Original investigation

Brain Responses to Cigarette-Related and Emotional Images in Smokers During Smoking Cessation: No Effect of Varenicline or Bupropion on the Late Positive Potential

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Abstract

Introduction: Varenicline and bupropion are two effective smoking cessation pharmacotherapies. Researchers have hypothesized that they might be effective, in part, because they reduce cue reactivity and cue-induced cravings. Here, we used event-related potentials (ERPs) to directly measure brain responses to cigarette-related and other motivationally relevant images during a pharmacologically aided quit attempt.

Methods: Smokers involved in a 12-week placebo-controlled double-blind clinical trial of smoking cessation medications (varenicline, bupropion, placebo) took part in the study. We assessed participants at two time points: 24 h ($n = 140$) and 4 weeks ($n = 176$) after the quit date. At both sessions, we measured the amplitude of the late positive potential (LPP), an ERP component reliably associated with motivational relevance, and self-reported tonic craving using the brief version of the Questionnaire of Smoking Urges (QSU-Brief).

Results: At both sessions, emotional and cigarette-related images evoked significantly larger LPPs than neutral images. Neither drug type nor smoking abstinence altered this effect at either session. At both sessions, varenicline and bupropion significantly reduced self-reported tonic craving relative to the placebo condition.

Conclusions: While both varenicline and bupropion reduced self-reported tonic craving, neither medication altered the amplitude of the LPP to cigarette-related or emotional pictures in smokers attempting to quit. These medications may influence abstinence by means other than by reducing neuroaffective responses to cigarette-related cues. Smokers should be prepared for the likelihood that even after several weeks of successful abstinence, once treatment ends, cigarette-related cues may remain motivationally relevant and trigger cravings that might lead to relapse.

Implications: Bupropion and varenicline do not alter electrophysiological responses, as measured by the LPP, to cigarette-related and emotional images. These findings help explain why cigarette-related cues can trigger relapse when smoking cessation medication treatments end.

Introduction

In the United States, tobacco smoking is still the most prevalent cause of preventable disease, disability, and death.¹ Each year, half of the smokers in the United States try to quit, but only 7% of smoking cessation attempts result in successful abstinence of 6 months or longer.¹ Pharmacotherapies such as nicotine replacement therapy (NRT), bupropion, and varenicline significantly increase the likelihood of achieving smoking abstinence,^{2–4} yet, even when smokers receive intensive behavioral and pharmacological interventions, the relapse rate at 6 months is still 75%.^{5,6} A better understanding of the neurophysiological mechanisms underlying vulnerability and resilience to smoking relapse can contribute to the development of new and more effective treatment strategies for helping smokers maintain abstinence.

Both varenicline, a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs),⁷ and bupropion, a weak $\alpha 4\beta 2$ nAChRs antagonist with weak activity on both dopaminergic (DA) and noradrenergic (NE) systems,⁸ reduce general smoking urges and negative affect in smokers attempting to quit.^{6,9–11} However, notwithstanding its clinical relevance, the extent to which these medications reduce brain responses to cigarette-related cues (ie, stimuli associated with smoking, such as ashtrays, cigarette brands, or a person smoking) and cue-induced cravings is less clear. The presence of cigarette-related cues is one of the most common triggers of smoking relapse.^{12–16} Cue-induced cravings continue to trouble smokers even after weeks or months of continuous abstinence, when tonic background craving has subsided.¹⁷

To date, few studies have directly investigated the impact of bupropion or varenicline on smoking urges or brain activity evoked by cigarette-related cues. Two brain imaging studies^{18,19} reported that, relative to placebo, bupropion reduces both cue-induced brain activity and craving. However, the brain regions showing reduced cue-induced activation in smokers treated with bupropion were not the same in the two studies: striatum, thalamus, and midbrain in Weinstein et al.,¹⁸ and anterior cingulate in Brody et al.¹⁹ Furthermore, a subsequent double-blind randomized trial²⁰ did not replicate the observation that bupropion reduces cue-induced cravings relative to placebo. Although varenicline more consistently reduces cue-induced cravings,^{21,22} its effects on cue-evoked brain activity are not consistent across studies. Franklin et al.²² reported diminished responses in the medial orbitofrontal cortex for those on varenicline, compared to baseline while Hartwell et al.²³ reported no significant differences in activated brain regions for those on varenicline relative to baseline. In both cases, small sample sizes and differences among experimental paradigms likely contributed to the inconsistencies.

