

## Naltrexone attenuates acute cigarette smoking behavior

Alyssa M. Epstein<sup>a</sup>, Andrea C. King<sup>b,\*</sup>

<sup>a</sup>*Illinois Institute of Technology, Institute of Psychology, Chicago, IL, USA*

<sup>b</sup>*Department of Psychiatry, Pritzker School of Medicine, University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, USA*

Received 31 May 2003; received in revised form 14 September 2003; accepted 16 September 2003

### Abstract

This within-subjects, placebo-controlled laboratory study was designed to examine the effects of naltrexone on cigarette response in 44 chronic smokers (23 male, 21 female). Each participant received either 50-mg oral naltrexone or identical placebo during the morning of the session after maintaining overnight abstinence. Subsequently, the participant was administered a smoking cue (holding lit cigarette) to examine craving and associated features of smoking, and instructed to smoke a cigarette 1 h later. This was followed by a smoking interval in which participants could choose to smoke up to four more cigarettes over a 2-h period. Subjective measures (withdrawal, craving, affect, and side effects) and smoking behavior were assessed throughout the session. Naltrexone significantly reduced the total number of choice cigarettes smoked and expired carbon monoxide levels ( $P < .05$ ). Naltrexone significantly increased total side effects, especially for sedation ( $P < .01$ ). Further, naltrexone significantly increased overall negative affect, and decreased positive affect 1 h after smoking the first cigarette ( $P < .05$ ). However, naltrexone did not affect acute withdrawal or smoking urges. Despite mixed findings, women reported more overall naltrexone-induced withdrawal ( $P < .05$ ) and side effects ( $P < .08$ ) compared to men. Although the exact mechanism is unknown, the findings support an opioid antagonist attenuation of smoking behavior.

© 2003 Elsevier Inc. All rights reserved.

**Keywords:** Naltrexone; Opioid antagonist; Cigarette; Smoking; Laboratory paradigm; Subjective effects

### 1. Introduction

Smoking is paradoxical in nature because it simultaneously increases arousal and decreases self-reported stress levels (see Parrott, 1998, for review; Nesbitt, 1973). One of the challenges in treating nicotine dependence is that smoking urges may be derived from both positive reinforcement (i.e., increased concentration or alertness) as well as negative reinforcement (i.e., an avoidance of nicotine withdrawal symptoms; Baker et al., 1986; Niaura et al., 1988). Various neurobiological mechanisms have been proposed to underlie the reinforcing properties of cigarette smoking. Animal studies have shown that acute nicotine administration causes an elevation in plasma concentrations of beta-endorphin (Conte-DeVolx et al., 1981) and induces changes in the levels of the opioid met-enkephalin in the nucleus accumbens, an area involved in regulating reward (Houdi et al., 1991; Pierzchala et al., 1987). Furthermore, both animal and human

studies have indicated that administration of naloxone, a short-term opioid antagonist, precipitates a nicotine/opioid abstinence syndrome (i.e., withdrawal; Krishnan-Sarin et al., 1999; Malin et al., 1993, 1996) and blocks nicotine-induced antinociceptive effects (Tripathi et al., 1982). These findings offer support for the hypothesis that an opioid mechanism may play a role in the reinforcing effects of smoking.

Human studies have supported a nicotine-opioid interaction by demonstrating that the administration of methadone, an opioid agonist, increases smoking behavior (Chait and Griffiths, 1984; Mello et al., 1980), as well as tobacco craving and nicotine withdrawal symptoms (Story and Stark, 1991). Furthermore, two studies have demonstrated that naloxone reduces smoking behavior (Gorelick et al., 1989; Karras and Kane, 1980), but these results are mixed (Nemeth-Coslett and Griffiths, 1986). Although studies using naloxone have indicated some preliminary evidence for a nicotine–opioid link, more recent smoking administration studies have focused on the opioid antagonist naltrexone because of its longer half-life, oral administration, and potential relevance for clinical applications.

Similar to studies with naloxone, studies examining naltrexone's effects on smoking response are also mixed.

\* Corresponding author. Tel.: +1-773-702-6181; fax: +1-773-702-6454.

E-mail address: [aking@yoda.bsd.uchicago.edu](mailto:aking@yoda.bsd.uchicago.edu) (A.C. King).

Naltrexone has been found to decrease smoking satisfaction (Wewers et al., 1998), smoking desire and craving, (King and Meyer, 2000), perceived difficulty in abstaining from smoking (Sutherland et al., 1995), and negative affect to a smoking cue when combined with the nicotine patch (Hutchison et al., 1999a). Additionally, several studies have shown that naltrexone decreased the number of choice cigarettes smoked (King and Meyer, 2000; Wewers et al., 1998), corroborated by reduced expired air carbon monoxide and plasma nicotine levels (King and Meyer, 2000). However, other studies have not found an effect of naltrexone on smoking satisfaction or withdrawal measures (Brauer et al., 1999; Houtsmuller et al., 1997; Sutherland et al., 1995), or naltrexone attenuation of cigarette smoking (Brauer et al., 1999; Sutherland et al., 1995). This discrepancy may be due to differences across studies in the medication dose, time between naltrexone administration and cigarette smoking, period of abstinence required before the session, or differences in smoking paradigms within the session (i.e., smoking in the laboratory versus in a naturalistic setting). Furthermore, sample sizes generally have been small ( $Ns \leq 22$ , within-subjects), which may have increased the likelihood of type II error (i.e., failure to find truly significant results) in some studies.

