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A Randomized Clinical Trial of Nicotine Preloading for Smoking Cessation in People with Posttraumatic Stress Disorder

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Abstract

Objective—To determine whether augmenting standard smoking cessation treatment by wearing an active nicotine patch before the smoking quit date improves rates of smoking cessation in individuals with posttraumatic stress disorder (PTSD), and to explore mechanisms of treatment response such as decreased cigarette craving and symptom relief from smoking.

Methods—Double-blind parallel randomized controlled trial in 81 people with PTSD who smoked cigarettes. Participants were recruited from Veterans Affairs outpatient clinics and flyers in the community. Participants provided ecological momentary assessments (EMA) of PTSD symptoms, smoking withdrawal symptoms, and cravings before and after smoking a cigarette during one week of *ad lib* smoking, then three weeks of either a nicotine patch ($n = 37$) or placebo patch ($n = 44$) preceding the quit date. All participants received standard pharmacotherapy and behavioral treatment for smoking cessation after the quit date. To test the efficacy of nicotine patch preloading for engaging proposed treatment targets during the pre-quit phases, we used multilevel models to compare post-smoking changes in symptoms and cravings during the preloading phases to post-smoking changes reported during the *ad lib* smoking phase.

Results—There was no significant difference in quit rates across the two conditions on the primary outcome of 7-day point prevalence smoking abstinence bioverified with breath carbon monoxide (CO) at six weeks post-quit date. In a multivariable multilevel model pre- to post-cigarette changes in PTSD symptom clusters, smoking withdrawal symptoms, and cravings, there was a significant interaction between treatment phase and condition. Relative to participants in the placebo condition, participants in the nicotine patch condition experienced diminished relief from

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Disclosures

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Conflict of Interest

The authors have no conflicts of interest to disclose.

PTSD re-experiencing symptoms, smoking withdrawal symptoms, and cigarette craving after smoking a cigarette.

Conclusions—Relative to placebo patch preloading, nicotine patch preloading diminished the reinforcing effects of smoking cigarettes. However, the low quit rates in both conditions suggest that nicotine patch preloading is not a sufficiently intensive treatment for achieving smoking cessation in people with PTSD.

Trial Registration—Clinical Trials NCT00625131

Keywords

smoking cessation; tobacco; posttraumatic stress disorder; nicotine replacement therapy; ecological momentary assessment

INTRODUCTION

Despite the fact that smoking rates in the general United States population have substantially decreased over the past 30 years from 42% to 15% (Centers for Disease Control & Prevention, 2016), nearly half of individuals with PTSD continue to smoke (Cook, McFall, Calhoun, & Beckham, 2007; Feldner, Babson, & Zvolensky, 2007; Lasser et al., 2000). Individuals with PTSD are less likely than those in the general population to quit smoking (Hapke et al., 2005), despite their desire to stop smoking (Kirby, 2009). There is a clear need to test treatment innovations that might improve smoking cessation rates for people with PTSD.

To increase the efficacy of nicotine replacement, several trials have tested the strategy of initiating nicotine replacement prior to the quit date, an approach often termed “preloading.” A meta-analysis found that using the nicotine patch prior to the quit date resulted in a moderate increase in the rate of abstinence (Stead et al., 2012), though the effect was not statistically significant when combining nicotine patch trials with trials using other forms of nicotine replacement (e.g., gum, lozenges, inhalers). In trials reported to date, results have been mixed, with some trials reporting significantly improved smoking abstinence (Rose, Behm, Westman, & Kukovich, 2006; Rose, Herskovic, Behm, & Westman, 2009; Schuurmans, Diacon, van Biljon, & Bolliger, 2004), and other trials reporting no significant advantage of nicotine preloading (Bullen et al., 2010; Etter, Huguelet, Perneger, & Cornuz, 2009; Dennis et al., 2016).

