to injection, the microcapsule preparation was reconstituted in a suspending medium, to a total volume of 2.4 ml. The preparation was administered subcutaneously as a single injection in the gluteal region. The active SRP contained 206 mg of NTX, the maximal dose previously administered to humans.¹³ The PLA preparation contained vehicle and microcapsules, but no NTX. A research pharmacist randomly assigned subjects to a medication group, with double-blind conditions maintained throughout the study.

Laboratory Analysis

Blood was collected nine times over the course of the 8 weeks after injection (i.e., during the Injection and Follow-up Periods). Solid-phase

Table 1. Pretreatment Demographic and Clinical Features by Medication Group

	NTX (n = 15)	PLA (n = 5)	Test	p
Demographics				
Gender (% male)	73.3	80.0	FET	1.00
Employment (% full time)	66.7	80.0	FET	1.00
Marital status (% married)	80.0	40.0	FET	0.13
Age (years)	47.0 (9.0)	48.2 (4.3)	$F = 0.08$	0.77
Education (years)	14.9 (2.8)	15.0 (4.1)	$F = 0.00$	0.96
Clinical Features				
BDI* score	1.7 (2.5)	1.0 (1.7)	$F = 0.24$	0.63
DSM-IV† criteria	4.9 (1.0)	5.2 (1.3)	$F = 0.24$	0.63
MAST‡ score	21.9 (8.4)	24.0 (14.0)	$F = 0.17$	0.69
ADS§ score	13.1 (3.1)	15.2 (8.2)	$F = 0.49$	0.49
Years of heavy drinking#	19.8 (10.6)	23.2 (7.2)	$F = 0.44$	0.51
Prior treatments for alcoholism#	0.47 (0.64)	0.80 (0.45)	$F = 1.15$	0.30

* BDI, Beck Depression Inventory (Beck et al., 1961).

† Alcohol Dependence Criteria (American Psychiatric Association, 1994).

‡ MAST, Michigan Alcohol Screening Test (Selzer, 1971).

§ ADS, Alcohol Dependence Scale (Skinner and Allen, 1982).

From the Addiction Severity Index (McLellan et al., 1988).

extraction and derivitization, followed by gas chromatography-negative ion chemical ionization-mass spectrometry, were used to measure plasma concentrations of NTX and 6- β -naltrexol.²⁴ The precision and accuracy of this procedure have previously been demonstrated.²⁴

Data Analysis

A two-tailed criterion of $p < 0.05$ was used to define statistical significance. One-way analysis of variance (ANOVA) was used to compare groups on continuous measures and Fisher's Exact Test (FET) was used for categorical measures. Paired t tests were used to compare mean weekly adverse effects during the Oral NTX Period with those occurring during the Injection and Follow-up Periods. The Pearson correlation coefficient was used to examine the degree of association between changes in GGTP level and changes in total alcohol consumption during the Oral/Washout, Injection, and Follow-up Periods and to examine the association between adverse effects and changes in alcohol consumption.

Hierarchical multiple regression was used to examine the effect of the SRP (i.e., NTX versus PLA) on adverse effects and drinking outcomes, after controlling for the respective measures during the Oral NTX and Washout Periods. Measures from these periods were entered into the analyses prior to medication group to examine change from the time of random assignment through the end of the study (i.e., the only time over which the injection could have exerted its effects). Because drinking measures from the Pretreatment Period did not contribute significantly to the variance in drinking outcomes during the study, they were not included in the regression equations. Regression analyses were conducted separately for the Injection and Follow-up Periods. Based on prior reports,^{1,2} we hypothesized that the SRP of NTX would exert its greatest effects on the percentage of heavy drinking days.

RESULTS

Plasma Concentrations

Plasma concentrations of NTX and 6- β -naltrexol were obtained after the Washout Period (i.e., immediately prior to the depot injection), and then a mean of 1, 3, 8, 13, 20, 27, 34, 42, and 64 days after the injection. As can be seen in Fig. 2, the mean plasma NTX concentration exceeded 1 ng/ml, the concentration thought to produce opioid antag-

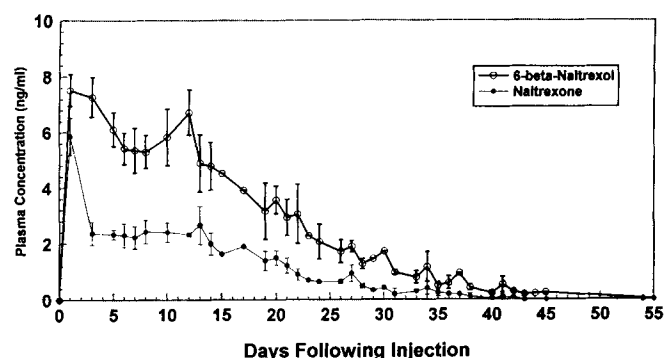


Fig. 2. Naltrexone and 6- β -naltrexol plasma concentrations after a single depot injection in 15 alcoholics. Values are mean (SEM) for days on which multiple measurements were taken.

onist effects,^{10,25} for 21 days after the active SRP was administered.

