

# A Controlled Trial of Naltrexone Augmentation of Nicotine Replacement Therapy for Smoking Cessation

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**Background:** Many smokers remain refractory to current therapies, which only partially address weight gain after smoking cessation. Thus, this study evaluated whether naltrexone hydrochloride augmentation of nicotine patch therapy improves smoking abstinence and reduces postcessation weight gain more than nicotine patch therapy alone and at what dose.

**Methods:** Six-week double-blind placebo-controlled trial with follow-up in an outpatient research center. Four hundred individuals who smoked 20 or more cigarettes daily were randomly assigned to treatment for 6 weeks with a 21-mg nicotine patch and oral naltrexone hydrochloride (0, 25, 50, or 100 mg/d) after equal random treatment assignment and followed up for 1 year after randomization. The a priori specified primary end points were prolonged 4-week cigarette abstinence after a 2-week grace period in the intent-to-treat sample and weight gain in these abstainers.

**Results:** We found no significant differences in prolonged 4-week abstinence ( $P=.49$ ) or 6-week continu-

ous abstinence after the quit date ( $P=.12$ ) during treatment in the intent-to-treat analysis. Among 295 treatment completers, the 100-mg dose was associated with higher continuous abstinence rates (71.6%) compared with placebo (48%) (odds ratio, 2.73; 95% confidence interval, 1.39-5.39;  $P<.01$ ). Among continuous abstainers, the 25-mg naltrexone hydrochloride group gained significantly less weight (mean  $\pm$  SEM,  $0.7 \pm 0.31$  kg) than the placebo group (mean  $\pm$  SEM,  $1.9 \pm 0.33$  kg;  $P<.01$ ). Similar naltrexone dose effects on weight were found for those with prolonged abstinence and treatment completers, irrespective of abstinence.

**Conclusions:** The 100-mg dose of naltrexone hydrochloride appears the most promising for augmenting the efficacy of the nicotine patch on smoking cessation outcomes but requires further study. The significant weight reduction with low-dose naltrexone therapy suggests that it may be useful as a second-line treatment for weight-concerned smokers.

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**T**HE CLINICAL PRACTICE guidelines for treating tobacco use and dependence from the Agency for Healthcare Research and Quality recommend screening for tobacco use and treating all tobacco users.<sup>1</sup> Although pharmacological interventions for tobacco dependence are available, many patients remain refractory to approved treatments. Moreover, although advised to quit, many smokers are reluctant because of the perceived risk of gaining weight after smoking cessation,<sup>2,3</sup> a problem only partially addressed by current therapies.

Naltrexone hydrochloride, an opiate antagonist, has the potential to promote smoking cessation and reduce weight gain based on the documented role of the endogenous opioid system in regulating these behaviors.<sup>4</sup> However, clinical trials of naltrexone therapy for smoking cessation have

been small in scale and inconclusive,<sup>5-9</sup> leading a recent Cochrane review<sup>10</sup> to conclude that larger trials are needed. Moreover, to our knowledge, only 1 published study has reported effects on weight gain.<sup>9</sup> Finally, no clinical trial we are aware of has examined the effects of naltrexone as a function of dose, with most studies using the 50-mg dose approved for alcoholism and opiate dependence.

Thus, we designed the first large, prospectively randomized dose-ranging study of naltrexone for smoking cessation. Naltrexone was tested in combination with the nicotine patch, a treatment to reduce nicotine withdrawal and aid smoking cessation, based on data suggesting that opioid antagonists can precipitate a withdrawal syndrome in nicotine-dependent animals<sup>11</sup> and human subjects.<sup>12</sup> Our a priori specified hypotheses were that, compared with placebo, naltrexone would increase 4-week prolonged absti-

nence rates after a 2-week grace period in the intent-to-treat (ITT) population and reduce weight gain in those who abstained from smoking during the last 4 weeks of treatment.

## METHODS

### PARTICIPANTS

We enrolled 400 cigarette smokers, including 344 at the University of Connecticut Mental Health Center, Farmington, and 56 at the Veterans Affairs Connecticut Healthcare System, Newington. Institutional review board approval was obtained from the Veterans Affairs Connecticut Healthcare System, Yale University School of Medicine, New Haven, Conn, and the University of Connecticut Health Center. We recruited subjects via advertisements, press releases, and mailings to physicians. Eligible smokers were 18 years or older, spoke English, weighed at least 45 kg ( $\geq 100$  lb), smoked 20 or more cigarettes daily for at least 1 year, and had an expired carbon monoxide (CO) level of 10 ppm or more and at least 1 previous quit attempt. One person per household could enroll. Women were excluded if pregnant, nursing, or not using reliable birth control. Other exclusion criteria were unstable cardiac disease; history of dermatoses; aspartate aminotransferase or alanine aminotransferase levels of more than 3 times the reference range or elevated bilirubin levels; current serious neurological, psychiatric, or medical illness; use of psychotropic medications; current alcohol dependence; use of opiates; drug screen findings that were positive for an opiate, pain conditions requiring use of opiates, or current use of other tobacco products or smoking cessation medications.

