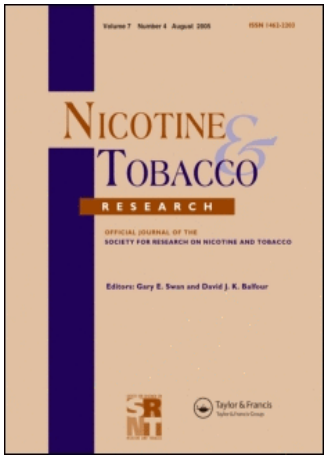

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Efficacy of naltrexone in smoking cessation: A preliminary study and an examination of sex differences

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Efficacy of naltrexone in smoking cessation: A preliminary study and an examination of sex differences

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This double-blinded, placebo-controlled trial evaluated the efficacy of naltrexone as an adjunct to standard smoking cessation treatment. Participants ($N=110$) were adult male and female nicotine-dependent smokers who expressed interest in quitting smoking. All subjects received six sessions of behavioral counseling (1 hr/session for 6 weeks), and 1 month of the nicotine patch (21 mg for the first 2 weeks, 14 mg the third week, 7 mg the fourth week). Subjects were randomly assigned to the naltrexone or placebo group. The naltrexone group started at 25 mg daily for 3 days prior to the quit date, and increased to 50 mg/day on the quit date and following 8 weeks. At the end of medication treatment, the naltrexone group had better quit rates versus the placebo group (48% quit on naltrexone vs. 41% on placebo), but this difference was not statistically significant. However, men and women differed on several measures: in the placebo group, women had significantly lower quit rates than men (39% vs. 67%, $p<.05$), but in the naltrexone group, women had quit rates comparable with those of men (58% vs. 62%, $p=ns$). Further examination revealed that naltrexone significantly reduced men's and women's cessation-related weight gain and selectively reduced women's urge to smoke to relieve negative affect and withdrawal. The results suggest continued examination of naltrexone as an adjunct in smoking cessation, particularly in female smokers, who have historically shown worse outcomes with traditional treatment methods.

Introduction

Cigarette smoking is the number one preventable cause of death and disease in the United States (U.S. Department of Health and Human Services, 2000). Quit rates are significantly improved with use of FDA-approved medications, such as nicotine replacement or bupropion, either alone or in combination (Fiore et al., 2000; Jorenby et al., 1999). However, because some patients either do not respond to these treatments or have contraindications for their use, additional medication adjuncts are needed for smoking cessation. One possible medication for smoking cessation may be naltrexone, a primary mu-opioid receptor antagonist that is currently FDA approved for the treatment of opioid and alcohol dependencies.

The rationale for the use of naltrexone in smoking cessation comes from animal and basic science studies showing an association between opioids and nicotine (Almeida et al., 2000; Gianutsos, Drawbaugh, Hynes, & Lal, 1975; Malin, Lake, Carter, Cunningham, & Wilson, 1993; Opitz & Weischer, 1988; Pomerleau, 1998; Tripathi, Martin, & Aceto, 1982). However, the results of studies of opioid antagonists and smoking behavior in humans have been mixed. Although several laboratory studies have shown that naltrexone attenuates smoking pleasure and craving, as well as reduces cigarette consumption and other smoking topography measures (Epstein & King, 2004; Houtsmuller,

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Clemmy, Sigler, & Stitzer, 1997; King & Meyer, 2000; Sutherland, Stapleton, Russell, & Feyerabend, 1995; Wewers, Dhatt, & Tejwani, 1998), other studies have failed to show changes in smoking reinforcement and related behaviors with opioid antagonists (Brauer, Behm, Westman, Patel, & Rose, 1999; Nemeth-Coslett & Griffiths, 1986; Sutherland et al., 1995). The discrepancies in findings may be related to differences in methodology, subject characteristics, or the types of measures employed. The effects of naltrexone also may be specific to certain subgroups. Finally, results from acute administration paradigms may not correspond with the drug's potential effectiveness in the clinical setting of smoking cessation.

Results also have been mixed in the few published clinical studies of naltrexone in smoking cessation. Naltrexone did not decrease smoking in alcoholic smokers receiving the drug for alcohol treatment (Rohsenow et al., 2003). Also, in a study designed to compare naltrexone with placebo in smoking cessation, both with and without concurrent treatment with nicotine patch, naltrexone did not improve quit rates (Wong et al., 1999). However, other studies have shown that naltrexone may improve quit rates when used either with (Krishnan-Sarin, Meandzija, & O'Malley, 2003; O'Malley et al., 2006) or without the patch (Covey, Glassman, & Stetner, 1999). In the latter study, naltrexone improved quit rates in women but not in men (Covey et al., 1999). This finding is of particular clinical interest, given that numerous studies have shown that female smokers may be less successful in quitting than male smokers, particularly with standard treatments, nicotine replacement, or less intensive support (Bjornson et al., 1995; Cepeda-Benito, Reynoso, & Erath, 2004; Royce, Corbett, Sorensen, & Ockene, 1997; Scharf & Shiffman, 2004; Senore et al., 1998; Wetter et al., 1999). Two of the studies showing positive effects of naltrexone were preliminary in nature and therefore limited by variable dosing schedules or small sample sizes (30 or fewer naltrexone-treated clients; Covey et al., 1999; Krishnan-Sarin et al., 2003). However, a more recent and larger dose-ranging trial showed that smoking quit rates were significantly higher with adjunct treatment of 100 mg oral daily naltrexone compared with placebo, both in conjunction with patch, but this effect was evident only among treatment completers and not in the intent-to-treat sample (O'Malley et al., 2006).

