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ORIGINAL INVESTIGATION

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Depot naltrexone: long-lasting antagonism of the effects of heroin in humans

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Abstract *Rationale:* Naltrexone, an opioid antagonist, is currently approved as a treatment for heroin dependence. However, naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment. A sustained-release form of naltrexone may improve compliance. *Objective:* The present study was designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®). *Methods:* Twelve heroin-dependent individuals participated in an 8-week inpatient study. After a 1-week detoxification period, six participants received 192 mg naltrexone base and six participants received 384 mg naltrexone base. For safety, the low dose of depot naltrexone was tested before the high dose. The effects of heroin (0, 6.25, 12.5, 18.75, 25 mg, IV) were evaluated for the next 6 weeks. One dose of heroin was tested per day on Mondays through Fridays, and the entire dose range was tested each week. Active heroin doses were administered in ascending order during the week, while placebo could be administered on any day. Subjective, performance, and physiological effects were measured both before and after heroin administration. The hypotheses were that depot naltrexone would antagonize the effects of heroin, and that the high dose of depot naltrexone would produce a more effective and longer-lasting antagonism than the low dose. *Results:* The low and high doses of depot naltrexone antagonized heroin-induced subjective ratings for 3 and 5 weeks, respectively. Plasma levels of naltrexone remained above 1 ng/ml for approximately 3 and 4 weeks after administration of 192 mg and 384 mg naltrexone. Other than the initial discomfort associated with the injection of depot naltrexone, there were no untoward side-effects. *Conclusions:* These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.

Keywords Heroin · Human · Naltrexone · Opioid · Subjective effect · Sustained-release · Depotrex

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Introduction

Naltrexone, an orally effective opioid antagonist, was approved in 1984 by the Food and Drug Administration as a maintenance medication for the treatment of heroin dependence. Naltrexone potently antagonizes the effects of opioid agonists, while producing no agonist effects of its own (Jaffe and Martin 1990). Tolerance does not develop to naltrexone's antagonist effects and the drug has few side effects, even after chronic administration of over 1 year (Kleber et al. 1985). Because of its ability to antagonize the effects of mu opioid agonists, its long duration of action, and its favorable pharmacokinetic and metabolic characteristics (Martin et al. 1966, 1973), naltrexone initially held great promise as a treatment for opioid dependence. The early rationale for using a pure antagonist was that once the individual was maintained on naltrexone, subsequent attempts to self-administer the illicit opioid would not produce euphoria (Wikler 1965; Martin et al. 1966) and the user would eventually discontinue opioid use altogether.

Although the use of naltrexone as a maintenance therapy for opioid abuse can be effective (Martin et al. 1973; O'Brien et al. 1975; Judson et al. 1981), it has been used most successfully with only a select subpopulation of highly motivated individuals. Because of the problems with medication non-compliance, naltrexone therapy has not lived up to its initial promise. This may be in part because opioid users are accustomed to self-administering potent reinforcers, and, by contrast, the complete absence of opioid-induced reinforcing effects may be unacceptable. Another factor that may contribute to noncom-

Table 1 Participant demographics. Numbers in parentheses represent+1 SEM

	192 mg naltrexone	384 mg naltrexone
Age (average; years)	33.8 (2.5)	29.2 (3.2)
Years of heroin use (average)	10.7 (2.5)	9.1 (3.5)
Amount spent for heroin (average; $/day)	$39 (4)	$55 (12)
Tobacco cigarette use (range; no. per day)	8–20	10–20
Cocaine use (range; occasions/week)	0–1	0–3
Amphetamine use (range; occasions/week)	0–1	0
Marijuana use (range; occasions/week)	0–1	0–3
Alcohol use (range; occasions/week)	0–1	0–3
Sedative use (range; occasions/week)	0–1	0–1

pliance is that, unlike methadone, discontinuation of naltrexone maintenance has no adverse consequences (e.g. withdrawal effects). Furthermore, naltrexone itself may induce adverse neuropsychiatric and gastrointestinal effects, such as dysphoria, nausea, and abdominal pain (Hollister et al. 1981; Crowley et al. 1985; Oncken et al. 2001).

Sustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness (Martin and Sandquist 1974; Abrahams and Ronel 1975; Chiang et al. 1985a, 1985b). Chiang et al. (1985a, 1985b), for example, administered biodegradable beads containing a dose of 63 mg naltrexone to normal, healthy volunteers. Following an initial burst of release, this formulation yielded relatively constant plasma levels of naltrexone (0.3–0.5 ng/ml) for up to 1 month. However, when these investigators administered challenge doses of morphine (15 mg IM), the results were variable. In some participants, morphine was completely ineffective, while in others, morphine-like effects were observed. In addition, three of the five participants who completed the study developed tissue inflammation near the site of bead implantation (Chiang et al. 1985b). Although the adverse tissue reaction and the variable antagonist effectiveness of the naltrexone beads limited its clinical utility, the rationale behind the development of a sustained-release form of naltrexone was sound.

A new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side-effects (Heishman et al. 1994; Alim et al. 1995; Kranzler et al. 1998). In an early tolerability study, Alim and colleagues (1995) reported blockade of the physiological and subjective effects of 10 mg intravenous (IV) morphine in cocaine-dependent participants who received 206 mg depot naltrexone; side-effects associated with naltrexone were minimal in these participants. Kranzler and colleagues (1998) further showed that 206 mg depot naltrexone significantly reduced the percentage of heavy drinking days in alcoholics. Adverse effects reported after depot naltrexone were comparable to those reported after oral naltrexone administration. Although this formulation of depot naltrexone appears to be safe and effective in treating alcohol dependence, it has not yet been tested with heroin. The purpose of the current study was 1) to determine whether the new formulation of depot naltrexone will antagonize the effects of heroin at doses comparable to those used on the streets today, and 2) to assess the duration of antagonist effect of 192 mg and 384 mg depot naltrexone. The hypothesis was that depot naltrexone would dose-dependently antagonize the effects of heroin.

Materials and methods

Participants

Fifteen heroin-dependent men, who were not seeking treatment for their drug use, began the 8-week protocol. Three participants left the study prior to depot naltrexone administration: one was discharged for aggressive behavior toward the staff, and two left for personal reasons. Twelve participants (eight non-Hispanic Caucasian, three Hispanic, and one African American) completed the study: six received 192 mg depot naltrexone, and six received 384 mg depot naltrexone (Table 1). The low dose of depot naltrexone was tested in the first six participants. The groups did not differ in age, years of heroin use, and amount of money spent on heroin per day. All participants had experience using heroin IV. One participant in the low-dose group and two in the high-dose group preferred to use heroin intranasally; all other participants preferred to use heroin IV. All participants were dependent on heroin at the start of the study, as verified by a naloxone challenge test (Wang 1974).

After an initial telephone interview, eligible participants completed detailed questionnaires on drug use, general health and medical history, and a medical and psychological evaluation in the laboratory. An electrocardiogram and Mantoux test or chest X-ray were also performed. Routine laboratory analyses included a blood chemistry panel, thyroid function test, syphilis and hepatitis (A, B, and C) screening, and urinalysis. Urine drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines) were also performed using a radiative energy attenuation and fluorescence polarization immunoassay system (AD_x System; Abbott Laboratories, Abbott Park, Ill., USA). Participants were told that they would be detoxified from heroin during the first week of the study, that they would receive one of two doses of a depot formulation of naltrexone, and that a range of IV heroin doses would be tested each week for the 6 weeks following depot naltrexone administration.

Participants were excluded from the study if they were seeking drug treatment, dependent on alcohol or illicit drugs other than opioids, or had a major Axis I psychiatric diagnosis other than opioid dependence. Those who had recent histories of violence or who were on parole/probation were excluded from the study. Participants were required to be physically healthy, and fully able to perform all study procedures. Although both men and women were screened for the study, none of the women met the eligibility requirements. Prior to admission, participants completed a training session, during which the study procedures were explained to them in detail. Volunteers were paid $25 per inpatient day and an additional $25 per day bonus if they completed the study. Participants signed consent forms describing the aims of the study, and

the potential risks and benefits of participation. Free HIV testing and education were offered, and during the last week of the study, participants were offered referrals for treatment. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI).

Apparatus

During experimental sessions, participants were seated in a room equipped with Macintosh computers. All computer activities, vital signs and behaviors were continuously monitored by the experimenters in an adjacent control room via a continuous on-line computer network, video cameras, and vital signs monitors (cardiovascular function was measured using a Sentry II Vital Signs Monitor, NBS Medical, Costa Mesa, Calif., USA; arterial oxygen saturation was measured using a pulse oximeter Model 400, Palco Laboratories, Santa Cruz, Calif., USA). Communication between the staff and participants was kept to a minimum during experimental sessions.