### PROCEDURES

After giving written informed consent, patients underwent baseline assessments, a physical examination, and laboratory testing. Eligible participants were randomized in blocks to treatment arms, with stratified (for sex) randomization implemented after the first 150 participants to ensure that the important predictor, sex, would be distributed similarly among treatment groups. Random sequence was provided to the pharmacist, who assigned participants; others were blinded to treatment assignment.

### MEDICATION CONDITIONS

Participants received 21-mg transdermal nicotine patches (Nicoderm CQ, GlaxoSmithKline, Research Triangle Park, NC) for 6 weeks, beginning on their quit date. They also received placebo or 1 of the following 3 dosages of naltrexone hydrochloride (Depade; Mallinckrodt Pharmaceuticals, Hazelwood, Mo): 25, 50, or 100 mg/d. Naltrexone hydrochloride dosages were titrated during the first week (12.5 mg for 1 day, 25 mg for 1 day, 50 mg for 2 days, and 100 mg thereafter) to the target dose. Naltrexone medication in opaque capsules was dispensed in bottles, with the first 7 doses in individual glassine envelopes within the bottle. Participants began naltrexone therapy on the second day of nicotine patch therapy approximately 4 hours after patch placement, when steady-state nicotine levels would be close to peak. On subsequent days, they took naltrexone and replaced their patch at the same time. Dose reductions or discontinuation of the drug based on tolerability were permitted with the option to continue nicotine patch therapy and counseling.

### COUNSELING

The counseling was developed from clinical practice guidelines<sup>1</sup> and was based on protocols of the National Cancer Institute.<sup>13</sup>

The first session with the nurse lasted 45 minutes, and subsequent weekly sessions with a research assistant supervised by an investigator (J.L.C.) lasted 15 minutes. A handout described the benefits of quitting smoking relative to the risk of weight gain and tips to eat a balanced diet, drink water, and exercise.

### ASSESSMENTS

Participants completed a core battery with questions about demographics, smoking variables, mood, alcohol use, and other areas of functioning. Diagnostic information was obtained with the Fagerstrom Test for Nicotine Dependence,<sup>14</sup> an alcohol screening questionnaire (Alcohol Use Disorders Identification Test),<sup>15</sup> and the Structured Clinical Interview for DSM-IV [Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition] Axis I Disorders, Research Version, Patient Edition<sup>16</sup> alcohol and depression modules. At each weekly appointment, weight, CO levels, and reports of daily tobacco and alcohol consumption were obtained, the latter using the Timeline Follow-back Interview beginning 30 days before screening.<sup>17</sup> Alcohol consumption will be presented in future reports. Serum cotinine level was measured at intake and posttreatment follow-ups. Other weekly self-reports included the Questionnaire of Smoking Urges,<sup>18</sup> Center for Epidemiological Studies Depression Scale,<sup>19</sup> and Minnesota Nicotine Withdrawal Scale.<sup>20</sup>

A checklist of common adverse events for naltrexone and nicotine patch therapy was administered weekly with other concerns elicited with questioning. Liver function test results were obtained at intake and 1, 4, and 6 weeks after randomization.

Naltrexone therapy compliance was monitored with eDEM caps, which recorded the time of bottle openings (APREX [AARDEX USA], Union City, Calif). The percentage of days compliant equaled the number of days on which the bottle was opened divided by 41 (the number of possible doses). Levels of naltrexone and 6- $\beta$ -naltrexol, a metabolite of naltrexone used as an independent compliance marker, were measured by means of high-performance liquid chromatography<sup>21</sup> at 1 and 4 weeks after the quit date.

Follow-up assessments similar to weekly assessments were conducted 3, 6, and 12 months after randomization.

### STATISTICAL CONSIDERATIONS

All patients who were randomized and attended their first session at which study medications were dispensed constituted the primary ITT population. Although this population served as the primary population for analysis of smoking abstinence, secondary analyses were conducted in treatment completers, defined as those who attended the final treatment session. The following 2 major smoking cessation outcomes were specified: (1) prolonged 4-week abstinence following a 2-week grace period after the quit date and (2) continuous 6-week abstinence from the quit date. Self-reported abstinence (not even a puff) was verified by an exhaled CO level of 10 ppm or less. Participants who dropped out or missed multiple appointments were considered failures. A single missed appointment was coded as abstinent only if abstinence was verified at the appointments before and after the missed session. For baseline group comparisons,  $\chi^2$  tests and analyses of variance were used for categorical and continuous variables, respectively. Smoking abstinence outcomes (yes or no) were analyzed using the logistic regression model, with the treatment variable coded such that each naltrexone plus nicotine patch assignment was compared with the placebo plus nicotine patch assignment. Exploratory analyses of 7-day point prevalence abstinence at the posttreatment follow-up periods were conducted using the same approach.

