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Effects of the opioid receptor antagonist naltrexone on smoking and related behaviors in smokers preparing to quit: a randomized controlled trial

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ABSTRACT

Aims To determine if naltrexone affects smoking behaviors in smokers preparing to quit, and whether or not such pre-quit responses predict post-quit date outcomes. **Design** Double-blind, placebo-controlled, randomized study. The current study focused on smoking-related outcomes in the pre-quit phase, which was 1 week prior to the quit date, and these findings were linked with reductions in the same outcomes demonstrated in the post-quit phase published previously for this randomized controlled trial (RCT) in mediation analyses. **Setting** Community sample of adult smokers desiring to quit in Chicago, Illinois, USA. **Participants** Participants were 315 smokers randomized to naltrexone ($n = 161$; mean age = 42.58 years; 60% Caucasian) or placebo ($n = 154$; mean age = 41.32 years; 55% Caucasian). **Measurements** The difference from baseline in the number of cigarettes smoked during the pre-quit phase interval was the primary outcome. Secondary pre-quit outcomes were assessed using Likert scales of subjective responses and consumption of cigarettes, alcohol and food. Number of cigarettes smoked, alcoholic drinks consumed and the Brief Questionnaire of Smoking Urges were assessed in the post-quit phase. **Findings** Relative to placebo, naltrexone decreased the number of cigarettes smoked (–4.21 versus –2.93, $P < 0.05$), smoking urge ($P = 0.02$) and number of alcoholic drinks consumed ($P = 0.04$). Exploratory mediation analyses linking outcomes of the pre-quit and post-quit phases found that naltrexone's effects on reducing smoking urge, cigarettes smoked and alcoholic drinks consumed in the pre-quit phase demonstrated full mediation of their respective effects during the post-quit phase. **Conclusions** Naltrexone taken in the week before a quit attempt reduces cigarette consumption, urges to smoke and alcohol consumption relative to placebo. The size of the effect mediates statistically the size of similar effects after the quit date.

Keywords Alcohol, cigarette smoking, cotinine, naltrexone, opioid antagonist, smoking urge.

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INTRODUCTION

Currently, 19% of adults in the United States smoke cigarettes and tobacco use remains the leading preventable cause of death [1]. Despite the fact that more than two of every three smokers report a desire to quit smoking [2], most are unsuccessful in achieving this goal even when using currently approved pharmacotherapies [3]. As there is evidence for interactions between the nicotinic and endogenous opioid systems [4,5], a potential target for novel treatments might involve antagonism of opioid receptors to alter cigarette reward and related consummatory behaviors, such as alcohol consumption, that often precedes smoking [6] and reduces the likelihood of treatment success [7–9]. Naltrexone, a mu opioid receptor antagonist that is approved for the treatment of opioid and alcohol dependencies, has shown efficacy to improve quit rates and decrease smoking behaviors during active treatment in some trials [10–14], but not in others [15,16]. Naltrexone might also decrease women's long-term weight gain associated with quitting smoking [17]. However, the 2013 Cochrane Report [18]

concluded that naltrexone did not increase long-term smoking abstinence. A greater understanding of specific biobehavioral mechanisms of naltrexone on smoking and other consummatory behaviors during the early treatment phase may enable more targeted use of the drug to optimize outcomes and allow comparisons with novel medications. The current study examined the effects of naltrexone on behavioral, objective and subjective responses among treatment-seeking smokers participating in a clinical trial evaluation of naltrexone for smoking cessation during the naltrexone dose initiation phase prior to their quit date.

Results from acute human laboratory studies examining naltrexone effects on smoking behaviors have been mixed. Some studies have shown naltrexone attenuation in the number of cigarettes smoked, responses to smoking cues or self-report craving [19–23], but other studies have failed to find effects of naltrexone on these indices [19,24–26]. While acute human laboratory paradigms are an important tool to characterize drug effects [27], conflicting results for naltrexone on cigarette smoking could be the result of assessments being limited to several hours after a single drug administration and samples consisting largely of non-treatment seekers. Examining naltrexone effects in a clinically relevant paradigm and on a variety of domains in smokers desiring to quit might enable better elucidation of the mechanisms facilitating the opioid system to smoking behavior change, and allow for comparisons with other therapeutics.