Detoxification procedures

Participants were admitted into the hospital, and detoxified during the first week after admission. Buprenorphine (8 mg sublingual tablet; National Institute on Drug Abuse, Rockville, Md., USA) was administered on the first 1–2 days after admission. Two days after the last buprenorphine dose, oral naltrexone (DuPont Pharma, Wilmington, Del., USA) was administered for 3 consecutive days (25, 50, and 50 mg per day) to ensure that participants were willing and able to tolerate its effects. Clonidine HCl (0.2 mg PO, every 6 h; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn., USA), ketorolac tromethamine (30 mg IM, every 6 h; Roche Laboratories, Nutley, N.J., USA), prochlorperazine (10 mg PO or IM, every 8 h; SmithKline Beecham Consumer Healthcare, Pittsburgh, Penn., USA) and clonazepam (2 mg PO, every 8 h; Roche Laboratories) were available, as needed, during the detoxification week. Thereafter, trazodone (50–100 mg PO, at bedtime; Warner Chilcott, Morris Plains, N.J., USA) was available if participants reported having trouble sleeping. Depot naltrexone was administered on a Monday morning, 2 days after the last oral naltrexone dose.

General procedures

The effects of IV heroin (placebo, 6.25, 12.5, 18.75, and 25 mg) were evaluated each week for 6 weeks following depot naltrexone administration. The entire dose range was tested each week, and one dose of heroin was tested each day on weekdays. For safety, active heroin doses were administered in ascending order within each week, with the exception that the day of placebo injection was varied across weeks. On the day that depot naltrexone was administered, placebo was tested during the experimental session.

Experimental sessions

During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate and blood pressure were measured every 2 min, and blood oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. Participants received breakfast between 0800 and 0900 and lunch between 1230 and 1330 hours. Experimental sessions occurred between 0930 and 1130 hours. Participants were not allowed to smoke tobacco cigarettes during experimental sessions.

Physiologic, subjective and performance effects were measured both before and after drug administration (see descriptions below). Heroin or placebo was administered only if vital signs were within safe limits (SpO_2 >93%). A photograph was taken of the right pupil before and 4, 10, 20, 40 and 60 min after drug administration. The subjective-effects battery (see description below) was administered before and 4, 40 and 90 min after drug administration. The performance battery (see description below) was administered before and 10 and 60 min after drug administration. The Subjective Opioid Withdrawal Scale was administered before drug administration. The Drug Effects Questionnaire was administered 90 min after drug administration.

Subjective measures

Four questionnaires were used to assess subjective effects throughout the experimental sessions. The first questionnaire was a 26-item visual analog scale (VAS) designed to assess subjective and physiological effects (modified from Foltin and Fischman 1995). The first 18 lines were labeled with adjectives describing mood states (e.g., “I feel...:” “high”) and four additional lines, labeled with questions about the dose just received (i.e. “I liked the dose,” “For this dose, I would pay”). Participants also indicated, by making a mark along a 100 mm line, how much they “wanted” each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rated each item on the VAS from “Not at all” (0 mm) to “Extremely” (100 mm), except for the “For this dose, I would pay” question, which ranged between $0 (0 mm) to $20 (100 mm). The second questionnaire was a 13-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects (e.g. “My skin is itchy,” etc.; Fraser et al. 1961; Foltin and Fischman 1992). The VAS and opioid symptom checklist together constituted the subjective-effects battery. The third questionnaire was the 16-item Subjective Opioid Withdrawal Scale (SOWS; Handelsman et al. 1987). Participants rated each item on a scale from 0 to 4, with 0 being “Not at all” and 4 being “Extremely” (e.g. “I have gooseflesh,” etc.). The fourth questionnaire was a 6-item Drug Effects Questionnaire (DEQ; Evans et al. 1995). Participants described drug effects by selecting among a series of possible answers ranging from 0 (“No effects at all”) to 4 (“Very strong (good, bad, etc.) effects”). Ratings of drug liking ranged between –4 (“Dislike very much”) to 4 (“Like very much”).

Task battery

The task battery consisted of four tasks: the first task was a 3-min digit-symbol substitution task, during which participants were required to emulate a series of patterns on a keypad (McLeod et al. 1982). The second task was a 10-min divided attention task, which consisted of concurrent pursuit-tracking and vigilance tasks (Miller et al. 1988). The third task was a 10-min rapid information processing task, during which a series of digits was displayed rapidly on the computer screen (100 digits/min), and participants were instructed to press a key as quickly as possible after three consecutive odd or even digits (Wesnes and Warburton 1983). The fourth task was a 3-min repeated acquisition of response sequences task, during which four buttons were illuminated, and participants were instructed to learn a ten-response sequence of button presses (Kelly et al. 1993).