The present study examined the extent to which varenicline and bupropion affected brain responses evoked by cigarette-related, emotional (pleasant and unpleasant), and neutral visual stimuli during a smoking cessation attempt. Participants were a subset ($N = 210$) of the 294 smokers that took part in a double-blind placebo-controlled smoking cessation medication clinical trial.⁶ In this study, we used event-related potentials (ERPs) to measure brain responses at two time points: 24 h and/or 4 weeks after the scheduled quit date. ERPs are a noninvasive, millisecond-resolution measure of neurotransmission-related neural activity. Previous studies have shown that the presentation of emotional images modulates the amplitude of several

ERP components that are associated with perceptual, attentional, and affective processes.²⁴ To evaluate the effects that medications might have on neuroaffective responses evoked by neutral, emotional, and cigarette-related cues, we analyzed the amplitude of the late positive potential (LPP), the most replicable and reliable index of motivational relevance.^{24–26} Affectively charged images (both pleasant and unpleasant) increase the amplitude of the LPP relative to neutral images as a function of their motivational relevance.^{26–30} Several studies also showed that images depicting cigarette-related cues (eg, smoking paraphernalia, people smoking cigarettes) prompt larger LPPs than images depicting neutral objects or people engaged in mundane activities.^{31,32} Even though, on average, cigarette-related cues evoke smaller LPPs than highly arousing emotional stimuli such as erotic images or mutilations,^{33,34} cigarette-related cues consistently evoke brain responses that are comparable to those evoked by other motivationally relevant images.^{35,36} These findings support the idea that, for some smokers, cigarette-related stimuli can acquire motivational relevance by being paired with nicotine delivery.^{37,38}

Hence, to better understand the neuropsychological underpinnings of cue-induced relapse, here we used the LPP, a valid and reliable index of motivational relevance, to investigate the extent to which bupropion and varenicline influence neuroaffective responses to both cigarette-related and non-nicotine related emotional stimuli in a relatively large group of smokers attempting to quit.

Methods

Participants

Participants were a subset ($N = 210$) of the 294 smokers who participated in a double-blind placebo-controlled smoking cessation medication clinical trial.⁶ The current study reports results only from the participants who completed at least one ERP session after their target quit date while in the clinical trial. One visit was scheduled 24 h after the target quit date ($n = 140$), the other visit 4 weeks after the target quit date ($n = 176$). It is important to note that we did not have ERP data from both visits for all participants: 106 participants provided data at both visits, 34 participants only at the 24-h visit and 70 only at the 4-week visit. The demographic characteristics of the sample at the 24-h post-quit visit did not differ from those at the 4 weeks post-quit, thus Table 1 shows demographics for the total sample. Participants were recruited in Houston, Texas through public service announcements, radio, and newspaper advertisements from August 31, 2006 to October 27, 2010. Inclusion criteria included smoking at least five cigarettes per day with a baseline expired carbon monoxide (CO) level greater than 6 parts per million (ppm), having no uncontrolled chronic medical illness, being fluent in English, having a working phone, being 18–65 years old, and being able to provide written consent. Exclusion criteria included taking psychotropic medication, having a lifetime history of a psychotic disorder, being hospitalized in the past year for a psychiatric condition, being involved in a concurrent smoking cessation program, having a current psychiatric disorder, scoring high or moderate on a suicidality scale of the Mini-International Neuropsychiatric Interview,³⁹ or having a medical exclusion in which the person could not use varenicline or bupropion sustained release (SR). This research and procedures