Although to date no laboratory studies have examined sex differences in the effects of naltrexone on cigarette smoking, a preliminary clinical smoking cessation trial suggested that women smokers may benefit more from adjunct treatment with naltrexone than their male counterparts (Covey et al., 1999). In addition, clinical studies involving nonnicotine based pharmacotherapies have suggested that women smokers show greater reductions in craving and/or improved quit rates compared to men (Lerman et al., 2001; Covey and Glassman, 1991; Rose et al., 1999). Non-nicotine based pharmacotherapy may be particularly beneficial for women because they are less able to discriminate nicotine compared to their male counterparts (Perkins, 1995), and may smoke more in response to non-nicotine factors, such as escape from dysphoria, alleviating negative affect, and social pleasure (Grunberg et al., 1991; Perkins, 1996). Therefore, an examination of sex differences in response to naltrexone under well controlled laboratory conditions is warranted.

The present investigation was a human laboratory study comparing the effects of naltrexone versus placebo on various subcomponents of acute smoking. It is unclear whether naltrexone's potential attenuation of smoking parameters may be mediated through direct exposure to nicotine or to general associated features of the cigarette (i.e., handling of a cigarette and smoking cues). To explore these components, four phases of smoking were examined, including effects of naltrexone during short-term abstinence, after a smoking cue, immediately after smoking a single cigarette of the participant's preferred brand, and during a choice cigarette phase. The primary goal of this study was to replicate previous findings in our laboratory (King and

Meyer, 2000), in which naltrexone reduced behavioral choice for smoking and attenuated subjective craving and smoking desire. The secondary goal was to extend prior findings showing naltrexone attenuation of subjective response to a smoking cue (Hutchison et al., 1999a) relative to placebo. Finally, exploratory analyses stratified the sample by sex on smoking measures, and it was hypothesized that women would show greater naltrexone-induced attenuation of smoking behaviors compared to their male counterparts.

## 2. Methods

### 2.1. Participants

The final sample consisted of 44 regular cigarette smokers (23 male, 21 female), who were recruited through flyers and advertisements in local Chicago newspapers. Interested candidates were first screened over the telephone to determine their eligibility based on the following criteria: age between 21 and 65 years, a minimum of smoking 13 cigarettes (up to two packs) daily for a minimum of 2 years, body mass indices between 19 and 34, and be in general good health. Those participants who met these basic criteria were subsequently invited for an in-lab screening session, which included a physical examination by the resident physician, questionnaires, and a diagnostic interview. Standard cut-off thresholds were used for questionnaires, which included the Beck Depression Inventory (BDI; Beck et al., 1961), Symptom Checklist-90 (SCL-90; Derogatis, 1983), State-Trait Anxiety Inventory (STAI; Spielberger et al., 1987), Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991), Short Michigan Alcoholism Screening Test (SMAST; Selzer et al., 1975), a drug and health history questionnaire, and the Mood Episodes and Alcohol Use Disorders modules from the Structured Diagnostic Interview for the DSM IV (SCID; First et al., 1995). Participants were excluded from participation if they reported any major medical or psychiatric conditions, including current drug and/or alcohol dependence. Participants 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), or if they were pregnant, breast-feeding, or taking psychotropic medications.

### 2.2. Procedure

During the screening session, the participant signed informed consent, which was approved by the University of Chicago Internal Review Board. To minimize medication expectancy, the consent form explained that the participant could receive naltrexone or placebo on either or both sessions. Each participant in fact received preadministration of either 50 mg oral naltrexone (Depade Mallinckrodt, St.

Louis, MO) or identical placebo in random order. This dose was chosen to be consistent with our prior study (King and Meyer, 2000), and is the current FDA-approved dose for the treatment of alcohol and opioid dependence. The two identical testing sessions occurred on average 9 days apart (range 3–21 days). Participants were asked to maintain their regular smoking patterns before arriving to the laboratory and in between sessions, and they were instructed to abstain from alcohol and drug use 48 h prior to each session, and prescription medication 12 h before the session. Female participants were given additional pregnancy tests before each session, and all results were negative.

The evening prior to each session, the participant arrived between 1700 and 1830 h for an overnight stay in a private room at the University of Chicago Clinical Research Center (CRC). This ensured overnight smoking abstinence and allowed participants to acclimate to the stress-minimized hospital environment. The participant received dinner (40% daily calories) upon arrival and was allowed to smoke until 2000 h, whereupon the nurse took the cigarettes to avoid temptation for the subject. The participant awoke at 0700 h the following morning and consumed a small breakfast (20% daily calories). At 0720 h, the CRC nurse inserted an intravenous catheter into the forearm vein for blood sampling. Participants were allowed to read or watch television or movies during periods when study measures were not being taken.

The testing session began at 0745 h, with the CRC nurse obtaining vital signs and blood samples and the research technician obtaining the participant's baseline measures, including questionnaires and carbon monoxide (CO) levels. At 0800 h, the participant received either 50-mg naltrexone or an identical placebo tablet. As seen in Table 1, questionnaires were obtained at various intervals throughout the session. Participants were allowed to rest or watch television between time intervals. At the 120-min time point, the smoking cue was introduced, in which the technician instructed the participant to light a cigarette of his/her brand, hold it for 60 s without smoking it, then extinguish the

cigarette in the ashtray. The participant completed questionnaires immediately following and 50 min postcue. At the 180-min time point, the technician told the participant to smoke one cigarette of his/her preferred brand at the usual rate. The participant completed the measures immediately following and 50 min postcigarette. At 1145 h, the participant consumed a snack (15% daily calories) to avoid effects of hunger on mood state.

The final segment of testing included a choice smoking interval commencing at 240 min. During this 90-min period, the participant was given the option of smoking a cigarette at half-hour intervals (i.e., maximum four choice cigarettes). The technician recorded each cigarette smoked and removed the pack of cigarettes from the room between smoking choice trials. At the end of the session, the participant completed a final set of questionnaires and CO readings. The nurse obtained a final blood sample outside of the subject's private room (to avoid contamination of nicotine molecules in the air after smoking), then removed the intravenous catheter and discharged the subject. The second session was identical to the first session with the exception of an exit interview at the end of the study. The participant was debriefed and paid US\$175 within several weeks of participation.