The present study was a preliminary randomized aid-to-cessation trial of the efficacy of 50 mg oral naltrexone for smoking cessation using a fixed dosing schedule. Initial findings from the first 41 subjects in the trial were described in an earlier paper of workshop proceedings (National Institute on Alcohol Abuse and Alcoholism–sponsored workshop, "Alcohol and tobacco: Mechanisms and treatment"). The early data observations in that paper (King, 2002) suggested that naltrexone may show promise in smoking cessation, with an approximately 20% increase in 1-month quit rates compared with placebo. The present paper is based on the data from the entire sample of 110 nicotine-dependent smokers in that trial. Subjects were randomized to receive either 50 mg oral naltrexone or identical placebo, along with standard comprehensive smoking cessation treatment including nicotine patch and counseling. This standard treatment platform (nicotine replacement and behavioral counseling) was chosen to be consistent with clinical practice guidelines (Fiore et al., 2000). Preliminary evidence also suggests that naltrexone combined with nicotine patch may produce optimal outcomes, compared with naltrexone alone, in terms of reduction in cravings, cue responsivity, or withdrawal symptoms (Hutchison et al., 1999; Krishnan-Sarin et al., 2003; O'Malley, Krishnan-Sarin, & Meandzija, 1997; O'Malley et al., 2006). A secondary goal was to examine sex differences in outcome. We hypothesized that women may benefit more from naltrexone than men.

Method

Participants

Cigarette smokers reporting a desire to quit were recruited via advertisements in local newspapers; flyers in hospitals, medical clinics, and community organizations; and word of mouth. Initial screening was conducted over the telephone to determine eligibility based on a score of 7 or higher on a 10-point scale of self-reported desire to quit, good general health, age between 21 and 65, smoking between 15 and 40 cigarettes/day for at least the past 2 consecutive years, body mass index between 19 and 34, no current or recent past major medical or psychiatric disorder, and no use of psychotropic medications in the previous year. Female candidates who were pregnant or lactating or had plans to become pregnant in the next 3 months were excluded.

Candidates found eligible from phone screening attended an in-laboratory screening where they received a physical examination by the study physician, blood chemistry/hepatic function tests, a urine toxicology test, pregnancy screening (female only), and an expired-air carbon monoxide (CO) test (Bedfont EC50 Microsmokerlyzer II, Medford, New Jersey). Candidates also provided demographic information and were given the following questionnaires: The Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), a Smoking

Contemplation Ladder (Biener & Abrams, 1991), a modified version of the Short Michigan Alcoholism Screening Test (SMAST; Selzer, Vinokur, & Can Rooijen, 1975), the Beck Depression Inventory (BDI; Beck, Ward, Menderson, Mack, & Erbaugh, 1961), and the Structured Clinical Interview for the *DSM*-IV nonpatient edition (SCID-NP; First, Spitzer, Gibbon, & Williams, 1995), as well as selected SCID modules for current/past mood disorders, alcohol and substance use disorders, and nicotine dependence. Standard cutoff thresholds were used to exclude subjects with significant major current or past psychiatric symptomatology (i.e., lifetime history of psychotic or bipolar disorder, opioid dependence, or major Axis II disorder, or a past-year history of other Axis I disorders). Additionally, candidates having abnormal levels (± 2.5 *SD*) on the blood chemistry or hepatic panels, a positive urine toxicology screen (cocaine, opiates, benzodiazepines, amphetamine, barbiturates, and PCP), or a positive pregnancy result were excluded.

Procedure

Study design and overview. During the screening session, participants signed an informed consent form approved by The University of Chicago Institutional Review Board. Once eligibility was confirmed, all participants agreed to attend eight visits during the first 10 weeks and a follow-up session 6 months after the quit date. The first six weekly visits included a 30-min assessment by the research assistant followed by a 45- to 60-min individual behavioral counseling session with a study therapist. These visits started 2 weeks prior to the quit date (weeks -2 and -1) and continued for four more sessions weekly during the first month after the quit date (weeks 0–4). The last two visits consisted of only the 30-min assessments conducted every other week during the second month after the quit date (weeks 6 and 8). Medications included open-label nicotine patch, which was given with instructions to commence on the morning of the quit date and continue for the next 4 weeks. Subjects were randomly assigned via a computer-generated random number list to receive either naltrexone or identical placebo tablets. Subjects began taking tablets 3 days prior to the quit date and continued for 8 weeks (see "Medications" section for details).

The initial enrollment consisted of 124 smokers. Fourteen of these subjects did not continue through initial medication randomization, which resulted in 110 subjects randomized to either naltrexone ($n=52$; 26 men, 26 women) or placebo ($n=58$; 30 men, 28 women). The 14 "enrollment failures" did not differ from enrolled participants on the majority of background characteristics, such as sex, race, education, body mass index, desire to quit rating, and baseline FTND and BDI scores. However, they were significantly younger than enrolled subjects (35.4 vs. 43.6 years), smoked for fewer years (15.8 vs. 24.7 years), and reported higher daily cigarette usage (25.1 vs. 21.0 cigarettes daily; all p values $<.05$).

Medications. Subjects assigned to the naltrexone group received 25 mg daily for the first 3 days prior to the quit date and then 50 mg on the quit date and every day for the next 2 months. Subjects assigned to the placebo group received identical placebo tablets on the same schedule. The lower initial naltrexone dose was chosen to reduce the incidence of adverse side-effects, which may be more prevalent during initial dosing. Both subjects and trial staff were blinded to study medication assignment. Tablets (naltrexone and placebo) were prepared by Mallinckrodt, Inc., St. Louis, Missouri.

Nicotine patches (Nicoderm CQ; GlaxoSmith-Kline Consumer Healthcare, Pittsburgh, Pennsylvania) were administered to all participants for 1 month beginning on the quit date. Participants were instructed to apply a new patch daily to a hairless portion of the body above the torso after removing the old patch. The patch doses were as follows: 21 mg for 2 weeks, 14 mg for 1 week, and 7 mg for the final week. The study physician was on call in case of adverse effects associated with study medications.