While mixed results from previous trials prevent definitive conclusions, there is reason to expect that nicotine preloading will be helpful for people with PTSD. EMA research suggests that PTSD symptoms are associated with urges to smoke and are significant antecedents of smoking (Beckham et al., 2005). Individuals with PTSD retrospectively report that their smoking behavior is driven by negative reinforcement motives such as reducing distress (Calhoun et al., 2011). Though these data support the idea that smoking reduces PTSD symptoms, these reductions are short-lived and continue to increase in response to trauma-related cues (Beckham et al., 2007). By disrupting the connection between smoking behavior and decreased psychiatric and smoking withdrawal symptoms

before the quit date, nicotine preloading could make individuals less likely to seek relief from smoking withdrawal after the quit date (Schuz & Ferguson, 2014).

In this study of nicotine patch preloading, side effects from combining nicotine patch with regular nicotine yield cigarettes can be minimized by providing participants with low nicotine cigarettes to reduce their dependence on inhaled nicotine while wearing nicotine patches, a method utilized in a previous trial (Rezaishiraz, Hyland, Mahoney, O'Connor, & Cummings, 2007). In addition, to match standard smoking cessation pharmacotherapy, it is important to evaluate the influence of patch preloading in the presence of bupropion in the pre-quit week of nicotine patch preloading (Lindson-Hawley et al., 2014). The lone previous trial to test nicotine patch preloading in people with PTSD did not use low nicotine cigarettes or bupropion in the preloading phase and did not find an effect of preloading on smoking abstinence (Dennis et al., 2016), suggesting the utility of alternative approaches. With this in mind, we aimed to test the efficacy of nicotine patch preloading by using low nicotine cigarettes for two weeks, then adding bupropion in a third week before the quit date.

We hypothesized that, relative to participants assigned to wearing the placebo patch prior to the quit date, participants assigned to preloading with a nicotine patch would have a higher rate of smoking abstinence at the 6-week follow-up. Regarding targeted treatment mechanisms, we hypothesized that, relative to participants assigned to wearing the placebo patch prior to the quit date, participants preloading with a nicotine patch would be more likely to report reduced smoking, and diminished smoking-related relief from PTSD symptoms, withdrawal symptoms, and cigarette craving when they move from *ad lib* smoking to patch preloading phases.

METHODS

Participants

All participants discussed study procedures with study personnel, then provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. The study was reviewed, approved, and monitored by the Duke University and Durham VA Health Care System Institutional Review Boards. Participant characteristics are reported in Table 1. Participant flow through the study is illustrated in Figure 1. Thirteen participants were missing a large proportion of EMA data, primarily due to early dropout, resulting in 68 participants who were included in EMA analyses. Eighty-one participants were randomized and included in intent-to-treat analyses. This sample size was designed to detect a difference in smoking abstinence at six weeks post-quit date, based on quit rates observed in previous smoking cessation studies in people with PTSD (12–40% in preloading group vs. 0–5% in placebo group; (Hertzberg, Moore, Feldman, & Beckham, 2001; McFall et al., 2010)).

Eligibility criteria included smoking at least 10 cigarettes daily for the past year, willingness to make a smoking cessation attempt, interview-based diagnosis of PTSD, age 18–70 years, and fluency in English. Potential participants were excluded if they smoked non-cigarette forms of nicotine (non-combustible forms of nicotine such as electronic cigarettes were not excluded), were pregnant, had major unstable medical problems or unstable medication

regimens, current manic syndrome, psychotic disorder, current drug or alcohol use disorder, or used bupropion or benzodiazepines.

Procedures

Recruitment and Screening—The study timeline is illustrated in Figure 2. Participants were military Veterans and civilians who were invited to participate from outpatient clinic providers or saw Institutional Review Board-approved flyers advertising a study on PTSD and smoking cessation. Potentially eligible participants were also mailed a series of invitational letters using an approach described by Dillman and colleagues (Dillman, Smyth, & Christian, 2009). At the screening session, each participant provided sociodemographic information, smoking history, completed the Fagerström Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), and completed the Structured Clinical Interview for DSM-IV for Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1996). Bupropion was added in the final week of the patch preloading phases in those with no medical contraindication who were willing to take it ($n = 22$ in the nicotine patch condition; $n = 31$ in the placebo patch condition), with no statistically significant difference in bupropion prescription rates across conditions ($p = 0.353$, Fisher's exact test).

