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ORIGINAL INVESTIGATION

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Effects of naltrexone with nicotine replacement on smoking cue reactivity: preliminary results

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Abstract Although several studies have examined the effects of opioid antagonists on smoking behavior, there have been no reports of the potentially therapeutic combination of naltrexone and nicotine replacement therapy. The primary objective of the present study was to determine whether naltrexone reduced reactivity to smoking cues among abstinent smokers treated with nicotine replacement. Twenty participants were instructed to abstain from smoking cigarettes for 9 h while using nicotine replacement therapy. Participants were subsequently treated with either naltrexone (50 mg) or placebo before being exposed to smoking cues. Results indicated that the smokers who received the placebo responded to smoking cue exposure with increases in urge to smoke and increases in negative affect. Participants who received naltrexone did not show any increase in urge or negative affect and showed a decrease in withdrawal symptoms after exposure to smoking cues. Although preliminary, the findings suggest that naltrexone may work in combination with nicotine replacement therapies to block the effects of smoking stimuli in abstinent smokers.

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Introduction

Smoking remains the leading preventable cause of death in the United States, increasing mortality through a variety of diseases including coronary heart disease, chronic obstructive pulmonary disease, stroke and cancer (USDHHS 1988, 1990). Transdermal nicotine replacement (TNR) has demonstrated modest efficacy in the treatment of nicotine dependence (e.g., Rose 1996). The effects have in part been attributed to TNR's ability to attenuate craving and relieve withdrawal (Hurt et al. 1993; Levin et al. 1994; Dale et al. 1995; Jorenby et al. 1996). Lower subjective ratings of cigarette satisfaction and taste have also been associated with TNR (Levin et al., 1993). While treatment of nicotine addiction has been improved by the advent of TNR, nicotine replacement is still far from a panacea. Seventeen million smokers per year attempt to quit; however, the majority of these individuals fail with or without nicotine replacement. Long term abstinence rates are at best only 10–30% even with nicotine replacement therapy (e.g., Rose 1996). Clearly, novel approaches to enhancing treatment outcome for this serious public health problem are warranted (Shiffman 1993).

From a clinical standpoint, an intervention that could be used in combination with TNR to produce additive reductions in craving and dysphoria would be particularly useful in the treatment of nicotine dependence. One possible candidate is naltrexone, a pharmacotherapy that has demonstrated safety and efficacy as an adjunct in the treatment of alcohol dependence (O'Malley et al. 1992; Volpicelli et al. 1992; Berg et al. 1996). Although the mechanisms by which naltrexone works are not well understood, naltrexone's

effectiveness has been attributed to its ability to reduce activation of the mesolimbic dopamine system through the antagonism of mu-opiate receptors. For example, naltrexone blocks the activation of mesolimbic dopamine after alcohol administration in animals (Benjamin et al. 1993), and naltrexone reduces the stimulatory and reinforcing effects of alcohol in humans (e.g., Swift et al. 1994).

Research on the effects of naltrexone on smoking is scant. Two small studies found naloxone (an opiate antagonist similar to naltrexone) to reduce smoking (Karras and Kane 1980; Gorelick et al. 1989), while a third study failed to replicate the effects of naloxone on smoking rate (Nemeth-Coslett and Griffiths 1986). Another study with a sample of 12 heavy smokers reported that naltrexone had no significant effect on smoking behavior or satisfaction from smoking, but significantly reduced the perceived difficulty of abstaining from smoking during 24-h smoking deprivation (Sutherland et al. 1995). Naltrexone was also reported to decrease alertness and increase dysphoria (Sutherland et al. 1995). While Sutherland et al. (1995) reported no statistically significant reduction in craving or actual smoking due to naltrexone, the effect sizes for naltrexone on several measures of smoking were substantial, with a medium effect size suggesting that naltrexone reduced the number of puffs smoked ($f = 0.24$) and a large effect size suggesting naltrexone reduced craving ($f = 0.45$). Another recent report suggested that naltrexone may reduce urges to smoke (Houtsmuller et al. 1997).

There has been only one report of the effects of naltrexone when combined with TNR. The results of the study suggested that naltrexone may be useful for augmenting the efficacy of TNR (O'Malley et al. 1997). In fact, several lines of reasoning suggest that combining naltrexone with transdermal nicotine may result in greater effectiveness. Nicotine replacement results in norepinephrine release and occupation of nicotinic receptors. Naltrexone occupies the mu-opiate receptors which may diminish the activation of the mesolimbic dopamine system and may thereby reduce craving. Thus, TNR and naltrexone could produce additive effects by reducing craving through their respective mechanisms of action. Because opiate antagonists are known to precipitate nicotine withdrawal symptoms in nicotine dependent animals (Malin et al. 1993, 1996), TNR may also have the added benefit of counteracting the dysphoria, sedation, and increased withdrawal that may be caused by opioid antagonists such as naltrexone (O'Malley et al. 1997).