Table 1. Baseline Demographics, Smoking Characteristics, and Abstinence in All Participants

Measure	Placebo (<i>n</i> = 68)		Bupropion (<i>n</i> = 71)		Varenicline (<i>n</i> = 71)		Total (<i>N</i> = 210)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age	45.7	(11.4)	44.7	(9.5)	43.5	(11.2)	44.6	(10.7)
FTND	4.3	(2.2)	4.7	(1.9)	4.4	(2.2)	4.5	(2.1)
Cigarettes per day	18.5	(8.7)	20.1	(9.4)	18.9	(8.3)	19.2	(8.8)
	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>
Sex								
Female	32.4	22	40.8	29	32.4	23	35.2	74
Male	67.6	46	59.2	42	67.6	48	64.8	136
Race/ethnicity								
African American, non-Hispanic	20.6	14	21.1	15	21.1	15	21.0	44
White, non-Hispanic	69.1	47	69.0	49	59.2	42	65.7	138
Hispanic	8.8	6	5.6	4	9.9	7	8.1	17
Other	1.5	1	4.2	3	9.8	7	5.2	11

Age, FTND, cigarettes per day, were each compared across the two visits (24-h post-quit and 4-weeks post-quit) using independent-samples *t*-tests (because not all participants contributed data to both visits). There were no significant differences between the two time points on any of these measures.

were approved by the University of Texas MD Anderson Cancer Center Internal Review Board.

Given that our main interest was to study the effects of the medications on brain responses, our analyses at each time point only included participants who took the full dosage of the medication. In the 24-h post-quit analyses, five participants were excluded (two in placebo; two in bupropion; one in varenicline) because they had stopped taking medication or were on a reduced dose, while in the 4-week post-quit analyses, 15 participants were excluded (eight in placebo; two in bupropion; five in varenicline).

Treatment

Participants enrolled in the 12-week placebo-controlled double-blind clinical trial of smoking cessation medications took either active or matching placebo varenicline capsules or active or matching placebo bupropion SR tablets according to the following dosage: varenicline tartrate, 0.5 mg/day for days 1–3, followed by 0.5 mg twice a day for days 4–7, and 1 mg twice per day thereafter; bupropion hydrochloride SR, 150 mg/day for days 1–3, followed by 150 mg twice per day thereafter. At the baseline visit, participants were randomized to treatment (double-blind randomization), scheduled the target quit date (approximately 2 weeks after the beginning of treatment), and received instructions to begin treatment the following day. Participants followed the recommended dosage for a total of 12 weeks and were monitored by the (blinded) physician to control for any adverse effects. During the clinical trial, participants also received individual behavioral counseling, including six in-person visits and four telephone calls. As described in the main outcomes article,⁶ counseling sessions involved training in strategies for maintaining abstinence in high-risk situations for smoking, coping skills, relapse prevention, management of withdrawal symptoms, and stress management.

Laboratory Sessions

At baseline, participants completed the Fagerström Test for Nicotine Dependence (FTND)⁴⁰ and other mood and demographic questionnaires, and then completed a psychophysiological assessment that included either ERPs or functional magnetic resonance imaging (we reported results from the baseline recordings in Minnix³⁴ and Versace³⁶). We also collected facial electromyography, heart rate,