### 2.3. Measures

The Brief Questionnaire of Smoking Urges (BQSU; Cox et al., 2001) is a brief, 10-item version of the Questionnaire of Smoking Urges (Tiffany and Drobes, 1991), which measures smoking craving and urges. Individuals respond to each statement using a Likert scale from 10 (*strongly disagree*) to 70 (*strongly agree*). The Positive Affect/Negative Affect Schedule (PANAS; Watson et al., 1988) is a 20-item questionnaire measured on a Likert Scale from 1 (*very slightly*) to 5 (*extremely*). The PANAS is divided into two subscales: Positive Affect reflects the extent to which the individual feels alert or enthusiastic, and Negative Affect reflects general subjective distress that is accompanied by

Table 1  
Timeline of session

Measures	Time									
	0 min (Prepill)	110 min (Precue)	120 min (Postcue)	170 min (Precigarette)	180 min (Postcigarette)	230 min (1-h rest)	240–330 min (choice cigarettes)			
							1	2	3	4
Questionnaires										
BQSU, VAS, PANAS,	X	X	X	X	X	X				
Withdrawal										
Side Effects	X	X								X
Exit										X
CO Reading <sup>a</sup>	X				X	X	X	X		X
Blood Draws	X									X

The "postcue" at T-120 = immediately after subject held the lit cigarette for 60 s; the "postcigarette" at T-180 = immediately after fixed cigarette in which the subject was instructed to smoke one cigarette of his/her own brand; "choice cigarettes" at the end of the session = subject was given a choice to smoke one cigarette every 30 min for 1.5 h.

<sup>a</sup> Carbon monoxide was monitored throughout the session, with analyses performed only on end of session readings.

various aversive mood states. Further, participants were given several 10-cm-long visual analogue scales (VAS; Aitken, 1969), which evaluated feelings such as dizzy, light-headed, head rush, ability to concentrate, relaxed, irritable, desire to smoke, and pleasure from cigarette. Participants also completed an updated version of the Withdrawal Symptoms Checklist (Hughes and Hatsukami, 1986) and a side effects scale, which has been used in prior clinical and preclinical trials with naltrexone (King et al., 1997a,b), and consists of 10 items (nausea, vomiting, headache, sexual desire, erections, anxiety, light-headedness, flushing, sedation, and other).

Blood samples (approximately 20–25 ml) were drawn during the study. Samples obtained at two time points were analyzed to determine plasma nicotine levels (pretablett baseline and end of session) and its major metabolite cotinine (pretablett baseline only). All samples were drawn in a smoke-free environment to minimize 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  $-20^{\circ}\text{C}$  and later packed on dry ice and shipped to the University of Vermont Clinical Research Center laboratories 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. (1987). The intra- and interassay %CV for cotinine were 6.2 and 8.4, respectively, and for nicotine, 9.3 and 10.8, respectively. Three of the 44 subjects were excluded from the plasma nicotine level analysis because of catheterization or measurement problems.

Expired air CO levels were obtained using a hand-held monitor (Smokerlyzer, Bedford, Medford, NJ). For each trial, the subject was instructed to slowly exhale into a stop-chambered valve attached to the monitor for approximately 10 s, and the peak reading was recorded. Due to measurement error, CO levels were available for only 31 subjects. Additionally, vital signs (blood pressure and heart rate) were monitored throughout the session by the CRC nurse.

#### 2.4. Statistical analyses

Student's *t* tests were utilized to compare the naltrexone versus placebo session on total number of choice cigarettes smoked, objective verification measures (CO, nicotine), and the VAS item 'pleasure from cigarette' (only given after the first fixed cigarette). Subjective variables were analyzed using two-factor repeated-measures analyses of variance (ANOVAS), examining within-subject factors of medication and time. When appropriate, simple effects tests were performed to examine significant main effects and interactions. Based on previous investigations, the primary variables of interest in this study were behavioral/objective measures (i.e., number of choice cigarettes smoked as well as CO and plasma nicotine), and subjective measures (BQSU, VAS 'pleasure' and 'desire to smoke,' side effects, and PANAS scales). Variables of secondary interest were the

other VAS items (i.e., dizziness, light-headedness, and irritability), withdrawal scores, and exit interview items. Secondary exploratory analyses examined sex as a between-subjects factor.

### 3. Results

Participant demographics are displayed in Table 2. Planned comparisons for most dependent measures indicated that the effects of naltrexone were primarily evident during the period of experimental manipulation, with little change noticed between the first and second baseline periods or to the cue. Therefore, the ensuing results on the effects of naltrexone refer mainly to the fixed cigarette interval through the end of the session, unless otherwise indicated.

#### 3.1. Behavioral/objective measures

Results on smoking behavior showed that naltrexone reduced the mean number of total choice cigarettes smoked [ $t(43)=2.36$ ,  $P<.05$ ]. As seen in Fig. 1, naltrexone decreased choice for the first and second cigarettes ( $P<.05$ , and  $P<.01$ , respectively), but not the latter two choice cigarettes. Fig. 2 shows that the overall naltrexone-related decrease in cigarette smoking was supported by reduced CO levels at the end of the session [ $t(30)=2.08$ ,  $P<.05$ ], and a trend for a decrease in plasma nicotine levels [ $t(40)=1.66$ ,  $P=.10$ ].