The primary objective of the present study was to examine the effects of naltrexone on urge to smoke and withdrawal among deprived smokers who were provided TNR using a rigorous laboratory based assessment paradigm that involves in vivo exposure to smoking cues. Exposure to smoking cues produces reliable increases in urges to smoke and in negative affect (e.g., Niaura et al. 1988, 1998; Drobes and Tiffany 1997) and provides a test of the effects of naltrexone in a simulated high risk situation that is commonly associated with relapse (Shiffman 1982). It was postulated that smoking cues would precipitate increases in urge to smoke and dysphoria in deprived smokers treated with TNR and placebo, while smoking cues would produce smaller increases in urges to smoke and dysphoria in smokers treated with TNR and naltrexone.

Materials and methods

Participants

Participants were recruited from the Providence Veteran Affairs Medical Center and the greater Providence, R.I. community through advertisements and flyers and gave their written informed consent before participating. Participants were excluded if they had a history of opioid dependence, were positive on a urine opiate screen, were currently taking medications with opiates, had liver function tests (SGOT, bilirubin) greater than three times normal, had any symptoms of an acute medical problem, or had a chronic medical problem that could contraindicate participation (e.g., cardiac disease). In addition, smokers were only included if they smoked at least 20 cigarettes per day and were contemplating quitting in the next 6 months. This criterion was included to increase the treatment relevance of the results by including only regular smokers with some motivation to quit. Participants were compensated with $40 in grocery store gift certificates. Of the 20 participants, ten (five women) were randomly assigned to the placebo group and ten (five women) to the naltrexone group. Table 1 summarizes the demographic and smoking variables by group. *t*-Tests were used to confirm that the groups did not differ significantly on any of these variables.

Procedure

Baseline demographic, smoking history, and expired carbon monoxide (CO) measures were collected on the day before participants were scheduled for an experimental session. Participants were instructed to smoke their last cigarette upon waking on the following morning. Participants were given a 21 mg nicotine replacement patch (Nicoderm) and were instructed to place the patch on a hairless portion of their upper arm after smoking their last cigarette on the following morning. Nicotine blood levels typically peak at 2–3 h after the patch is placed on the skin (Russell 1990). Participants remained abstinent from cigarettes throughout the day. This resulted in approximately 9 h of smoking deprivation with concurrent TNR. Participants were administered a capsule containing either 50 mg naltrexone or placebo at 12:00 p.m. and returned to the laboratory at 4:00 p.m. for the experimental session. The participants and the experimenter were blind to the medication condition. A second expired CO measure was taken immediately prior to the experimental session in order to verify smoking deprivation. Expired CO decreased significantly after smoking deprivation, and there were no differences in expired CO between the naltrexone and placebo groups before deprivation or after deprivation, indicating that compliance was consistent across the two groups (see Table 1).

In the experimental session, participants were seated at a desk and instructed to relax. After the relaxation period (5 min), participants completed measures of urge to smoke, affect, and withdrawal. Following the smoking cue exposure procedure outlined in a previous study (e.g., Sayette and Hufford 1994), participants were then

Table 1 Demographic and smoking variables for naltrexone and placebo groups

	Placebo		Naltrexone			
	Mean	SD	Mean	SD	*t*	*P*
Age	37.2	10.9	42.2	9.7	1.08	0.29
Education	13.7	1.2	13.4	2.1	0.81	0.43
Age when started smoking	13.9	2.5	14.8	3.5	0.66	0.52
Number of years smoked	20.3	11.3	26.1	9.2	1.26	0.22
Number of quit attempts	4.1	2.0	4.6	4.0	0.35	0.73
Average number of daily cigarettes in last 7 days	25.8	11.3	26.5	8.2	0.16	0.88
Number of cigarettes in last 24 h	23.3	7.5	23.3	8.6	0.01	0.99
Fagerstrom Tolerance questionnaire score	7.7	1.9	7.8	1.5	0.13	0.81
Expired CO before 9 h of deprivation	31.4	11.5	27.8	11.2	0.68	0.51
Expired CO after 9 h of deprivation	8.3	4.1	10.0	4.8	0.85	0.41

provided with a cigarette of their preferred brand, a lighter, and an ashtray and were instructed to light and hold the cigarette without taking a puff. The participants held the cigarette for 60 s before extinguishing it. Participants were then instructed to repeat the measures of urge to smoke, affect, and withdrawal. Finally, participants were allowed to relax for 10 min before repeating the measures a third time to investigate the degree of recovery after cue exposure.

