Original Investigation

Impact of bupropion and cognitive–behavioral treatment for depression on positive affect, negative affect, and urges to smoke during cessation treatment

David R. Strong, Christopher W. Kahler, Adam M. Leventhal, Ana M. Abrantes, Elizabeth Lloyd-Richardson, Raymond Niaura, & Richard A. Brown

Abstract

Introduction: Bupropion and cognitive–behavioral treatment (CBT) for depression have been used as components of treatments designed to alleviate affective disturbance during smoking cessation. Studies of treatment-related changes in precessation affect or urges to smoke are needed to evaluate the proposed mechanisms of these treatments.

Methods: The present report examines affective trajectories and urges to smoke prior to, on quit day, and after quitting in a sample of 524 smokers randomized to receive bupropion versus placebo and CBT versus standard smoking cessation CBT.

Results: Bupropion and/or CBT did not affect the observed decreases in positive affect and increases in negative affect prior to cessation. However, on quit day, observed levels of negative affect and urges to smoke were diminished significantly among individuals receiving bupropion. Decreases in positive affect prior to quitting, lower levels of positive affect, and increased levels of negative affect and urges to smoke on quit day were each related to higher risk of smoking lapse. Depression proneness was an independent predictor of lower positive affect and higher negative affect but did not moderate the effects of bupropion on outcomes. In mediational analyses, the effect of bupropion was accounted for in part by lower negative affect and urges to smoke on quit day.

Discussion: Results support the efficacy of bupropion in reducing relapse risk associated with urges to smoke and negative affect and suggest the need to better understand the role of low positive affect as a risk factor for early lapse.

Introduction

Relapse to smoking is a common problem in cessation treatment. Research on the processes underlying smoking relapse has often focused on the role of affective disturbance and nicotine withdrawal symptoms that occur during a quit attempt (Piasecki, 2006). The motives underpinning relapse risk are dynamic and vary in accordance with affective fluctuations over the course of a cessation attempt (Piasecki, Jorenby, Smith, Fiore, & Baker, 2003a, 2003b; Shiffman et al., 2007). Given the strong link between fluctuations in affect and relapse to smoking (Kenford et al., 2002; Shiffman et al., 2007), affect processes have been implicated as a primary motivational basis for contributing to urges to smoke, maintaining smoking behavior, and derailing cessation attempts.

Significant affective changes occur during smoking cessation. For the average smoker, mood disturbance increases on quitting and then decreases gradually over the next several weeks (Piasecki et al., 2003a). However, significant interindividual variability exists in affective trajectories, suggesting that many smokers do not follow this typical pattern (Burgess et al., 2002; Kahler et al., 2002; McCarthy, Piasecki, Fiore, & Baker, 2006; Piasecki & Baker, 2000; Piasecki, Fiore, & Baker, 1998; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003c). Observed variability

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in affective trajectories may suggest a potential role for examining whether pretreatment levels of affective vulnerability, such as proneness to depression (Cook, Spring, McChargue, & Hedeker, 2004; Spring et al., 2007; Zelman, Brandon, Jorenby, & Baker, 1992), may help to explain differences in initial levels and time course of affective changes. These individual differences may be clinically relevant, given evidence that levels of distress on entering treatment (Blondal, Franzon, & Westin, 1997; Cinciripini et al., 2003; Kinnunen, Doherty, Militello, & Garvey, 1996; Swan et al., 2003) and the rate of change in affective distress during a cessation attempt predict relapse (McCarthy et al.; Piasecki et al., 2003b). Additional data suggest that certain smoking cessation treatments may alter the course of affective trajectories during cessation (Piasecki et al., 2003b), which may account for some of their efficacy (Catley et al., 2005; Lerman et al., 2002; Piper et al., 2007).

Although most data on dynamic affective processes in smoking cessation have focused on affective changes that occur after quitting (Burgess et al., 2002; Kahler et al., 2002; Piasecki & Baker, 2000; Piasecki et al., 1998, 2003a; Shiffman et al., 2007), often overlooked is the fact that affective changes that occur prior to quit day also may influence cessation success. McCarthy et al. (2006) found that increases in negative affect during the 3 weeks prior to quit day were associated with increased risk for relapse 3 months postquit. This finding is of considerable clinical interest because it suggests that treatments administered prior to quit day that target precessation affective disturbance may improve quit rates. To further extend the clinical relevance of this finding, three points could be clarified.

First, studies examining early affective trajectories have often focused solely on negative affect (Brown et al., 2001; Kahler et al., 2002; McCarthy et al., 2006). However, a common view is that affect can be parsed into two primary dimensions of negative and positive affect (Watson & Tellegen, 1985). Negative affect is defined as an aversive emotional state including feelings of nervousness, sadness, and irritation, whereas positive affect is a pleasant and energized mood state that reflects feelings of joy, interest, and alertness (Watson & Tellegen). The two-dimensional model postulates that positive and negative affective states are independent and not mutually exclusive. Empirical evidence suggests that positive and negative affect are psychometrically distinct (Watson & Clark, 1997), are associated with different neural underpinnings (Davidson, Ekman, Saron, Senulis, & Friesen, 1990), and have unique psychosocial correlates (Watson & Clark), supporting a two-dimensional view. Further, decreases in positive affect have been observed in smokers during early cessation (Cook et al., 2004), and decreases in positive affect have been related to relapse (al'Absi, Hatsukami, Davis, & Wittmers, 2004). Therefore, it is important to examine whether changes in positive affect, as well as negative affect, prior to quitting may play a role in cessation outcomes.

Second, it is not entirely clear whether treatments designed to alleviate affective disturbance administered prior to cessation can influence affective changes during this period. Two common mood-targeted treatments for smoking cessation are bupropion and cognitive–behavioral treatment (CBT) for depression. Bupropion is an antidepressant medication with noradrenergic and dopaminergic properties. It has been shown to increase (or buffer reductions in) positive affect (Piper et al., 2007; Shiffman et al., 2000), reduce negative affect (Lerman

et al., 2002; Piasecki et al., 2003b; Shiffman et al., 2000), and decrease urges to smoke (Brody et al., 2004; Hurt et al., 1997; Piper et al., 2008; Wileyto et al., 2005) following cessation, although this finding has not always been replicated (e.g., Lerman et al.). Changes in urges to smoke also may be relevant prior to cessation, given evidence that bupropion may disrupt the reinforcing effects of nicotine (Bruijnzeel & Markou, 2003; Glick, Maisonneuve, & Kitchen, 2002; Paterson, Balfour, & Markou, 2007). Little is known clinically about the influence of bupropion on precessation affect or urges to smoke, and additional studies are needed to examine changes in affect and urges to smoke as potential mediational processes that underlie the effects of bupropion.