#### 3.2. Subjective

Fig. 3 illustrates that naltrexone increased total side effect scores over time, relative to placebo [Med  $\times$  Time  $F(2,86)=3.55$ ,  $P<.05$ ]. Naltrexone significantly elevated

Table 2  
Characteristics of participants

<i>General characteristics</i>	
Age (years)	37.0 (5.6)
Sex (M/F)	23 M/21 F
Education (years)	14.5 (2.2)
BMI ( $\text{kg}/\text{m}^2$ )	25.5 (4.1)
Race (Caucasian/African American/Other)	52%/30%/18%
<i>Smoking characteristics</i>	
FTND	5.2 (3.8)
Cigarettes per day	20.7 (3.1)
Smoking duration (years)	18.7 (2.8)
<i>Session baseline average levels</i>	
CO readings (ppm)	8.2 (1.2)
Cotinine levels (ng/ml)	197.1 (29.7)
Nicotine levels (ng/ml)	1.2 (0.2)

Data indicate mean (S.E.M.). BMI = Body Mass Index. FTND = Fagerström Test for Nicotine Dependence. Session baseline measures were taken after 14 h of smoking abstinence.

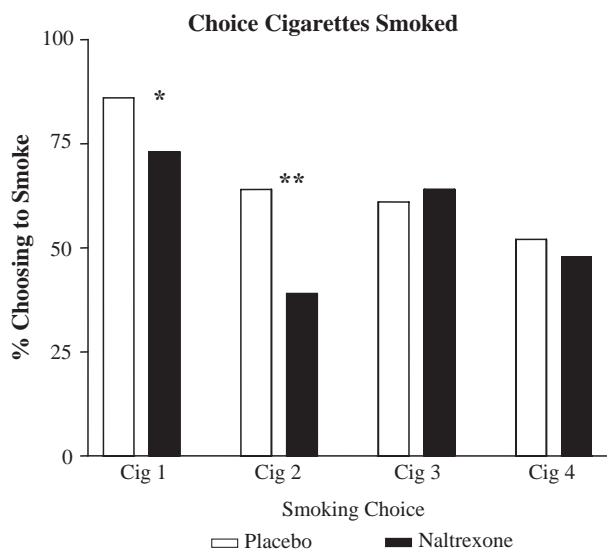


Fig. 1. Choice smoking behavior. Naltrexone significantly decreased the number of first and second cigarettes chosen in the smoking choice phase of the session ( $P < .05$  and  $P < .01$ , respectively).

total side effects at 6 h ( $P < .05$ ), but not 2 h post pill administration. Post hoc analyses of specific side effects that comprise the total score revealed that naltrexone produced increases in sedation [Med  $\times$  Time  $F(2,86) = 5.78$ ,  $P < .005$ ], with 45% of participants reporting sedation by the end of the naltrexone session compared to only 23% during the placebo session. Naltrexone did not significantly alter other specific side effects (i.e., nausea, vomiting, headaches, dizziness/light-headedness, etc.) [Med  $\times$  Time  $F_s(2, 84) \leq 2.20$ ,  $P_s = ns$ ] or total withdrawal symptoms [Med  $\times$  Time  $F(5,215) = 1.18$ ,  $P_s = ns$ ].

Results from the PANAS scale showed that participants reported decreasing positive affect during the presmoking phase of the session, reaching its nadir just prior to smoking the first cigarette (simple effects,  $P_s < .01$ ) and then in-

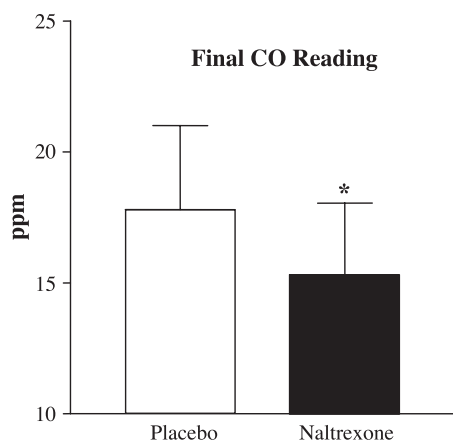


Fig. 2. Objective verification of smoking behavior. There was a significant main effect of naltrexone reducing the end of session carbon monoxide levels ( $P < .05$ ).

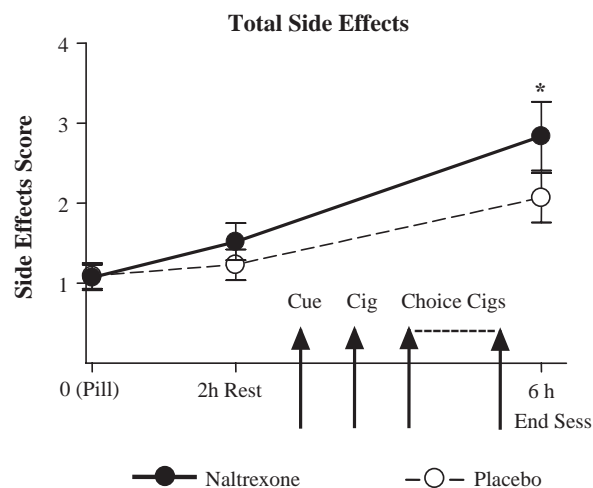


Fig. 3. Total reported side effects score during the session measured at baseline, 2 h postbaseline, and at the end of the session. Naltrexone significantly increased total side effects at end of session. [Med  $\times$  Time,  $P < .05$ , simple effects  $P < .05$  (at 6 h)].

creased immediately after the cigarette [time  $F(5,215) = 4.16$ ,  $P < .005$ ; simple effects,  $P < .01$ ]. As shown in Fig. 4, although naltrexone did not alter positive affect during the presmoking interval or cue, it did significantly attenuate positive affect 1-h after smoking the fixed cigarette [Med  $\times$  Time,  $F(5,215) = 4.34$ ,  $P < .001$ ; simple effects  $P < .005$ ]. On the PANAS negative affect scale, the highest levels of negative affect were evident after the smoking cue, which gradually decreased after smoking [time,  $F(5,215) = 3.55$ ,  $p < .005$ ]. Naltrexone produced more overall negative affect compared to placebo [med  $F(1,43) = 4.40$ ,  $P < .05$ ], but there was no Med  $\times$  Time interaction ( $P = ns$ ). Post hoc analyses revealed that participants who reported naltrexone-induced