Measures

The Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom and Schneider 1989), and a smoking history questionnaire were administered prior to the experimental session as descriptive measures of the severity of nicotine dependence and smoking history. The primary measure of urge to smoke was a single item scale from 0 to 100. This measure of urge to smoke has been validated in several cue reactivity studies and predicts smoking outcomes (Abrams et al. 1988; Niaura et al. 1989, 1992). The Positive Affect/Negative Affect Scale (PANAS) is a 20-item measure with subscales for Positive Affect and Negative Affect and was used as a measure of mood before and after smoking cue exposure. The PANAS is a reliable and valid measure of both positive and negative affect with Cronbach alphas of 0.84–0.90 (Watson et al. 1988). An updated version of the Minnesota Withdrawal scale (Hughes and Hatsukami 1986) was used to measure withdrawal before and after cue exposure by asking participants to rate eight symptoms of withdrawal on a scale from 0 (none) to 4 (severe).

Design and analysis

A 2×2 mixed-subjects design was utilized. Prior to analysis, the distributions of the four dependent variables (i.e, urge, withdrawal, negative affect, positive affect) were checked and found to be normally distributed. The postulated effects of naltrexone and cue exposure were analyzed with four separate repeated measures analyses of variance (ANOVAs). The two factors in each ANOVA were Drug (naltrexone versus placebo) as the between-subjects factor and Trial (pre-exposure versus post-exposure to smoking cues) as the within-subjects factor. Additional *t*-tests were used to check for group differences prior to exposure and after the recovery period.

Results

A 2 × 2 (Drug × Trial) repeated measures ANOVA with urge to smoke as the dependent variable revealed a significant interaction, ($F1,\ 18 = 4.90,\ P < 0.05$). without significant main effects for Drug or Trial ($P > 0.05$). The effect size for the interaction was $f = 0.52$, indicating a large effect (Cohen 1988). Simple effects tests indicated that urge to smoke increased in the group that received placebo, ($F1,\ 9 = 5.44,\ P < 0.05$), but did not increase significantly in the group that received naltrexone after exposure to smoking cues ($P > 0.05$). Figure 1a presents the means and standard error of the means for urge to smoke.

A 2 × 2 (Drug × Trial) repeated measures ANOVA on the withdrawal scale showed a significant Drug × Trial interaction ($F1,\ 18 = 6.94,\ P < 0.01$), but did not demonstrate a significant main effect for Drug or Trial ($P > 0.05$). The effect size for the interaction was $f = 0.62$, indicating a large effect (Cohen 1988). Simple effects tests indicated that withdrawal decreased from the pre-exposure trial to the exposure trial in the group that received naltrexone, ($F1,\ 9 = 37.55,\ P < 0.01$), but did not change in the group that received placebo ($P > 0.05$). Figure 1b depicts the means and standard errors for the withdrawal scores.

A 2 × 2 repeated measures ANOVA with negative affect as the dependent variable demonstrated a significant Drug × Trial interaction, ($F1,\ 18 = 8.11,\ P < 0.05$), but did not reveal a significant main effect for Drug or Trial ($P > 0.05$). The size of the interaction effect was $f = 0.67$. Simple effects tests showed that negative affect increased after smoking cue exposure in the group that received placebo ($F1,\ 9 = 7.63,\ P < 0.05$), and did not change in the group that received naltrexone ($P > 0.05$) (see Fig. 1c). A 2 × 2 repeated measures ANOVA with positive affect as the dependent variable did not demonstrate a significant main effect for Drug, Trial, or the interaction ($P > 0.05$).

Separate analyses were conducted to exclude methodological confounds regarding whether naltrexone may have affected the dependent measures irrespective of the smoking cues. Comparisons showed no significant differences between the naltrexone and placebo groups on urge to smoke, withdrawal, or negative affect prior to exposure and no differences 10 min after terminating exposure to smoking cues ($P > 0.05$), indicating that the effects of naltrexone were specific to the smoking cues. Tests were also conducted to exclude the explanation that there may have been a differential