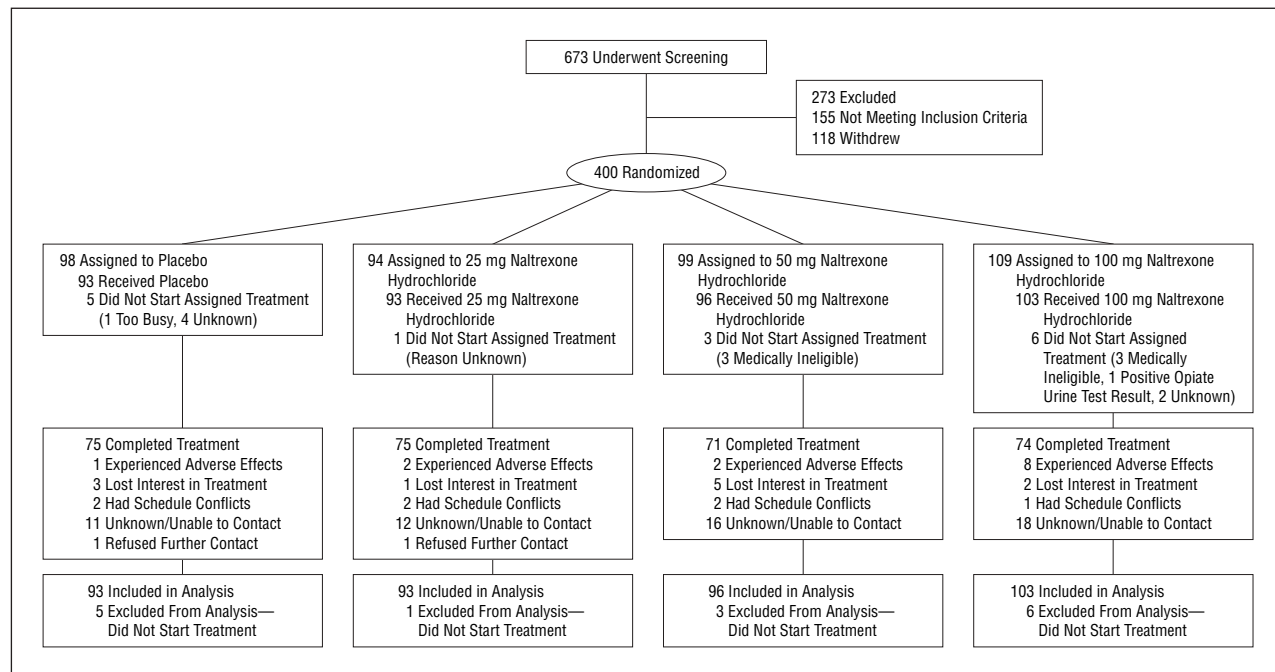


Figure 1. Study participant flow.

Change in weight from baseline was analyzed with 1-way analyses of variance general linear models with planned comparisons between each dose and placebo for abstainers and treatment completers. A sensitivity analysis was performed using a linear mixed-effects model with weight as the response and time, treatment, and time  $\times$  treatment entered as fixed effects with baseline weight entered as a covariate.<sup>22</sup>

Secondary analyses of cigarettes smoked per week, craving, depression, and withdrawal were analyzed using linear mixed-effects models with planned contrasts between each dose and placebo over time. Given the secondary nature of these analyses, we did not require that the overall test be significant to examine the contrasts with placebo.

This study was powered to detect a moderate effect size of  $w=0.25$  (power=0.80;  $\alpha=.017$ ), with a sample size of 200 for each comparison of placebo and active drug. With the prespecified  $\alpha$ , the 3 preplanned comparisons of each active drug dose vs placebo were accounted for during the planning of the study. No other adjustments to sample size due to multiple comparisons of multiple primary end points were made in the planning phase. Interim monitoring to assess safety and efficacy was performed by an independent data and safety monitoring board. We implemented a 2-look investigation of the primary efficacy end points, using a strict significance level of .005 at the first look roughly halfway through enrollment, to maintain virtually all of the initially specified significance for the final analysis. We used SAS software, version 8.0 for Windows,<sup>23</sup> and S-Plus, version 6.1 for Windows.<sup>24</sup> All *P* values are 2-tailed.