Behavioral therapy. A master's- or doctoral-level clinician conducted six 45- to 60-min semistructured, individual behavioral therapy sessions encompassing cognitive-behavioral, motivational, and addiction/12-step techniques (King & Riley, 2001). This treatment manual, developed in our clinical laboratory, was founded on evidence-based treatments, including the *Clinical Practice Guidelines for Treating Tobacco Use and Dependence* (Fiore, et al., 2000), the *Freedom from Smoking* guide (Strecher & Rimer, 1999), and the *Tobacco Dependence Treatment Handbook: A Guide to Best Practices* (Abrams et al., 2003). Sessions 1 and 2 focused on behavioral and motivational skills in preparation for the quit date; session 3 (quit date) focused on withdrawal symptoms, cravings, and relapse prevention; and sessions 4–6 covered rationalizations, high-risk situations, obtaining support, and emergency plans. All sessions were audiotaped and an independent master's-level clinician reviewed a randomly selected subset (5%) of the tapes. From a checklist of therapy components, 91% of the reviewed sessions were deemed fully adherent to the treatment elements in the manual, with the remaining 9% of the sessions rated as 80%–83% adherent.

Presession interviews. The 30-min presession assessments by the bachelor's-level research assistant consisted of questionnaires and an interview, an expired-air CO reading, and pill and patch counts and disbursements. The research assistant also distributed parking or travel reimbursements and study compensation. After completing the first 2 months of the study, participants received US$35 in gift cards and eligibility to participate in an individualized raffle (i.e., able to select one of four envelopes with three each containing a $50 gift card and one containing a $100 gift card).

Follow-up session. At 6 months after the quit date, participants returned to the clinical laboratory for a 30-min follow-up interview to determine smoking status and psychosocial functioning and to obtain a final breath CO reading. Participants who attended the follow-up took part in an individual raffle by selecting one of four envelopes, with three envelopes each containing a $35 gift card and one envelope containing a $75 gift card.

Measures. Substance-related measures were obtained regularly during the study and included weekly substance use patterns, current state ratings of urge to smoke, and objective verification of smoking status via expired-air CO measures ($\leqslant$10 ppm for abstinence). At each weekly visit (starting at week -2), cigarette use for each day since the last visit was obtained via a modified timeline followback interview (Sobell, Maisto, Sobell, & Cooper, 1979; Sobell & Sobell, 1995). Subjective smoking urge ratings at each visit were assessed by the 10-item Brief Questionnaire of Smoking Urges (B-QSU; Cox, Tiffany, & Christen, 2001), which yields a total score and two subscores (i.e., factor 1 assesses cigarette urges for reward, and factor 2 assesses urges to relieve negative affect or withdrawal).

Tobacco withdrawal was assessed by an expanded version of the Minnesota Withdrawal Scale (MWS; Hughes & Hatsukami, 1986, 1998) on the quit date, and at weeks 1 and 4. This scale was not given at each week's assessments to avoid subject overburden with measures. The expanded MWS included 14 total items scored on five-point Likert scales (ratings 0–4) with several additional items included so that two subscales, a withdrawal negative affect scale and a sleep/fatigue scale, could be computed (Piasecki et al., 2000). A total MWS score was computed using the standard items for the scale (i.e., six of the seven items from the *DSM*-IV for nicotine withdrawal excluding heart rate decreases, which cannot be determined by subject self-report). The craving item from the MWS also was excluded for the MWS total score.

Side-effects of the medications were assessed weekly by a 14-item side-effects scale based on those used in prior studies (Ahluwalia, McNagny, & Clark, 1998; King, Volpicelli, Gunduz, O'Brien, & Kreek, 1997; Volpicelli, Alterman, Hayashida, & O'Brien, 1992). Five items measured effects related to nicotine patch (skin itching, welts, insomnia, constipation, muscle pain), and nine items measured side-effects associated with naltrexone (nausea, vomiting, headache, light-headedness, flushed/warm, sedation, vague symptoms of agitation/anxiety, increased sexual desire, increased erections). Response choices were 0 (absent), 1 (mild), and 2 (severe). Subjects were weighed by the research assistant at baseline and 1 month after the quit date.

Data analyses

The treatment groups were compared on demographic and baseline data via *t* tests and chi-square tests, as appropriate. For outcome data, intent-to-treat analyses were conducted. All randomized participants were included, and participants who did not complete the study or were lost to follow-up were conservatively classified as relapsed. The primary outcome variable was the quit rate, which was determined by two primary definitions (Hughes et al., 2003): (a) *Success*=not smoking even a puff daily for 1 week *and* not smoking even a puff at least 1 day in each of 2 consecutive weeks at any point in the trial, and (b) *prolonged abstinence*=not smoking even a puff at any point during the trial, after a 1-week grace period after the quit date. Chi-square tests were used to compare quit rates between medication groups. To examine sex differences in outcome for placebo and naltrexone conditions, logistic regression included sex, medication, and their interaction as predictors. Analyses were repeated excluding several participants who were unable to provide biochemical verification (n=2 at week 8; n=4 at week 24), but the results were not significantly different from the main analyses presented.

Analysis of variance was used to test the effects of sex and medication on weight gain (baseline to 1 month). Withdrawal and smoking urge scores were modeled to investigate the effect of sex and medication using Generalized Estimating Equation (GEE) models (Liang & Zeger, 1986), which considered the correlation among multiple measurements over time. To maximize the data collected for analysis, we used imputation procedures. Scores were imputed for missing data ($\leqslant$5% of data) at week 1 or 4 by taking the mean of the subjects' surrounding datapoints or carrying forward the last observation, as appropriate.