The current study examined the effects of naltrexone on smoking and related behaviors among treatment-seeking smokers participating in a randomized, placebo-controlled, double-blind trial of naltrexone for smoking cessation during the naltrexone dose initiation phase prior to their quit date. As this was the period of medication initiation, the dose was gradually up-titrated to minimize adverse effects, with the full therapeutic dose (50 mg) taken on the fourth to sixth day of the pre-quit phase. Naltrexone was hypothesized to reduce the number of cigarettes smoked in this phase [19,21,23]. Naltrexone was also hypothesized to reduce subjective effects of smoking, including cigarette urge, taste and pleasure and the number of alcoholic drinks consumed in the pre-quit phase [20–23,28,29]. Exploratory analyses were conducted to examine whether naltrexone effects during the pre-quit week mediated outcomes after the quit date.

METHODS

Participant screening

Candidates were recruited by advertisements in print and radio media, mass transit, the internet and by word-of-mouth referrals. In-person screening included completion of questionnaires and psychiatric and medical screening (for details, see King *et al*. [13]). Participants were eligible if they were aged 18–65 years; smoked 12–40 cigarettes daily for at least 2 years and reported a desire to quit smoking; had a body mass index of 19–38 kg/m^2; had hepatic transaminase concentrations within normal range (<2.5 times normal); were able to read and write English; were not currently taking opioid or psychotropic medications; and did not have a past-year history of a major medical or psychiatric disorder, lifetime diagnosis of opioid abuse or dependence, and were not nursing or pregnant.

Treatments and procedures

This pre-quit interval study was designed a priori as part of a larger smoking cessation trial. The study was located at three Chicago area sites, including the University of Chicago (58% of sample), as well as the Respiratory Health Association (26%) and the Howard Brown Health Center (16%). Participants were enrolled from June 2006 to March 2009, with follow-ups completed by April 2010. All participants consented to randomization to receive either naltrexone or placebo, attend behavioral counseling and take open-label nicotine patches after the quit date [13]. Details of the computer-generated randomization and post-quit phase results are reported in King *et al*. [13]. Naltrexone or placebo group assignment was stratified by sex. The study was fully approved by the University of Chicago Institutional Review Board.

Participants were given their assigned tablets in a daily pill box organizer 1 week prior to the quit date. The titrated dose included: 12.5 mg on day 1, 25 mg daily on days 2 and 3 and 50 mg on days 4–6. The 50-mg dose was also continued daily on the quit date and throughout the post-quit date phase to be consistent with the Food and Drug Administration (FDA)-approved dose of naltrexone for alcohol and opioid dependence. To decrease nausea and other adverse effects, participants were encouraged to consume food prior to taking each tablet.

Participants completed a short questionnaire each evening prior to going to sleep during the pre-quit phase. The primary dependent measure was the number of cigarettes smoked ('today, how many cigarettes did you smoke?'). Other secondary measures included subjective ratings of smoking urge ('what was your urge to smoke?'), cigarette pleasure and taste ('what was your pleasure or enjoyment of smoking', 'what was the appealing taste of your cigarettes?'), and other consummatory behaviors, including alcohol, eating and caffeine consumption (the latter as a control item). To standardize consumption quantifications, subjects were informed

that a cigarette included a single puff up to an entire cigarette, a caffeinated drink was 8 oz coffee/tea or a 12 oz caffeinated soda, and a standard alcoholic drink was 1½ oz of liquor, 5 oz of wine or 12 oz of beer. The subjective effects were rated on five-point scales from 'a lot less than usual' [1] to 'a lot more than usual' [5]. Adverse effects were each rated from 'none' [1] to 'severe' [5] and included three common naltrexone effects: 'today, how much did you feel' to assess the items light-headed/dizzy, tired/sedated and nauseated. As a check of naltrexone effects on general functioning, three additional items were included to assess anxious mood, depressed/sad mood and the amount of sleep.

Tablet adherence was assessed by interview on the quit date and by collection of any unused tablets, and quantified as each participant's ratio of the number of tablets taken to the number disbursed. Adherence to naltrexone was also confirmed by objective measures, i.e. a urine and saliva test to determine naltrexone and its main metabolite, 6-β-naltrexol. The samples were collected by each participant on the morning of day 7, i.e. the designated quit date. The instructions included having the participant void upon awakening to empty the bladder. This was followed by tablet administration and collection of their urine for the next 180 minutes, and their saliva at 90 minutes. The participants brought all their samples to the study visit on the quit date and were compensated $35.