Physiological measures

A blood pressure cuff was attached to the non-dominant arm, which recorded automatically every 2 min. Participants were also connected to a pulse oximeter via a soft sensor on a finger of the dominant hand, which monitored arterial blood oxygen saturation ($\%SpO_2$). For safety, supplemental oxygen (2 l/min) was provided via a nasal cannula during all experimental sessions. A specially modified Polaroid camera with a close-up lens (×2 magnification) was used to take pupil photographs. All photographs were taken under ambient lighting conditions. Horizontal and vertical measurements of pupil diameter were made using calipers, and then these two measurements were averaged and divided by 2 to correct for the ×2 magnification.

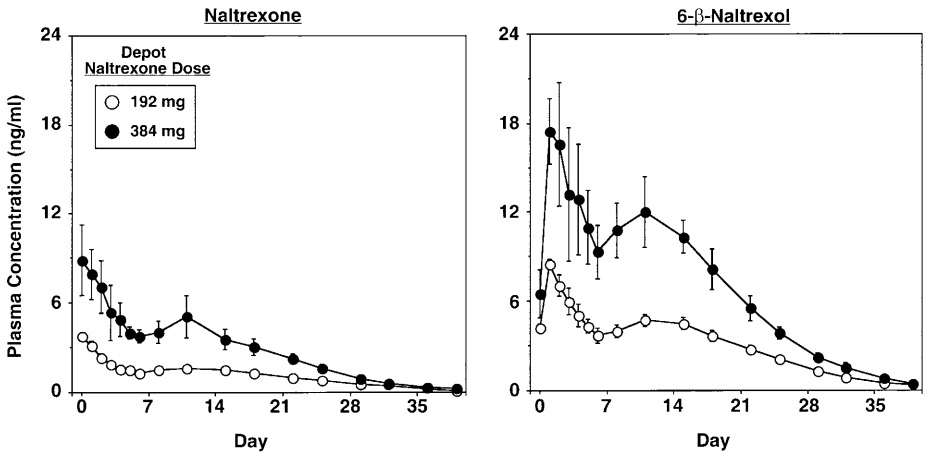

Fig. 1 Mean plasma levels of naltrexone (*left panel*) and 6-β-naltrexol (*right panel*) as a function of depot naltrexone dose and days after administration of depot naltrexone. Data points represent the mean across 6 participants per group. Error bars represent±1 SEM

Blood was drawn 2 h, 1, 2, 3, 4, 5, 6, 8, 11, 15, 18, 22, 25, 29, 32, 36, and 39 days after administration of depot naltrexone, and immediately centrifuged at 3000 rpm for 15 min. Plasma was drawn off and stored at –20°C until it was shipped by overnight mail on dry ice for analyses of naltrexone and 6-β-naltrexol (Center for Human Toxicology, University of Utah, Salt Lake City, Utah, USA). Analyses were performed by solid phase extraction and negative ion chemical ionization gas chromatography/mass spectrometry, as described by Huang and colleagues (1997). The lower limit of detectability for both analytes was 0.1 ng/ml.

Blood was also drawn prior to, and at weekly intervals after administration of depot naltrexone for analyses of liver enzymes (AST, ALT, GGT).

Drugs

Depot naltrexone (Depotrex®) was manufactured by Biotek Inc. (Woburn, Mass., USA) and provided by the National Institute on Drug Abuse. Depotrex is a registered trademark of Biotek, Inc. 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. The active formulation contained drug equivalent to 192 mg naltrexone base. The placebo formulation contained the equivalent weight in polymer microspheres. Injections were administered subcutaneously into the buttocks (one injection per buttock), using an 18 gauge needle. 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). For safety, the low dose of Depotrex was tested in the first six participants, and the high dose of Depotrex was tested in the next six participants.

Heroin HCl was provided by the National Institutes on Drug Abuse and prepared by the Columbia-Presbyterian Medical Center research pharmacy. A 25 mg/ml heroin concentration was prepared in a 5% dextrose solution to enhance stability. Dose calculations were based on the hydrochloride salt form. Heroin was stored in a freezer and used within 3 months of preparation. The stock solution was diluted in 5% dextrose to produce each dose. Placebo (5% dextrose solution) or heroin (6.25, 12.5, 18.75, and 25 mg) was administered intravenously over a 30-s period in a total volume of 2 ml. Heroin doses were administered in a double-blind fashion. Physiological saline solution was infused continuously during experimental sessions, except during drug administration. Between 1 and 2 ml heparinized saline (10 IU/ml) was flushed into the catheter four to eight times each day. All venous catheters were maintained as heplocks and were removed within 72 h of insertion.