Medication Tolerance

Seven subjects [5 NTX (33.3%) and 2 PLA (40%)] complained of a burning sensation at the time of the injection (FET = 0.59). In three of these cases (2 NTX and 1 PLA), soreness at the injection site persisted over the week after injection. An area of induration was evident at the injection site among 13 subjects [11 NTX (73%) and 2 PLA (40%) (FET = 0.29)], with the size of the induration ranging from 0.5 cm (NTX subject) to 4.0 cm (PLA subject) in diameter. The induration resolved completely to palpation over a period of 2.8 (SD = 1.3) weeks (range = 1 to 5 weeks).

Nine subjects [2 PLA (40%) and 7 NTX (46.7%)] reported other adverse effects during the Injection Period (FET = 0.60). The mean number of weekly complaints during this period was 0.40 (SD = 0.54) for the PLA group and 1.33 (SD = 1.95) for the NTX group. Adverse effects reported after depot NTX were comparable in frequency to those reported during the Oral NTX Period (mean = 1.80, SD = 1.82, paired $t_{14} = 1.07$, $p = 0.30$). Although the number of adverse effects during the Oral NTX Period predicted the number of adverse effects during the Injection Period [$\beta = 0.457$, $F(1,18) = 4.74$, $p = 0.043$], the depot NTX and PLA groups did not differ significantly on this measure [$\beta = 0.257$, $F(1,16) = 1.59$, $p = 0.23$].

Of the adverse effects reported during the Injection Period, fatigue was most common ($n = 3$: no PLA subjects and 20% of NTX subjects), followed by complaints of mood changes ($n = 2$: no PLA subjects and 13.3% of NTX subjects). Rash, palpitations, headache, nausea, vertigo, and insomnia were each reported by one NTX subject. No complaints of a severe nature were reported during the Injection Period. All adverse effects resolved spontaneously.

During the Follow-up Period, eight NTX subjects (40%) and no PLA subjects reported adverse effects (FET = 0.051). The mean number of weekly complaints by NTX subjects during this period was 1.27 (SD = 1.67), which

Table 2. Means for Drinking Measures by Study Period and Medication Group Prior to Depot Injection

	NTX (<i>n</i> = 15)	PLA (<i>n</i> = 5)	<i>p</i> Value*
Pretreatment Period (4 weeks)			
% drinking days	68.1 (19.1)	71.3 (16.1)	0.73
% heavy drinking days	50.2 (30.0)	64.7 (29.0)	0.36
Average drinks/day	4.9 (3.6)	6.1 (4.0)	0.61
Oral NTX Period (2 weeks)			
% drinking days	11.4 (14.9)	5.8 (7.4)	0.44
% heavy drinking days	2.9 (9.3)	0	0.51
Average drinks/day	0.3 (0.5)	0.1 (0.2)	0.37
Washout Period (2 weeks)			
% drinking days	21.0 (24.3)	19.1 (19.4)	0.88
% heavy drinking days	7.3 (13.6)	0	0.26
Average drinks/day	0.8 (1.1)	0.5 (0.6)	0.57

* Using ANOVA.

does not differ statistically from the comparable measure during the Oral NTX Period (paired $t_{14} = 0.81$, $p = 0.43$). There was a trend for the number of complaints reported during the Follow-up Period to be correlated with both the number of complaints during the Oral NTX Period [$\beta = 0.455$, $F(1,18) = 4.22$, $p = 0.055$] and with the medication group [$\beta = 0.402$, $F(1,16) = 4.16$, $p = 0.059$]. During the Follow-up Period, 1 NTX subject reported severe vomiting, which resolved spontaneously.

Validation of Self-Reported Drinking

NTX subjects' GGTP levels ($n = 15$) declined from 40.9 units/liter (SD = 28.9) at baseline to 29.4 units/liter (SD = 21.3) for the Injection Period and 30.1 units/liter (SD = 21.4) for the Follow-up Period. PLA subjects' levels ($n = 4$; one subject failed to provide one specimen) declined from 43.0 units/liter (SD = 19.9) at baseline to 33.5 units/liter (SD = 16.4) for the Injection Period and 38.5 units/liter (SD = 7.1) for the Follow-up Period. Between-group comparisons of GGTP levels were nonsignificant (p 's all > 0.10). However, change in GGTP level was significantly correlated with change in total alcohol consumption during the Oral and Washout Periods combined [$r = 0.48$, $p = 0.017$] and during the Injection Period [$r = 0.47$, $p = 0.021$]. There was also a trend for an association between the change in these measures during the Follow-up Period [$r = 0.33$, $p = 0.084$].