CBT is a psychotherapy that has been incorporated into standard smoking cessation treatment (ST). It promotes coping skills for mood disturbance, including elements that purportedly target deficient positive affect (e.g., pleasant event scheduling) and elevated negative affect (e.g., cognitive restructuring of negative thoughts). In an earlier report, we found that CBT did not influence negative affect prior to cessation (Brown et al., 2001), although the influence of CBT on positive affect was not examined. Additional research is required to clarify whether either bupropion or CBT can influence precessation and quit-day positive and negative affect. Furthermore, it is unclear whether bupropion and CBT have synergistic effects on mood fluctuations or urges to smoke during this period. Accordingly, the present study examined the individual and synergistic effects of bupropion and CBT on positive affect, negative affect, and urges to smoke prior to and on quit day.

Third, in addition to examining affective changes prior to quitting, it is also important to identify for whom these changes may be particularly relevant. Increases in negative affect (Brown et al., 2001; Hall et al., 1996; Spring et al., 2008) and decreases in positive affect (al'Absi et al., 2004; Cook, Spring, & McChargue, 2007; Spring et al., 2008) during cessation have been proposed as mechanisms for relapse that may be concentrated among depression-prone smokers. For example, depression-prone smokers are more likely to report smoking when experiencing negative affect (Brandon, 1994) and have demonstrated an enhanced response to positive affect situations when self-administering nicotine (Spring et al., 2008). Further, smokers who reported higher levels of depression proneness by self-report (Zelman et al., 1992) or by evidence of a history of recurrent depression (Brown et al., 2001) and smokers who report a day-to-day pattern of smoking when emotionally upset have been shown to be at heightened risk for relapse after cessation (Shiffman et al., 2007; Zelman et al.). The potential for an enhanced functional role of smoking among depression-prone smokers also suggests a potential for a differential response to affective changes that accompany early withdrawal and a potential for improved response to CBT and bupropion. Therefore, the study also examined whether changes in negative and positive affect were related to depression proneness and if levels of depression proneness moderated the effectiveness of CBT and bupropion.

The present report examined affective trajectories and urges to smoke prior to and on quit day in a sample of 524 smokers participating in a smoking cessation trial studying the individual and combined effects of bupropion versus placebo and CBT versus ST using a 2×2 design (Brown et al., 2007). Previous analyses of quit rates in this sample at the end of 12 weeks of treatment

and across 2-, 6-, and 12-month follow-ups indicated that bupropion was significantly more effective than placebo, that CBT did not outperform ST, and that there were no synergistic effects (i.e., no interaction). We also found that neither CBT nor bupropion, either alone or in combination, was differentially effective for smokers with a history of a depression diagnosis (major depressive disorder [MDD]) or elevated depressive symptoms. Findings with regard to MDD and elevated depressive symptoms should be interpreted with caution given the low rate of MDD and the low level of depressive symptoms in our sample.

The aims of the present study were (a) to investigate whether bupropion and CBT individually or synergistically altered the rate of change in positive affect, negative affect, and urges to smoke over the 3 weeks prior to quitting, on quit day, and after quitting; (b) to investigate whether individual differences in depression proneness helped to explain rates of change in affect and urges to smoke over the 3 weeks prior to quitting, on quit day, and after quitting; (c) to examine whether changes in positive affect, negative affect, and urges to smoke increased the risk for failure to quit on quit day, smoking lapse, and relapse; and (d) to examine whether changes in affect and urges to smoke mediated the relationship between bupropion and cessation outcomes.

Methods

Participants

Participants were 524 smokers recruited via newspaper, radio, and television advertisements to participate in a randomized, double-blind placebo-controlled 2×2 clinical trial comparing (a) standard, cognitive–behavioral smoking cessation treatment plus bupropion sustained release (SR) (ST–BUP); (b) ST plus placebo (ST–PLAC); (c) ST combined with CBT for depression plus bupropion SR (CBT–BUP); and (d) ST combined with CBT for depression plus placebo (CBT–PLAC).

All participants in this study were smoking 10 or more cigarettes per day over the past year. Exclusion criteria were (a) current Axis I disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*; American Psychiatric Association, 1994); (b) *DSM-IV* diagnosis of past-year psychoactive substance abuse or dependence (other than nicotine); (c) current use of psychotropic medication or medication that may interact adversely with bupropion; (d) current weekly (or more frequent) psychotherapy; or (e) use of other tobacco products. Participants also were screened by a study physician to rule out the following: any unstable medical condition; hypertension; pregnancy, lactation, or refusal to use contraception while on study medication; history of seizure disorder or head injury with loss of consciousness; eating disorder; or panic disorder. Of the 778 potential participants screened with baseline interviews, 198 were excluded: 104 for medical exclusions, 34 for acute psychiatric treatment, and 60 for other reasons such as lack of transportation or inability to participate in English-only group treatments. All participants provided written informed consent prior to study participation.

Participants' assignment to medication condition was stratified by gender, current depressive symptoms, and level of nicotine dependence, using the urn randomization technique (Wei, 1978). Participants were randomized to treatment conditions as follows: ST–PLAC ($n = 157$), CBT–PLAC ($n = 112$), ST–BUP ($n = 147$), and CBT–BUP ($n = 108$). We were able to balance the drug and placebo conditions on an individual basis, but behavioral treatments were randomized by group and thus were more susceptible to fluctuations in recruitment and to the paring of a junior and senior therapist trained in CBT. These fluctuations prevented us from implementing four full groups within each cohort (two ST and two CBT).

Psychosocial treatment conditions

Participants were randomized to receive one of two intensive group counseling interventions: ST or standard cessation treatment combined with CBT for depression. Both group treatment conditions provided twelve 2-hr sessions and were equated for participant and Ph.D.-level therapist contact time. Six sessions occurred twice weekly for 3 weeks before the scheduled quit day (s1–s6), two sessions occurred during the week of quit day (s7 and s8), followed by two sessions weekly for 2 weeks (s9 and s10), one session 2 weeks later (s11), and then a final session 4 weeks later (s12), for a total of 12 weeks. Quit date began upon awakening on the morning of the seventh session, 3 weeks after s1. The ST and CBT conditions encouraged practicing of skills prior to quit date and skills training continued throughout treatment. The treatments are described in detail elsewhere (Brown et al., 2001). On average, participants attended 9.19 sessions ($SD = 2.53$). Session attendance was not significantly different in any of the four treatment groups ($p > .05$).