## RESULTS

### BASELINE CHARACTERISTICS

Figure 1 presents the flow of participants. Recruitment occurred from November 1, 2000, through April 2, 2003. Of 400 subjects randomized, 385 attended their first session and constitute the ITT sample. Baseline characteristics were comparable for the 4 groups (Table 1).

### TREATMENT EXPOSURE

The groups were similar on the percentage of participants who completed treatment (Figure 1;  $P=.34$ ), number of counseling appointments attended, and number of weeks nicotine patch therapy was used (Table 2). As the dose increased, there were nonsignificant trends toward a decrease in the number of weeks when naltrexone was used ( $P=.10$ ) and the percentage of days compliant ( $P=.06$ ) and a significant difference in the percentage of subjects who reduced or discontinued naltrexone therapy ( $P=.01$ ).

Serum naltrexone and 6- $\beta$ -naltrexol concentrations were approximately dose proportional (Table 2). Concentrations of the parent drug and metabolite at the highest (100-mg) dose were slightly lower than would be predicted by linear disposition, which may reflect slightly poorer compliance at this dose. Naltrexone and 6- $\beta$ -naltrexol concentrations and the percentage positive for 6- $\beta$ -naltrexol did not differ significantly between 1 and 4 weeks.

### SMOKING ABSTINENCE

There was no significant naltrexone effect on prolonged abstinence across the last 4 weeks of the trial for any dose in the ITT population (Table 3). The analysis of continuous abstinence across the 6-week trial revealed a nonsignificant dose trend ( $P=.12$ ) that favored the 100-mg group compared with the placebo group ( $P=.07$ ).

In the secondary population of 295 treatment completers, the 4 groups differed significantly on continuous abstinence ( $P=.007$ ). Treatment completers in the 100-mg group were significantly more likely to be continuously abstinent (71.6%) compared with those in the placebo group (48.0%;  $P=.004$ ).

**Table 1. Baseline Characteristics by Treatment Condition\***

Characteristic	Placebo Group (n = 93)	Naltrexone Hydrochloride Groups			P Values
		25 mg (n = 93)	50 mg (n = 96)	100 mg (n = 103)	
Age, y	45.9 ± 1.16	45.2 ± 1.16	45.2 ± 1.14	47.2 ± 1.10	.55
Female, No. (%)	47 (50.5)	45 (48.4)	46 (47.9)	47 (45.6)	.92
White, No. (%)	83 (89.2)	85 (91.4)	81 (84.4)	87 (84.5)	.36
BMI	27.8 ± 0.52	27.6 ± 0.52	27.6 ± 0.51	28.0 ± 0.49	.94
Education, No. (%)					.10
High school graduate or less	33 (37.5)	35 (38.9)	28 (30.4)	45 (45.5)	
Some education after high school	42 (47.7)	33 (36.7)	37 (40.2)	31 (31.3)	
≥College graduate	13 (14.8)	22 (24.4)	27 (29.3)	23 (23.2)	
Marital status, No. (%)					.31
Married or cohabitating	53 (57.0)	53 (57.6)	52 (55.3)	62 (60.2)	
Divorced or separated	14 (15.1)	17 (18.5)	24 (25.5)	27 (26.2)	
Never married	23 (24.7)	21 (22.8)	16 (17.0)	13 (12.6)	
Widowed	3 (3.2)	1 (1.1)	2 (2.1)	1 (1.0)	
Full-time employment, No. (%)	65 (71.4)	64 (72.7)	62 (70.5)	77 (77.0)	.75
No. of cigarettes smoked per day	26.9 ± 1.15	28.1 ± 1.18	26.4 ± 1.15	28.2 ± 1.08	.62
Years of smoking cigarettes	29.3 ± 1.13	29.1 ± 1.14	28.3 ± 1.12	30.2 ± 1.08	.66
No. of previous attempts to quit	7.6 ± 1.56	5.1 ± 1.54	5.7 ± 1.57	8.2 ± 1.52	.41
Expired CO level, ppm	25.3 ± 1.03	25.0 ± 1.03	24.7 ± 1.01	24.6 ± 0.98	.97
Serum cotinine level, ng/mL	293.1 ± 13.27	317.4 ± 13.49	319.1 ± 13.12	292.9 ± 12.65	.30
Fagerstrom score	4.9 ± 0.16	5.1 ± 0.16	5.0 ± 0.16	5.2 ± 0.16	.39
Previous use of nicotine replacement, No. (%)	64 (68.8)	63 (67.7)	69 (71.9)	78 (75.7)	.60
Other smokers in household, No. (%)	38 (40.9)	30 (33.0)	32 (34.0)	45 (44.6)	.29
CES-D score	13.0 ± 0.58	13.3 ± 0.58	12.6 ± 0.57	14.1 ± 0.55	.32
AUDIT score	2.4 ± 0.31	1.9 ± 0.31	2.1 ± 0.30	2.5 ± 0.29	.42

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CES-D, Center for Epidemiological Studies Depression Scale; CO, carbon monoxide.

