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Naltrexone Alteration of Acute Smoking Response in Nicotine-Dependent Subjects

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KING, A. C. AND P. J. MEYER. *Naltrexone alteration of acute smoking response in nicotine-dependent subjects.* PHARMACOL BIOCHEM BEHAV **66**(3) 563–572, 2000.—There are mixed results on the effects of opioid antagonists on acute nicotine response in humans. The present study examined the effects of a single dose of 50 mg oral naltrexone relative to placebo on smoking response in 22 chronic smokers during short-term nicotine abstinence, after acute smoking and subsequent smoking deprivation, and on smoking behavior in a choice paradigm. The results showed that naltrexone significantly reduced immediate postcigarette ratings of smoking craving and desire to smoke and increased light-headedness, dizziness, and head rush ($ps < 0.05$). Reductions in craving and smoking desire persisted during a subsequent 1 h nonsmoking interval. Naltrexone also was found to significantly reduce the total number of cigarettes smoked in the choice interval, which was supported by objective measures of both reduced CO and plasma nicotine levels ($ps < 0.01$). Exploratory analyses on potential individual difference factors revealed that smokers with the highest levels of craving during abstinence showed the most pronounced naltrexone attenuation of smoking response. The results support the continued exploration of naltrexone as an adjunct to smoking cessation, especially in identified smoker subgroups most sensitive to the effects of opioid antagonism.   © 2000 Elsevier Science Inc.

Opioid antagonist   Naltrexone   Cigarette smoking   Nicotine   Craving   Urge
Human laboratory study   Smoking cessation

NICOTINE, the active ingredient in tobacco, affects various neuroregulatory systems, including the endogenous opioid system (39,40). Support for nicotine–opioid system interactions derives from several lines of animal studies, including dose-dependent inhibition of nicotine intake by opioid antagonists (33) and blockage of nicotine-related antinociception by the opioid antagonist naloxone (1,46). Also, there is similarity in the withdrawal symptoms occurring during opioid and nicotine deprivation, which can be precipitated by naloxone infusion (23,25). However, these results are equivocal, as other animal studies failed to show dose-dependent effects of opioid antagonists on nicotine administration (6), and results in human studies are mixed.

In general, human laboratory studies of opioid–nicotine interactions have utilized variable methods, including choice of opioid antagonist, cigarette smoking parameters, and dependent variables. There are several human laboratory studies indicating that preadministration of intravenous naloxone alters one or more aspects of cigarette smoking. These effects include naloxone-related decreases in number of cigarettes smoked (11), number of puffs taken, and/or trials in which cigarettes were smoked (18), and reduced subjective pleasure in smoking

(34). In contrast, another investigation failed to show significant dose–response effects of naloxone on subjective and behavioral indices during an ad lib smoking paradigm (29). Differences in study timing parameters, small sample sizes (i.e., $ns < 10$), and the relatively short half-life of naloxone ($\sim$60–90 min) (3,10) might explain these discrepant results.

In contrast to naloxone, naltrexone is a longer acting opioid antagonist with a plasma terminal half-life of $\sim$2–6 h (27,48), can be administered orally, and has been FDA approved for the treatment of opioid and alcohol dependence. Several human laboratory studies have investigated the effects of naltrexone alone or in combination with nicotine patch on smoking behavior and, as with naloxone, results have been mixed. Two recent pilot clinical trials of naltrexone in smoking cessation treatment have indicated some potential benefits of naltrexone alone (7) or in combination with the patch (31). In studies examining smokers during short-term smoking abstinence (i.e., 0.5–3 days), naltrexone decreased perceived difficulty in abstaining (44) and reduced craving and urge to smoke (15). Also, in combination with nicotine replacement, naltrexone blocked subjective responses (urge, withdrawal, and negative affect) to smoking-related cues (17).

However, other studies have shown that naltrexone reversed the inhibitory effects of the nicotine patch on smoking, failed to alter ad lib smoking, and produced unpleasant mood changes similar to some aspects of tobacco withdrawal (4,44). Taken together, these studies suggest an interaction between the opioid antagonist naltrexone and some effects during acute cigarette smoking or abstention; however, the exact nature and mechanism of this interaction is unclear. Additionally, identification of those smokers most sensitive to opioid antagonist effects on smoking has not been discerned.

The present study employed a within-subject design to examine the acute effects of naltrexone compared to placebo during three phases of smoking: a precigarette phase to examine craving and mood after overnight smoking abstinence; a postcigarette phase to examine effects after smoking a single cigarette (5 and 60 min); a choice smoking phase to examine cigarette self-administration. The smoking paradigm was chosen to closely resemble clinical aspects during an initial period of smoking cessation, including overnight abstinence, craving for the first cigarette of the day, reintroduction of a single cigarette or "slip" to smoking, and maintenance of nicotine self-administration (i.e., subsequent relapse).

In addition, we examined several nicotine- and alcohol-related subject variables as potential indicators of naltrexone sensitivity to smoking response based on prior studies indicating potential individual difference factors in opioid antagonist sensitivity (20,21,51). These included between-subject comparisons of naltrexone and smoking response based on subjects' severity of nicotine dependence, baseline morning craving for cigarettes, family history of alcoholism, and drinking history. Selection of these variables derived mainly from prior reports of heightened opioid antagonist sensitivity in at-risk groups, individual differences in endogenous opioid tone, and opioid system mediation of the brain reward pathway components and/or aspects of craving (14,41,52).

METHOD

Subjects

Subjects were regular cigarette smokers ($n = 22$; 10 male, 12 female) aged 19–50. They were recruited through flyers and advertisements in the local Chicago area newspapers. After a telephone interview to exclude those persons with potential major health and psychiatric problems, subjects were invited for in-lab screening, which included questionnaires, an interview conducted by the study psychologist (A.K.), and a short physical examination by a resident physician. The questionnaires consisted of the Symptom Checklist (SCL-90) (9), the Fagerström Test of Nicotine Dependence (FTND) (13), the Short Michigan Alcoholism Screening Test (SMAST) (43), and a drug and health history questionnaire and interview. Standard cutoff thresholds were used to eliminate those persons with significant current or past alcohol, drug, or psychiatric symptomatology. In addition, individuals identified with current or past major medical or psychiatric disorders from the clinical interview or physical exam were excluded from participation. Subjects were also excluded for abnormal levels on screening blood chemistry indices (chemistry and/or hepatic panel) or positive urine toxicology (cocaine, opiates, benzodiazepines, amphetamine, barbiturates, and PCP).