Medication

Participants were randomized to receive one of two medications: bupropion SR or placebo. Participants received identically packaged bupropion or placebo pills, prepared by the manufacturer of Zyban (GlaxoSmithKline, Research Triangle Park, NC). Two sessions of psychosocial treatment that included instructions for medication usage were delivered in the first week. Bupropion was initiated during the second week of treatment, 2 weeks prior to quit day, and was delivered according to the standard therapeutic dose (150 mg/day for the first 3 days initiated at s3, followed by 300 mg/day) for a total of 12 weeks.

Measures

Measured domains included (a) descriptive and diagnostic measures, (b) level of nicotine dependence, (c) candidate mediators of smoking outcomes: positive and negative affect and urge to smoke, (d) depression proneness as a candidate moderator of affect or craving trajectories and smoking outcomes, and (e) smoking outcomes.

Descriptive and diagnostic measures. At a baseline assessment session prior to treatment, participants provided demographic and background information, such as age, gender, years of education, marital status, number of years of regular smoking, and average number of cigarettes per day. Current and past Axis I diagnoses were determined with the Structured Clinical Interview for *DSM-IV* Non-patient Edition (First, Spitzer, Gibbon, & Williams, 1995).

Nicotine dependence. Severity of nicotine dependence was assessed during the baseline assessment using the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), a six-item measure with total scores ranging from 0 to 10, with higher scores indicating higher levels of nicotine dependence.

Measure of positive and negative affect. Positive and negative affects were measured using the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS was administered at the baseline assessment and at treatment sessions in the week before quitting (s1, s3, and s5), on quit day (s7), 3 days after quitting (s8), and at all remaining treatment sessions (s9, s10, s11, and s12). The PANAS items are rated on a 5-point scale ranging from "very slightly" to "extremely." At the baseline assessment, internal consistency reliability for the 10-item positive and 10-item negative scales was .90 and .79, respectively, and the correlation between the positive and negative scales was $r = .01$.

Measure of urges to smoke. Ratings of urges to smoke were collected at each treatment session in the 3 weeks before quitting (s1, s3, and s5), on quit day (s7), 3 days after quitting (s8), and at all remaining treatment sessions (s9, s10, s11, and s12). The urges to smoke scale included items that index wanting or craving a cigarette (rated 1–4, "none" to "severe"); urges throughout the day (rated 1–6, "none" to "all the time"); and thinking about cigarettes more than usual, immediate desire to smoke, missing a cigarette, and immediately accepting a cigarette offer, all rated on a 6-point scale ("definitely not" to "definitely"). Total scores on this measure range from 6 to 34. Validity of the scale has been established in factor analyses and prospective studies of the time course of withdrawal (Piasecki et al., 2000). At the baseline assessment, an internal consistency measure of reliability for this scale was .74, using Cronbach's alpha.

Depression proneness. The Depression Proneness Inventory (DPI; Alloy, Hartlage, Metalsky, & Abramson, 1987) is a face valid measure of proneness to depression that was administered to all participants at the baseline assessment. The 10 items are rated on a 7-point scale and tap individual perceptions of how frequently the respondent experiences depression, feelings of inadequacy, and a negative view of the future, and whether the respondent is more likely than others to experience depressive symptoms. The DPI has demonstrated predictive associations with depression vulnerability, history of MDD, and poor smoking cessation outcomes in adult smokers seeking cessation (Strong, Brown, Kahler, Lloyd-Richardson, & Niaura, 2004; Zelman et al., 1992). In this sample, an average item score was used (range = 1–7), and the standardized coefficient alpha of the DPI was .89. The mean DPI total score for this sample was 2.38 ($SD = 0.83$).

Smoking outcomes. Self-reports of smoking status were obtained at each treatment session, as well as by telephone at 2-, 6-, and 12-month follow-ups using the timeline follow-back for smoking, which has been shown to have good reliability and validity for assessing retrospective reports of daily smoking (Brown et al., 1998). Participants' reports of abstinence were verified biochemically via two methods: alveolar carbon monoxide (CO), using CMD/CO Carbon Monoxide Monitors (Spirometrics, Inc., Auburn, ME), and salivary cotinine assay, using a 2-ml saliva sample, collected during treatment and at the 6- and 12-month follow-ups and assayed by American Health Foundation (Valhalla, NY). During follow-up, biochemical measures were obtained in person only from participants reporting 7-day abstinence. Abstinence was confirmed by a combination of a CO level of 10 parts per million or less and a cotinine level of 15 ng/ml or less. In those few cases in which biochemical verification could not be obtained (8.2%), self-reported abstinence was verified through significant-other interview.

Data analyses

We used a latent variable framework that included growth curve models to examine individual changes in positive affect, negative affect, and urges to smoke in two time periods, one before quitting and one after quitting. Individual variation in affect and urge trajectories was captured with continuous latent variables representing the initial value upon entry into treatment s1 (prequit intercept), the amount of change during treatment sessions before quitting (prequit slope: s1–s5), the value recorded on the assigned quit day (postquit intercept: s7), and the postquit changes assessed through the end of treatment (postquit slope: s7–s12). By using a latent variable modeling framework, we were able to examine covariate-adjusted treatment effects on positive affect, negative affect, and urges to smoke and simultaneously assess the association of these growth parameters with smoking outcomes.

Latent growth models were used to test (a) whether bupropion, CBT, or depression proneness were associated with significant decreases in positive affect as well as increases in negative affect and urges to smoke prior to attempts at cessation (prequit slope: s1–s5), on the scheduled quit day (postquit intercept: s7), and throughout treatment (postquit slopes: s7–s12); (b) whether changes (prequit slopes) in positive affect, negative affect, and urges to smoke predicted a failure to quit on quit day (coded 0 and 1 for verified abstinent and failed to quit on quit day, respectively); and (c) whether changes (prequit slopes and postquit intercepts) in positive affect, negative affect, and urges to smoke predicted survival to smoking lapse (e.g., any report of smoking) and relapse to seven consecutive days of smoking after quit day.