Clinician-Administered PTSD Scale (CAPS-IV)—PTSD was assessed with the CAPS-IV diagnostic interview (Blake et al., 1995). Total scores for the CAPS-IV were summed using both frequency and intensity for the 17 items (Cronbach's $\alpha = .86$). We divided symptoms into four symptom clusters based on a four-factor model of PTSD (King, Leskin, King, & Weathers, 1998): 5 re-experiencing items, 2 avoidance items, 5 numbing items, and 5 hyperarousal items.

Ad lib EMA, Randomization, and Preloading Phase—After the baseline session, participants were asked to complete one week of baseline EMA monitoring that would capture participants' *ad lib* smoking behavior. See "Ecological Momentary Assessment" section below for procedures. One week later, participants returned and were randomly assigned using a pre-study list of computerized random numbers maintained by pharmacists who were not involved in study conduct. Participants were randomized to wear either an active 21mg nicotine patch or a placebo patch prior to the scheduled quit date. Randomization was stratified by gender and presence of current major depressive disorder. Both staff members and participants were masked to the treatment condition until after the trial was completed. To maintain treatment condition masking, placebo and active nicotine patches had the same packaging. Throughout the patch preloading phases, participants used low nicotine cigarettes yielding 0.2 mg nicotine and 1 mg tar when smoked.

Behavioral Counseling—During the pre-quit period, all participants received two sessions of cognitive behavioral smoking cessation counseling. Behavioral counseling sessions lasted 50 minutes each and included psychoeducation about the physiological effects of smoking, behavioral strategies for coping with withdrawal symptoms, diaphragmatic breathing exercises, identification of social support, and plans for reinforcing abstinence.

Post-Quit Phase—Beginning at the quit date, study coordinators assessed smoking frequency, including lapse dates and times, bioverified smoking status with a carbon monoxide monitor, and reviewed the EMA data provided by participants. During the post-quit phase, all participants received a standard course of nicotine patches at decreasing doses of 21 mg for the first two weeks, 14 mg for next two weeks and 7 mg for last two weeks. Participants received one form of rescue nicotine replacement (e.g., gum, lozenge) while continuing bupropion as previously prescribed. Participants also began post-quit EMA procedures. Participants returned weekly after the quit date until 6 weeks post-quit, when they returned study equipment. Lapse dates and times were recorded via EMA and at weekly study visits. Study visits were scheduled at weeks 1–6 post-quit, and at six months post-quit. Seven-day abstinence was self-reported and verified by exhaled carbon monoxide < four parts per million (Cropsey et al., 2014).

Ecological Momentary Assessments—EMA data collection procedures were designed to evaluate the influence of patch preloading condition on: 1) smoking frequency and craving throughout *ad lib*, patch preloading, and post-quit phases of a quit attempt and; 2) change in craving, withdrawal symptoms, and PTSD symptoms that occur when smoking a cigarette during the patch preloading phase. Using procedures described in a previously published trial (Dennis et al., 2016), participants were asked to respond to random alarms throughout the day and initiated their own assessments before and after smoking, as well as after resisting a craving. Random readings only assessed time of most recent cigarette and current craving; while self-initiated readings included smoking craving, setting, activity, and withdrawal and PTSD symptoms. PTSD symptoms were assessed with one question per symptom cluster. Participants had a two-minute window after the alarm to begin the assessment. They were instructed to ignore any signal that occurred during an incompatible activity (e.g., driving), could delay an assessment with a 5-minute delay function. Participants could also inactivate daytime alarms for 15–120 minutes when they expected to be unavailable and for 4–11 hours overnight for sleeping.