Procedure

Each subject participated in two identical testing sessions in this double-blind study. The sessions were spaced on average 8 days apart (range 4–19 days). Each subject received preadministration of either 50 mg oral naltrexone (ReVia, Dupont Merck Pharmaceutical Company, Wilmington, DE) or identical placebo in random order. The dose was chosen to be consistent with prior lab studies of naltrexone in acute smoking (4,17,44). It is also the standard dose used for its currently approved clinical indications in the treatment of opioid and alcohol dependence. The subjects were told to maintain cigarette smoking at normal levels before arriving to the session and to refrain from using alcohol, recreational drugs, and medications for 48 h prior to and 12 h after each session. Alcohol breathalyzer (Alco-Sensor III, Intoximeters, Inc.), and hCG pregnancy tests (female subjects) were negative for all subjects upon study arrival.

The subject arrived at the University of Chicago Clinical Research Center (CRC) at 1830 h the evening before the testing session to ensure overnight abstinence (i.e., 12 h) from smoking. The subject stayed in his/her own private room at the CRC. Shortly after admission, the subject received a dinner (40% daily calories) and was allowed to relax and read or watch television but not allowed to smoke after 2000 h. The subject was awoken at 0700 h the following morning and given a small breakfast (20% daily calories). At approximately 0720 h, the CRC nurse inserted an intravenous catheter into a forearm vein for blood sampling at various intervals and the subject was allowed to relax for an adaptation period.

The testing session began at 0740 h, with the subject submitting to baseline measures (questionnaires, blood, CO levels, vital signs) administered by the CRC nurse and the bachelor's level research technician. Table 1 depicts the overall session time line and measures. At approximately 0800 h, the subject was administered the capsule, which contained 50 mg naltrexone or identical placebo. The subject was allowed to relax and read or watch videos provided for the next 2 h, but not allowed to smoke cigarettes (postcapsule period). Questionnaires and blood sampling were repeated at approximately 0945 h. At 1000 h (2 h postcapsule), the subject was provided with a cigarette of his/her own brand and instructed to smoke it at the usual rate. The subject was administered questionnaires and CO tests immediately after smoking the cigarette and also at the end of a 1-h postcigarette rest interval (postcigarette measures taken at 5 and 60 min after the single cigarette). To reduce the effects of hunger on mood, the subject was given a light snack (15% daily calories) at approximately 1045 h.

The final portion of testing (choice smoking period; 1100–1300 h) was conducted after the postcigarette rest period. This interval consisted of a choice smoking paradigm in which the subject was given the option whether or not to smoke a cigarette of his/her brand each half-hour for a total of 2 h. Therefore, up to four more additional cigarettes could have been smoked in the session, in addition to the first cigarette at 1000 h. Each cigarette was offered from a pack of the subjects' usual brand, and the research technician carefully recorded each cigarette smoked. The technician had the cigarette pack in his possession at all times to avoid excessive temptation to the subject. The subject was allowed to read or watch television or videos provided during this time. At the end of the session, a final set of questionnaires, CO levels, and blood samples were obtained. The nurse removed the intravenous catheter and the subject was discharged. The second session was identical to the first session (i.e., naltrexone or placebo), with the addition of an exit interview, where the subject was asked to compare the sessions in terms of everyday smoking, pleasure, taste, and which session they thought

TABLE 1
TIMELINE OF SESSION EVENTS

	Time 0: capsule	(2 h Rest)	Fixed Smoke	(1 h Rest)	Smoking Choice			
	↓		↓		↓	↓	↓	↓
Measures:		cig 1			cig 1	cig 2	cig 3	cig 4
Questionnaires	X	X	X	X			X	
CO Reading	X		X	X			X	
Blood draws	X	X						X

"Fixed smoke" = subject smoked one cigarette of their own brand of cigarettes at their normal rate; "smoking choice" = subject given choice to smoke one cigarette each 30 min for 2 h.

they received the medication. The subject was then debriefed and paid for participation.

MEASURES

Subjective Measures

The Brief Questionnaire of Smoking Urges (B-QSU) (8) is a 10-item brief version of the Questionnaire of Smoking Urges (45) that measures acute smoking craving and urges. The B-QSU was given at baseline (pre- and postcapsule), and also at 5 and 60 min postsmoking. Each item on the B-QSU contains a smoking-urge statement for the subject to endorse with a Likert-type scale, scored from 10 (strongly disagree) to 70 (strongly agree). The B-QSU consists of two factor-derived subscales, with factor 1 reflecting desire to smoke for stimulation, and factor 2 reflecting urge to smoke to relieve nicotine withdrawal.

Several 10 cm-long adjective visual analogue scales (VAS) (2) were administered at baseline, 2 h postcapsule, and during several postsmoking intervals (5 and 60 min) to assess the following subjective states: dizzy, light-headed, jittery, head-rush, relaxed, ability to concentrate, irritable, feeling stimulated, desire to smoke, and pleasure from cigarette. The Stress-Arousal Checklist (SACL) (24) was also administered at the same intervals, and consists of four bipolar adjective pairs (tense–relaxed, nervous–calm, energetic–tired, alert–drowsy). Scores on the two former related pairs are combined into a single "stress" score, and scores on the latter two pairs combined into a single "arousal" score. The VAS and SACL scales have been shown in prior studies to be sensitive to acute nicotine (32,35,37,38).