and skin conductance (which will be reported elsewhere). After the baseline session, participants attended two laboratory-based follow-up visits. During the follow-up visits, scheduled for 24 h post-quit and 4 weeks post-quit, participants first indicated whether they had abstained from smoking (24 h of not smoking at the 24-h post-quit visit and 7 days without smoking at the 4-weeks post-quit visit). Self-reported abstinence was biochemically confirmed (expired carbon monoxide (CO) level of less than 10 ppm at both visits and salivary cotinine <15 ng/ml at the 4-week visit). When self-reported abstinence and biochemical verification were not concordant, biochemical verification took precedence. There were no discrepancies at the 24-h visit. Five discrepancies were recorded at the 4-week visit (1 in the varenicline, 1 in the bupropion, and 3 in the placebo condition). Tonic craving was assessed at each visit before the picture-viewing task using the brief form of the Questionnaire of Smoking Urges (QSU-B).⁴¹ At both follow-up visits, we also collected ERPs to estimate the motivational relevance of cigarette-related, pleasant, unpleasant, and neutral images using LPP amplitude.

Materials and Design

During the electroencephalogram (EEG) recording session, participants were shown one of three equivalent picture sets. Each set included 96 pictures: 24 pleasant (8 erotica, 8 romantic, 8 pleasant objects), 24 unpleasant (8 mutilations, 8 sad, 8 unpleasant objects), 24 neutral, and 24 cigarette-related images. The images were selected from the International Affective Picture System⁴² and from other sets used in previous studies.⁴³ At each visit, participants saw a different picture set and the order of presentation was randomized across participants. At each visit, the frequency of each order presentation was similar across the three medication groups (Both *ps* > .40). Participants viewed the picture slideshow on a plasma television screen at a viewing distance of approximately 1.5 m. E-Prime software (version 1.4; Psychology Software Tools, PST, Inc., Pittsburgh, PA), running on a Pentium 4 computer, controlled the picture presentation. The images appeared in a pseudo-random order with no more than two images of the same category being presented consecutively. Each trial began with a variable interval of 3–5 s that consisted of a black background with a white fixation cross, which was presented in the center of the screen. Images were presented for four seconds each; the entire presentation lasted approximately 30 min.

Compensation

Participants were compensated at each visit and received a maximum of \$290 at the end of the study.

Data Reduction and Statistical Analyses

EEG was recorded using a 129-channel Geodesic Sensor System (Geodesic EEG System 250; Electrical Geodesics, Inc., Eugene, OR). Data reduction followed the same procedures as previous studies from our laboratory.^{34–36} Briefly, data were filtered offline using a 30 Hz low pass filter. Data were visually inspected, and channels contaminated by artifacts for more than 50% of the recording were interpolated using spherical splines. Eye blinks were corrected using a spatial filtering method implemented in BESA ver. 5.1.8.10 (MEGIS Software GmbH, Gräfenberg, Germany). Next, the data were transformed to the average reference and segmented in 900 ms epochs starting 100 ms before picture onset. After baseline correction, artifacts were identified using gradient (25 μ V/ms maximal allowed voltage step), difference (100 μ V maximal allowed difference within a segment), and amplitude ($\pm$ 100 μ V absolute voltage allowed within a segment) criteria, and segments with more than 10% of channels containing artifacts were discarded. Then, segments were averaged and the amplitude of the LPP was computed by averaging the voltage recorded across 10 centroparietal sensors (EGI electrodes: 7, 31, 37, 54, 55, 79, 80, 87, 106, 129) between 400 and 700 milliseconds (ms) postpicture onset.

We analyzed the LPPs separately for each session using a $3 \times 2 \times 4$ analysis of variance (ANOVA), with drug type (placebo, bupropion, varenicline) and smoking abstinence (abstainer, nonabstainer) as between-subjects factors, and picture category (cigarette-related, pleasant, neutral, unpleasant) as a within-subjects factor.

The results from the QSUB collected at each session were analyzed using a 3×2 ANOVA, with drug type (placebo, bupropion, varenicline) and smoking abstinence (abstainer, nonabstainer) as between-subjects factors.

All post hoc pairwise comparisons were corrected using the Bonferroni procedure.

Results

Even though not every participant attended both visits, the 24-h and the 4-week post-quit samples did not differ with regard to any of the dependent variables, baseline demographics, or the smoking measures. See Table 1 for demographic characteristics.