Results

Demographic and baseline characteristics

The demographic and clinical characteristics for naltrexone and placebo groups are shown in Table 1. The groups were similar on most background variables including age, years of education, sex, ethnic/racial composition, marital status, and body mass index. The groups did not differ on average number of cigarettes smoked daily, duration of smoking, and other relevant smoking-related characteristics (Table 1). However, the average FTND score was higher in the naltrexone group, compared with placebo, $t(110)=2.48$, $p<.05$. Given this baseline difference, logistic regression analyses were conducted to examine the effect of FTND on end of treatment smoking outcomes, controlling for sex and medication, but revealed no significant association; success, $\beta(SE)=-0.14$ (0.10), $p=.19$; prolonged abstinence, $\beta(SE)=-0.15$ (0.10), $p=.13$.

Medication compliance

Compliance with the nicotine patches and medication was computed by taking the total number of patches or pills reported taken divided by the total number disbursed during that period (i.e., a maximum total of 29 patches and 59 pills). Nicotine patch and pill compliance did not differ significantly between treatment groups: The naltrexone group participants reported using 87% of patches and 78% of pills, and the placebo group participants reported using 75% of patches and 70% of pills. Post-hoc analyses of data from participants who completed the program (i.e., excluding dropouts, who were noncompliant by definition) revealed that medication or patch compliance included as an independent factor did not significantly alter outcome results.

Table 1. Demographic and baseline smoking characteristics in the naltrexone vs. placebo group ($N=110$).

	Naltrexone group ($n=52$)	Placebo group ($n=58$)
Demographic variables		
Age (years)	44.23±1.41	42.97±1.59
Education (years)	14.17±0.32	14.72±0.25
Sex (male)	26 (50)	28 (52)
Race (White)	37 (71)	35 (60)
Married or living with partner	28 (54)	25 (43)
Body mass index (kg/m^2)	26.88±0.70	26.30±0.62
Smoking variables		
Duration of smoking (years)	25.94±1.43	23.49±1.76
Average cigarettes/day	22.28±1.11	19.85±0.91
Previous number of quit attempts	4.82±1.11	2.84±0.24
Baseline carbon monoxide level[a]	23.96±1.53	21.31±1.28
Baseline B-QSU score[a]	33.79±1.82	30.97±1.71
Baseline MWS total score[b]	6.52±0.70	5.61±0.66
FTND score (0–10)	6.35±0.27*	5.41±0.26
Motivation to quit (1–10)	7.24±0.10	7.19±0.11
Other smokers in household	19 (37)	17 (30)
Clinical background[c]		
History of major depression	17 (33)	17 (30)
History of alcohol dependence	7 (13)	6 (10)
History of current or past alcohol abuse	19 (37)	14 (24)
History of substance dependence	7 (13)	4 (7)
Beck depression score (baseline)	5.16±0.70	4.78±0.66

Note. B-QSU, Brief Questionnaire of Smoking Urges; MWS, Minnesota Withdrawal Scale; FTND, Fagerström Test for Nicotine Dependence. [a]Data are mean±*SE* or frequencies (percentage), unless otherwise noted. Comparisons by *t*-test or chi-square, where appropriate. [a]2 weeks before quit date. [b]On quit date. [c]History of at least 1 year since meeting criteria for the particular diagnosis. *$p<.05$.

Adequacy of study medication blinding and medication guessing

Participants were given a questionnaire to assess whether they thought they were on the active medication or placebo on the quit date and at the end of medication treatment. On the quit date, 52% (27/52) of naltrexone-treated participants correctly identified being randomized into the medication group, whereas 40% of subjects in the placebo group (23/57; one subject did not complete the survey) also believed they were taking naltrexone. Data were similar at 2 months, with 58% (25/43) of naltrexone-treated and 55% (24/44) of placebo-treated participants believing they were in the active medication group. Participants who correctly identified being in the active treatment group had significantly more side-effects on the quit date ($p<.001$) and tended to have higher quit rates than participants who incorrectly believed they were not taking active medication or who were not sure (74% vs. 56% quit rates at 1 month, respectively).

Adverse effects and retention in the trial

In the first week after the quit date, the main side-effects associated with naltrexone were nausea, sedation, light-headedness, and feeling flushed/warm (Table 2). However, 4 weeks after the quit date, only light-headedness remained significantly elevated in the naltrexone group, compared with placebo. Most side-effects ratings were mild and not severe. On the quit date, 80% of the side-effects reported in the naltrexone group were rated as mild (i.e., rated a "1" on the three-point scale) compared with 92% in the placebo group, $\chi^2(1)=12.00$, $p<.001$; and at week 4, 86% and 89% of the side-effects were rated as mild in the naltrexone group versus the placebo group, respectively, $\chi^2(1)=0.92$, $p=ns$.

At the end of the first month, the dropout rate was 13.6% (15/110) and did not differ between the naltrexone (11.5%, $n=6/52$) and placebo groups (15.5%, $n=9/58$). An additional 6.3% (6/95) dropped

Table 2. Subjects reporting side-effects in the naltrexone and placebo groups.