Participants were paid \$25 per week for EMA monitoring and up to \$25 in incentive pay during the post-quit weeks for good EMA protocol adherence (i.e., no more than two missed alarm readings per day and at least two pre- and post- cigarette readings per day until the quit date). Participants were also paid an additional \$25 at each of the post-quit visits for completing the study session. Participants remained enrolled in treatment until they relapsed, which was defined as smoking at least five cigarettes a day for at least three consecutive days.

Smoking frequency was assessed using the self-initiated smoking entries and nightly entries indicating number of cigarettes smoked. Both sets of estimates were summed over the course of each pre-quit phase (*ad lib*, patch-only, and patch + bupropion preloading phases). The larger estimate of the two was retained and divided by time elapsed to generate an estimate of the number of cigarettes smoked per day.

Analysis Plan

The primary outcome was intent-to-treat analyses of smoking abstinence at the 6-week follow-up, with 6-month follow-up included as a secondary outcome. To evaluate how effectively nicotine preloading engaged proposed treatment mechanisms, we evaluated changes in smoking and craving during patch preloading and symptom change after smoking a cigarette. This was done to inform models of smoking cessation in PTSD as well as patch preloading treatments. To analyze data that included multiple observations (e.g., smoking occasions) nested within individual participants, we used multilevel modeling (MLM; (Snijders & Bosker, 1999). The output from MLM can be interpreted in a similar manner as that from ordinary least-squares regression and generalized linear modeling, with coefficients representing the modeled effect of the corresponding variable on the outcome variable.

To model change in symptoms from pre- to post-cigarette, change scores were tabulated by subtracting pre-cigarette symptoms from post-cigarette symptoms. As such, a negative score would represent greater symptom reduction and relief following smoking. Due to its robust inverse relationship with smoking cessation (Vangeli, Stapleton, Smit, Borland, & West, 2011), nicotine dependence was included as a covariate in analyses of CO levels, cravings, and symptom changes. The change scores were modeled with pre-cigarette symptoms as a covariate. Log-linked negative binomial MLM was also used to model smoking frequency and CO level during the three pre-quit phases. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Ecological Momentary Assessment Entries

Participants completed a total of 5,415 self-initiated and 13,563 random-alarm entries during the pre-quit period. The response rate to random alarms was high (76%). During the *ad lib* phase, 68 participants completed entries for a mean of 8.2 days ($SD = 3.0$), 7.9 random alarm entries a day ($SD = 5.1$), and 3.8 self-initiated entries a day ($SD = 2.5$). During the patch-only preloading phase, 67 participants completed entries for a mean of 15.5 days ($SD = 4.6$), 5.2 random alarm entries a day ($SD = 5.6$), and 2.5 self-initiated entries a day ($SD = 1.9$). During the patch + bupropion phase, 49 participants completed entries for a mean of 9.1 days ($SD = 5.9$), 13.1 random alarm entries a day ($SD = 9.6$), and 2.1 self-initiated entries a day ($SD = 1.8$). Entries per day of self-initiated and random-alarm entries did not vary by patch treatment condition during any of the pre-quit phases (p s $\geq .29$). Additional descriptive statistics for EMA-measured variables are provided in Table 2.

Smoking Lapse and Relapse

Analysis of abstinence rates were based on intent-to-treat principles, with missing data classified as currently smoking cigarettes. At 6 weeks post-quit, 42 participants (22 in the placebo-patch condition and 20 in the active patch condition) provided bio-verified 7-day abstinence data. Of those providing 6-week follow-up data, 7/22 (32%) in the placebo-patch condition and 5/20 (25%) in the active patch condition were abstinent. In the intent-to-treat analysis, 7/44 (16%) in the placebo-patch condition and 5/37 (14%) in the active patch

condition reported smoking abstinence that was bioverified by CO. Odds of 6-week abstinence in the intent-to-treat analysis were not significantly greater for the active-patch condition in comparison to the placebo-patch condition, $OR = 0.83$, 95% CI : 0.24–2.86. Thirty-eight participants (19 in each treatment condition) attended the 6-month follow-up ($n = 36$) or confirmed by phone ($n = 2$) that they were currently smoking cigarettes. Of those providing 6-month follow-up data, 6/19 (32%) in the placebo-patch condition and 1/19 (5%) in the active patch condition were abstinent. In the intent-to-treat analysis, 6/44 (14%) in the placebo-patch condition and 1/37 (3%) in the active patch condition were abstinent. Odds of 6-month abstinence in the intent-to-treat analysis were not significantly greater for the active-patch condition in comparison to the placebo-patch condition, $OR = 0.18$, 95% CI : 0.02–1.53.