All growth models included latent prequit intercepts and prequit slopes, and separate models were used to evaluate the failure to quit using a logistic regression and survival analysis to evaluate smoking lapse and relapse outcomes. The moderating effects of depression proneness were tested in each model by including terms representing the interaction with prequit slopes and postquit intercepts when predicting smoking outcomes. Gender and level of nicotine dependence were included as covariates, and postquit changes in examined mediators (postquit intercepts and postquit slopes) were estimated in all analyses. The inclusion of postquit changes simultaneously in the models allows for evaluation of the prequit and quit-day changes across each of the examined mediators with control for any continued relationship of these mediators on smoking outcomes after quitting.

We also conducted two formal tests of mediation to evaluate whether the effect of bupropion on the risk of smoking lapse was mediated by the effect of bupropion on prequit changes or quit-day increases in positive affect, negative affect, and urges to smoke. Mediational tests included the joint significance test (MacKinnon, 1994) and a product of coefficients test (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). The use of two distinct mediational tests increases the confidence in findings regarding rejection of the null hypothesis (MacKinnon et al.). Extensive simulation studies (MacKinnon & Dwyer, 1993; Tein & MacKinnon, 2003) have supported the method for examining the distribution of the product of coefficients from binary logistic and survival models in which the residual variance is not normal.

Table 1. Baseline characteristics of participants in each treatment condition

Characteristics	ST + PLAC ($n = 157$)	CBT + PLAC ($n = 112$)	ST + BUP ($n = 147$)	CBT + BUP ($n = 108$)
Age, years	45.16 (10.98)	44.40 (9.89)	43.89 (9.95)	43.36 (10.57)
Female (%)	4.10	44.60	51.0	46.30
Cigarettes per day	25.54 (9.62)	25.40 (11.34)	24.46 (9.88)	24.06 (9.30)
CES-D score	6.31 (5.99)	5.44 (6.70)	6.53 (6.73)	5.77 (6.09)
MDD history (%)	22.9	23.4	19.0	16.8
Depression proneness	2.42 (0.84)	2.31 (0.78)	2.41 (0.82)	2.33 (0.87)
PANAS positive	34.97 (7.73)	35.39 (7.78)	34.27 (7.68)	35.61 (6.98)
PANAS negative	14.15 (4.80)	14.72 (5.70)	14.81 (4.80)	13.86 (4.73)
Urge to smoke	20.71 (5.60)	19.65 (5.87)	19.94 (5.98)	20.08 (5.41)

Note. Values are means with *SD*s or percentages. BUP, bupropion; CBT, cognitive–behavioral treatment for depression; CES-D, Center for Epidemiological Studies Depression Scale; MDD, major depressive disorder; PANAS, Positive and Negative Affect Schedule; PLAC, placebo; and ST, standard smoking cessation treatment.

Results

Participants

Of the 524 participants randomized to treatment, 249 (47.5%) were women and 322 (61.4%) were married. The mean age of the sample was 44.27 years ($SD = 10.38$), and the mean number of years of education was 13.61 ($SD = 2.25$). The majority of participants identified themselves as White ($n = 482$, 92%), with 3.8% Black ($n = 20$), 2.3% Hispanic ($n = 12$), and 1.9% ($n = 10$) identifying themselves as coming from other racial/ethnic origins. Prior to treatment, participants reported smoking on average of 24.6 cigarettes each day ($SD = 10.0$), and they had smoked for an average of 26.0 years ($SD = 10.6$).

The sample mean on the FTND (Heatherton et al., 1991) was 6.41 ($SD = 1.9$). The majority of participants (94.5%) had made at least one quit attempt that lasted more than 12 hr. Most participants (79.0%, $n = 414$) had no history of MDD, 17.6% of participants ($n = 92$) had a single episode of MDD, 3.1% of participants ($n = 16$) had recurrent MDD, and information on history of MDD was missing for two participants (0.4%). Overall, rates of any history of substance use disorder were high (43.7%). Specifically, 39.5% met criteria for lifetime alcohol abuse ($n = 120$) or dependence ($n = 87$), and 19.1% met criteria for lifetime drug abuse ($n = 41$) or dependence ($n = 59$). Table 1 lists characteristics of each treatment condition.

Latent variable models

Longitudinal data for growth curve models were available for 98%, 95%, and 89% of participants for prequit assessments and for 98% of participants on quit day. Among participants abstinent on quit day and included in primary mediation analyses, data were available for 80%, 89%, 82%, 75%, and 84% of participants across postquit session assessments 8, 9, 10, 11, and 12, respectively. We fit a separate latent variable model to evaluate relationships of prequit changes in positive affect, negative affect, and urge to smoke on the failure to quit on quit day using all available data from randomized participants ($n = 524$). To assess the time to lapse and relapse, we restricted analyses to smokers who achieved CO-verified abstinence on the target quit day ($n = 395$) to limit confounding of smoking status with self-reports of positive affect, negative affect, and urges to smoke on quit day. Although a full 12 months of assessments following

quit day were available, examination of Schoenfeld residuals (Grambsch & Therneau, 1994) from initial survival models using the follow-up data suggested that these data failed to meet assumptions for survival analyses due to a significant decrease in the effect of bupropion treatment on smoking outcomes in the period of time after medication was discontinued ($\chi^2 = 14.98$, $p < .001$). We therefore confined analyses to the primary period of interest during the 12-week period of active treatment.

Changes in positive affect, negative affect, and urges to smoke prior to quit day

Table 2 lists the growth model estimates of the relationships among gender, FTND, depression proneness, and bupropion and CBT treatment effects with levels of affect or craving upon entry into treatment (prequit intercept), changes in affect or craving prior to quitting (prequit slopes), levels of affect or craving on quit day (postquit intercept), and changes in affect or craving after quitting (postquit slopes). These results are separated for three candidate mediators: positive affect, negative affect, and craving. The prequit intercept and slope effects in the left-hand portion of Table 2 indicate effects relevant to prequit affect and craving.