	1 week postquit		4 weeks postquit	
Reported side-effect	Naltrexone (n=51)	Placebo (n=58)	Naltrexone (n=46)	Placebo (n=48)
Nausea	23 (45)*	13 (22)	9 (20)†	3 (6)
Vomiting	4 (8)	1 (2)	2 (4)	1 (2)
Headache	25 (48)	18 (31)	15 (33)	12 (25)
Light-headed/dizzy	32 (62)*	25 (43)	13 (28)*	4 (9)
Flushed/warm	30 (58)*	25 (43)	18 (39)	16 (34)
Sedation	33 (65)**	18 (31)	15 (33)	12 (25)
Agitation/anxiety	28 (55)	23 (40)	21 (46)	19 (40)
Increased sexual desire	9 (18)	13 (22)	13 (28)	15 (32)
Increased erections[a]	9 (36)	8 (27)	12 (52)†	6 (25)
Skin irritation	4 (8)	9 (16)	16 (35)	13 (27)
Welts/hives	1 (2)	0 (0)	2 (4)	4 (8)
Insomnia	11 (22)	13 (22)	16 (35)	17 (35)
Gastrointestinal distress	12 (24)	16 (28)	10 (22)	13 (27)
Joint/muscle pain	17 (33)	12 (21)	14 (30)	15 (31)

Note. Data are frequencies (percentage) that were rated either 1 (mild) or 2 (severe) on the side-effects scale. Analyses conducted with chi-square tests. [a]Data on erections include male participants only (i.e., week 1: n=25 naltrexone, n=30 placebo subjects; week 4: n=23 naltrexone, n=24 placebo subjects). **p<.01; *p<.05; †p=.06.

out by the end of treatment at 2 months (naltrexone: 4.3%, n=2/46; placebo 8.2%, n=4/49). Reasons stated for study discontinuation before the end of treatment were as follows: No reason cited or not interested (n=11), not ready to quit (n=3), didn't need the program (n=2), moved or scheduling problems (n=3), medication contraindication (n=1), and side-effects (i.e., gastrointestinal distress, n=1). At the 6-month follow-up, data were obtained on the remaining 97% (86/89) of eligible participants. As stated earlier, participants who dropped out or were lost to follow-up were classified conservatively as relapsed to smoking immediately after the moment of last contact.

Quit rates in the overall sample

Table 3 shows the quit rate data for success and prolonged abstinence (biochemically verified) at 1, 2, and 6 months after the quit date. Although quit rates were directionally higher in naltrexone-treated patients than in placebo-treated participants, they were not statistically significant (OR=1.18–1.57).

Sex differences in quit rates

Quitting rates were further compared with the groups stratified by sex, using logistic regression models with medication, sex, and their interaction as predictors. No interaction term was significant for the smoking cessation outcome at week 4, 8, or 24. Men had better overall quit rates than women in terms of success, sex: $\beta(SE)$=1.13 (0.55), p=.04; and marginally significant for prolonged abstinence, sex: $\beta(SE)$=1.05 (0.56), p=.06. Further inspection of the data indicated that the sex difference in the week 8 outcome occurred mainly in the placebo group. Post-hoc chi-square analyses with the groups stratified by sex revealed that women had lower quit rates than men in the placebo condition but not in the naltrexone condition (Table 4 and Figure 1).

Weight gain

Analyses were conducted to examine effects of medication and sex on potential contributors to the observed treatment effects. In terms of weight gain in

Table 3. Overall sample quit rates in the naltrexone and placebo groups.

	Naltrexone	Placebo	χ^2	p-value	Odds ratio (95% confidence interval)
Success					
Week 4	73%	66%	0.73	0.39	1.43 (0.59–3.53)
Week 8	60%	53%	0.42	0.52	1.28 (0.56–2.94)
Week 24	37%	33%	0.17	0.68	1.18 (0.50–2.80)
Prolonged abstinence					
Week 4	63%	57%	0.49	0.48	1.32 (0.57–3.05)
Week 8	48%	41%	0.50	0.50	1.31 (0.58–2.97)
Week 24	27%	19%	0.99	0.32	1.57 (0.58–4.30)

Note. Quit rates in this table are for success and prolonged abstinence. S*uccess* was defined as not smoking even a puff daily for 1 week *and* not smoking even a puff at least 1 day in each of two consecutive weeks at any point in the trial; *prolonged abstinence* was defined as not smoking even a puff at any point during the trial, after allowing for a 1-week grace period after the quit date (Hughes et al., 2003). Quit rate data were biochemically verified by subjects' expired-air CO $\leqslant$10 ppm.

Table 4. Quit rates (success) in the naltrexone and placebo groups by sex.

	Men	Women	χ^2	*p*-value	Odds ratio (95% confidence interval)
Placebo group					
Week 4	77%	54%	3.42	0.06	2.85 (0.82–10.39)
Week 8	67%	39%	4.37	0.04	3.09 (0.94–10.39)
Week 24	40%	25%	1.48	0.22	2.00 (0.57–7.31)
Naltrexone group					
Week 4	73%	73%	0.00	0.99	1.00 (0.25–4.08)
Week 8	62%	58%	0.08	0.78	1.17 (0.33–4.45)
Week 24	35%	38%	0.08	0.77	0.85 (0.02–3.03)

Note. Quit rates in this table are for success, defined as not smoking even a puff daily for 1 week *and* not smoking even a puff at least 1 day in each of 2 consecutive weeks at any point in the trial. Data for prolonged abstinence were similar for differences between the sexes but are not included for ease of presentation.