SI conversion factor: To convert cotinine to nanomoles per liter, multiply by 5.68.

\*Unless otherwise indicated, data are expressed as mean ± SEM.

**Table 2. Treatment Exposure\***

Treatment	Placebo Group (n = 93)	Naltrexone Hydrochloride Groups			df	χ <sup>2</sup> /F	P Value
		25 mg (n = 93)	50 mg (n = 96)	100 mg (n = 103)			
No. of weeks in treatment	5.3 ± 0.18	5.2 ± 0.18	5.2 ± 0.18	4.9 ± 0.18	3	0.95†	.42
No. of weeks using nicotine patch	5.2 ± 0.19	5.1 ± 0.19	5.0 ± 0.19	4.9 ± 0.18	3	0.46†	.71
No. of weeks receiving naltrexone	5.2 ± 0.20	5.0 ± 0.20	4.9 ± 0.20	4.5 ± 0.19	3	2.11†	.10
Days medication taken during 6 wk of treatment, %§	80.2 ± 3.19	75.8 ± 3.19	75.3 ± 3.14	68.4 ± 3.03	3	2.49†	.06
Naltrexone therapy reduced or discontinued by patient or provider, No. (%) of patients	3 (3.2)	8 (8.6)	11 (11.5)	18 (17.5)	3	11.12‡	.01
Naltrexone level at wk 1, µg/L	0	1.7 ± 1.19	3.8 ± 1.18	7.7 ± 1.15	2	6.77†	.001
Naltrexone level at wk 4, µg/L	0	1.3 ± 0.99	4.5 ± 0.96	7.9 ± 0.97	2	11.36†	<.001
6-β-Naltrexol level at wk 1, µg/L	0	16.3 ± 3.80	32.9 ± 3.75	56.7 ± 3.64	2	30.00†	<.001
6-β-Naltrexol level at wk 4, µg/L	0	14.6 ± 3.92	38.2 ± 3.82	67.2 ± 3.89	2	45.45†	<.001
6-β-Naltrexol level detected at wk 1, No. (%) of patients	0/86	64/82 (78.0)	72/84 (85.7)	79/89 (88.8)	2	3.89‡	.14
6-β-Naltrexol detected at wk 4, No. (%) of patients	0/72	59/72 (81.9)	69/76 (90.8)	66/73 (90.4)	2	3.40‡	.18

\*Unless otherwise indicated, data are expressed as mean ± SEM.

†F value.

‡χ<sup>2</sup> Value.

§Subjects without eDEM caps monitoring data were coded as 0.

||Missing values and values below the detection level were coded as 0. The mean concentration of naltrexone at the lowest dose was below our lower limit of quantification. Analyses of naltrexone and 6-β-naltrexol levels are based on the active drug conditions. As expected, these levels were equal to 0 for participants in the placebo group.

**WEIGHT GAIN**

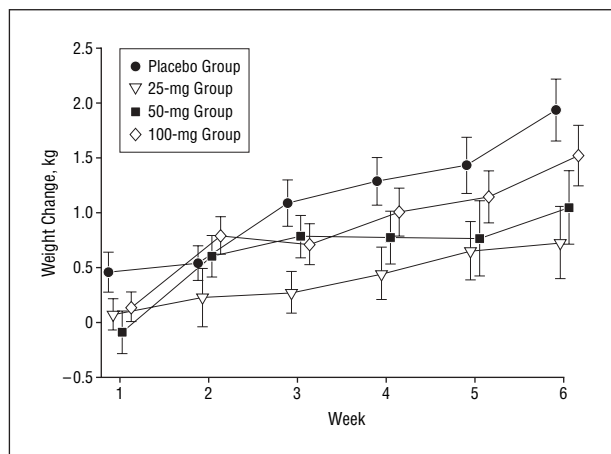
A significant dose effect ( $P < .05$ ) was found in weight gain from baseline to week 6 in those who were continu-

ously abstinent ( $n = 157$ ; 4 were missing weight measurements at baseline or at week 6). Mean ± SEM weight gain was significantly less in the 25-mg group ( $0.7 \pm 0.31$ ;  $n = 38$ ;  $P < .01$ ), marginally lower in the 50-mg group ( $1.1 \pm 0.33$ ;