Finally, subjects also completed the updated version of the Withdrawal Symptoms Checklist (16) and a side effects scale (21,22,49). The withdrawal scale consists of eight items closely related to the subjective withdrawal symptoms listed in the DSM-IV (APA, 1994). The side effects scale has been used in prior clinical and preclinical studies of naltrexone, and includes items rated from 0 (none) to 2 (severe) for nausea, vomiting, headache, sexual desire, erections, anxiety, lighted-headedness, flushing, and sedation. An exit interview was given at the end of participation and asked if the subject could estimate which session he/she received a medication, and if there were any session differences in several general effects (liking, cigarette taste, etc.).

Objective Measures

Blood samples (7 ml) were drawn at various intervals throughout the study. Samples obtained at three time points were used for determination of plasma nicotine levels (precapsule baseline, 2 h postcapsule, and at the end of the session) and its major metabolite cotinine (baseline only). All samples were drawn in a smoke-free environment to minimize sample contamination. The blood was drawn into lithium heparin (green top) tubes, and immediately set on ice and centrifuged within 30 min. Samples were stored at $-65°C$ and later packed in dry ice and shipped to the University of Vermont Clinical Research Center laboratory for assays. The radioimmunoassays, employing tritium as a tracer, for the measurement of cotinine and nicotine were performed using the methods of Van Vunakis et al. (47). The intra- and interassay %CV for cotinine were 6 and 9.5, respectively, and for nicotine, 3 and 11, respectively.

Expired CO levels were obtained using a carbon monoxide monitor (Vitalograph Breathco, Lenexa, KS). For each test, the subject was instructed to slowly exhale into a stop-chambered valve attached to the monitor for approximately 20 s, and the peak CO reading (in ppm) was recorded by the research assistant. Vital signs (blood pressure and heart rate) were monitored by the CRC nurse at baseline, after the medication, and upon session completion. Due to methodological problems, complete data for blood pressure and heart rate were available for only thirteen subjects.

Statistical Analyses

Subjective data were summarized into scale scores when appropriate. The primary dependent variables in this study were craving (B-QSU factors), pleasure and desire to smoke (VAS items), total nicotine withdrawal severity, and stress and arousal scores from the SACL. Secondary dependent measures included other VAS items shown to increase during acute smoking (dizzy, light-headed, and jittery), side effects, and exit interview items. Analyses of objective measures, such as CO and plasma nicotine, were performed to further support significant differences that were detected in subjective effects.

Initial analyses on the main dependent variables examined the overall sample on subjective data using repeated-measures analyses of variance (ANOVAs), with medication (naltrexone, placebo) and time (baseline, 2 h postcapsule, and 5 and 60 min postcigarette) as the within-subject factors. When appropriate, simple effects tests were used to examine significant main effects and interactions. A *t*-test was employed to compare the effects of naltrexone on ratings of the single

	Total Sample ($n = 22$)
General characteristics	
Age (years)	32.5 (2.0)
Education (years)	13.6 (0.4)
Height (cm)	169.0 (2.8)
Weight (kg)	78.7 (3.1)
SCL-90 global index	0.3 (0.1)
Race (% Caucasian)	68%
Gender (M/F)	12 M/10 F
S-MAST	1.6 (0.5)
Smoking characteristics	
Baseline B-QSU score	49.5 (2.5)
Cigarettes per day	25.3 (2.3)
Smoking duration (yrs)	13.9 (1.8)
Baseline CO readings (ppm)	10.0 (0.7)
Baseline nicotine readings (ng/ml)	0.8 (0.1)
Baseline cotinine levels (ng/ml)	274.5 (30.0)
FTND score	5.8 (0.5)

Data indicate mean (SEM). S-MAST = Short Michigan Alcoholism Screening Test; SCL-90 = symptom checklist-90; B-QSU = brief questionnaire of smoking urges; FTND = Fagerström test for nicotine dependence.

VAS item "pleasure from cigarette," which was only administered after the first cigarette. Objective measures (CO and nicotine) were analyzed upon finding a significant pattern of results on the subjective data for additional support for these findings. Nonparametric chi-square analyses were conducted on the side effects and exit interview data.

Exploratory analyses were conducted to identify those subjects with potentially greater naltrexone sensitivity, as indicated by greater placebo–naltrexone craving composite change scores at the postsmoking time points (5 and 60 min). A one-way ANOVA was conducted on this composite craving measure, with subject subgroups derived from high and low split on the following variables: FTND score, baseline B-QSU craving score, quantity frequency of alcohol consumption, and family history of alcoholism (i.e., FH+/FH−). Because these analyses were largely exploratory in nature, we only examined the main variable of interest, cigarette craving, as the dependent variable.

RESULTS

The racial composition for the sample was 68% Caucasian, 23% African-American, and 9% Hispanic. The subjects smoked an average of 25.2 cigarettes daily (range 10–60; nicotine yield average = 0.98, range 0.70–1.35) for a duration of 13.9 years (range 1.5–32 years) with an average FTND score of 5.8 (range 2–10). Complete demographics and subject characteristics are listed in Table 2.

As expected, craving scores (B-QSU total, factors 1 and 2) did not change prior to smoking but declined immediately after the first cigarette and began rising again after the 1-h rest period [time main effect, $Fs(3, 63) > 29.0$, $ps < 0.001$. Although there were no medication effects on craving during the presmoking interval, naltrexone significantly attenuated craving postsmoking, which was evident at the 1-h postsmoking rest period [med × time (B-QSU total, factor 1), $Fs(3, 63) > 4.25$, $ps < 0.05$; see Fig. 1]. Thus, naltrexone, compared to placebo, significantly reduced craving increases observed 1 h after subjects smoked a cigarette.