Effects on Craving and Symptoms

Smoking Frequency and CO Levels Across Patch Preloading Phases—

Participants reported smoking a mean of 16.7 cigarettes per day ($SD = 9.5$) during the *ad lib* phase, 13.8 per day ($SD = 7.6$) during the patch-only phase, and 12.6 per day ($SD = 7.6$) during the patch + bupropion phase. In negative binomial MLM analyses, nicotine dependence was positively associated with mean cigarettes smoked per day ($B = 0.16$, $p < .001$). There was not a significant decrease in smoking from the *ad lib* phase to the patch-only phase ($B = -0.17$, $p = .064$). The decrease in smoking from the *ad lib* phase to the patch + bupropion phase was significant ($B = -0.41$, $p < .001$), and the moderation of this decrease by treatment condition was only marginally significant in the full model ($B = 0.28$, $p = .065$). As illustrated in Figure 3, participants using the active nicotine patch had a decrease in smoking from the *ad lib* phase to the patch-only phase ($B = -0.21$, $p = .038$), whereas participants in the placebo patch condition had only a marginally significant decrease ($B = -0.17$, $p = .064$).

We used negative-binomial MLM to model CO levels as a function of pre-quit phase, treatment condition, and their interaction. According to this analysis, neither nicotine dependence, $B = 0.02$, $p = .70$, nor nicotine preloading condition, $B = 0.01$, $p = .94$, were associated with CO level. CO did not decrease significantly from the *ad lib* phase to the patch-only preloading phase ($B = -0.11$, $p = .26$). However, the decrease from the *ad lib* phase to the patch + bupropion phase was significant ($B = -1.00$, $p < .001$). Neither of these changes in CO level were moderated by treatment condition, ($p > .96$).

Symptom Change Following Smoking—To determine whether immediate changes in PTSD and withdrawal symptoms as well as cigarette craving associated with smoking varied by treatment condition and/or pre-quit phase, we modeled difference scores calculated by subtracting pre-cigarette symptom/craving levels from post-quit levels *via* linear MLM. Initially, we analyzed a multivariate multilevel model examining PTSD symptom clusters, smoking withdrawal, and craving. According to that model, there were significant main effects of pre-cigarette symptom level ($F[6, 37782] = 2498.61$, $p < .001$) and pre-treatment phase ($F[6, 672] = 3.29$, $p < .001$), with a marginally significant effect of nicotine dependence ($F[6, 37782] = 2.03$, $p = .058$) and no significant effect of treatment condition ($F[6, 328] = 0.95$, $p = .46$). The interaction between pre-treatment phase and treatment

condition was significant ($F[12, 672] = 3.29, p < .001$). As illustrated in Figure 4, there were also significant differences across study phases in the degree of symptom and craving relief provided by smoking. There was no difference between treatment conditions in symptom and craving relief provided by smoking, but the effects of pre-treatment study phase on symptom and craving relief provided by smoking depended on treatment condition. To clarify the direction of the main effects and the nature of the interactions (see Table 3), we then examined the univariate multilevel models. Higher pre-smoking symptoms and craving were related to greater symptom and craving relief (i.e., drops in symptoms and craving following smoking). Across treatment conditions, smoking during the patch preloading phases was related to greater relief from PTSD re-experiencing, PTSD numbing, and smoking withdrawal symptoms. The interactions between pre-quit phases and study condition were significant for models of PTSD re-experiencing symptoms, smoking withdrawal symptoms, as well as cigarette craving. Plotting these interactions illustrated that, relative to the placebo patch condition, participants in the nicotine patch condition experienced diminished relief from PTSD re-experiencing symptoms, smoking withdrawal symptoms, and cigarette craving in the patch-only preloading phase and patch + bupropion preloading phase (see Figure 4). Generally, participants with greater symptoms and cravings experienced greater relief from smoking. In addition, relief provided by smoking was greater during the patch preloading phase, especially for participants who were in the placebo patch condition.