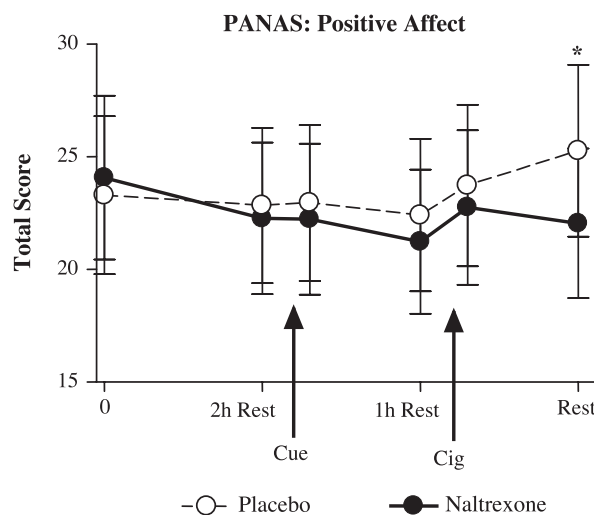


Fig. 4. PANAS Positive Affect ratings for the total sample. Naltrexone significantly decreased positive affect ratings, specifically 1 h after smoking the fixed cigarette. [Med  $\times$  Time,  $P < .001$ , simple effects,  $P < .01$  (at postcigarette rest)].

side effects, sedation, or decreased positive affect prior to the choice smoking phase did not differ from participants who did not report these effects on the number of cigarettes chosen in the naltrexone session [ $F_s \leq .58$ ,  $P_s = \text{ns}$ ].

Ratings for 'desire to smoke' significantly increased following the smoking cue and as anticipated, declined after smoking the first cigarette [time  $F(5,215) = 34.17$ ,  $P < .001$ ; simple effects,  $P_s < .05$ ]. Also, BQSU cigarette craving scores remained consistently high during the presmoking interval, and as expected, craving decreased after the participant smoked the fixed cigarette and began rising again after the 1-h rest interval [time  $F(5,215) = 48.58$ ,  $P < .001$ ; simple effects,  $P_s < .001$ ]. Although naltrexone did not alter either craving or desire to smoke compared to placebo during the session [Med  $\times$  Time  $F_s \leq 1.11$ ,  $P_s = \text{ns}$ ], an examination of the effects of medication order on these variables revealed a significant three-way interaction [Med Order  $\times$  Med  $\times$  Time  $F_s(5, 210) \geq 2.75$ ,  $P_s < .05$ ]. Naltrexone given at session 1 reduced subsequent session 2 baseline ratings of cigarette craving (simple effects,  $P < .05$ ) and desire to smoke (simple effects,  $P = .05$ ), but placebo given at session 1 did not alter session 2 baseline scores. No other subjective or behavioral variables interacted with session order.

For the other VAS items, the smoking cue significantly decreased feelings of relaxation [time  $F(5,215) = 3.10$ ,  $P < .05$ ; simple effects,  $P < .001$ ], and a significant pattern of mood effects was also evident after participants smoked the fixed cigarette: dizziness, light-headedness, and head rush increased immediately after smoking [time  $F_s(5,215) \geq 33.92$ ,  $P_s \leq .001$ ]. Additionally, ability to concentrate and irritability decreased immediately after the cigarette [time  $F_s(5,215) \geq 5.93$ ,  $P_s \leq .001$ ]. Naltrexone increased overall feelings of light-headedness [med  $F(1,43) = 10.02$ ,  $P < .01$ ], but did not significantly alter items such as dizziness, head rush, irritability, or ability to concentrate. Further, naltrexone did not significantly alter ratings of pleasure from cigarette immediately after the first cigarette [med  $t(43) = 0.41$ ,  $P = \text{ns}$ ]. Additionally, on the exit interview, participants were not able to discriminate which session they thought they received naltrexone (i.e., 50% correct) or which session had less craving, pleasure, taste of cigarettes, or smoking like everyday life.

### 3.3. Sex differences

Exploratory subgroup analyses on sex revealed that men and women were similar on baseline demographics such as age, weight, body mass index, FTND, cigarettes smoked per day, and years smoked. There was some evidence for increased sensitivity to naltrexone in women compared to men, in terms of women's significantly greater withdrawal symptoms [Sex  $\times$  Med  $F(1,42) = 4.77$ ,  $P < .05$ ] and a trend for greater side effects [Sex  $\times$  Med  $F(1,42) = 3.24$ ,  $P < .08$ ]. Post hoc analyses for specific items that comprise the withdrawal scale revealed that women tended to report

greater naltrexone induced irritability, difficulty concentrating, and restlessness [ $F_s(1,42) \geq 2.87$ ,  $P_s \leq .10$ ], whereas there were no sex differences on craving, anxiety, increased appetite, sadness, or insomnia [ $F_s(1,42) \leq 2.44$ ,  $P_s = \text{ns}$ ]. Further, in women, naltrexone decreased VAS ratings of relaxation immediately after the smoking cue, but did not alter men's ratings [Sex  $\times$  Med  $\times$  Time  $F(5,210) = 2.41$ ,  $P < .05$ ; simple effects,  $P < .05$  (women)]. However, in contrast, men appeared more sensitive than women on naltrexone's attenuation of the PANAS positive affect scale [Sex  $\times$  Med  $F(1,42) = 4.39$ ,  $P < .05$ ]. There were no naltrexone-related sex differences on cigarette craving (BQSU), PANAS negative affect, other VAS scales, discrimination responses, or behavioral choice.