For the VAS items, we found a significant pattern of mood effects after subjects smoked the single cigarette. As expected, immediately after smoking the first cigarette, ratings were decreased for "desire to smoke" [time, $F(3, 63) = 3.38$, $p < 0.001$]. Significant modest increases were also found after smoking the cigarette for the VAS scales for dizzy, light headed, and head rush [time main effect, $Fs(3, 63) > 12.00$, $ps < 0.001$] with values peaking at the immediate postcigarette time point (Figs. 2c–d).
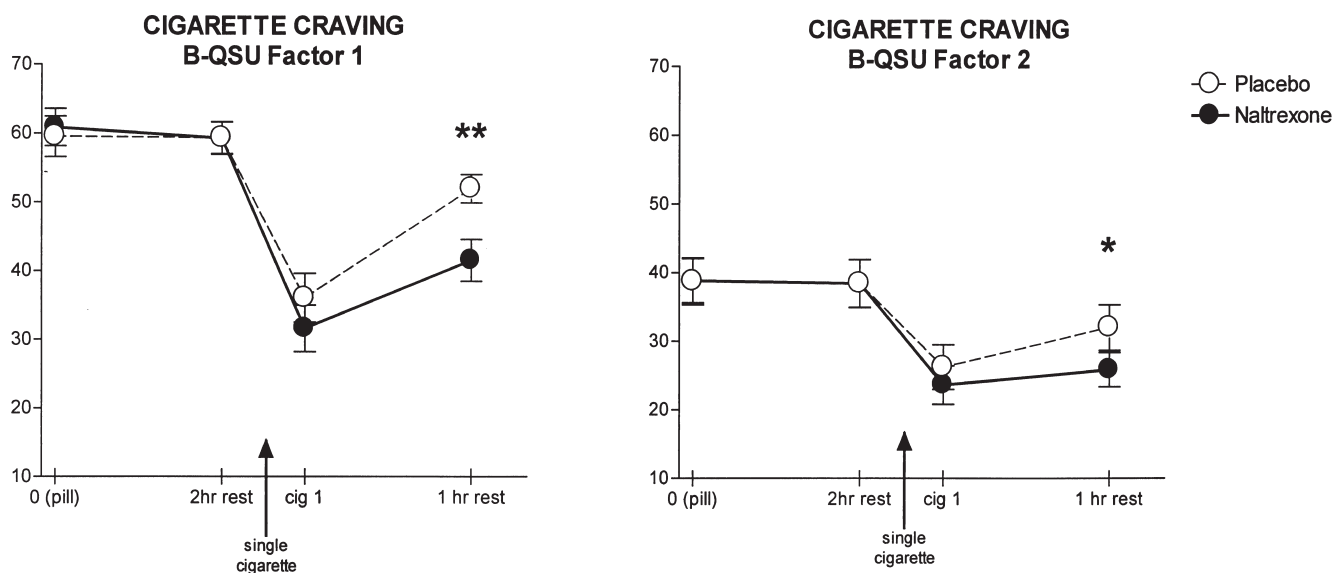

FIG. 1. Cigarette craving ratings for total sample. B-QSU Craving factor 1 = craving for smoking stimulation; B-QSU craving factor 2 = craving to relieve withdrawal; B-QSU administered prior to the capsule (2 hr rest), 2 h after the capsule, immediately after the cigarette (cig 1), and after a 1 h postsmoking rest period (1hr rest). *$p < 0.05$, **$p < 0.01$ (simple effects tests).
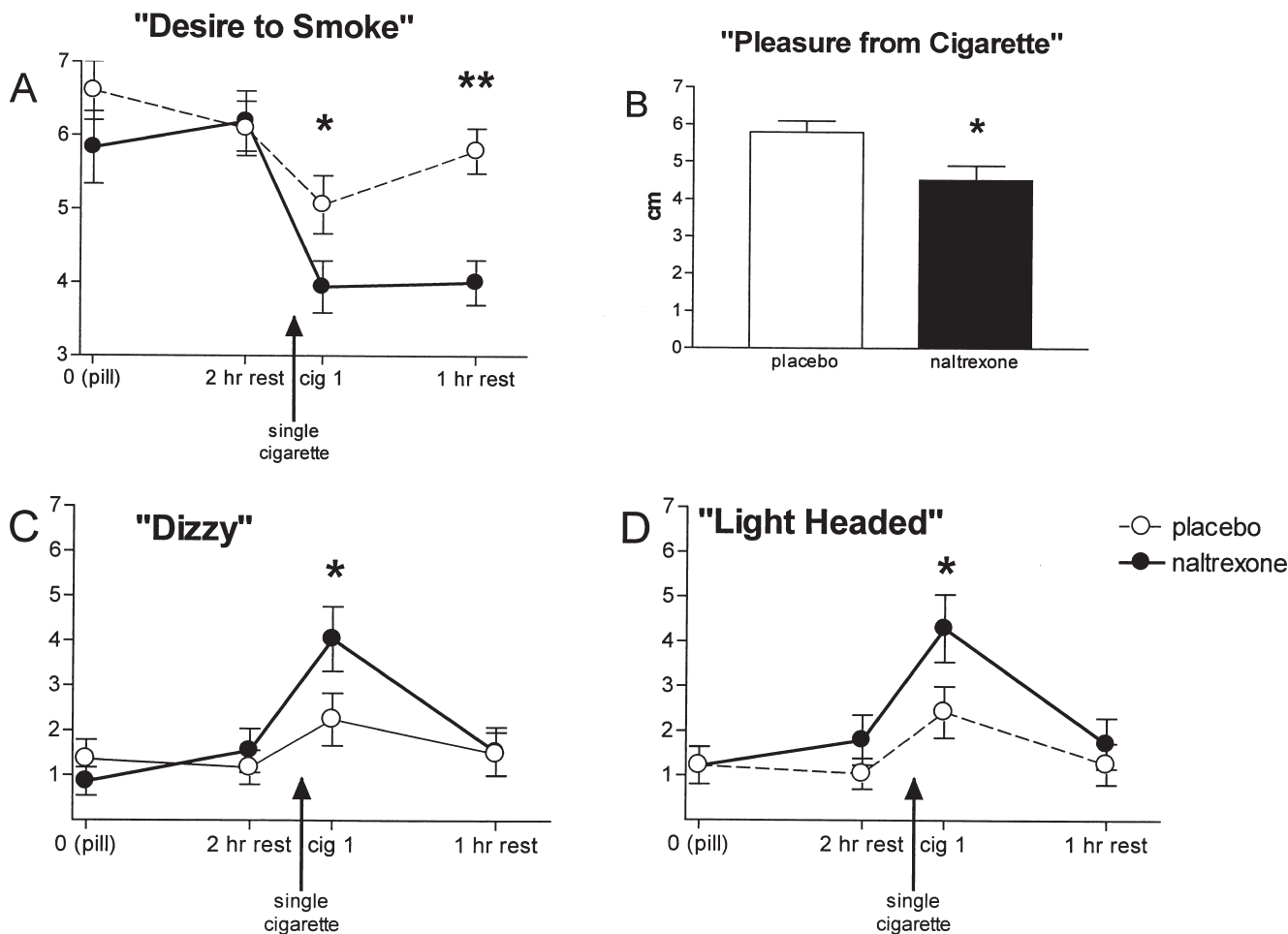
FIG. 2. Visual analog ratings (100 mm) for total sample. Item for "pleasure from cigarette" only given at the immediate postcigarette time point (cig 1). All other VAS items administered prior to the capsule (2 hr rest), 2 h after the capsule, immediately after the cigarette (cig 1), and after a 1-h postsmoking rest period (1 hr rest). $*p < 0.05$, $**p < 0.01$ (simple effects tests).