Supplemental medications available to all participants for the duration of the study included: Mylanta, acetaminophen, ibuprofen, Colace, Milk of Magnesia and multi-vitamins with iron.

Morning urine samples were collected daily and one random sample per week was screened for the presence of other illicit substances. No illicit substances were found in the participants' urine samples.

Statistical analyses

Repeated-measures analyses of variance (ANOVA) with planned comparisons were used to address the following questions: 1) What was the duration of antagonism of heroin's effects? 2) Did the low and high doses of depot naltrexone differ in ability to antagonize the effects of heroin? In order to address the first question, the data for each group were analyzed separately as a function of week (1–6) and heroin dose (0, 6.25, 12.5, 18.75, 25 mg). Twenty-five planned comparisons were made: each week (2–6) was compared to week 1 for each dose (e.g. placebo-week 2 versus placebo-week 1, placebo-week 3 versus placebo-week 1, placebo-week 4 versus placebo-week 1, etc.) because it was likely that virtually complete antagonism would occur during week 1. In order to address the second question, an overall analysis was performed with one between-group factor (group) and two within-group factors (week, heroin dose): the main effect of group, and the week×group and dose×group effects were evaluated. Interaction effects were examined using post-hoc comparisons. Peak subjective ratings, peak performance effects, trough pupil diameter, liver enzyme levels, average arterial oxygen saturation, and plasma levels of naltrexone and 6-β-naltrexol were analyzed. Liver enzymes (AST, ALT, GGT) were also analyzed: each week post-depot naltrexone was compared to a pre-depot naltrexone baseline. Due to an excessive number of missing data points, the cardiovascular data were not analyzed. To control for type I errors, a modified Bonferroni test was used in that only those comparisons with $P<0.01$ were considered statistically significant.

Results

Plasma drug levels

Figure 1 shows mean plasma levels of naltrexone (left panel) and 6-β-naltrexol (right panel) for each group as a function of time since the depot naltrexone injection. Two hours after administration of 192 mg and 384 mg depot naltrexone, plasma levels of naltrexone were 3.8 (±0.2) and 8.9 (±1.4) ng/ml. Plasma levels of 6-β-naltrexol were 8.5 (±0.3) and 17.4 (±1.3) ng/ml, respectively, 24 h after administration of 192 mg and 384 mg depot naltrexone. Across individual participants, plasma levels