Positive affect. Treatment conditions did not differ in levels of positive affect upon entering treatment, $F(3, 511) = 0.77$, $p > .10$ (Table 1). Overall, there was a statistically significant decrease in positive affect between s1 and s5 (i.e., the week prior to quit date; $\text{mean}_{s1} - \text{mean}_{s5} = -2.87$; 95% $CI = -3.56$ to -2.17, $d = -0.35$, $p < .001$). In growth model analyses of prequit changes in positive affect (prequit slope), neither bupropion nor CBT were related to changes in positive affect prior to quit day. Level of depression proneness was related strongly to levels of positive affect upon entry into treatment (prequit intercept) and was not related to differential changes in positive affect (prequit slope) prior to quit day (Table 2). When entered as a block after all other terms, there were no significant interactions between treatment conditions and baseline level of nicotine dependence, gender, or depression proneness in predicting changes in positive affect prior to quitting (prequit slope). To illustrate these results, Figure 1 displays changes in positive affect during treatment for smokers receiving bupropion and placebo who were

Table 2. Relationships among gender, nicotine dependence, depression proneness, and treatment groups on changes in positive affect, negative affect, and urges to smoke when predicting risk for smoking lapse

	Prequit intercept		Prequit slope		Postquit intercept		Postquit slope	
	Effect	SE	Effect	SE	Effect	SE	Effect	SE
Positive affect								
Female	−0.44	0.68	−0.60	0.42	−1.67*	0.83	0.08	0.12
FTND	0.01	0.17	−0.05	0.11	−0.22	0.22	0.01	0.03
Depression proneness	−2.45**	0.43	−0.41	0.27	−2.23**	0.54	−0.03	0.07
Treatment effects								
CBT	0.60	0.67	−0.55	0.40	0.62	0.83	−0.05	0.12
BUP	−0.36	0.68	0.15	0.40	0.52	0.83	0.15	0.12
Negative affect								
Female	0.22	0.49	0.04	0.30	0.92	0.55	−0.01	0.09
FTND	0.26*	0.11	0.08	0.07	0.53**	0.13	−0.04	0.02
Depression proneness	1.73**	0.33	−0.01	0.18	0.78*	0.38	0.02	0.05
Treatment effects								
CBT	0.27	0.51	−0.26	0.30	−0.24	0.56	0.01	0.09
BUP	−0.34	0.49	−0.03	0.29	−1.85**	0.56	0.06	0.10
Urge to smoke								
Female	0.44	0.52	−0.23	0.24	1.27*	0.54	0.09	0.10
FTND	1.06**	0.14	−0.11	0.06	0.66*	0.14	−0.03	0.03
Depression proneness	−0.00	0.34	0.15	0.15	0.15	0.15	0.03	0.06
Treatment effects								
CBT	0.14	0.52	−0.09	0.23	0.17	0.54	−0.08	0.09
BUP	0.01	0.52	−0.05	0.23	−2.16**	0.53	−0.03	0.06

Note. FTND, Fagerström Test for Nicotine Dependence; BUP, bupropion; and CBT, cognitive–behavioral treatment for depression.
    $*p < .05; **p < .01$.

classified as high and low using the median score from the DPI assessed prior to treatment.

Negative affect. Treatment conditions did not differ in levels of negative affect upon entering treatment, $F(3, 511) = 1.02$, $p > .10$ (Table 1). Overall, there was a small and statistically significant increase in negative affect between s1 and s5 in the week prior to quit date (mean$_{s1}$ − mean$_{s5}$ = 0.85, 95% CI = 0.33–1.38, $d = 0.17$, $p < .001$). As demonstrated in Table 2, in growth model

analyses, neither bupropion nor CBT were related to changes in negative affect prior to quit day (prequit slope). Level of depression proneness was related strongly to higher levels of negative affect upon entry into treatment (prequit intercept) and was not related to changes prior to quit day. When entered as a block after all other terms, there were no significant interactions between treatment conditions and baseline covariates or depression proneness in predicting changes in negative affect prior to quitting (prequit slope). Figure 1 displays changes in negative
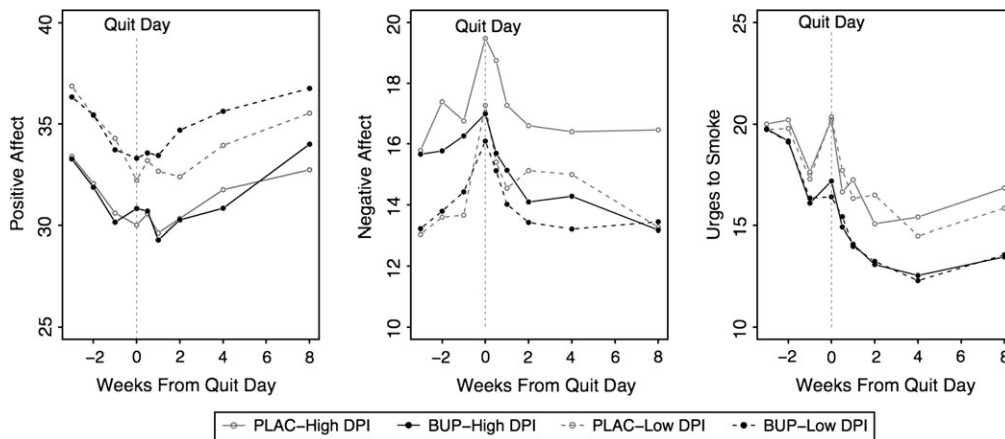
Figure 1. Changes in positive affect, negative affect, and urges to smoke among smokers with high and low levels of depression proneness (median split). BUP, bupropion; PLAC, placebo; and DPI, Depression Proneness Inventory.

affect during treatment for smokers receiving bupropion and placebo who were classified as high and low using the median score from the DPI assessed prior to treatment.

Urges to smoke. Treatment conditions did not differ in levels of urges to smoke upon entering treatment, $F(3, 511) = 0.83$, $p > .10$ (Table 1). Overall, there was a statistically significant decrease in urges to smoke between s1 and s5 in the week prior to quit date (mean$_{s1}$ − mean$_{s5}$ = −3.04; 95% $CI = -3.64$ to -2.43, $d = -0.57$, $p < .001$). As illustrated in Table 2, in growth model analyses, bupropion and CBT were not related significantly to changes in urges to smoke prior to quit day (prequit slope). Level of dependence was strongly related to level of urges upon entry into treatment. Level of depression proneness was not related to urges to smoke upon entry into treatment or changes in urges prior to quit day. There were no significant interactions between treatment conditions and baseline covariates or depression proneness in predicting changes in urges to smoke prior to quitting (prequit slope). Figure 1 displays changes in urges to smoke during treatment for smokers receiving bupropion and placebo who were classified as high and low using the median score from the DPI assessed prior to treatment.