## 4. Discussion

The findings of the present study show that participants smoked significantly less total choice cigarettes in the naltrexone compared to placebo session, which was confirmed by reduced CO levels and a trend for reduced plasma nicotine levels. This overall naltrexone-related decrease in cigarette smoking was driven by less first and second choice cigarettes smoked. Further, naltrexone significantly increased negative affect and self-reported side effects (i.e., specifically in sedation), and decreased positive affect 1 h after smoking the first cigarette. However, in contrast to prior research (King and Meyer, 2000; Wewers et al., 1998; Hutchison et al., 1999a), naltrexone did not significantly alter measures of acute cigarette craving, pleasure in smoking, or response to a smoking cue. Therefore, the current study provides a partial replication for studies showing naltrexone attenuation of smoking response. Lack of change in smoking urge and pleasure has been found in other studies with naltrexone (Brauer et al., 1999; Houtsmuller et al., 1997; Sutherland et al., 1995). Also, the study that showed an effect of naltrexone in response to a cue included nicotine replacement therapy in addition to naltrexone, and further research is needed to determine if transdermal nicotine is necessary for naltrexone's ability to decrease subjective response to a smoking cue.

Although it is difficult to compare across studies given disparate methodologies, there are potential differences that may explain some of the discrepancies. First, while the observed naltrexone-induced reduction in desire to smoke immediately after the first cigarette was similar to our prior study (King and Meyer, 2000; i.e., both studies showed 33% decreases in desire to smoke), results from the placebo sessions differed across studies (i.e., 40% decrease in the current study vs. 23% in the prior study). In other words, in the present study, desire to smoke ratings after the placebo session's first cigarette decreased to a lower relative level and did not rebound 1 h later to approach baseline presmoking levels as they did in our prior study. Reasons for this discrepancy include possible differences in paradigm or

participant characteristics. The addition of a smoking cue in the current study could have affected or blunted subsequent craving and subjective responses to the first cigarette. Smoking cues, particularly in vivo, have been shown to increase heart rate and blood pressure (Niaura et al., 1998) as well as alter (postcue) craving and negative affect (Hutchison et al., 1999b; Niaura et al., 1988, 1998). Therefore, it is possible that the addition of a cue in the present study may have affected subsequent subjective responses to acute smoking. Also, subjects in the present study were somewhat less nicotine dependent (e.g., 20.7 cigarettes per day; mean cotinine = 197.1; mean FTND = 5.2), than in the prior study (e.g., 25.3 cigarettes per day; mean cotinine = 274.5; mean FTND = 5.7). Heavier levels of nicotine dependence have been shown to be associated with greater craving and urge to smoke (Niaura et al., 1994), and may have been a factor in the prior study's results.

Overall, the finding of naltrexone-related reduction in smoking supports a possible role of the endogenous opioid system in smoking behavior. In terms of physiological mechanisms, it is possible that opioid blockade partially reduces an endorphin-mediated mechanism of cigarette smoking reward (see Pomerleau and Pomerleau, 1984, for review). Alternatively, electrophysiological (Gysling and Wang, 1983; Matthews and German, 1984) and behavioral data (David et al., 2002; Phillips and LePaine, 1980) have shown evidence for an opiate–dopamine interaction, and therefore naltrexone's action may be possibly mediated via a secondary or interneuron effect at mesolimbic dopamine receptors. Further, opioid antagonist alteration of the function and expression of neuronal nicotinic receptors (Almeida et al., 2000) and/or hypothalamic–pituitary–adrenocortical axis responsivity (King and Meyer, submitted for publication; Krishnan-Sarin et al., 1999) could also contribute to reductions in smoking behavior. In terms of behavioral mechanisms, naltrexone-induced unpleasant states (i.e., increased sedation and negative affect and decreased positive affect) have been postulated to play a role in its effects on appetitive consummatory behaviors. However, post hoc analyses revealed that cigarette choice in the naltrexone session was not different between participants with and without side effects. The present study's mixed findings in terms of subjective measures reflect the possible complexity of nicotine–opioid interactions, and underscore the dissociation of behavioral and subjective effects, particularly as related to the multidimensional nature of smoking response.

Mixed support was also observed for sex differences in response to naltrexone. Women experienced significantly greater withdrawal symptoms and a trend for greater total side effects during the naltrexone session than men. Alternatively, naltrexone reduced positive affect in men but not in women, and no differences were found in negative affect, cigarette craving, VAS scales, or number of choice cigarettes smoked. One caveat of the present study is that sex effects were examined in the context of a smoking paradigm

in a CRC hospital environment. There is evidence that women may smoke more in response to nonnicotine factors, such as escape from dysphoria, alleviating negative affect, and social pleasure than in male smokers (Grunberg et al., 1991; Perkins, 1996). Consequently, the removal of such factors may have reduced the ecological validity of women's compared to men's smoking.

Another notable finding was the medication order effect on craving and desire to smoke. While one advantage of a within-subjects design is the ability to directly compare participant data across medication conditions, one disadvantage is the possible confound of repeated sessions affecting participants' responses. In the current study, naltrexone administered during the first session may have attenuated craving and desire to smoke during the baseline on the subsequent (placebo) session. However, this was not found for participants receiving placebo on their first session. Carry-over effects attributed to extant levels of naltrexone or its metabolite in the second session may be ruled out because sessions were spaced on average 9 days apart (range 3–21 days). It may be speculated that naltrexone produced latent post-session smoking alterations because naltrexone decreased smoking behavior in the first session. Participants were told that they might receive naltrexone or placebo on either or both sessions, in contrast to our first study in which they were told that they would receive the medication on one session and placebo on the other session. This methodology might have led participants with naltrexone on their first session to expect further reductions in craving and desire to smoke in their second (placebo) session.