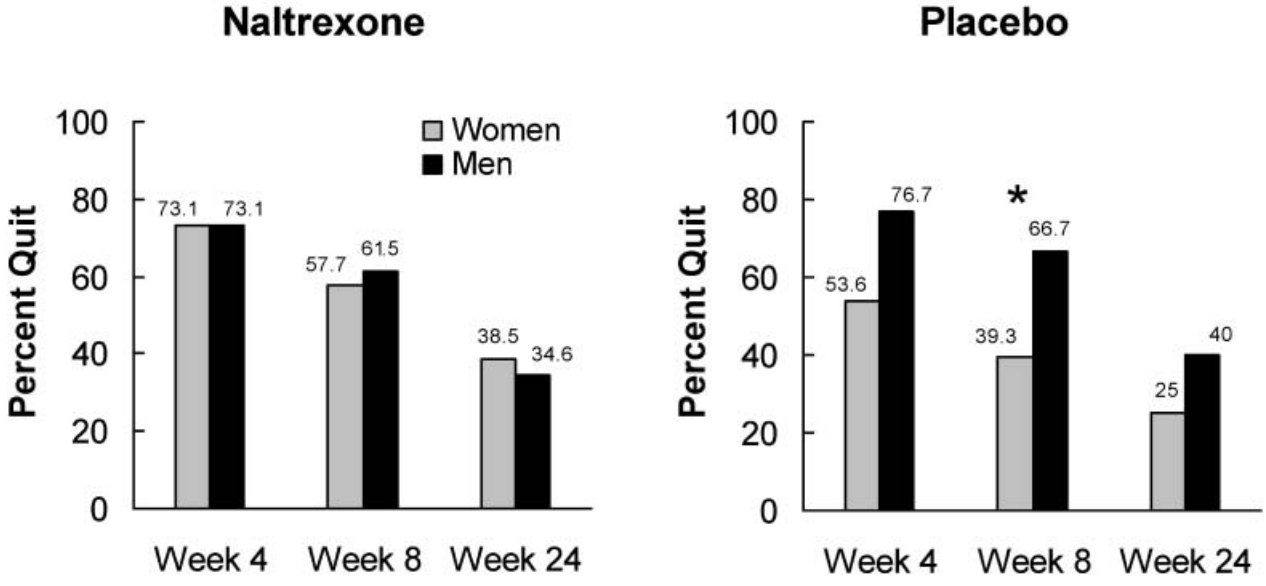

Figure 1. Quit rates (success) for men and women in naltrexone and placebo groups. *$p<.05$.

the first month after the quit date (Figure 2), weight increases were significantly greater in the placebo compared with the naltrexone group: 4.2 ± 0.6 pounds vs. 1.5 ± 0.7 pounds, respectively; medication: $F(1, 75)=7.89$, $p<.001$. We found no significant main effect of sex or interaction of sex with medication, given that both men and women showed this naltrexone-related effect.

Withdrawal and smoking urges

Participants' reported withdrawal symptoms and cigarette craving scores at their respective baselines were in the mild to moderate range (Table 1), which would be expected based on their smoking patterns and degree of nicotine dependence. The patterns of MWS and B-QSU total and subscale scores were assessed over time as difference scores from their first respective baseline measurements through the first month of treatment. Data were analyzed by GEE models examining sex, medication, and measurement time and their two-way and three-way interaction as independent variables. Women scored higher than men on the MWS total—sex: $\beta(SE)=-3.18$ (1.60), $p=.047$—after controlling for the other factors in the model. Withdrawal scores tended to decrease over

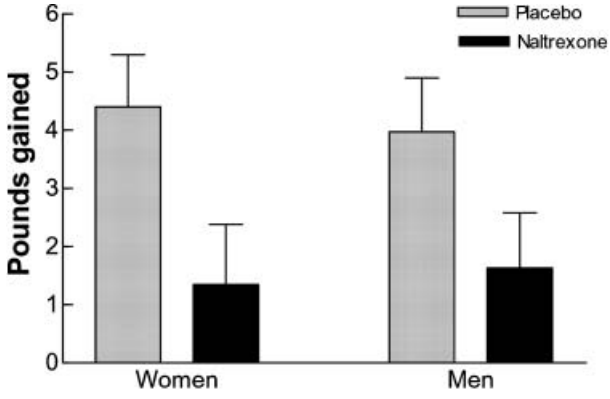

Figure 2. Weight gain during the first month of treatment. Results shown are the mean ($\pm$SEM) weight gain in pounds (change from baseline to week 4) for men and women in naltrexone and placebo groups. Data are shown for the 97 participants who completed the first month of the study, which includes both abstinent and nonabstinent subjects. **Medication, $p<.001$.

the first month of treatment—time: $\beta(SE)=-0.57$ (0.32), $p=.08$—and naltrexone tended to decrease scores more than did the placebo condition—medication: $\beta(SE)=-2.72$ (1.66), $p=.10$.

For the MWS affect subscale (Figure 3A), the interaction term between sex and medication was marginally significant, sex × medication: $\beta(SE)=3.72$ (2.08), $p=.07$, whereas the effects of sex, medication, and time were all significant, sex: $\beta(SE)=-3.21$ (1.43), $p=.02$; medication: $\beta(SE)=-3.00$ (1.48), $p=.045$; time: $\beta(SE)=-0.49$ (0.25), $p=.05$. The results indicate that MWS affect scores were lower in the naltrexone versus placebo group for female smokers but not for male smokers (Figure 3A). Analyses were repeated including only abstinent subjects during the first month ($n=66$; defined by prolonged abstinence), and results yielded similar patterns as observed for the total sample for the MWS affect subscale, but with larger p values for each term because of reduced statistical power. We found no significant effects for the MWS sleep/energy subscale.

In terms of smoking urge assessed by the B-QSU, the medication × time interaction was significant for the B-QSU total score and the factor 1 and 2 subscales (all p values $<.01$). The smoking urge scores decreased over time, but the rates differed between the groups, in that craving decreased faster over time in the naltrexone group than in the placebo group. No other interaction term was significant for the B-QSU total and factor 1 subscale. For the B-QSU factor 2 subscale (Figure 3B), the three-way interaction (sex × medication × time) was significant, $\beta(SE)=0.73$ (0.37), $p=.05$. Further examination