No smoking-related changes were noted for the other VAS items in our paradigm (i.e., jittery, relaxed, ability to concentrate, feeling irritable, etc.). Naltrexone produced a significant pattern of mood alteration on the VAS items found to be sensitive to the single cigarette, including significant diminished ratings for "desire to smoke" immediately after smoking, which persisted through the one hour post-smoking break [med × time, $F(3, 63) = 3.16$, $p < 0.05$; see Fig. 2a] and reduced self-reported "pleasure from cigarette," $t(21) = 2.50$, $p < 0.05$ (see Fig. 2b).

Naltrexone also appeared to augment postsmoking ratings for dizzy [med × time, $F(3, 63) = 4.27$, $p < 0.01$], light headed, and head rush [med main effect, $Fs(1, 21) > 6.34$, $ps < 0.05$; simple effects (5 min postsmoke): $p < 0.05$]. These effects do not appear to be related to autonomic changes, as naltrexone moderately reduced both diastolic blood pressure and heart rate 1 h after medication administration (naltrexone DBP = 64 mmHg, HR = 67 bpm; placebo DBP = 68 mmHg, HR = 73 bpm; $ps < 0.05$) when subjective effects were not apparent. There were no naltrexone-related alterations of vital signs data after cigarette smoking, when significant mood effects were noted.

As anticipated, results from the withdrawal scale showed that ratings of self-reported withdrawal symptoms declined significantly after smoking the cigarette [time, $F(2, 42) = 12.21$, $p < 0.001$]. Naltrexone did not alter ratings of withdrawal symptoms during any of the pre- or postsmoking intervals (ps = NS, Fig. 3). Chi-square analyses indicated no differences in incidence of reported side effects in the naltrexone compared to placebo sessions prior to smoking (i.e., 2-h postcapsule: naltrexone session, 41% of subjects with one or more side effect; placebo session, 32%). However, 1 h after smoking the single cigarette, there was an increased incidence of naltrexone-related side effects (68%) compared to placebo (32%) [$\chi^2(1) = 5.82$, $p < 0.05$]. The most common side effects during naltrexone included light headed ($n = 7$ naltrexone; $n = 2$ placebo), sedated ($n = 5$ naltrexone; $n = 2$ placebo), and nausea ($n = 4$ naltrexone; $n = 0$ placebo); all but one subject indicated that these effects were in the mild range. Similar to prior work indicating some mild increases in sedation after naltrexone administration (21,26,44), we found naltrexone produced decreased ratings for arousal (SACL) and feeling stimulated (VAS), particularly after the 1-h smoking break [med × time, $F(3, 63) = 7.28$, $p < 0.001$].

Results on smoking behavior during the choice interval showed similar naltrexone-related attenuation of smoking
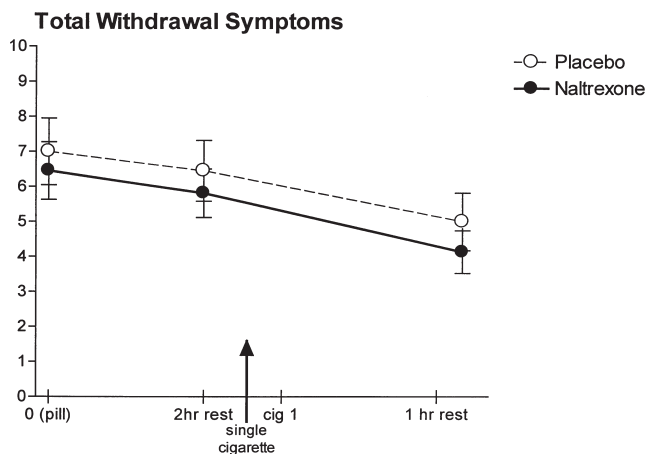
Total Withdrawal Symptoms

FIG. 3. Total withdrawal symptoms for total sample. Updated version of the Hughes-Hatsukami Withdrawal Scale administered prior to the capsule, 2 h after the capsule, and after a 1-h postsmoking rest period. No significant main effects or interactions.

(Fig. 4). During the naltrexone session, there was a significant reduction in number of choice cigarettes smoked (2.6 ± 0.17 cigarettes) compared to placebo (3.2 ± 0.23 cigarettes), $t(21) = 3.78$, $p < 0.01$. This naltrexone-induced reduction of cigarette smoking was corroborated by objective indicators, including significantly reduced CO and plasma nicotine levels, $ts(21) > 4.55$, $ps < 0.01$. Presmoking (baseline and 2-h postcapsule) levels of CO, nicotine, and cotinine (baseline only) did not differ between sessions, $ts(1, 21) < 1.26$, $ps = $ NS. Therefore, in addition to altering subjective response to the first cigarette of the day, naltrexone also reduced subsequent choice smoking behavior.