Assay methods

The methods for identification of naltrexone and its major metabolite, 6-β-naltrexol, in the saliva or urine sample were performed by Ammon Laboratories (Linden, NJ, USA) using the Immunalysis Naltrexone Direct enzyme-linked immunosorbent assay (ELISA) Kit (Immunalysis Corporation, Pomona, CA, USA), and confirmed by gas chromatography-mass spectrometry (Agilent Technologies, Santa Clara, CA, USA).

Post-quit date procedures

As stated earlier, the pre-quit interval was the 6 days leading to each participant's designated quit date. During this pre-quit interval, no instructions were given on smoking behaviors. However, starting on the quit date, the participant was expected to achieve abstinence from smoking. Participants initiated open-label nicotine patch starting on the quit date, and attended once-weekly behavioral counseling, both of which ended 4 weeks after the quit date. Nicotine patch was included to reduce potential withdrawal-like effects that might be augmented in smokers given an opioid antagonist [30] and reduce dropout rates, which have been high in trials of naltrexone alone [11]. During weeks 5–12, naltrexone or placebo groups continued as a monotherapy for relapse prevention. Details of the post-quit phase portion of the trial can be found in King *et al.* [13].

Statistical analyses

Analysis was based on the intent-to-treat sample of 315 smokers ($n = 161$ naltrexone, $n = 154$ placebo), which we defined a priori as a subject who took at least one tablet [see CONSORT (CONsolidated Standards of Reporting Trials) diagram, Fig. 1]. Twenty participants (6%) did not complete any data recording for the questionnaire, so mean imputation was used separately for participants in the naltrexone and placebo groups to replace these missing values. For other pre-quit measures, baseline values were used to replace missing values. Linear regression was used to assess the medication effect on the primary outcome (the change in number of cigarettes smoked during full dose phase from baseline) and the secondary outcomes (ratings for subjective effects, the change in number of alcoholic or caffeinated drinks versus baseline levels). Analyses included the unadjusted differences between groups and were then repeated in several hierarchical models adjusting for demographic variables (sex, age, education and race), adverse effects and baseline smoking variables (nicotine dependence, carbon monoxide, number of prior quit attempts and smoking duration). For the latter, only ratings of nausea were included as the adverse effect because nausea is the most widely reported adverse effect of naltrexone and to avoid collinearity as ratings of nausea, dizziness and sedation were intercorrelated significantly ($rs \geq 0.36$, $Ps < 0.01$). The intent-to-treat sample was used in all analyses except for analysis of the number of alcoholic drinks, which included only current drinkers, i.e. the 75% of the sample who drank at least one alcoholic beverage in the 2 weeks prior to enrollment.

Mediation analyses [31] were conducted to determine if various pre-quit effects served as mediators of their corresponding post-quit outcomes [13]. For each post-quit outcome, three regression models were conducted sequentially for testing mediation [31], including examination of whether the medication effect was associated with the post-quit outcome and whether the medication effect was associated with the pre-quit measure. If these were significant, then the third model was conducted to examine whether the medication effect on the post-quit outcome was still significant while including the pre-quit measure, with mediation demonstrated if the medication effect was no longer significant.

This study was powered to detect an estimated hazard ratio of 1.97 (power = 0.80; $\alpha = 0.05$) for the second-phase outcome of the comparison of prolonged abstinence quit rates at 12 weeks for the interactions of medication and sex [32].