Changes in positive affect, negative affect, and urges to smoke on quit day and after quitting

The postquit intercept and slope estimates in the right-hand portion of Table 2 indicate effects relevant to quit-day and postquit affect and craving.

Positive affect. After controlling for levels of nicotine dependence and female gender, we found that neither bupropion nor CBT were related to levels of positive affect on quit day (Table 2). Examination of postquit intercepts indicated that level of depression proneness was strongly related to lower levels of positive affect on quit day relative to baseline. There were no significant relationships among female gender, level of dependence, depression proneness, or treatment conditions on changes in positive affect after quitting, and no significant interactions related to the postquit positive affect slope.

Negative affect. After controlling for levels of nicotine dependence and female gender, we found that smokers receiving bupropion had lower levels of negative affect on quit day (see postquit intercepts in Table 2). Smokers with higher levels of depression proneness also related higher levels of negative affect on quit day (postquit intercept). There were no significant interactions between treatment conditions and baseline covariates or depression proneness in predicting levels of negative affect on quit day.

Urges to smoke. After controlling for levels of nicotine dependence and female gender, we found that bupropion was significantly related to reduce urges to smoke on quit day (see postquit intercept in Table 2). Level of depression proneness was not related to the level of urge to smoke on quit day (postquit intercept). There were no significant relationships among gender, level of dependence, depression proneness, or treatment conditions on changes in level of urge to smoke after quitting (postquit slope). Of the examined interactions with treatments, CBT had a significant interaction with levels of depression proneness ($B = -0.30$, $SE = 0.14$, $p < .04$), suggesting that smokers with lower levels of depression proneness who received CBT

had lower urges to smoke on quit day than did those who received ST. There were no other significant interactions.

Changes in positive affect, negative affect, and urges to smoke and the risk for smoking lapse

Failure to quit on quit day. Of the 524 randomized smokers, 121 smokers reported smoking on the target quit date, and 8 smokers did not provide any follow-up data. We used the latent variable model to conduct logistic regression analyses to evaluate whether changes in positive affect, negative affect, and urges to smoke prior to quit day (s5) were related to a failure to quit on quit day. Table 3 lists point estimates of effects from the models. In separate logistic regressions, level of dependence ($OR = 1.16$, 95% $CI = 1.02–1.31$, $p < .02$) and bupropion ($OR = 0.36$, 95% $CI = 0.23–0.56$, $p < .01$) was related to the likelihood of failing to quit on quit day. Rates of failing to quit on quit day were not significantly different for women versus men ($OR = 0.85$, 95% $CI = 0.55–1.32$, $p > .10$), by levels of depression proneness ($OR = 0.95$, 95% $CI = 0.71–1.28$, $p > .10$), or among participants in CBT versus ST psychosocial treatments ($OR = 1.24$, 95% $CI = 0.81–1.90$, $p > .10$). Prequit changes (prequit slopes) in positive affect ($OR = 0.98$, 95% $CI = 0.95–1.01$, $p > .18$), negative affect ($OR = 0.75$, 95% $CI = 0.35–1.61$, $p > .46$), and urges to smoke ($OR = 3.22$, 95% $CI = 0.26–39.79$, $p > .18$) were not related to the likelihood of failing to quit on quit day. Postquit changes in positive affect, negative affect, and urges to smoke were not related to failure to quit on quit day.

Prospective risks of smoking lapse and relapse. Consistent with outcomes reported previously (Brown et al., 2007; Wileyto et al., 2004, 2005), after including female gender and level of nicotine dependence as covariates (Table 3), smokers receiving bupropion had significantly lower risk of smoking lapse (relative risk [RR] = 0.55, 95% $CI = 0.42–0.72$, $p < .001$) and a lower risk of smoking relapse ($RR = 0.48$, 95% $CI = 0.36–0.68$, $p < .001$) than smokers receiving placebo. There was no significant difference in the risk of lapse or relapse across CBT and ST psychosocial treatments. Examination of the interaction of treatments suggested that the effect of bupropion over placebo on smoking lapse was consistent across CBT and ST psychosocial treatments ($RR = 1.46$, 95% $CI = 0.90–2.37$, $p < .14$), across levels of dependence ($RR = 0.96$, 95% $CI = 0.84–1.10$, $p < .33$), and across women and men ($RR = 0.85$, 95% $CI = 0.53–1.39$, $p < .53$). Figure 2 plots the probability of smoking lapse and relapse during treatment for smokers receiving bupropion and placebo. Level of depression proneness was not related to the risk for smoking lapse ($RR = 1.04$, 95% $CI = 0.88–1.23$, $p < .64$) or relapse ($RR = 1.03$, 95% $CI = 0.86–1.23$).

Using the latent variable models that included simultaneous estimates of growth parameters that controlled for covariates and treatment effects, we examined the relationship between smoking (re)lapse and prequit changes, levels on quit day, and postquit changes in positive affect, negative affect, and urges to smoke. Positive affect changes prior to quit day were related to smoking lapse ($RR = 1.27$, 95% $CI = 1.08–1.53$, $p < .001$). Quit day (postquit intercept) levels of positive affect ($RR = 0.95$, 95% $CI = 1.03–1.07$, $p < .001$), negative affect ($RR = 1.15$, 95% $CI = 1.11–1.20$, $p < .05$), and urges to smoke ($RR = 1.14$, 95% $CI = 1.09–1.18$, $p < .001$) all had significant

Table 3. Results of logistic regression and combined individual growth and proportional hazards regression models assessing the associations among planned covariates; psychosocial and bupropion treatment effects; and changes in positive affect, negative affect, and urges to smoke on quit day