DISCUSSION

In this study of nicotine patch preloading among smokers with PTSD, we did not find that smokers attempting to quit by using a nicotine patch during the preloading phases were more likely to quit smoking than smokers using a placebo patch. Results are consistent with a previous trial of nicotine patch preloading (Dennis et al., 2016), which did not use low nicotine cigarettes or bupropion.

While nicotine patch preloading was unrelated to improved quit rates, analyses provided limited support to the utility of nicotine patch preloading for engaging proposed treatment targets. During the patch preloading phase, smoking produced greater relief of PTSD re-experiencing symptoms, smoking withdrawal symptoms, and cigarette craving in participants wearing the placebo patch, relative to participants preloading with a nicotine patch. Further, smokers preloading with a nicotine patch reported diminished relief from craving during the preloading phases. Thus, mechanisms were generally in favor of the nicotine patch condition. However, it is important to replicate this finding in people with PTSD who have comorbid non-tobacco substance use disorders.

This study was limited by the use of low nicotine cigarettes and bupropion during the patch preloading phases, as this cessation process might differ from those reported in most previous trials. However, nicotine patch preloading also did not provide an advantage in a trial of people with PTSD that asked people to continue smoking their usual brand of cigarettes during the preloading phase (Dennis et al., 2016). Effects of patch preloading could have also been limited by the small sample size, termination of treatment when participants fully relapsed, and the absence of PTSD treatment.

This trial did not support the use of nicotine patch preloading to improve quit rates among smokers with PTSD. It is possible that the addition of nicotine preloading alone is not a sufficiently intensive intervention for people with PTSD, who suffer from low rates of smoking cessation. Future intervention studies on smoking in PTSD might focus more strongly on psychiatric and behavioral aspects of smoking cessation, such as addressing PTSD symptoms and habitual aspects of smoking. Interventions using more intensive counseling could be required to effectively assist individuals with PTSD to achieve smoking abstinence (Dedert et al., 2016). Additional innovative approaches are needed to promote smoking cessation in people with PTSD.

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Figure 1.
CONSORT Trial Flow Diagram

Figure 2.

Study recruitment, screening, and data collection timeline.

Notes: Durations for each phase were standardized across participants so that phases had the same durations across participants. *Ad lib* = Latin phrase that means “as often as desired.”

EMA = ecological momentary assessment. mg = milligrams.

Figure 3.

Mean cigarettes smoked per day by pre-quit phase and treatment condition. Cigarettes per day are drawn exclusively from random alarm ecological momentary assessments.

Notes: *Ad lib* = Latin phrase that means “as often as desired.” Bup = bupropion.

Figure 4.

Post-cigarette change in PTSD Re-experiencing symptoms, withdrawal symptoms, and cigarette craving by treatment phase and condition.

Notes: Notes: Re-Experiencing and Craving were measured by ecological momentary assessment on a 5-point scale ranging from 1 (“not at all”) to 5 (“extremely”). Withdrawal Symptoms were measured by ecological momentary assessment on a 5-point scale ranging from 0 (“none”) to 4 (“severe”). Negative scores indicate drop in levels after smoking. *Ad lib* = Latin phrase that means “as often as desired.” Bup = bupropion.

Table 1

Participant Characteristics.