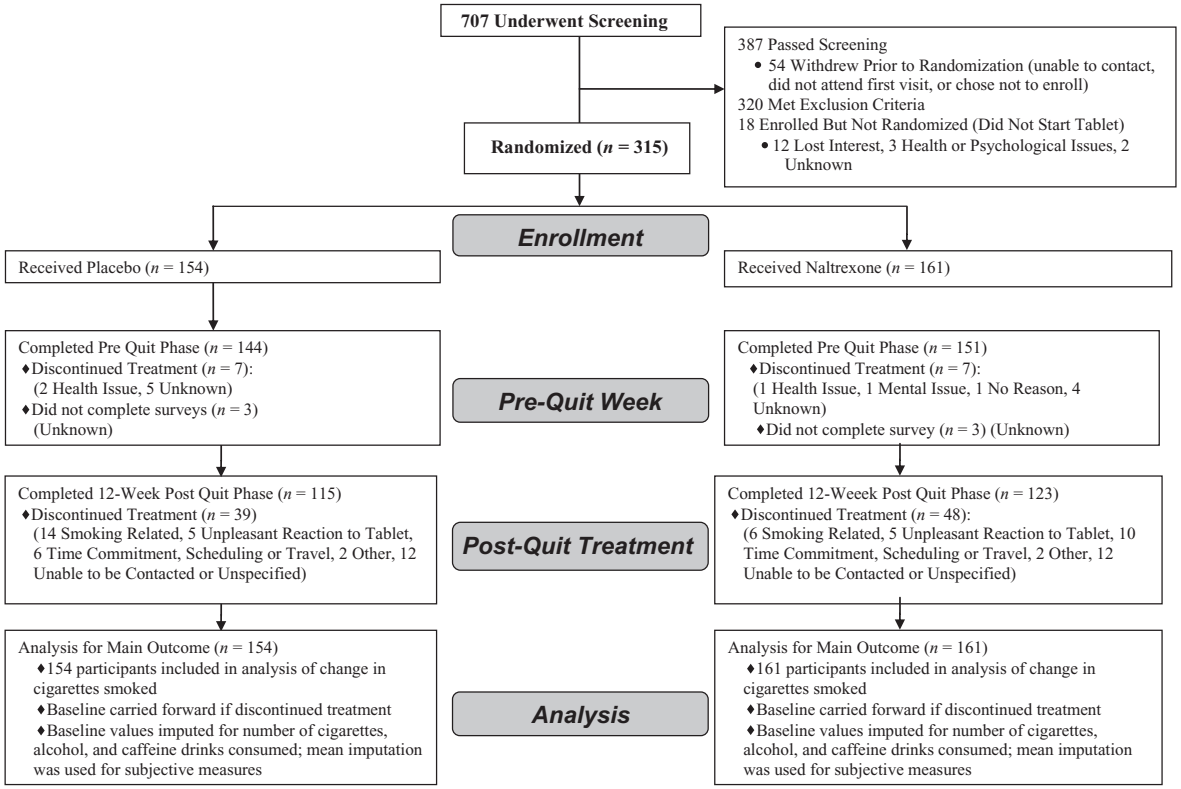

Figure 1 CONSORT (CONsolidated Standards of Reporting Trials) diagram. Flow diagram of the process through the phases of a randomized trial of naltrexone versus placebo groups

Table 1 Demographic and smoking characteristics.

	Placebo (n = 154)	*Naltrexone (n = 161)*
Demographic variables		
Age (years)	42.58 (10.87)	41.32 (11.61)
Education (years)	15.04 (2.19)	15.12 (2.37)
Sex (male)	71 (46)	76 (47)
Marital status (married/living with partner)	53 (34)	49 (30)
Race (Caucasian)	93 (60)	88 (55)
Smoking and alcohol variables		
Smoking urge (baseline BQSU score)	26.17 (12.30)	28.30 (13.01)
Nicotine dependence (Fagerström score)	5.31 (2.03)	5.11 (1.73)
Baseline carbon monoxide level (p.p.m.)	24.35 (13.00)	22.09 (10.90)
Number of prior quit attempts[a]	4.08 (5.47)	4.56 (8.93)
Cigarettes smoked per day (in past month)	16.55 (5.33)	15.99 (5.12)
Smoking duration (years)	24.88 (11.36)	23.36 (11.90)
Alcohol drinking days per week[b]	2.39 (1.53)	2.25 (1.57)
Drinks per drinking occasion[b]	3.53 (2.29)	3.41 (2.38)

Data are mean (standard deviation) or *n* (%) as indicated. [a]Number of prior quit attempts defined as each attempt of intending to quit and remaining smoke-free for at least 12 hours. [b]Drinks per drinking occasion and alcohol drinking days per week were based on the 1-month time-line follow-back interview prior to enrollment and summarized for current drinkers only (*n* = 123 naltrexone, 109 placebo). BQSU = brief questionnaire for smoking urge; p.p.m. = parts per million.