As a manipulation check, we used a chi-square test to examine drug impact on smoking abstinence where the independent variable was drug type (placebo, bupropion, varenicline) and abstinence was the

dependent variable (abstainer, nonabstainer). The abstinence results from this subsample were consistent with those from the complete sample.⁶ Those on varenicline reported the highest abstinence rate, followed by bupropion, and placebo at both the 24 h [$\chi^2(2) = 14.06$, $p < .001$, Cramer's $V = .32$, $N = 140$] and 4-week post-quit sessions [$\chi^2(2) = 11.43$, $p = .003$, Cramer's $V = .25$, $N = 176$], Table 2.

Twenty-Four-Hour Post-Quit

Late Positive Potentials

As expected, picture category had a significant effect on the LPP amplitude, $F(3, 402) = 55.21$, $p < .001$. Both cigarette-related and emotional images evoked significantly larger LPPs than neutral pictures ($ps < .001$; Figure 1A). Neither abstinence nor drug type altered this reactivity pattern, as evidenced by nonsignificant picture category $\times$ abstinence [$F(3, 402) = .16$, $p = .92$] and picture category $\times$ abstinence $\times$ drug type interactions [$F(6, 402) = .78$, $p = .59$]. To evaluate whether medications differentially affected the amplitude of the LPPs evoked by the different picture categories relative to baseline, we used mixed effects modeling in which baseline served as the intercept for the trajectory of change from baseline to 24-h post-quit. This analysis showed that pharmacotherapy did not significantly modify the change of LPP amplitude over time ($p = .72$).

Questionnaire of Smoking Urges—Brief

Using ANOVA to examine the role of drug type and abstinence on smoking cravings, a main effect of drug type emerged. Specifically, drug type significantly affected self-reported cravings, $F(2, 129) = 7.41$, $p = .001$. Post hoc pairwise comparisons indicated that those treated with varenicline reported significantly less craving than those on placebo ($p = .002$), and less, but not significantly less, craving than those on bupropion ($p = .82$). There was also a tendency for those on bupropion to report less craving than those in the placebo condition ($p = .05$). There was no main effect of abstinence status on self-reported craving, $F(1, 129) = .15$, $p = .69$, but the interaction between drug type and abstinence was significant, $F(2, 129) = 3.03$, $p = .05$. Post hoc pairwise comparisons indicated that those abstinent in the placebo condition reported significantly more craving than those who were abstinent in the bupropion treatment condition ($p = .01$) and those abstinent ($p = .002$) or not abstinent ($p = .04$) in the varenicline treatment condition. When we added gender to the model, the results described above did not change, but there was a significant gender $\times$ valence interaction, $F(3, 402) = 5.92$, $p = .0006$. Males responded more strongly than females to pleasant and cigarette-related cues (uncorrected $ps = .015$ and $.16$, respectively), but these differences did not reach statistical significance when corrected for multiple comparisons.

Table 2. Biochemically Confirmed Smoking Abstinence Rates at 24 h 4 Weeks Post-quit

	Placebo ($n = 45$)		Bupropion ($n = 45$)		Varenicline ($n = 50$)		Total ($N = 140$)	
24-h Post-quit	%	(n)	%	(n)	%	(n)	%	(N)
Abstinence	31.1	14	60.0	27	68.0	34	53.6	75
	Placebo ($n = 55$)		Bupropion ($n = 60$)		Varenicline ($n = 61$)		Total ($N = 176$)	
4 weeks post-quit	%	(n)	%	(n)	%	(n)	%	(N)
Abstinence	30.9	17	48.3	29	62.3	38	47.8	84

Note: Overlap exists with those participating at 24 h and 4 weeks post-quit (total unique participants = 210): 106 participants provided data at both visits, 34 participants only at the 24-h visit and 70 only at the 4-week visit.