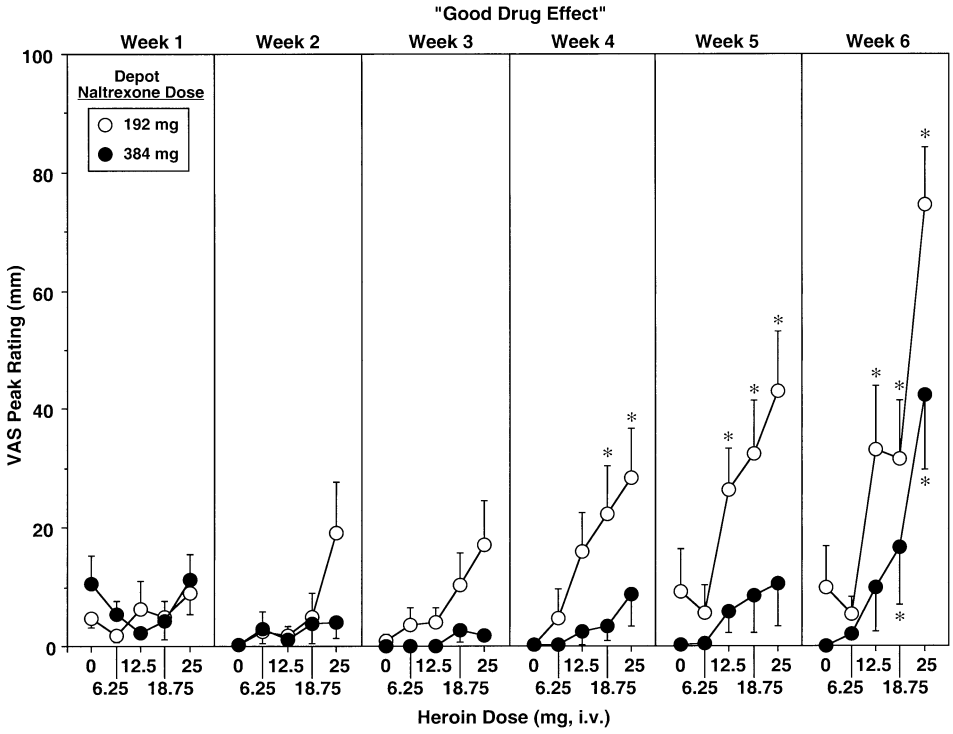

Fig. 2 Mean peak VAS ratings of "Good Drug Effect" after administration of heroin (0–25 mg) as a function of depot naltrexone dose and study week (week 1: *left panel*; week 6: *right panel*). Maximum rating=100 mm. Data points represent mean peak ratings (n=6 per group). Error bars represent±1 SEM. * Indicates significant differences from week 1

of naltrexone ranged between 3.1 and 4.5 ng/ml after administration of 192 mg depot naltrexone, and 5.6 and 14.2 ng/ml after administration of 384 mg depot naltrexone. After administration of 192 mg and 384 mg of depot naltrexone, plasma levels of naltrexone were less than 1 ng/ml on day 22 and 29, respectively. The group and group×day effects for naltrexone [group: $F(1,10)$= 48.5, P<0.0001; group×day: $F(1,10)$=8.6, P<0.0001] and 6-β-naltrexol [group: $F(1,10)$=33.8, P<0.0002; group× day: $F(1,10)$=8.3, P<0.0001] were significant.

Subjective effects

Figure 2 shows mean peak visual analog scale ratings of "Good Drug Effect" for each group as a function of heroin dose and week. After low-dose depot naltrexone, ratings of "Good Drug Effect" significantly increased by week 4, relative to week 1, after administration of 18.75 mg [$F(1,100)$=6.4, P<0.01] and 25 mg heroin [$F(1,100)$=7.9, P<0.006]; ratings of "Good Drug Effect" significantly increased by week 5 after administration of 12.5 mg heroin [$F(1,100)$=8.4, P<0.004]. In the high-dose group, ratings of "Good Drug Effect" did not significantly increase until week 6, after 18.75 mg [$F(1,100)$=7.5, P<0.007] and 25 mg heroin [$F(1,100)$= 47.3, P<0.0001]. Both the week×group [$F(5,50)$=4.8, P<0.001] and dose×group [$F(4,40)$=4.4, P<0.005] effects were significant for ratings of "Good Drug Effect." Several other VAS ratings showed a similar pattern including ratings of "High," "Liking," drug "Potency," drug "Quality," and how much they would be willing to pay for the dose (data not shown). The dose×group effect was significant [$F(4,40)$=4.2, P<0.006], and the week×group effect approached statistical significance [$F(5,50)$=2.9, P<0.02] for ratings of "High." Although ratings tended to be higher in the low-dose group for VAS ratings of "Liking," drug "Potency," and drug "Quality," the week×group and dose×group effects were not statistically significant for these items.

VAS ratings of "I feel..." "Gooseflesh," "Depressed," "Muscle Pain," "Anxious," and "Restless" were elevated in both groups during the first week after receiving depot naltrexone, and were higher in the high-dose group (data not shown). The week×group effect was statistically significant for ratings of "Gooseflesh" [$F(5,50)$=3.4, P<0.01] and "Depressed" [$F(5,50)$=3.5, P<0.009], while the week×group effect for ratings of "Muscle Pain" (P<0.03), "Anxious" (P<0.04), and "Restless" (P<0.04) approached statistical significance. Ratings of "I Want Heroin," which did not vary across study weeks or heroin doses, were significantly elevated in the high-dose group [main effect of group: $F(1,10)$=26.3, P<0.0004]. Ratings of "I Want Heroin" ranged between 26 and 37 in the low-dose group, and 86 and 95 in the high-dose group.

The pattern of results obtained from the opioid symptom checklist and DEQ (data not shown) were similar to the VAS ratings of "Good Drug Effect" (Fig. 2) in that total scores on the opioid symptom checklist and DEQ ratings of drug "Liking," "Good Drug Effect," strength of drug effect, and desire to take the drug again increased as a function of heroin dose and across study weeks. The week×group effect was statistically significant for the opioid symptom checklist [$F(5,50)$=3.2, P<0.01]. Although ratings tended to be higher in the

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