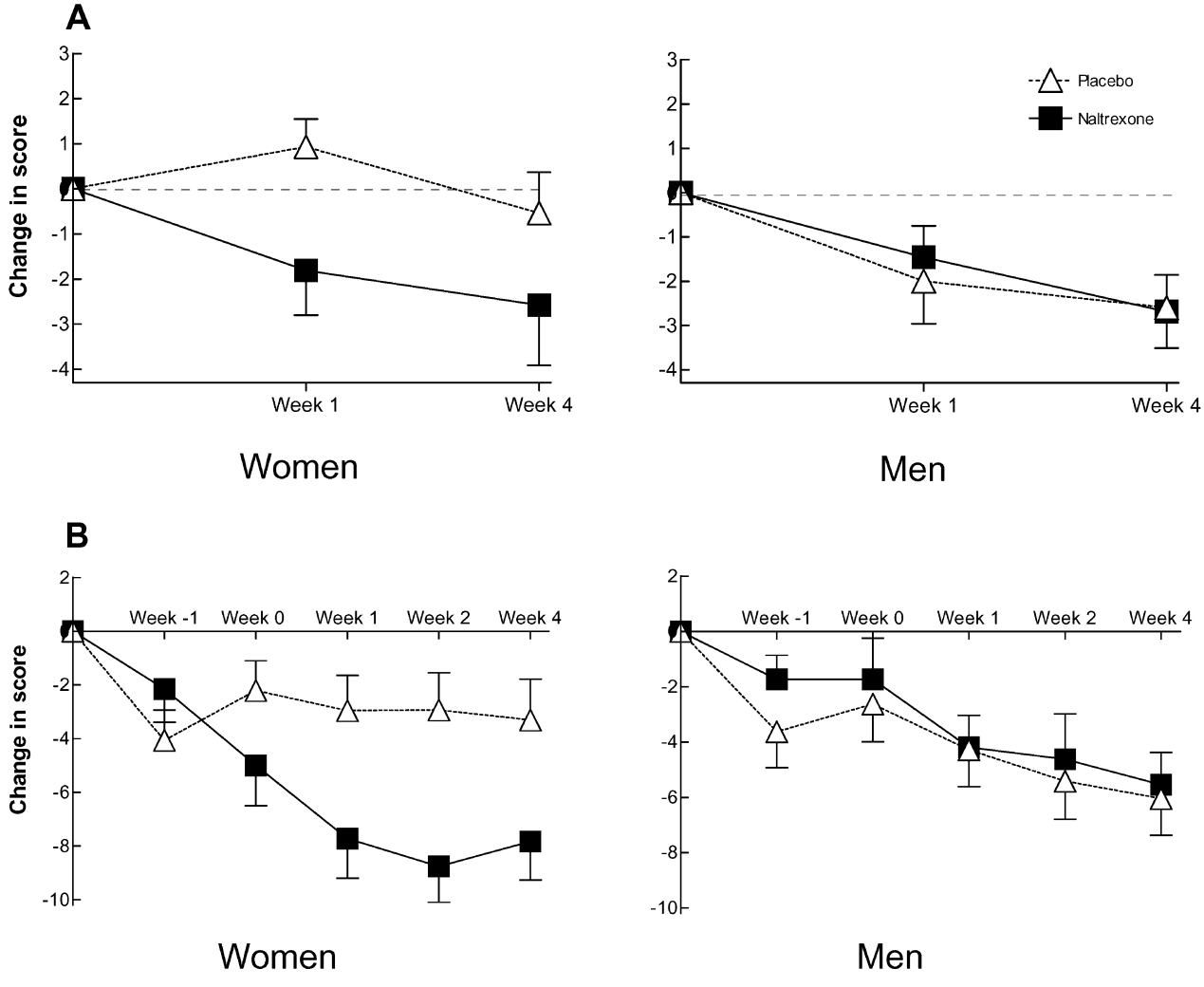

Figure 3 (A, B). Change from baseline (±SEM) in withdrawal affect and smoking urge during the first month of treatment. Withdrawal measured by the Minnesota Withdrawal Scale, negative affect subscale; smoking urge measured by the Brief Questionnaire of Smoking Urges, factor 2 subscale. Data are shown for the 97 participants who completed the first month of the study, which includes both abstinent and nonabstinent subjects. For withdrawal, sex × medication, $p=.07$. For smoking urge, sex × medication × time, $p=.05$; in women: medication × time, $p<.001$; in men: medication × time, $p=ns$.

indicated that naltrexone significantly decreased craving through the first month compared with placebo in the female smokers, medication × time, $\beta(SE) = -1.07$ (0.29), $p < .001$, but not in the male smokers, medication × time, $\beta(SE) = -0.34$ (0.24), $p = .15$.

Discussion

The present study showed that although naltrexone produced an overall modest improvement in smoking cessation quit rates, potential interesting sex differences were observed, with the gender gap (women showing worse outcome than men) apparent in the placebo group but not in the naltrexone group. It is possible that the lack of significance for an overall effect could have been related to the relatively small sample size and obscured by potential sex differences in outcome. At the end of medication treatment, in the placebo group, women were less likely than men to quit smoking (39% vs. 67%), but in the naltrexone group, quit rates were comparable between women and men (58% vs. 62%, respectively). While this finding was statistically significant at 8 weeks, it was no longer significant at the 6-month follow-up, which may suggest the need for longer duration of treatment. The results provide initial evidence for a possible role for naltrexone as an adjunct in smoking cessation, primarily in female smokers, who may show worse outcomes with standard or less intensive treatments (Bjornson et al., 1995; Cepeda-Benito et al., 2004; Royce et al., 1997; Scharf & Shiffman, 2004; Senore et al., 1998; Wetter et al., 1999).