**Table 3. Odds of Prolonged and Continuous Abstinence\***

Outcome	Naltrexone Hydrochloride Groups											
	Placebo Group			25 mg			50 mg			100 mg		
	No. (%)	OR (95% CI)†	P Value	No. (%)	OR (95% CI)†	P Value	No. (%)	OR (95% CI)†	P Value	No. (%)	OR (95% CI)†	P Value
Prolonged (4-wk) abstinence	42/93 (45.2)	NA	NA	42/93 (45.2)	1.00 (0.56-1.78)	>.99	39/96 (40.6)	0.83 (0.47-1.48)	.53	53/103 (51.5)	1.29 (0.73-2.26)	.38
Continuous (6-wk) abstinence	36/93 (38.7)	NA	NA	38/93 (40.9)	1.09 (0.61-1.97)	.76	34/96 (35.4)	0.87 (0.48-1.57)	.64	53/103 (51.5)	1.68 (0.95-2.96)	.07
Continuous (6-wk) abstinence among treatment completers	36/75 (48.0)	NA	NA	38/75 (50.7)	1.11 (0.59-2.11)	.74	34/71 (47.9)	1.00 (0.52-1.91)	.99	53/74 (71.6)	2.73 (1.39-5.39)	.004

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.  
 \*All groups also received 21-mg transdermal nicotine replacement therapy (nicotine patch).  
 †Indicates comparison of each active dose with placebo and 2-sided 95% CIs.



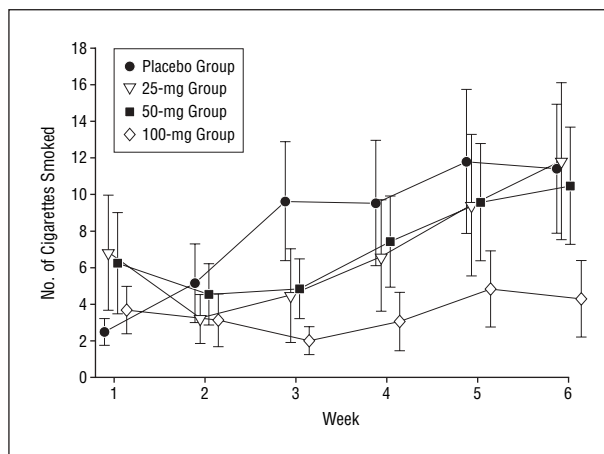
**Figure 2.** Mean  $\pm$  SEM weight change from baseline by week and treatment condition in participants who were continuously abstinent (n=161; numbers of participants at each week ranged from 151 to 159, depending on missing data). The 3 naltrexone treatment groups received 25, 50, or 100 mg/d of naltrexone hydrochloride.

n=33; P=.06), but not different in the 100-mg group (1.5 $\pm$ 0.27 kg; n=52; P=.33) compared with the placebo group (1.9 $\pm$ 0.34 kg; n=34). The longitudinal linear mixed-effects model results were consistent with the baseline to week 6 comparison (**Figure 2**). Similar findings were seen among those who had prolonged abstinence during the final 4 weeks of therapy.

Among 295 treatment completers, irrespective of smoking abstinence, 287 subjects had complete weight data in which a similar dose effect was seen (P<.01). Mean $\pm$ SEM weight gain in the 25-mg dose (0.8 $\pm$ 0.21 kg; n=75; P<.001) and the 50-mg dose (1.0 $\pm$ 0.23 kg; n=67; P=.006) but not the 100-mg dose (1.4 $\pm$ 0.22 kg; n=73; P=.13) was significantly less than in the placebo group (1.9 $\pm$ 0.22 kg; n=72).

**NUMBER OF CIGARETTES SMOKED**

In an exploratory analysis of the number of cigarettes smoked each week in the ITT sample with smoking during the week before the quit date entered as a covariate,



**Figure 3.** Mean  $\pm$  SEM number of cigarettes smoked from the first week in treatment by week and treatment condition (n=364; numbers of participants at each week ranged from 364 to 309, depending on missing data). The 3 naltrexone treatment groups received 25, 50, or 100 mg/d of naltrexone hydrochloride.

the number smoked in the placebo group increased compared with the number smoked in the 100-mg group, which remained low (P=.04; **Figure 3**) during treatment.