	Failure to quit[a]			Lapse			Relapse		
	Effect	*SE*	*OR*	Effect	*SE*	*RR*	Effect	*SE*	*RR*
Covariates[a]									
Female	−0.16	0.22	0.85	0.39	0.14	1.50**	0.46	0.17	1.58**
FTND	0.14	0.06	1.16*	0.11	0.04	1.12**	0.16	0.04	1.17**
Treatment effects[a]									
CBT	0.22	0.22	1.24	0.26	0.14	1.30	0.09	0.16	1.09
BUP	−1.03	0.23	0.36**	−0.60	0.14	0.55**	−0.73	0.17	0.48**
Depression proneness	−0.05	0.15	0.95	0.04	0.08	1.04	0.03	0.09	1.03
Examined mediators[b]									
PANAS positive									
Prequit changes	−0.02	0.176	0.98	0.25	0.09	1.27**	0.30*	0.12	1.35*
Postquit intercepts	0.02	0.023	1.02	−0.05	0.01	0.95**	−0.08	0.02	0.92**
Postquit changes	−0.37	0.427	0.69	−0.05	0.30	0.95	−0.55	0.34	0.58
PANAS negative									
Prequit changes	−0.29	0.39	0.75	−0.42	0.26	0.66	−0.63	0.39	0.53
Postquit intercepts	0.04	0.05	1.04	0.14	0.02	1.15**	0.18	0.04	1.20**
Postquit changes	−0.62	0.59	0.54	0.42	0.41	1.52	0.14	0.38	1.15
Urge to smoke									
Prequit changes	1.17	1.28	3.22	−0.11	0.16	0.84	−0.58	0.25	0.56*
Postquit intercepts	0.17	0.06	1.18**	0.09	0.02	1.14**	0.33	0.04	1.39**
Postquit changes	−0.64	0.83	0.53	0.62	0.19	1.87**	1.42	0.42	4.14**

Note. OR, odds ratio; *RR*, relative risk; FTND, Fagerström Test for Nicotine Dependence; CBT, cognitive–behavioral treatment for depression; BUP, bupropion; and PANAS, Positive and Negative Affect Schedule.
[a]Model estimates are not adjusted for the effects of the examined mediators.
[b]Model estimates adjusted for the effects of covariates and treatment effects.
*$p < .05$; **$p < .01$.

relationships to smoking lapse in their respective models. There were no significant interactions between treatments and quit-day levels of positive affect, negative affect, or urges to smoke in predicting smoking lapse. Results were similar in a subsequent model predicting time to relapse to seven consecutive smoking days (Table 3), with levels of positive affect, negative affect, and urges to smoke predicting time to relapse. However, a greater reduction in positive affect prior to quit day ($RR = 1.35$, 95% $CI = 1.07–1.70$, $p < .05$) was related to increased risk of relapse, and a greater reduction in urges to smoke prior to quit day ($RR = 0.56$, 95% $CI = 0.34–0.92$, $p < .05$) was related to a reduced risk of smoking relapse. Although postquit changes in positive affect and negative affect were not related to relapse, postquit increases in urges to smoke were related to increased risk for smoking relapse ($RR = 4.14$, 95% $CI = 1.81–9.86$, $p < .01$).
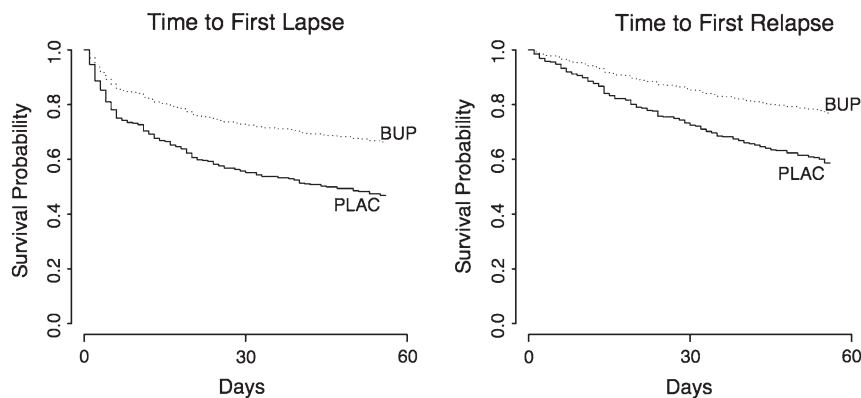
Figure 2. The probability of smoking lapse and smoking relapse to seven consecutive smoking days during treatment for smokers receiving bupropion (BUP) and placebo (PLAC).

Evaluating negative affect and urges to smoke as potential mediating mechanisms

We used two mediation tests to evaluate the potential mechanism of the observed effect of bupropion in increasing the odds of abstinence at the end of the 12-week treatment. We examined only the effect of bupropion on negative affect and urges to smoke, given a lack of demonstrated bupropion effect on positive affect either before (prequit slope) or on the target quit day (postquit intercept). For the first mediational evaluation, we examined the joint significance test, which evaluated the relationship between the bupropion and the mediator and the relationship between the mediator and the smoking outcome. Bupropion had significant effects on levels of negative affect and levels of urge to smoke on quit day. Further, levels of negative affect and urges to smoke had significant relationships to the risk for smoking lapse (Table 3). This joint significance test suggested that the effect of bupropion in reducing risk for smoking lapse may be mediated by the medication's effect in reducing levels of negative affect and urges to smoke on quit day.

In the second evaluation, we examined the product of two effect coefficients: (a) the effect of bupropion on quit-day levels (postquit intercepts) of negative affect ($B = -1.85$, $SE = 0.56$, $p < .01$) and urges to smoke ($B = -2.16$, $SE = 0.53$, $p < .001$) and (b) the effect of quit-day levels (postquit intercepts) of negative affect ($B = 0.14$, $SE = 0.02$, $p < .001$) and urges to smoke on risk for smoking lapse ($B = 0.09$, $SE = 0.02$, $p < .001$). The product of these coefficients represents the amount of change in the effect of bupropion on reducing the risk for smoking lapse that can be attributed to negative affect and smoking urges. The product of coefficients must be different from zero to support the mediation hypothesis. We constructed asymmetric *CI*s around each of the products of coefficients derived above ($a_{\text{negative affect}} \times b_{\text{negative affect}} = -0.26$; $a_{\text{urge}} \times b_{\text{urge}} = -0.19$) and observed that the *CI*s of -0.44 to -0.10 and -0.33 to -0.08 did not include zero, suggesting a rejection of the null hypothesis of no mediating effects (MacKinnon et al., 2002).