RESULTS

Demographic and background characteristics of the intent-to-treat sample are included in Table 1. Tablet adherence during the pre-quit week was high for both groups, with full adherence reported in 94% of those in the placebo group and 93% of those in the naltrexone group. Further, in the naltrexone group, 96%

of participants were confirmed positive for detection of naltrexone or the metabolite 6-β-naltrexol.

Adverse effects and moods

Naltrexone did not affect general mood or health states, including anxiety, depressed mood or amount of sleep. However, naltrexone increased adverse effects that have been reported previously in alcohol dependence studies [33], including nausea, dizziness and sedation. Nausea was reported in 45% of naltrexone participants versus 22% of placebo participants and when it was experienced, it was most often rated as mild, i.e. in 88% of naltrexone and 94% of placebo participants. Further, a comparison of cigarette smoking (number of cigarettes smoked, smoking urge, pleasure and taste) in a median split of high and low nausea participants showed no differences ($|t|$s ≤ 1.38, Ps ≥ 0.17).

Outcomes

In unadjusted analyses naltrexone, compared with placebo, reduced significantly the number of cigarettes smoked in the pre-quit phase (see Table 2 for estimated effect size). The reduction in smoking in the naltrexone group was 4.21 fewer cigarettes daily (26% reduction) compared with 2.93 fewer cigarettes (17% reduction) in the placebo group. In terms of secondary outcomes, naltrexone also reduced smoking urge, cigarette taste and pleasure ratings, food pleasure, appetite, amount of sweet foods consumed and number of alcoholic drinks consumed (Table 2). Caffeine use was unaffected by naltrexone.

In analyses adjusting for demographic characteristics only, all the aforementioned effects of naltrexone remained. However, when adjusting for both demographic characteristics and nausea, the effects of naltrexone remained for number of cigarettes smoked, smoking urge, cigarette taste and number of alcoholic drinks consumed, but effects on cigarette pleasure, food pleasure, appetite and sweet food consumption were no longer significant (Table 2). In the final set of analyses adjusting for demographic characteristics, nausea and baseline smoking variables, naltrexone's significant reduction in smoking urge and number of cigarettes smoked and alcoholics drinks consumed remained (Table 2).

Mediators of treatment outcomes

As the first step of mediation, effects of naltrexone versus placebo during the pre- and post-quit phases were examined by regression analyses. Only those pre-quit effects reduced significantly by naltrexone in the final adjusted analyses (smoking urge and change in number of cigarettes and alcoholic drinks) were considered. For post-quit date outcomes, naltrexone reduced significantly the number of cigarettes smoked at 4 weeks post-quit compared with placebo (2.6 versus 5.2 cigarettes per week, respectively) and reduced smoking urge ratings [Brief Questionnaire for Smoking Urge (BQSU) peak scores 25.4 versus 28.7 placebo]. Naltrexone also reduced the number of alcoholic drinks consumed (19.2 drinks consumed over first 4 weeks for naltrexone versus 25.5 for placebo). In addition, naltrexone reduced the number of alcoholic drinks consumed at 12 weeks (53.1 drinks consumed over 12 weeks for naltrexone versus 68.4 for placebo). The final step of mediation analyses for these variables showed that the pre-quit effects fully mediated the naltrexone effects in the post-quit phase (Table 3).

DISCUSSION

To our knowledge, this study represents the first translational study of the acute mechanisms of opioid antagonism in nicotine-dependent participants examined in a clinically relevant context. The findings elucidated naltrexone's mechanism of action on smoking and other related indices. Consistent with our hypothesis, compared with placebo, naltrexone significantly reduced the number of cigarettes smoked. Naltrexone (versus placebo) also decreased smoking urge and cigarette hedonics (pleasure, taste) during these days before the designated quit date. Naltrexone also reduced other consummatory behaviors during this pre-quit phase, including alcohol drinking, appetite and food pleasure ratings. After controlling for nausea, only the reduction in alcohol drinking remained. Naltrexone had no effects on mood, sleep or caffeine use, suggesting that the medication did not produce malaise or dampening of all consummatory behaviors. Caffeine, a methylzanthine and central nervous system stimulant, binds primarily to adenosine receptors and is not involved directly with the opioid system [34] so, neurobiologically, an opioid receptor antagonist would not be expected to alter intake within this substance class. Conversely, preclinical research implicates the role of the endogenous opioid system in feeding behaviors, food hedonics and sucrose intake [35–39]. However, these effects appear to be associated with nausea, as they were no longer significant in the adjusted analyses. Given that gut and gastrointestinal processes are tied inherently to feeding behaviors and appetite, it was not surprising that naltrexone-induced nausea was associated with those effects, even if such effects were mild and generally tolerable. Overall, the behavioral and subjective effects observed in the present study are supported by the neurobiological circuitry of the opioid system and its connections to dopaminergic pathways underlying