In sum, naltrexone reduced choice smoking behavior and positive affect and increased total side effects (i.e., sedation). In contrast to prior studies (Hutchison et al., 1999a; King and Meyer, 2000), naltrexone did not affect subjective response to the smoking cue, craving, or desire to smoke during the session. However, postsession latent effects of naltrexone were observed for craving and desire to smoke. The findings support a potential increased sensitivity to naltrexone in women, although an examination in more real-world settings is warranted. Overall, this study provides partial support for an opioid–smoking interaction; however, the exact nature of this effect is complex. Further research is needed to discern whether naltrexone-related decreases in cigarette smoking are due to smoking-specific subjective effects or to a nonspecific effect (i.e., increases in sedation or decreases in positive affect).

## Acknowledgements

This research was supported by an NIH grant #K08-AA-00276 to the second author and an NIH Clinical Research Center (CRC) grant to the University of Chicago (M01-RR00055). The authors would like to thank the staff of the

University of Chicago Clinical Research Center, including the nursing staff (Jacqueline Imperial, Julie Turgeon, and Lynda Bartlett) and nutritionist Linda Trumbore, M.S., R.D. Assistance was also provided by the CRC Core Laboratory (Sujata Patel, Regina Wan, and Andrew Ellis) for preparation and handling of the blood samples, and by Susan Lang at the University of Vermont CRC for performing nicotine and cotinine assays. Appreciation is extended to Dr. Theodore Karrison at The University of Chicago, Department of Health Sciences for consultation on statistical analyses, to Dr. Farr Curlin at The University of Chicago for conducting the medical screenings, to Dr. Lori Rokicki at The Illinois Institute of Technology for a critical review of the manuscript, to Elizabeth Chilton for data management, and to Katie Jorgensen and Kelly Maxwell for assisting in data collection.

## References

- Aitken RC. Measurement of feelings using visual analogue scales. *Proc R Soc Med* 1969;62:989–93.
- Almeida LEF, Pereira EFR, Alkondon M, Fawcett WP, Randall WR, Albuquerque EX. The opioid antagonist naltrexone inhibits activity and alters expression of  $\alpha 7$  and  $\alpha 4\beta 2$  nicotine receptors in hippocampal neurons: implications for smoking cessation programs. *Neuropharmacology* 2000;39:2740–55.
- Baker TB, Morse E, Sherman JE. The motivation to use drugs: a psychological analysis of urges. *Nebr Symp Motiv* 1986;34:257–323.
- Beck AT, Ward CH, Mednelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
- Brauer LH, Behm FM, Westman EC, Patel P, Rose JE. Naltrexone blockade of nicotine effects in cigarette smokers. *Psychopharmacology (Berl.)* 1999;143:339–46.
- Chait LD, Griffiths RR. Effects of methadone on human cigarette smoking and subjective ratings. *J Pharmacol Exp Ther* 1984;229:636–40.
- Conte-DeVolx B, Oliver C, Giraud P, Gillioz P, Casteanas E, Lissitzky JC, et al. Effect of nicotine on in vivo secretion melanocorticotrophic hormones in the rat. *Life Sci* 1981;28:1067–73.
- Covey LS, Glassman AG. A meta-analysis of double-blind placebo-controlled trial of clonidine for smoking cessation. *Br J Addict* 1991;86:991–8.
- Covey LS, Glassman AH, Stetner F. Naltrexone effects on short-term and long-term smoking cessation. *J Addict Dis* 1999;18:31–40.
- Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res* 2001;3:7–16.
- David V, Durkin TP, Cazala P. Differential effects of the dopamine D<sub>2</sub>/D<sub>3</sub> receptor antagonist sulpiride on self-administration of morphine into the ventral tegmental area or the nucleus accumbens. *Psychopharmacology (Berl.)* 2002;160:307–17.
- Derogatis L. SCL-90-R manual II. Towson (MD): Clinical Psychometric Research; 1983.
- First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID-I/P, Version 2.0). New York (NY): Biometrics Research Department; 1995.
- Gorelick DA, Rose J, Jarvik ME. Effects of naloxone on cigarette smoking. *J Subst Abuse* 1989;1:153–9.
- Grunberg NE, Winders SE, Wewers ME. Gender differences in tobacco use. *Health Psychol* 1991;10:143–53.
- Gysling K, Wang RY. Morphine-induced activation of A 10 dopamine neurons in the rat. *Brain Res* 1983;277:119–27.
- Heatherington TF, Kozlowski LT, Frecker RC, Fagerström K. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict* 1991;86:1119–27.
- Houdi AA, Pierzchala K, Marson L, Palkovits M, Van Loon GR. Nicotine induced alteration in Tyr-Gly-Gly and met-enkephalin in discrete brain nuclei reflects altered enkephalin neuron activity. *Peptides* 1991;12:161–6.
- Houtsmuller EJ, Clemmy PA, Sigler LA, Stitzer ML. Effects of naltrexone on smoking and abstinence. In: Harris LS, editor. *Problems of Drug Dependence 1996, Proceedings of the 58th Annual Scientific Conference*. NIDA Research Monograph 174. Washington (DC): US Department of Health and Human Services; 1997. p. 68.
- Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986;43:289–94.
- Hutchison KE, Monti PM, Rohsenow DJ, Swift RM, Colby SM, Gnys M, et al. Effects of naltrexone with nicotine replacement on smoking cue reactivity: preliminary results. *Psychopharmacology (Berl.)* 1999a;142:139–43.
- Hutchison KE, Niaura RS, Swift R. Smoking cues decrease prepulse inhibition of the startle response and increase subjective craving in humans. *Exp Clin Psychopharmacol* 1999b;7:250–6.
- Karras A, Kane JM. Naloxone reduces cigarette smoking. *Life Sci* 1980;27:1541–5.
- King AC, Meyer PJ. Naltrexone alteration of acute smoking response in nicotine-dependent subjects. *Pharmacol Biochem Behav* 2000;66:563–72.
- King AC, Meyer PJ. Post-cigarette smoking stress hormone response is heightened by naltrexone preadministration. [2003, submitted for publication].
- King AC, Volpicelli JR, Frazer A, O'Brien CP. Effects of naltrexone on alcohol subjective response in subjects at high and low risk for future alcohol dependence. *Psychopharmacology (Berl.)* 1997a;129:613–5.
- King AC, Volpicelli JR, Gunduz M, O'Brien CP, Kreek MJ. Naltrexone biotransformation and incidence of subjective side effects: a preliminary study. *Alcohol Clin Exp Res* 1997b;21:906–9.
- Krishnan-Sarin S, Rosen MI, O'Malley SS. Naloxone challenge in smokers: preliminary evidence of an opioid component in nicotine dependence. *Arch Gen Psychiatry* 1999;56:663–8.
- Lerman C, Audrain J, Crystals S. Gender differences in response to bupropion for smoking cessation. Poster presented at the 7th Annual Meeting of the Society for Research on Nicotine and Tobacco, San Diego, CA; 2001.
- Malin D, Lake J, Carter V, Cunningham J, Wilson O. Naloxone precipitates nicotine abstinence syndrome. *Psychopharmacology (Berl.)* 1993;112:339–42.
- Malin D, Lake J, Payne M, Short P, Carter V, Cunningham J, et al. Nicotine alleviation of nicotine abstinence syndrome is naloxone-reversible. *Pharmacol Biochem Behav* 1996;53:81–5.
- Matthews RT, German DC. Electrophysiological evidence for excitation of rat ventral tegmental area dopamine neurons by morphine. *Neuroscience* 1984;11:129–52.
- Mello NK, Mendelson JH, Sellers ML, Kuehnle JC. Effects of heroin self-administration on cigarette smoking. *Psychopharmacology (Berl.)* 1980;67:45–52.
- Nemeth-Coslett R, Griffiths RR. Naloxone does not affect cigarette smoking. *Psychopharmacology (Berl.)* 1986;89:261–4.
- Nesbitt PD. Smoking, physiological arousal and emotional response. *J Pers Soc Psychol* 1973;25:137–44.
- Niaura RS, Rohsenow DJ, Binkoff JA, Monti PM, Pedraza M, Abrams DA. Relevance of cue reactivity to understanding alcohol and smoking relapse. *J Abnorm Psychol* 1988;97:133–52.
- Niaura RS, Goldstein MG, Abrams DB. Matching high- and low-dependence smokers to self-help treatment with or without nicotine replacement. *Prev Med* 1994;23:70–7.
- Niaura RS, Shadel WG, Abrams DB, Monti PM, Rosenhow DJ, Sirota A. Individual differences in cue reactivity among smokers trying to quit: effects of gender and cue type. *Addict Behav* 1998;23:209–24.
- Parrott AC. Nesbitt's paradox resolved? Stress and arousal modulation during cigarette smoking. *Addiction* 1998;93:27–39.