Chi-square analyses conducted on the exit interview revealed that a significant majority of the subjects were able to correctly identify which session they received the medication and that the placebo session was more like everyday smoking (73%) [$\chi^2(1) = 4.54$, $p < 0.05$]. There was a trend for subjects' identifying the naltrexone session as the one producing overall less pleasure in smoking [$\chi^2(1) = 2.91$, $p < 0.09$]. Taste of cigarettes, session liking, and global craving did not differ between sessions ($ps = $ NS).

Exploratory analyses on subject subgroups to assess potential individual difference factors in naltrexone sensitivity revealed significant subgroup differences based on a split of baseline morning craving scores. The sample was divided into two near-equal sized subgroups using the baseline (overnight abstinence) craving scores, resulting in a high craving [baseline B-QSU = 57.4 (range = 52–60)] and a low craving subgroup [baseline B-QSU = 38.0 (range = 26–41)]. The subgroups did not differ significantly on general demographic characteristics (see Table 3). Results showed that for both factors of B-QSU, naltrexone significantly attenuated urge to smoke during the postsmoking phase in the high cravers but

Number of Cigarettes Smoked

Final CO reading
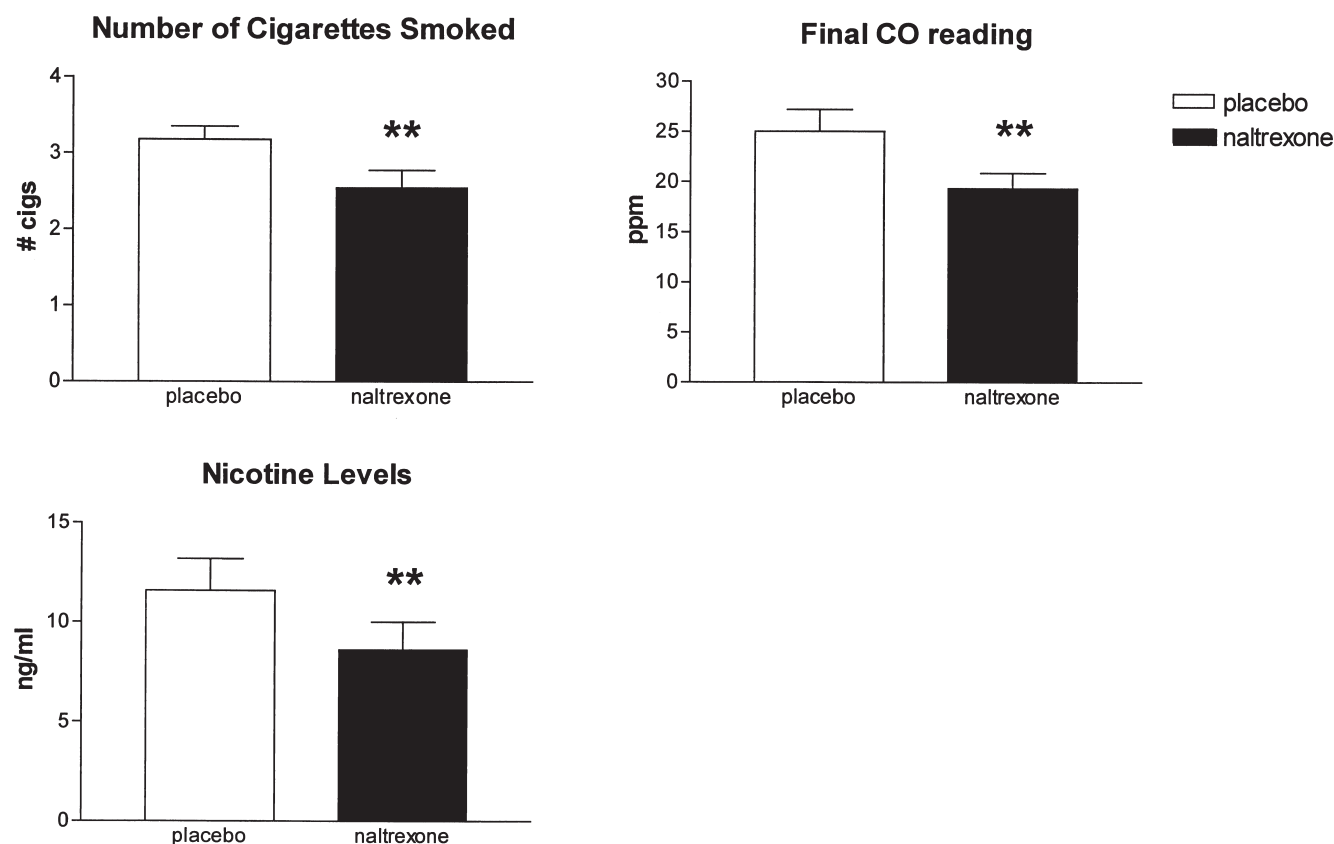

Nicotine Levels

FIG. 4. Objective measures during choice smoking in total sample. Naltrexone significantly reduced number of cigarettes smoked, CO levels (ppm), and plasma nicotine levels (ng/ml). Levels were measured at the end of the choice interval. **$ps < 0.01$ (t-tests).