Although several human laboratory studies have investigated the acute effects of naloxone or naltrexone on smoking, only a few published studies have examined naltrexone in smoking cessation clinical trials. Wong and colleagues found that the nicotine patch produced large increases in quit rates (56% patch vs. 23% no patch at 8 weeks) but that 50 mg naltrexone produced no further improvement. Mixed results were observed by O'Malley et al (2006): The 100-mg dose of naltrexone, but not the 50-mg or 25-mg dose, produced better continuous abstinence at 6 weeks in treatment completers compared with placebo (72% quit with 100 mg naltrexone vs. 48% with placebo, $OR = 2.73$). But the high dose was associated with greater discontinuation or dose reductions, and the two lower naltrexone doses produced weight reductions in treatment completers compared with placebo. Sample characteristics in our study and these two other studies were generally comparable, with the exception of smoking background (our sample averaged smoking approximately 7 less cigarettes per day) and racial diversity (our sample included significantly more non-Whites, i.e., 35%). These and other individual difference factors may explain, in part, the discrepant findings across studies.

Sex differences consistent with those suggested by the present study have been observed previously: Covey and colleagues (1999) demonstrated that naltrexone at doses of 50–75 mg selectively improved outcome for female smokers (39% naltrexone vs. 15% placebo quit rates at 4 weeks) but not for male smokers. They also found a benefit among smokers with a history of major depression (57% naltrexone vs. 14% placebo quit rates at 4 weeks) regardless of sex. Depression rates may be a possible factor in the difference between Covey's study and other studies, especially in those studies that specifically excluded persons with a history of major depression (Wong et al., 1999). Another important issue is the relatively high dropout rate in the naltrexone group in Covey's study (approximately 20% drop out because of adverse effects), which suggests potential limitations of opioid antagonist treatment alone for smoking cessation. However, several investigations, including the results of the present study, demonstrate that naltrexone combined with nicotine patch does not substantially increase dropout but does produce short-term improvement in quit rates compared with placebo and patch (Krishnan-Sarin et al., 2003; O'Malley et al., 2006). Although our own early data observations (King, 2002) suggested that naltrexone may improve 1-month outcomes, in the final dataset presented here, these effects were only directional with a lack of statistical power to detect significant differences with this sample size. Therefore, many questions remain on the efficacy of adjunct opioid antagonism treatment for smoking cessation, such as whether or not nicotine replacement and counseling are essential platforms with which to compare medication effects, if the effect may be replicated with other forms of nicotine replacement, and if naltrexone-related treatment effects are specifically sex based or based on another individual difference variable.

The potential difference in naltrexone response in female compared with male smokers may derive from several factors, including less weight gain, as well as amelioration of women's withdrawal affect and smoking urge to relieve negative affect. Consistent with two recent studies (Krishnan-Sarin et al., 2003; O'Malley et al., 2006), naltrexone significantly reduced the weight gain during the first month of cessation. Smoking-related weight concerns are highly prevalent in smokers (French & Jeffrey, 1995; Klesges et al., 1988) and may relate to early treatment dropout (Mizes et al., 1998; Streater, Sargent, & Wand, 1989) and a greater risk of relapse (Klesges et al., 1988; Korslund & Bowen, 1995; Meyers et al., 1997). Even though naltrexone reduced weight gain both for men and women, this issue may

be more salient for women (Meyers et al., 1997; Swan, Ward, Carmelli, & Jack, 1993), and it follows that women may preferentially respond to a medication that reduces cessation-related weight gain.

In addition, naltrexone significantly reduced cigarette craving for negative reinforcement (relief of withdrawal or negative affect), and withdrawal negative affect in women. These changes in subjective states after naltrexone may have influenced the subjects' ability to quit. Adjunct medications may be needed because nicotine replacement (2-mg nicotine gum) has been shown to be less effective in suppressing withdrawal symptoms in women compared with men (Hatsukami, Skoog, Allen, & Bliss, 1995). Therefore, opioid blockade may be useful during early cessation to reduce withdrawal symptoms and craving in women. Analyses in the approximate two-thirds of the sample who quit smoking during the first month (prolonged abstinence) revealed that naltrexone produced similar effects on these indices, although statistical power was reduced further. Although more in-depth analyses of the specific roles of withdrawal, craving, and weight gain could not be elucidated in this preliminary study with a modest sample size, future research in exploring the role of these possible underlying mechanisms in female and male smokers is warranted.

In terms of underlying neurobiological mechanisms of naltrexone effects on smoking response, both indirect dopamine pathways as well as direct opioid effects have been hypothesized. As suggested in a review by Pomerleau (1998), the opioid system may potentiate reinforcing effects of nicotine through the dopaminergic brain reward pathway. Some basic research supports this notion, in that electrophysiological (Gysling & Wang, 1983; Matthews & German, 1984) and behavioral studies (David, Durkin, & Cazala, 2002) show opioid stimulation of dopaminergic neurons in the ventral tegmental area, as well as dopaminergic mechanisms involved in opiate-induced reward in the same region. Alternatively, evidence indicates that nicotine induces the release of endogenous opioids in brain regions associated with opiate reinforcement (Dhart et al., 1995; Houdi, Pierzchala, Marson, Palkovits, & Van Loon, 1991; Pierzchala, Houdi, Van Loon, 1987), and human studies have also shown increased levels of endogenous opioids after nicotine administration (Pomerleau, Fertig, Seyler, & Jaffe, 1983). Taken together, these studies suggest that a direct opioidergic mechanism could be responsible for the underlying alterations in smoking-related behaviors with opioid antagonist treatment.

In sum, although prior research is mixed on the role of opioid antagonism in smoking-related behaviors, this preliminary study indicates that naltrexone may be beneficial as an adjunct to comprehensive smoking cessation treatment (counseling and patch), particularly for female smokers. Several mechanisms may underlie this effect, including reduction in cigarette craving or subjective smoking response, alleviation of negative affect and withdrawal, and less weight gain during cessation. Continued investigation, with larger sample sizes, of the role of naltrexone as an adjunct to comprehensive smoking cessation treatment is warranted.

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