- Perkins KA. Individual variability in response to nicotine. *Behav Genet* 1995;25:119–32.
- Perkins KA. Sex differences in nicotine versus nonnicotine reinforcement as determinants of tobacco smoking. *Exp Clin Psychopharmacol* 1996;4:166–77.
- Phillips AG, LePaine FG. Reinforcing effects of morphine micro-injections into the ventral tegmental area. *Pharmacol Biochem Behav* 1980;12:965–8.
- Pierzchala K, Houdi AA, Van Loon GR. Nicotine-induced alterations in brain regional concentrations of native and cryptic Met- and Leu-enkephalin. *Peptide* 1987;8:1035–43.
- Pomerleau OF, Pomerleau CS. Neuroregulators and the reinforcement of smoking: towards a biobehavioral explanation. *Neurosci Biobehav Rev* 1984;8:503–13.
- Rose JE, Behm FM, Westman EC. Brand-switching and gender effects in mecamylamine/nicotine smoking cessation treatment. *Proceedings of the Fifth Annual Society for Research on Nicotine and Tobacco Conference*; 1999. p. 73.
- Selzer ML, Vinokur A, Can Rooijen LA. A self-administered Short Michigan Alcoholism Screening Test (SMAST). *J Stud Alcohol* 1975;36:117–26.
- Spielberger CD, Edwards CD, Mantoun J, Lushene RE. *The State–Trait Inventory*. Windsor: NFER-Nelson; 1987.
- Story J, Stark MJ. Treating cigarette smoking in methadone maintenance clinics. *J Psychoactive Drugs* 1991;23:203–15.
- Sutherland G, Stapleton JA, Russell MAH, Feyerabend C. Naltrexone, smoking behaviour, and cigarette withdrawal. *Psychopharmacology (Berl.)* 1995;120:418–25.
- Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. *Br J Addict* 1991;86:1467–76.
- Tripathi HL, Martin BR, Aceto MD. Nicotine-induced antinociception in rats and mice: correlation with nicotine brain levels. *J Pharmacol Exp Ther* 1982;221:91–6.
- Van Vunakis H, Gjika HB, Langone JJ. Radioimmunoassay for nicotine and cotinine. In: O’Neil IK, Brunnemann KD, Dodet D, Hoffman B, editors. *Environmental Carcinogens Methods of Analysis and Exposure Measurements vol. 9*. Lyon (France): WHO International Agency for Research on Cancer; 1987. p. 317–30.
- Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;54:1063–70.
- Wewers ME, Dhatt R, Tejwani GA. Naltrexone administration affects ad libitum smoking behavior. *Psychopharmacology (Berl.)* 1998;140:185–90.