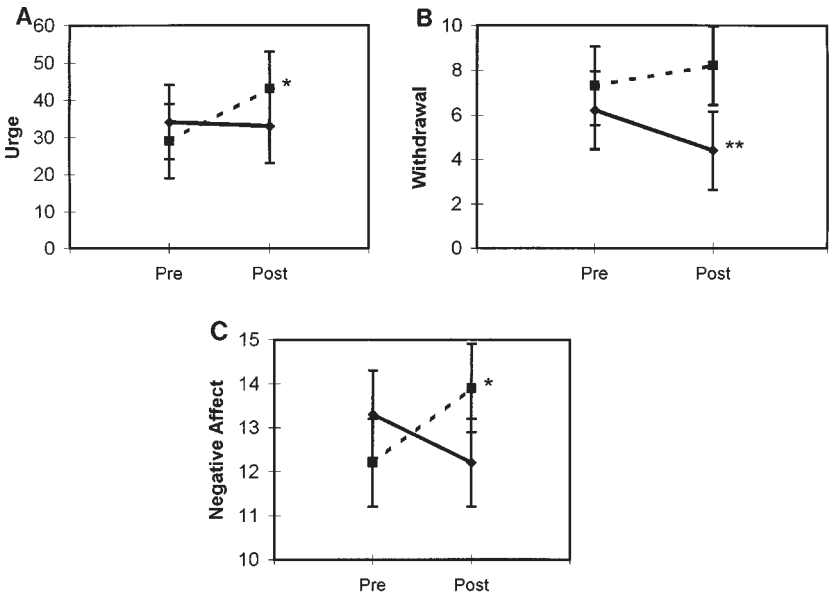

Fig. 1 **A** Mean subjective urge to smoke and standard error at pre-exposure and post-exposure to smoking cues for smokers treated with the combination of TNR and naltrexone (◆) or TNR and placebo (■). **B** Mean withdrawal score and standard error at pre-exposure and post-exposure to smoking cues for smokers treated with TNR and naltrexone or TNR and placebo. **C** Mean negative affect and standard error at pre-exposure and post-exposure to smoking cues Significant change from pre- to post-cue exposure is indicated by $*P < 0.05$ and $**P < 0.01$

change between the naltrexone and placebo groups as a function of time in the experimental room, irrespective of the presentation of smoking cues. Urge, withdrawal and affect did not show any significant differential change from the pre-exposure assessment to the assessment at 10 min after terminating exposure for the naltrexone or placebo groups, suggesting that these variables did not change simply as a function of time in the experimental room ($P > 0.05$). Finally, participants were asked to guess whether they received naltrexone or placebo at the end of the study. Only four of ten participants in the naltrexone group correctly guessed that they had received naltrexone, and only six of ten subjects in the placebo group correctly guessed that they received placebo. Thus, participants were unable to identify the medication with accuracy greater than would be expected by chance.

Discussion

The findings of the present study demonstrated that exposure to smoking cues increased urge to smoke in the group of deprived smokers that were treated with TNR and placebo but did not increase urge to smoke in the group of smokers that were treated with TNR and naltrexone. Furthermore, withdrawal scores decreased after exposure to smoking cues in the group of smokers who received TNR and naltrexone, but did not change in the group who received TNR and placebo, while negative affect increased after exposure to smoking cues in smokers treated with TNR and placebo, but did not change in smokers treated with TNR and naltrexone. The finding that the combination of naltrexone and TNR blocked an increase in urge after exposure to smoking cues, reduced withdrawal, and reduced negative affect, while TNR alone did not, suggests that naltrexone may have a beneficial effect when combined with TNR. Furthermore, the finding that the combination of naltrexone and TNR is superior to placebo and TNR is consistent with the underlying notion that the two interventions work through different mechanisms of action and consistent with the hypothesis that this pharmacotherapy combination may have an additive effect on urge to smoke and withdrawal after exposure to smoking stimuli, which is a common relapse precipitant that makes the temptation to smoke more difficult to resist (Shiffman 1982). The implication of this finding is that the applied combination of these two interventions may lead to improvements in smoking cessation treatment outcome. The effects of naltrexone with TNR that were noted in the present study stand in contrast to a previous report of the effects of naltrexone without TNR (Sutherland et al. 1995).

Given the small sample size of the current study, an alternative interpretation of the data is that the effects may be due to differences between the groups on other important variables (e.g., smoking history). However, the naltrexone and placebo groups were quite similar on demographic and smoking variables, indicating that this explanation cannot account for the substantial effects found in the present study. Several other limitations of this study should be noted. The conclusions of the present study are preliminary. A larger laboratory based study that includes a placebo TNR control is needed to test the putative mechanisms of TNR alone, naltrexone alone, and the combination of the two and to demonstrate the stability of the results reported here. In addition, the generalizability of these findings may be limited because the smokers in the pre-

sent study were not trying to quit permanently, which may have affected their urge to smoke and withdrawal. Thus, it is unclear from the present study whether naltrexone would alter smoking behavior during an actual quit attempt. The generalizability of these findings to a clinical population can only be determined in a clinical trial with smokers who are trying to quit permanently.

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