Figure 1. (A) Waveforms for each picture category at 24-h post-quit. The box highlights the time region of interest (ROI) used to compute the late positive potential (LPP) across the electrodes highlighted in the inset. The amplitude of the LPP evoked by neutral images was significantly lower than the LPP evoked by pleasant, unpleasant, and cigarette-related images (see bar graph). (B) Waveforms for each picture category at 4 weeks post-quit. The box highlights the time region of interest (ROI) used to compute the late positive potential (LPP) across the electrodes highlighted in the inset. The amplitude of the LPP evoked by neutral images was significantly lower than the LPP evoked by pleasant, unpleasant, and cigarette-related images (see bar graph). *Note:* CIG = cigarettes, PLE = pleasant, UNP = unpleasant, NEU = neutral. The error bars represent the 95% confidence intervals.

Four Weeks Post-Quit

Late Positive Potentials

Similar to what was observed 24-h post-quit, at 4 weeks post-quit, picture category had a significant effect on the amplitude of the LPP, $F(3, 510) = 59.37, p < .001$. Post hoc pairwise comparisons using Bonferroni correction showed that all picture categories (pleasant, unpleasant, cigarette-related) evoked significantly larger LPPs than neutral pictures (all $ps < .001$). Additionally, pleasant pictures evoked significantly larger LPPs than unpleasant ($p < .001$) and cigarette-related pictures ($p < .001$). The picture category $\times$ abstinence [$F(3, 510) = .44, p = .72$] and picture category $\times$ abstinence $\times$ drug type [$F(6, 510) = .90, p = .50$] interactions were not significant. Figure 1B shows the LPP mean responses for each picture category. To evaluate whether medications differentially affected the amplitude of the LPPs evoked by the different picture categories relative to the baseline, we used mixed effects modeling in which baseline served as the intercept for the trajectory of change from baseline to 4 weeks post-quit. This analysis showed that pharmacotherapy did not significantly modify the change of LPP amplitude over time ($p = .69$). Finally, when we added gender to the model, the results described above did not change, but there was a significant gender $\times$ valence interaction, $F(3, 510) = 3.19, p = .024$. Males responded somewhat more strongly than females to unpleasant, pleasant, and cigarette-related cues, but none of these differences reached statistical significance, even when no correction for multiple comparisons was applied.

Questionnaire of Smoking Urges—Brief

Using ANOVA to examine the role of drug type and abstinence on smoking craving, a significant main effect of drug type emerged [$F(2, 156) = 6.51, p = .002$]. Post hoc pairwise comparisons using Bonferroni correction indicated that those treated with varenicline ($p < .001$) or bupropion ($p = .01$) had significantly less craving than those on placebo. There was also a main effect of abstinence [$F(1, 156) = 3.92, p = .05$] such that those who were abstinent

reported less craving than those who were not abstinent. The drug type $\times$ abstinence interaction was not significant [$F(2, 156) = .15, p = .86$].

Discussion

The results from this study show that while both varenicline and bupropion reduced self-reported tonic craving intensity and enhanced abstinence rates relative to placebo, neither medication altered affective brain responses to cigarette-related or non-nicotine-related emotional pictures in smokers attempting to quit, as measured by the LPP. Replicating previous studies, we showed that for smokers, cigarette-related cues are motivationally relevant, as they evoke LPPs as large as those evoked by non-nicotine-related motivationally relevant images.^{35,36,44} However, our results also show that neither bupropion nor varenicline reduced the motivational relevance of cigarette-related cues relative to the placebo condition within 5 weeks of use. Together, these findings suggest that both medications may help smokers achieve and maintain abstinence by reducing tonic cravings and background urges to smoke rather than by specifically blunting cue-induced cravings, at least in the short term (up to 1 month post-quit). Nevertheless, it is also important to note that the motivational relevance held by cigarette-related cues and the cravings that they might induce are different constructs. Hence, even though the amplitude of the LPP reliably measures motivational relevance, it might not be an accurate measure of craving intensity. Although both cigarette-related cues and nonsmoking related emotional images prompt LPPs of similar amplitude, the LPP might not fully capture the cascade of neurophysiological events that is associated with cravings and smoking urges.