**SYMPTOMS OF WITHDRAWAL, DEPRESSION, AND CRAVING**

Analyses of total scores on the Minnesota Nicotine Withdrawal Scale<sup>20</sup> showed that withdrawal symptoms decreased for all groups (P<.001) over 6 weeks but that the 100-mg group showed a more rapid and greater reduction (from a mean of 9.91 to 4.90) compared with the placebo group (from a mean of 8.71 to 5.30 [P=.04]), with a trend observed for the 25-mg dose (P=.06). A similar pattern favoring the 100-mg group was observed on the Questionnaire of Smoking Urges<sup>18</sup> factor 2 subscale (craving for relief of withdrawal; P=.06). There was no effect of naltrexone on factor 1 scores (urge to smoke for positive reinforcement)<sup>18</sup> or on the Center for Epidemiological Studies Depression Scale.<sup>19</sup>



**Table 4. Moderate and Severe Events Reported During Treatment by Group\***

Adverse Event	All Groups	Placebo Group	Naltrexone Hydrochloride Groups		
			25 mg	50 mg	100 mg
Nausea	60 (15.6)	9 (9.7)	13 (14.0)	15 (15.6)	23 (22.3)
Vomiting	19 (4.9)	4 (4.3)	2 (2.2)	5 (5.2)	8 (7.8)
Diarrhea	16 (4.2)	5 (5.4)	3 (3.2)	3 (3.1)	5 (4.9)
Abdominal pain	35 (9.1)	8 (8.6)	6 (6.5)	11 (11.5)	10 (9.7)
Appetite changes	49 (12.7)	17 (18.3)	9 (9.7)	9 (9.4)	14 (13.6)
Headache	47 (12.2)	10 (10.8)	10 (10.8)	11 (11.5)	16 (15.5)
Dizziness	26 (6.8)	4 (4.3)	8 (8.6)	5 (5.2)	9 (8.7)
Fatigue	69 (17.9)	16 (17.2)	14 (15.1)	19 (19.8)	20 (19.4)
Nervousness/anxiety	42 (10.9)	11 (11.8)	6 (6.5)	11 (11.5)	14 (13.6)
Insomnia	60 (15.6)	18 (19.4)	14 (15.1)	13 (13.5)	15 (14.6)
Somnolence	15 (3.9)	1 (1.1)	3 (3.2)	4 (4.2)	7 (6.8)
Depression	70 (18.2)	14 (15.1)	20 (21.5)	20 (20.8)	16 (15.5)
Pruritus	11 (2.9)	7 (7.5)	2 (2.2)	1 (1.0)†	1 (1.0)†
Rash	14 (3.6)	9 (9.7)	4 (4.3)	1 (1.0)†	0†
Vivid dreams	73 (19.0)	19 (20.4)	14 (15.1)	17 (17.7)	23 (22.3)

\*All groups also received 21-mg transdermal nicotine replacement therapy (nicotine patch). Data are expressed as number (percentage) of patients.

†Statistically significant difference between the proportion of patients reporting adverse events compared with the placebo group (receiving nicotine patch therapy only).

## FOLLOW-UP EVALUATIONS

Exploratory analyses of 7-day point prevalence of abstinence during follow-up did not find substantial differences between the groups (3-, 6-, and 12-month rates for the placebo group, 32.3%, 21.5%, and 11.8%, respectively; for the 25-mg group, 29.0%, 21.5%, and 12.9%, respectively; for the 50-mg group, 29.2%, 15.6%, and 11.5%, respectively; for the 100-mg group, 35.0%, 21.4%, and 15.5%, respectively). Mean  $\pm$  SD weight gain in continuous abstainers continued to be somewhat lower ( $P = .02$ ) for the 25-mg group ( $1.42 \pm 0.54$  kg) at 3 months compared with the placebo group ( $3.17 \pm 0.55$  kg), although the overall test difference was not significant ( $P = .16$ ).

## SAFETY

Two serious adverse events involving overnight hospitalization for observation (nausea/vomiting and somnolence) occurred in the 50-mg group during treatment. Eight occurred during follow-up (in the placebo group, carotid angioplasty, chest pain, and hyperthyroidism; in the 25-mg group, fractured leg repair, mitral valve repair, and cardiac stent placement [ $n = 2$ ]; and in the 50-mg group, asthma attack).

**Table 4** presents the percentage of unique participants reporting nonserious adverse events rated moderate or severe for categories with a prevalence of 5% or more for at least 1 treatment condition. Only pruritus and rash showed a significant dose effect, with lower rates in the 50- and 100-mg groups compared with placebo.

Four subjects, 1 each in the 25- and 50-mg groups and 2 in the 100-mg group, developed liver function test values that exceeded entrance criteria. All values declined to within the reference range after the use of that medication was discontinued.