	Placebo Patch (<i>n</i> = 44)	Nicotine Patch (<i>n</i> = 37)	Tests of Difference
	Frequency (%)	Frequency (%)	Test statistic
Sex (Females)	21 (48%)	16 (43%)	Fisher's <i>p</i> = .823
Veteran Status	18 (41%)	16 (43%)	Fisher's <i>p</i> = 1.000
Race/Ethnic Category			Fisher's <i>p</i> = .180
African American	30 (68%)	20 (54%)	
Asian	0 (0%)	1 (3%)	
White	12 (27%)	10 (27%)	
Multiple Races	2 (5%)	6 (16%)	
Missing	0 (0%)	1 (3%)	
Employment Status			Fisher's <i>p</i> = .303
Full-time	5 (11%)	10 (27%)	
Part-time	8 (18%)	5 (14%)	
Unemployed	22 (50%)	15 (43%)	
Retired or Other	9 (20%)	5 (14%)	
	Mean (SD)	Mean (SD)	Test statistic
Age	44.5 (11.3)	45.0 (9.7)	<i>t</i> (77) = -0.21, <i>p</i> = .84
Education (years)	12.75 (2.55)	12.45 (2.18)	<i>t</i> (71) = 0.53, <i>p</i> = .60
Nicotine Dependence	2.42 (1.33)	2.33 (1.22)	<i>t</i> (77) = 0.30, <i>p</i> = .76
Index Trauma			
Combat	10 (0%)	11 (0%)	
Child Physical/Sexual Abuse	7 (0%)	6 (0%)	
Adult Physical/Sexual Abuse	8 (0%)	6 (0%)	
Accident	2 (0%)	2 (0%)	
Domestic Violence	1 (0%)	4 (0%)	
Death of Someone Close	6 (0%)	0 (0%)	
Witness Violence	9 (0%)	4 (0%)	
Other	1 (0%)	4 (0%)	
CAPS-IV Total	65.1 (20.5)	62.9 (17.3)	<i>t</i> (76) = 0.52, <i>p</i> = .61
Re-experiencing	19.0 (8.0)	17.5 (7.4)	<i>t</i> (76) = 0.86, <i>p</i> = .39
Avoidance	9.3 (4.1)	8.8 (4.3)	<i>t</i> (76) = 0.51, <i>p</i> = .61
Numbing	16.1 (8.2)	16.7 (6.0)	<i>t</i> (76) = -0.35, <i>p</i> = .73
Hyperarousal	20.7 (7.7)	19.9 (6.7)	<i>t</i> (76) = 0.50, <i>p</i> = .62
Current Major			
Depressive Disorder	15 (34%)	12 (34%)	$\chi^2(1) = 0.00$, <i>p</i> = .99
Current Panic Disorder	0 (0%)	2 (5%)	
Current Phobia (including Social Phobia)	8 (18%)	5 (14%)	Fisher's <i>p</i> = .763
Current Obsessive-Compulsive Disorder	0 (0%)	1 (3%)	

	Placebo Patch	Nicotine Patch	
	(<i>n</i> = 44)	(<i>n</i> = 37)	Tests of Difference
Current Generalized Anxiety Disorder	1 (2%)	0 (0%)	

Note. Means/frequencies and standard deviations/percentages (in parentheses).

CAPS-IV = Clinician-Administered PTSD Scale for DSM-IV. Fisher's exact test was not calculated for single-variable comparisons with cell sizes < 5.

Table 2

Descriptive Statistics for EMA Variables Across Phases of the Pre-quit Period.