Table 2 Pre-quit phase cigarette smoking and other behavioral and subjective effects.

	Pre-quit phase		*Linear regression models testing medication effect*				
				P-values			
	Placebo (n = 154)	*Naltrexone (n = 161)*	*Mean difference (95% CI)*	*Unadjusted: medication effect only*	*Adjusted for demographic characteristics*	*Adjusted for demographics and nausea*	*Adjusted for demographics, nausea and baseline*
Primary outcome[a]							
Cigarettes per day	−2.93 (4.54)	−4.21 (4.45)	1.28 (0.28 to 2.27)	0.01	0.02	<0.05	0.02
Secondary behavioral outcomes[a]							
Alcoholic drinks per drinking day	−1.98 (2.98)	−1.94 (2.77)	0.95 (0.21 to 1.70)	0.01	0.02	0.01	0.04
Caffeinated drinks per day	−1.22 (2.84)	−1.35 (2.21)	0.13 (−0.46 to 0.71)	0.7	0.83	0.95	0.9
Secondary subjective effects[b]							
Smoking urge	2.58 (0.64)	2.32 (0.65)	0.25 (0.11 to 0.40)	<0.01	<0.01	0.01	0.02
Cigarette pleasure	2.40 (0.62)	2.22 (0.63)	0.18 (0.04 to 0.32)	0.01	0.01	0.06	0.07
Cigarette taste	2.32 (0.61)	2.12 (0.63)	0.19 (0.05 to 0.33)	0.01	0.01	0.04	0.08
Appetite ratings	2.93 (0.58)	2.72 (0.66)	0.20 (0.07 to 0.34)	<0.01	<0.01	0.09	0.42
Food pleasure	2.88 (0.48)	2.72 (0.58)	0.17 (0.05 to 0.28)	0.01	0.01	0.08	0.30
Sweet food consumption	2.83 (0.65)	2.64 (0.69)	0.19 (0.05 to 0.34)	0.01	0.01	0.08	0.11

Data are mean change score [standard deviation (SD)] or mean score (SD). [a]Behavioral outcomes (cigarettes, alcoholic and caffeinated drinks) are expressed as change scores during pre-quit days 4–6 from baseline (2 weeks prior to enrollment). [b]Subjective effects were rating average on the 5-point scale and did not have a pre-treatment baseline.

Table 3 Mediation models of pre-quit effects of naltrexone to post-quit outcomes.

	Naltrexone predicting outcome post-quit phase[a]			*Naltrexone predicting effect in pre-quit phase*			*Prequit outcome as mediator*			
Outcomes	*B*	*SE*	*P*	*B*	*SE*	*P*	*B*	*SE*	*P*	*Mediation?*
At 4 weeks after quit date										
Δ cigarettes smoked	−2.60	1.24	0.04	−1.28	0.51	0.01	−2.31	1.25	0.07	Yes
Smoking urge ratings (BQSU)	−3.27	1.49	0.02	−0.25	0.07	<0.01	−2.50	1.43	0.08	Yes
Δ alcohol drinks consumed	−6.25	2.98	0.04	−0.95	0.38	0.01	−4.86	2.98	0.10	Yes
At 12 weeks after quit date										
Δ alcohol drinks consumed	−15.28	7.78	0.05	−0.95	0.38	0.01	−12.41	7.82	0.11	Yes

Data are the *B*, standard error (SE) and *P*-values in regression models for mediation analyses. [a]Post-quit phase refers to the period 4 weeks after the quit date for number of cigarettes smoked and smoking urge peak rating [Brief Questionnaire for Smoking Urge (BQSU)]. For alcohol drinks consumed the post-quit phase includes both 4 and 12 weeks after the quit date, as indicated.

motivational salience and hedonic pleasurable effects of nicotine, alcohol and eating behaviors [35,40–42].