## COMMENT

To our knowledge, this is the first study to systematically evaluate various doses of naltrexone for smoking cessation and reduction of weight gain after cessation in a large, prospectively randomized setting. We failed to confirm our hypothesis that naltrexone therapy would improve prolonged abstinence after a 2-week grace period.<sup>9</sup> In contrast, naltrexone's potential advantage was most apparent on continuous abstinence rates. Adding the 100-mg dose to nicotine patch therapy compared with nicotine patch therapy alone more than doubled the odds of achieving continuous abstinence in those who completed treatment and tended to improve short-term efficacy in the ITT sample. The results of the treatment completer analysis must be interpreted cautiously, however, given that we did not find significant effects in the ITT sample. Nonetheless, these findings provide support for additional testing of the 100-mg dose as an augmentation strategy in combination with the nicotine patch.

Reductions in tobacco withdrawal and the urge to smoke in response to withdrawal with the 100-mg dose may underlie effects of this dose on smoking-related outcomes. Consistent with this hypothesis, some but not all<sup>25-27</sup> laboratory studies have found that naltrexone reduced withdrawal symptoms<sup>28,29</sup> or attenuated self-reported difficulty in abstaining from smoking.<sup>30</sup> Reductions in the amount smoked per week is consistent with some laboratory studies that showed reductions in ad libitum smoking<sup>26,27</sup> but not others.<sup>25,28,30</sup>

On the coprimary outcome of postcessation weight gain, the daily addition of 25 and 50 mg of naltrexone hydrochloride to the nicotine patch resulted in less weight gain than placebo plus the nicotine patch, replicating our previous preliminary studies of 50 mg/d.<sup>9</sup> The 25-mg dose, which showed the largest effect, was essentially indis-

tinguishable from placebo on measures of tolerability. The fact that no single dose was efficacious in both reducing weight gain and improving smoking abstinence suggests that the optimal naltrexone dose may depend on the end point of greatest interest. For example, the expected reduction in short-term weight gain with low-dose naltrexone may help motivate weight-concerned smokers to make an attempt to quit.

The dose-dependent effects of naltrexone on smoking outcomes and weight gain may reflect opioid receptor specificity and changes produced by long-term naltrexone therapy and/or dose-dependent antagonism of nicotinic acetylcholine receptors. Naltrexone is more specific for the  $\mu$  opioid receptor (implicated in the reinforcing value of food<sup>4</sup>) at lower doses with increasing activity at  $\Delta$  and  $\kappa$  opioid receptors at higher doses. Moreover, long-term naltrexone treatment has been shown to result in greater up-regulation of  $\mu$  opioid receptors.<sup>31</sup> Perhaps tolerance to the weight-suppressing effect of naltrexone occurred with high-dose naltrexone through up-regulation of  $\mu$  opioid receptors. Alternatively, the 100-mg dose, which resulted in somewhat higher rates of continuous abstinence, may have helped a subgroup of smokers remain abstinent despite weight gain. Finally, the effects of the 100-mg dose on smoking outcomes may relate to potential antagonism of nicotinic acetylcholine receptors at higher doses.<sup>32</sup>

Although no single adverse event was significantly higher in the naltrexone groups, the incidence of individual events often increased as the dose increased. This pattern may account for the dose-dependent reduction in compliance with naltrexone therapy observed in a number of measures.

Several limitations of the design features warrant discussion. First, smoking abstinence was validated with CO levels with a 3- to 5-hour half-life. As a result, smoking abstinence rates could be inflated owing to undetected smoking lapses. Recruitment via advertisements and press releases likely yielded a highly motivated subset of smokers. The decision to recruit those who smoked 20 or more cigarettes daily also limits generalizability and may have contributed inadvertently to the predominantly white sample, because African Americans, for example, smoke on average fewer cigarettes per day.<sup>33</sup> An important limitation is that this study was not powered to detect effects on post-treatment outcomes, and maintenance of abstinence during follow-up was not seen. The short duration of treatment and the fact that all treatments (naltrexone, nicotine patch, and counseling) were discontinued simultaneously may have contributed to this finding.

Finally, there were several primary and secondary outcome measures as well as multiple study populations. As a consequence of these multiple comparisons, the overall type I error rate is affected, and any single nominal *P* value would need to be adjusted upward. For secondary and exploratory analyses, the issue of multiple comparisons is relevant but less important because such analyses generate hypotheses, with confirmation of these hypotheses tested in additional studies. Because the precise nature of this adjustment depends on the total number of comparisons performed, it is uncommon for adjusted *P* values to be reported. Thus, the statistically significant results reported herein may require independent con-

firmation in other studies because none of these results other than the effect on weight gain correspond to a priori specified primary hypotheses.

In conclusion, the results of this dose-ranging study provide support for further testing of the efficacy of the 100-mg dose for smoking cessation. In the meantime, the benefit of low-dose naltrexone therapy on reducing weight gain may have immediate clinical utility for the subset of weight-concerned smokers.

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