	Placebo Patch Condition				Nicotine Patch Condition			
	Ad lib Phase		Patch-only Preloading Phase		Ad lib Phase		Patch-only Preloading Phase	
	Week 1	Week 2-3	Week 2-3	Week 4	Week 1	Week 2-3	Week 2-3	Week 4
Cigarettes per day	17.08 (10.72)	14.38 (8.62)	14.38 (8.62)	11.14 (6.94)	16.16 (7.96)	13.08 (6.29)	13.08 (6.29)	14.65 (8.12)
Carbon Monoxide (CO)	20.36 (10.71)	18.76 (14.46)	18.76 (14.46)	7.76 (6.24)	18.91 (11.41)	18.12 (10.35)	18.12 (10.35)	7.32 (4.62)
Cigarette Craving	2.00 (1.26)	2.07 (1.15)	2.07 (1.15)	1.92 (0.99)	1.94 (1.39)	1.66 (1.27)	1.66 (1.27)	1.69 (1.21)
Smoking Withdrawal	7.81 (6.37)	7.39 (5.78)	7.39 (5.78)	7.77 (6.05)	8.72 (7.23)	8.29 (7.21)	8.29 (7.21)	11.94 (8.55)
PTSD Re-experiencing	1.77 (0.92)	1.77 (0.91)	1.77 (0.91)	1.79 (0.89)	1.90 (1.02)	1.87 (1.02)	1.87 (1.02)	2.42 (1.58)
PTSD Avoidance	1.93 (1.09)	1.83 (1.00)	1.83 (1.00)	1.78 (0.98)	2.02 (1.11)	1.93 (1.05)	1.93 (1.05)	2.48 (1.55)
PTSD Numbing	2.07 (1.29)	2.09 (1.24)	2.09 (1.24)	2.38 (1.31)	2.11 (1.20)	2.17 (1.18)	2.17 (1.18)	2.46 (1.29)
PTSD Hyperarousal	1.81 (1.01)	1.82 (1.00)	1.82 (1.00)	1.82 (0.99)	1.99 (1.01)	1.86 (0.99)	1.86 (0.99)	2.37 (1.43)

Note. All cells report the mean and standard deviation for each row by the corresponding phase listed in the column.

Table 3

Univariate Multilevel Models of Post-Smoking Symptom Change Across Treatment Phases.

	PTSD Re-experiencing	PTSD Avoidance	PTSD Numbing	PTSD Hyperarousal	Smoking Withdrawal	Cigarette Craving
Intercept	-0.04 (0.05)	-0.02 (0.08)	-0.04 (0.06)	-0.09 [†] (0.05)	-1.70 ^{**} (0.35)	-1.03 ^{**} (0.13)
Pre-Cigarette Symptom Level	-0.38 ^{**} (0.01)	-0.47 ^{**} (0.01)	-0.42 ^{**} (0.01)	-0.43 ^{**} (0.01)	-0.34 ^{**} (0.01)	-0.80 ^{**} (0.01)
Patch Preloading Phase ^a	-0.04 ^{**} (0.01)	-0.05 [†] (0.02)	-0.08 ^{**} (0.02)	-0.02 (0.02)	-0.38 ^{**} (0.12)	-0.05 [†] (0.03)
Patch + Bupropion Phase ^b	-0.01 (0.02)	-0.05 (0.03)	-0.04 (0.03)	-0.07 [*] (0.03)	-0.33 [*] (0.16)	-0.14 ^{**} (0.04)
Baseline Nicotine Dependence	0.03 (0.03)	0.07 (0.05)	0.04 (0.04)	0.06 [*] (0.03)	0.46 [*] (0.21)	0.22 ^{**} (0.07)
Preloading Condition	-0.00 (0.08)	0.03 (0.12)	0.03 (0.09)	0.07 (0.07)	0.11 (0.52)	-0.23 (0.18)
Patch ^a X Preloading Condition	0.06 ^{**} (0.02)	0.05 (0.04)	0.02 (0.03)	-0.02 (0.03)	0.44 [*] (0.18)	0.16 ^{**} (0.04)
Patch + Bupropion ^b X Preloading Condition	0.02 (0.03)	0.00 (0.05)	-0.02 (0.05)	0.01 (0.05)	0.33 (0.24)	0.23 ^{**} (0.06)

Note. Coefficients and standard errors (in parentheses). Coefficients are interpreted in the same manner as coefficients from ordinary least-squares regression. Change in symptoms and cigarette craving were calculated by subtracting pre-cigarette levels from post-cigarette levels. Consequently, negative change scores represent a decrease in level following smoking, whereas a positive change score represent an increase in level smoking. PTSD = posttraumatic stress disorder.

^a Patch phase vs. *Ad lib* phase.

^b Patch + Bupropion vs. *Ad lib* phase.

[†] $p < .10$.

^{*} $p < .05$.

^{**} $p < .01$.