The present study findings have translational significance, as pre-quit measures of number of cigarettes smoked and smoking urge mediated naltrexone's effects on their corresponding early post-quit outcomes. This demonstrates that smokers who are more sensitive to opioid antagonist effects before the target quit date may be likely to benefit, at least initially, from this pharmacotherapy in treatment. The findings are important, because prior research has shown that markers early in treatment [43,44] have better associations to post-treatment outcomes than do pre-treatment markers, so the challenges of identifying mediators of outcomes have been long-standing.

The results lend support to initiating naltrexone during a pre-quit interval not only to reduce adverse effects but also to enable a potential extinction phase of smoking reinforcement. The 1-week pre-quit week titration schedule for naltrexone in the current study represents the longest interval examined to date in trials examining the threshold dose of 50 mg naltrexone in treatment [11,12,14]. This interval was chosen a priori to facilitate the current investigation, as well as to reduce unpleasant side effects and to match the duration as recommended for other smoking cessation medications, such as bupropion and varenicline. It is plausible that a longer pre-quit initiation of naltrexone might further enhance post-quit date outcomes, as extended pre-loading could provide a longer extinction phase before the target quit date. For example, a recent study with varenicline demonstrated that pre-quit medication for 4 weeks improved post-quit date outcomes compared to the standard 1-week dosing before the quit date [45]. However, data are needed to determine if this is the case with naltrexone.

This study included several strengths, including both behavioral and subjective measures of smoking and other consummatory behaviors in a large sample and demonstration of the clinical significance of early sensitivity to naltrexone before the quit date to initial treatment outcomes after the quit date. However, there are some limitations worth noting. First, baseline data prior to randomization were included for behavioral measures but not for subjective measures. However, the groups did not differ on other measures of smoking at baseline, including nicotine dependence scores from the Fagerström scale, number of cigarettes smoked, number of prior quit attempts and BQSU smoking urge ratings [13]. Also, saliva and urine samples for medication adherence confirmation was collected by participants in their own environment, which may have affected validity, but was chosen to avoid undue burden on participants to have an extended visit on quit day considering their already stressful pre-quit week and demands on their time. Secondly, the main dependent variables were assessed during a period of behavior change with declines in many measures even in the placebo group. This was not entirely unexpected, as participants were anticipating and preparing for their quit date and taking a tablet daily without knowing whether or not it was the active medication. Finally, only one dose of naltrexone was examined (50 mg), so the study could not determine dose-ranging effects.

In sum, the current study demonstrated novel findings with regard to naltrexone effects on smoking indices and other behaviors in smokers preparing to quit. Naltrexone reduced cigarette smoking and urges and alcohol consumption before the designated quit date, and these effects mediated the medication's effect on these outcomes in the post-quit phase. The current findings lend pre-clinical support for continued research to evaluate the potential role for naltrexone as a treatment adjunct for smoking cessation on numerous clinically relevant outcomes, and to potentially extend pre-quit date medication initiation to examine if effects

after the quit date might be augmented with a longer extinction-type phase. Future research examining biomarkers in those more sensitive to naltrexone, such as opioid receptor mu 1 (OPRM1) and other genetic factors [46], is warranted to determine if genetic factors can help to identify those most likely to benefit from naltrexone in smoking treatment, as well as continued study of naltrexone effects on smoking and drinking outcomes in those with co-use of these substances [47–49]. Naltrexone is generally well tolerated and approved for the treatment of alcohol and opioid dependencies, and there may be a role for re-purposing the medication in the treatment of nicotine dependence. Further understanding of mechanisms may enable targeted and more effective use of this medication and/or facilitate comparisons with novel therapeutics.

Clinical trial registration

Clinicaltrials.gov identifier: Efficacy of Naltrexone in Women's Smoking Cessation: http://clinicaltrials.gov/ct2/show/NCT00271024?term=NCT00271024&rank=1 NCT0027102.

Declaration of interests

None.

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