	High Cravers (HCs; $n = 13$)	Low Cravers (LCs; $n = 9$)
General characteristics		
Age (years)	31.4 (2.5)	34.2 (3.4)
Education (years)	13.5 (0.6)	13.8 (0.5)
Height (cm)	165.9 (2.9)	174.6 (5.2)
Weight (kg)	74.1 (3.0)	83.3 (5.6)
SCL-90	0.4 (0.1)	0.2 (0.1)
Race (% Caucasian)	77	56
Gender (M/F)	5 M/8 F	7 M/2 F
S-MAST	1.3 (0.5)	2.2 (0.8)
Smoking characteristics		
Baseline B-QSU score	57.4 (1.2)*	38.0 (2.9)
Cigarettes per day	26.4 (3.5)	23.6 (2.7)
Smoking duration (yrs)	14.2 (2.6)	13.6 (2.6)
Baseline CO readings (ppm)	9.9 (0.8)	10.2 (1.4)
Baseline nicotine readings (ng/ml)	0.8 (0.1)	0.9 (0.3)
Baseline cotinine levels (ng/ml)	241.4 (25.1)	322.3 (63.2)
FTND score	6.2 (0.7)	5.0 (0.5)

Data indicated are mean (SEM).
*$p < 0.05$.

not in the low cravers, $Fs(3, 60) > 3.30$, $ps < 0.05$ (see Fig. 5). The results suggest greater naltrexone sensitivity in reducing smoking craving (5 and 60 min after one cigarette) in those smokers who are exhibiting high levels of cigarette craving after short-term abstinence.

Examination of other potential subject subgroups, based on severity of nicotine dependence and family history of alcoholism, failed to show any differences in naltrexone sensitivity to smoking response ($ps = $ NS). Rates of family history of tobacco use in the sample were so highly prevalent (i.e., 84%) that this variable could not be used in the analyses. However, there was a trend for heavier alcohol drinkers to have less cigarette craving reduction from naltrexone, $F(1, 20) = 3.55$, $p = 0.07$. This finding might relate to premorbid factors, effects of chronic exposure to both substances, and/or contextual factors. Relevant for the latter explanation is prior research demonstrating that drinkers have increased cigarette craving or intensity of smoking in the context of alcohol drinking or alcohol-related cues (5,28, 30,42), neither of which was present in our laboratory paradigm.

DISCUSSION

The findings of the present study show that preadministration of 50 mg oral naltrexone altered acute cigarette smoking reinstatement, as measured by subjective craving and mood effects, smoking choice behavior, and objective indicators, such as expired air CO and plasma nicotine levels. During the first 2 h of administration, naltrexone did not effect any of the baseline craving and mood effects measured in this study. However, naltrexone compared to placebo produced significant alteration in acute smoking response immediately after the first cigarette, including decreased desire to smoke and pleasure from cigarette and increased dizziness and light-headedness. Some of these acute effects, such as reduced

craving and desire to smoke, persisted during the 1-h post-smoking phase after the single cigarette. In contrast, during the placebo capsule session, 1 h after the cigarette, levels for both craving and desire to smoke appeared to be returning back to their relatively high baseline levels.

The results suggest an important interaction between opioid receptor blockade and nicotine reexposure after deprivation. Naltrexone produced significant changes in response to a single cigarette, including augmented levels of dizziness and light-headedness, which resulted in less pleasure from smoking. We might speculate that these effects could be the result of a reduction in the opioidergic or opioid–dopaminergic mechansims underlying nicotine reinforcement. This could conceivably render the smoker with either exaggerated or more salient aversive stimulant effects of nicotine through adrenergic mechanisms. It is also possible that opioid antagonist aversive effects caused a potentiation of these subjective effects during the single cigarette; however, subjects did not appear to try to compensate for this loss of nicotine reinforcement by increasing intake of cigarettes. To the contrary, desire to smoke as well as actual choice smoking behavior were attenuated by naltrexone, and corroborated by lower CO and plasma nicotine levels.

Given the relative heterogeneity present in chronic smokers and recent studies indicating individual difference factors in opioid antagonist sensitivity (20,21,51), we explored naltrexone response based on several potential between-subjects variables. Although caution must be taken in overinterpretation of the findings because of small subgroup sizes in split-sample analyses, our results suggest that those smokers exhibiting the highest levels of craving for cigarettes might be the most sensitive to the effects of opioid antagonism on nicotine exposure. This finding might simply reflect that the effects of a pharmacological agent are apparent only in those persons exhibiting the target symptom before administration of the agent. Similarly, there might be a floor effect in those smokers who experience mild craving after deprivation, with the effects of naltrexone less apparent compared to those smokers exhibiting the highest urge to smoke during abstinence. Further research will determine whether a high level of abstinence-induced cigarette craving is an important individual difference factor in opioid antagonist-nicotine sensitivity.