Drinking Measures

Table 2 shows drinking measures for the three study periods preceding the depot injection. ANOVA revealed no between-group differences on these measures (p 's all > 0.10).

Table 3 shows drinking measures for the Injection and Follow-up Periods. These comparisons control for the corresponding measures during the Oral NTX and Washout Periods.

Injection Period. During the Injection Period, the percentage of drinking days was predicted by the comparable

Table 3. Means for Drinking Measures by Study Period and Medication Group after Depot Injection

	NTX (n = 15)	PLA (n = 5)	p Value*
Injection Period (4 weeks)			
% drinking days	21.0 (25.5)	28.4 (34.5)	0.42
% heavy drinking days	3.7 (10.7)	5.3 (8.4)	0.03
Average drinks/day	0.7 (0.6)	0.9 (1.2)	0.08
Follow-up Period (4 weeks)			
% drinking days	28.2 (35.8)	44.6 (31.4)	0.58
% heavy drinking days	7.8 (18.2)	23.0 (32.8)	0.04
Average drinks/day	1.1 (1.7)	1.9 (1.7)	0.04

* Using linear regression, controlling for the corresponding measures during the Oral NTX and Washout Periods.

measure during the Oral NTX [$\beta = 0.72$, $F(1,18) = 19.25$, $p < 0.001$] and Washout [$\beta = 1.31$, $F(1,17) = 27.80$, $p < 0.001$] Periods. The medication group did not affect this measure [$\beta = -0.09$, $F(1,16) = 0.70$, $p = 0.42$].

The percentage of heavy drinking days during the Injection Period was predicted by the comparable measure during the Oral NTX Period [$\beta = 0.84$, $F(1,18) = 40.54$, $p < 0.001$], but not by heavy drinking days during the Washout Period [$\beta = 0.47$, $F(1,17) = 3.85$, $p = 0.067$]. However, as hypothesized, the SRP of NTX produced a significantly lower percentage of heavy drinking days during the Injection Period [$\beta = -0.26$, $F(1,16) = 5.46$, $p = 0.034$], an effect (f^2) = 0.269.²⁶

Mean drinks/day during the Injection Period was predicted by the comparable measure during both the Oral NTX Period [$\beta = 0.70$, $F(1,18) = 17.63$, $p = 0.001$] and the Washout Period [$\beta = 0.74$, $F(1,17) = 13.45$, $p = 0.002$]. There was a trend [$\beta = -0.23$, $F(1,16) = 3.4$, $p < 0.083$] for the SRP of NTX to reduce the mean number of drinks/day during the Injection Period.

Follow-up Period. During the Follow-up Period, there was a trend for the percentage of drinking days to be predicted by the comparable measure during the Oral NTX Period [$\beta = 0.45$, $F(1,18) = 4.45$, $p = 0.05$]. The comparable measure during the Washout Period was a significant predictor [$\beta = 1.65$, $F(1,17) = 24.72$, $p < 0.001$]. However, there was no effect of the SRP of NTX on the percentage of drinking days during the Follow-up Period [$\beta = -0.09$, $F(1,16) = 0.32$, $p = 0.58$].

The percentage of heavy drinking days during the Follow-up Period was predicted by the comparable measure during the Oral NTX Period [$\beta = 0.56$, $F(1,18) = 8.25$, $p = 0.010$], but not by heavy drinking days during the Washout Period [$\beta = 0.05$, $F(1,17) = 0.02$, $p = 0.88$]. Again, as hypothesized, individuals receiving the SRP of NTX had significantly fewer heavy drinking days during the Follow-up Period [$\beta = -0.43$, $F(1,16) = 5.18$, $p = 0.037$], an effect (f^2) = 0.245.²⁶

The mean number of drinks/day during the Follow-up Period was predicted by the comparable measure during both the Oral NTX Period [$\beta = 0.55$, $F(1,18) = 7.71$, $p = 0.012$] and the Washout Period [$\beta = 0.71$, $F(1,17) = 7.12$, $p = 0.016$]. A significant advantage for the SRP of NTX on

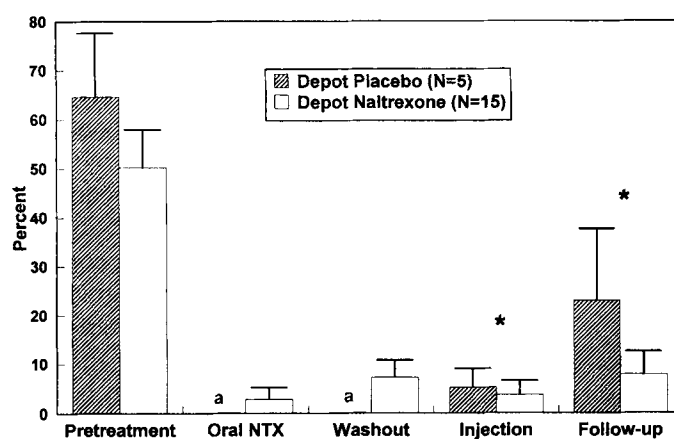


Fig. 3. Percent (mean + SEM) heavy drinking days by medication group and study period. * $p < 0.05$, after controlling for heavy drinking days during the Oral NTX and Washout Periods. ^aNo heavy drinking by placebo subjects during the Oral NTX and Washout Periods.