On the other hand, it is also possible that cigarette-related cues evoked LPPs of similar amplitude across groups and conditions because participants did not experience particularly intense cravings in the presence of cigarette-related cues during the experimental sessions. All participants were motivated to quit smoking and, in

line with the Clinical and Practice Guidelines,⁴⁵ received individual counseling that addressed coping with cue-induced cravings as part of the clinical trial.⁶ Cognitive strategies aimed at reducing craving intensity might blunt the amplitude of the LPP evoked by cigarette-related cues.⁴⁶ It is possible that during the EEG sessions, when facing cigarette-related cues, participants implemented the strategies that they were taught during the counseling sessions. As a result, this might have blunted the amplitude of the LPP evoked by cigarette-related cues across conditions. Furthermore, participants were not allowed to smoke during or immediately after the laboratory sessions. Wilson and Sayette⁴⁷ showed that craving intensity increases when participants think that cigarettes will be available immediately after the laboratory session. Thus, knowledge that smoking was not possible during or immediately after the EEG assessment might have also contributed to blunt the LPP amplitude evoked by cigarette-related cues.

By including noncigarette-related pleasant and unpleasant images in the experimental design, a key feature of our study, we also showed that neither bupropion nor varenicline alter the general pattern of emotional reactivity observed in smokers taking placebo. We do not attribute this effect to selection biases, because the attrition rate was similar across all study arms of the parent study⁶ and because the emotional reactivity pattern observed here is comparable to those observed in other groups of smokers not taking medications and in nonsmokers.³⁵ Interestingly, Robinson et al.³⁵ showed that current smokers tend to respond more than former smokers (ie, individuals abstaining for at least a year) to both cigarette-related and pleasant stimuli, supporting the idea that few weeks of smoking abstinence are not sufficient to alter reactivity to cigarette-related cues.

Finally, even though medication might not reduce reactivity to cigarette-related cues, it might improve smokers' ability to cope with cue-induced cravings.⁴⁸ For example, medications such as varenicline might improve the cognitive abilities⁴⁹ necessary to regulate emotional responses⁵⁰ and improve the likelihood of successfully resisting cravings in the presence of cigarette-related cues, a mechanism that we did not investigate in this study. We also did not assess cravings after the picture viewing task, but this aspect might deserve further investigation as it might be relevant for the interpretation of our results.

This study has several advantages relative to previous studies. It included a relatively large sample of smokers attempting to quit using bupropion, varenicline, or placebo, which allowed us to evaluate the effects of two of the most used medications for smoking cessation. It used a valid and reliable index of motivational relevance to measure neuroaffective responses to both cigarette-related and non-nicotine related emotional stimuli, allowing us to test whether varenicline and bupropion specifically reduce reactivity to cigarette-related cues or if they also alter reactivity to non-nicotine related emotional stimuli.

Notwithstanding the caveats mentioned above, we believe that this study makes an important contribution because it shows that, on average, neither bupropion nor varenicline alter electrophysiological responses to cigarette-related cues when measured using the LPP. This brings forth the problem of relapses occurring when medication treatments end.⁵¹ Smokers should be made aware that once treatment ends, cigarette-related cues will continue to capture attention and trigger responses that might lead to cravings and relapse even after several weeks of successful abstinence. If medications can not reduce cue reactivity, smokers must compensate with other means to successfully resist cue-induced cravings and relapse. By equipping smokers with strategies to deal with cue-induced cravings,

smoking cessation counselors can offer smokers the most effective ways to remain smoke free in the long-run, even when medications are withdrawn.

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Declaration of Interests

Varenicline for the parent clinical trial was provided by Pfizer. We are solely responsible for the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation and review of the manuscript.

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