The mechanisms of subjective cigarette craving during abstinence might relate to either acquired or premorbid factors, or both. Predictors or identifiers of high-craving smokers during abstinence remain to be determined, because no major subject-related factors (i.e., smoking levels, duration, FTND scores, etc.) differentiated the subgroups. However, there was a trend for a greater number of females represented in the high (eight females) versus low craver groups [two females; Fishers exact $p < 0.10$], consistent with other studies indicating higher levels of craving and withdrawal symptomatology in female compared to male smokers (12). Women have also been implicated as smoking more for nonnicotine influences, such as sensory or conditioned effects (36), and further studies will help determine whether they are also more sensitive to nonnicotine biological factors, such as opioid-related smoking reinforcement. Opioid antagonist sensitivity to smoking might also be reflective of low baseline endogenous opioid tone or other premorbid differences in opioid interactions with dopaminergic, serotonergic, or other neurotransmitter systems implicated in reward pathways and addictive disorders (52). Finally, there was a trend for those persons with higher alcohol drinking patterns to exhibit less craving reduction from naltrexone. This might be related in part to
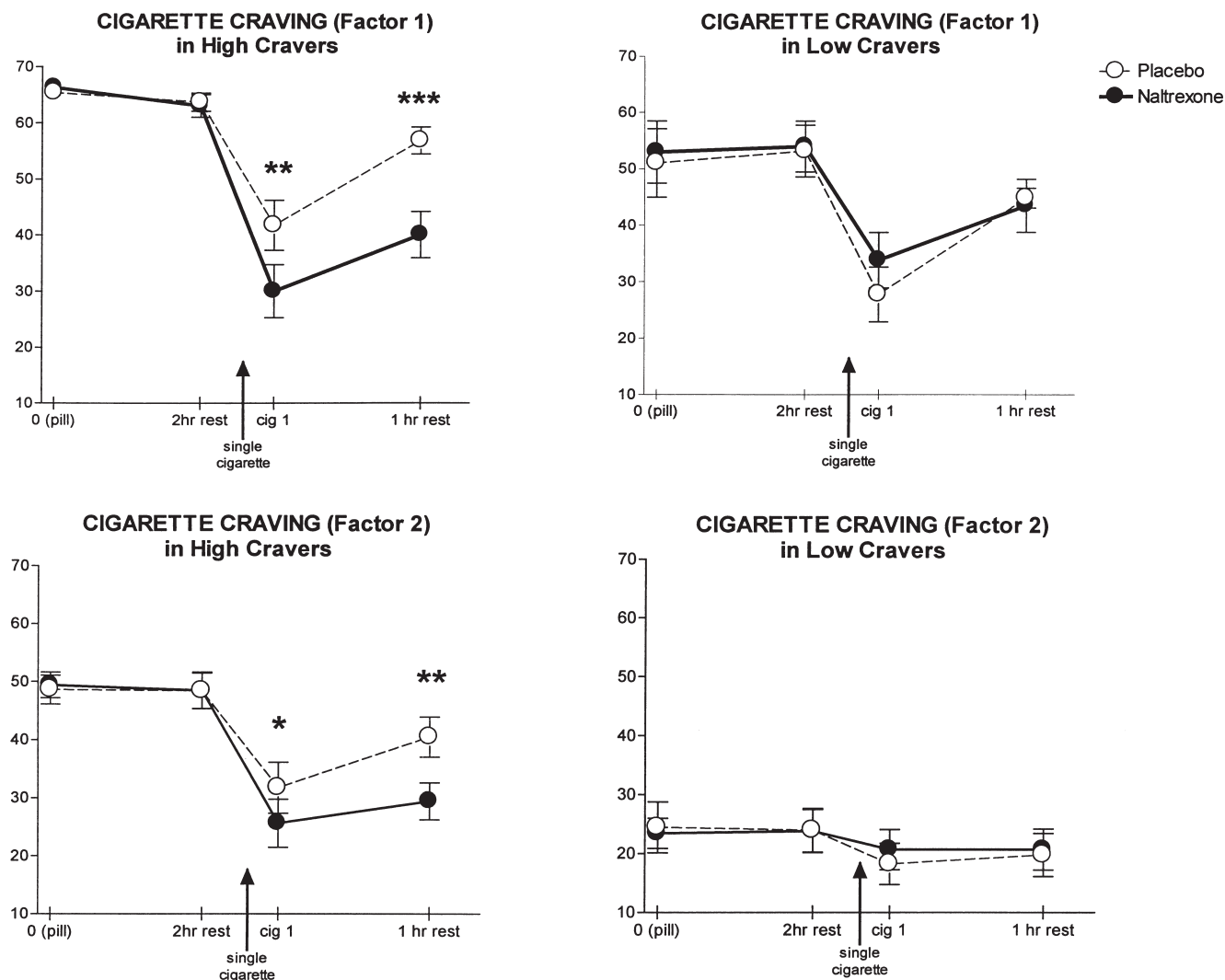
FIG. 5. Cigarette craving ratings comparing high- ($n = 13$) and low-craver ($n = 9$) subgroups. B-QSU craving factor 1 = craving for smoking stimulation; B-QSU craving factor 2 = craving to relieve withdrawal; B-QSU administered prior to the capsule, 2 h after the capsule (2 hr rest), immediately after the cigarette (cig 1), and after a 1-h postsmoking rest period (1 hr rest). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ (simple effects tests).

study parameters, such as lack of contextual factors (alcohol cues, time of day), or to differences in premorbid or acquired opioid sensitivity in those persons with chronic heavy drinking and smoking.

Comparison of the current study with other human laboratory studies of naltrexone and smoking is difficult given the differences in study design and parameters; however, some general comparison points are worth noting. First, naltrexone has been shown to increase negative mood and withdrawal-like features in some studies (4,44) but not in others (17). In the present study, naltrexone had no effect on subjective nicotine withdrawal, either before or after cigarette smoking. The withdrawal scale used in our study is commonly used in acute smoking research and measures DSM-related subjective withdrawal features (i.e., craving, irritability, anxiety, difficulty concentrating, restlessness, appetite changes, depressed mood, and insomnia). However, naltrexone did produce increases in some unpleasant physical effects, such as mild light-headedness, sedation, and nausea, similar to results in prior clinical and pre-

clinical studies. Although we did not show support for opioid antagonist elicitation of withdrawal (23,25), we did find some expected side effects, which cannot be ruled out as potential factors involved in naltrexone–smoking response.

The time course of naltrexone administration and sampling of acute smoking effects might be another important issue across studies. Naltrexone undergoes extensive biotransformation with plasma levels peaking within several hours and precipitously declining thereafter (19,50). Laboratory studies of oral naltrexone and cigarette smoking have varied in time course of acute smoking testing from 1 h (4) to 24 h (44) postmedication, which may affect results. We chose to examine the effects of naltrexone when the majority of subjects would be showing peak levels of naltrexone (i.e., study smoking interval 2–5 h postnaltrexone) and, therefore, the generalizability across studies may not be possible. A final comparison point relates to whether or not subjects can discern the effects of naltrexone. Contrary to one study (17), we found that a substantial proportion of our smokers were able

to distinguish which session they believed they thought they received the medication (i.e., naltrexone session) and which session was more like everyday smoking (i.e., placebo session). Subjects were not able to estimate above chance which session they preferred in terms of cigarette taste, session liking, or overall craving.

In sum, naltrexone compared to placebo augmented some of the acute effects of a single cigarette, and reduced subsequent craving, desire to smoke, and choice smoking behavior. Caution must be taken in interpretation of these findings due to small sample sizes and the potential resultant risk of finding a spurious result, although the results presented showed a consistent pattern of naltrexone altering smoking on subjective, objective, and behavioral indices. The results of this study support continued investigation of opioid antagonists for adjunct treatment in smoking cessation and a potential focus on high-risk smokers who may show difficulty in abstaining and are at risk for relapse.

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