this outcome measure emerged during the Follow-up Period [$\beta = -0.35$, $F(1,16) = 5.01$, $p = 0.040$], an effect (f^2) = 0.239.²⁶

Relations Between Adverse Events and Changes in Alcohol Consumption

When correlations between the number of adverse events reported and the change in each of the three drinking measures were examined separately for the Injection and Follow-up Periods, all were found to be nonsignificant (r 's all < 0.34 , p 's all > 0.10).

Integrity of the Double Blind

When subjects were asked to judge which medication they received, the majority (12, or 60%) guessed incorrectly. One PLA subject (20%) and 7 NTX subjects (46.7%) correctly identified their medication assignment (FET = 0.60).

DISCUSSION

This study provides preliminary evidence for the bioavailability, tolerability, and efficacy of an SRP of NTX for the treatment of alcohol dependence. A clinically significant effect of NTX on the frequency of heavy drinking was evident during the 4-week Injection Period. This effect persisted during the 4-week Follow-up Period (Fig. 3). An effect of similar magnitude was observed on the mean number of drinks per day, but only during the Follow-up Period. GGTP level did not differ by treatment group, which may be due to the fact that GGTP levels are a relatively insensitive measure of alcohol consumption,²⁷ and they were only modestly elevated in this subject sample at baseline. However, correlations with GGTP level observed herein support the validity of self-reported alcohol consumption. Because participants were no better able to

identify the medication they received and there was no correlation between adverse events and changes in self-reported drinking, it appears that there was a direct pharmacological effect of the SRP of NTX on alcohol consumption.

Olsen and Kincl²⁸ listed the following criteria for an ideal NTX sustained-delivery system: ease of administration, absence of an adverse tissue reaction, a relatively constant release of the drug for at least 30 days, and biodegradation within a short time after that. Using these criteria, the microcapsule formulation described herein, although promising, is not ideal. The volume of fluid that was injected produced discomfort. Although the induration lasted beyond the immediate Injection Period, in all cases it resolved spontaneously within 5 weeks of injection. Because an NTX concentration in excess of 1 ng/ml was maintained for 21 days, this preparation can be expected to block opioid agonist effects for at least that long.^{10,25} Furthermore, NTX was detectable in plasma, and clinical effects were present for >30 days after injection.

Although during the Follow-up Period, there was a trend toward a greater number of adverse effects among subjects receiving the active injection, the frequency of adverse effects of the SRP of NTX was comparable with that of oral NTX. Furthermore, the lack of association between adverse and therapeutic effects suggests that it may be feasible to increase tolerability without reducing the efficacy of the preparation. For example, by reducing the total dose of NTX in each injection, the volume injected and the peak plasma concentration would be reduced, which could reduce adverse effects. However, more frequent injections would be required to sustain the therapeutic effects.

Given the small number of subjects included and the fact that each subject received only one dose of the SRP, this study provides only preliminary data on this formulation of NTX. Nonetheless, a number of clinically significant therapeutic effects were observed. These were demonstrable despite the low level of drinking that was evident during the Oral NTX and Washout Periods, which served as the baseline against which the effects of the injection were evaluated. A larger study of this SRP should include patients with a wide range of alcohol dependence severity. Furthermore, because the medication effects were obtained in the context of weekly, individual psychotherapy, it may also be useful to evaluate the SRP in conjunction with a less intensive psychosocial intervention.

Based on the findings reported herein, an SRP of NTX may have an important place in the treatment of alcohol dependence, particularly in light of variable compliance with the oral medication in this patient population.^{4,5} Additional study of this formulation appears warranted. Ultimately, comparison with oral NTX therapy should help to determine which individuals might be most likely to benefit from the SRP of NTX.

ACKNOWLEDGMENTS

The authors thank the staff of the Clinical Research and Evaluation Unit, Alcohol Research Center, University of Connecticut School of Medicine, for their assistance in the conduct of this study. Special thanks go to Roberta Gline for help in conducting the clinical trial and Jeffrey Van Kirk, J.D., M.S., for help with data analysis. Joseph Burleson, Ph.D., Nancy Petry, Ph.D., and Cheryl Oncken, M.D., provided helpful comments on the manuscript.

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