To further describe the relationships among bupropion, levels of negative affect, and urges to smoke on quit day and smoking lapse, we examined patterns of treatment–mediator–outcome relationships among individual smokers (Collins, Graham, & Flaherty, 1998). We calculated a score using the quit-day indices of negative affect ($Mdn = 18$) and urges to smoke ($Mdn = 16$) and separated smokers into those who had high negative affect or urges (above median) and those who had low negative affect or urges (below median) on their quit day. Smokers assigned to bupropion ($n = 255$) relative to placebo ($n = 269$) were more likely to have reported low negative affect (bupropion = 53%, $n = 135$; placebo = 43%, $n = 116$) and low urges (bupropion = 52%, $n = 134$; placebo = 35%, $n = 95$) on quit day. Rates of abstinence at the end of treatment for smokers experiencing low negative affect were 55% and 29% among bupropion and placebo smokers, respectively. These rates are compared with abstinence rates of 45% and 26% among bupropion and placebo smokers who experienced high negative affect urges on quit day. Rates of abstinence at the end of treatment for smokers experiencing low urges to smoke were 54% and 38% among bupropion and placebo smokers, respectively. These rates are compared with abstinence rates of 46% and 21% among bupropion and placebo smokers who experienced high

urges on quit day. Thus, smokers receiving bupropion were more likely than smokers receiving placebo to have a pattern of low negative affect or low urge to smoke on quit day as well as higher rates of abstinence at the end of treatment.

Discussion

In this secondary analysis of data from a randomized clinical trial (Brown et al., 2007), we demonstrated that smokers receiving bupropion were significantly less likely to lapse and significantly less likely to relapse during 12 weeks of active treatment, compared with smokers receiving placebo medication. Prior to quit day, we observed significant decreases in positive affect and significant increases in negative affect. Higher levels of positive affect and negative affect prior to quitting were observed among smokers who identified themselves as prone to depression upon entering treatment. On the first day of quitting, higher levels of nicotine dependence predicted higher levels of negative affect and urge to smoke. We found that smoking cessation treatments with bupropion or CBT did not affect the observed decreases in positive affect and increases in negative affect during the 3 weeks of treatment prior to cessation. However, on the first day of the quit attempt, levels of negative affect and urges to smoke were significantly lower among individuals receiving bupropion. Lower levels of positive affect, higher levels of negative affect, and greater urges to smoke on the first day of the quit attempt were each related to higher risk of smoking lapse. Although strongly predicting lower levels of positive affect and higher levels of negative affect, levels of depression proneness were not directly predictive of subsequent smoking lapse and relapse outcomes and did not identify smokers who may benefit differentially from bupropion or CBT.

In mediational analyses, the positive effect of bupropion on reducing the risk for smoking lapse was accounted for in part by lower negative affect and urges to smoke on quit day specifically, with no evidence to suggest added effects through a change in positive affect. Despite intensive psychosocial and pharmacological treatment, decreases in positive affect that began in the weeks before quit day were unaffected and conveyed significant risk for both lapse and relapse during the 12 weeks of active treatment.

We hypothesized that bupropion and CBT, both of which targeted affective processes, would be particularly efficacious for smokers at increased risk for stronger affective responses to cessation. Specifically, we evaluated whether treatment effects were moderated by gender, level of nicotine dependence, and depression proneness. These characteristics were related to lower levels of positive affect, higher levels of negative affect, and stronger urges to smoke in the present study. We also found that women and individuals with higher levels of nicotine dependence were at greater risk for smoking lapse and relapse. We did not find a significant relationship between levels of depression proneness and risk for smoking lapse or relapse. Although gender, level of dependence, and depression proneness were related to the affective processes that predict risk for poor smoking outcomes, neither bupropion nor CBT significantly moderated the effects of any of these variables. Although CBT has been shown to be efficacious primarily in smokers with recurrent MDD (Brown et al., 2001; Haas, Muñoz, Humfleet, Reus, & Hall, 2004), only 3.9% of the study subjects met criterion for recurrent MDD.

Therefore, the present study could not test hypotheses about whether changes in affective process might contribute to the effect of CBT in smokers with recurrent MDD.

The positive effects of bupropion on risk for smoking lapse remained after controlling for changes in negative affect on quit day, but the effect of bupropion was no longer significant after controlling for changes in urges to smoke. This finding suggests that bupropion had significant effects that may be mediated primarily by a reduction in urges rather than by a reduction in negative affect alone or through other mechanisms not examined in the study. Further, increased urges to smoke and decreases in positive affect prior to quit day, as well as increases in urges after quit day, remained as significant risk factors for early lapse when controlling for bupropion effects, suggesting room for additional interventions to reduce the influence of positive affect and urges to smoke on early lapse.

Regarding relapse, only change in positive affect prior to quit day remained a significant predictor of the return to smoking. Previous studies that assessed urges to smoke throughout each day during cessation attempts found that levels of urges to smoke continued to mediate the effect of bupropion in improving rates of successful cessation for up to 6 months (Piper et al., 2008). More frequent assessments of urges to smoke may have allowed a more proximal assessment of rises in urges and relapse in the weeks following quit day. These conflicting findings may highlight the shortened time course or volatility of self-reported urges to smoke relative to the self-reported changes in global measures of positive affect and negative affect. Clinically, the risk for poor outcomes from heightened urges to smoke arises soon after quitting and is demonstrated here on the first day of cessation.

Changes in positive affect appeared to follow a gradual decline that began in the weeks before cessation and did not show the acute reactivity to quit day observed with self-reports of negative affect and urges to smoke. Levels of positive affect and negative affect appeared to return to baseline by the end of the 12-week treatment period. An increase in negative affect and urges to smoke and a declining course of positive affect through quit day each predicted initial lapses. This pattern of findings was consistent with both negative reinforcement (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004) and hedonic allostasis (Koob & Lemoal, 2008) models for motivational accounts of relapse. Negative reinforcement models would predict negative affect and accompanying urges to smoke rising acutely with cessation that would precipitate increased motivation to reinstate smoking behavior and thus predict initial smoking lapses. Hedonic allostasis accounts would suggest that cessation after periods of chronic nicotine self-administration would attenuate responsiveness to nonpharmacological rewards, leading to abstinence-induced anhedonia and low positive affect. These hedonic changes may underpin motivation to resume smoking in order to enhance reward responsiveness and positive affect and may therefore predict early smoking lapse. The relationship between changes in positive affect and risk for smoking lapse has received far less attention than negative affective processes. Although mechanisms for the functional role of nicotine and a nicotine withdrawal–related shift in the experience of rewards have been hypothesized (Cook et al., 2004; Spring et al., 2008), further research is needed to understand factors that may influence changes in positive affect clinically. Changes in positive affect prior to attempts at cessation may present a new target for improving treatment outcomes.

Limitations of the present study include the under-representation of non-White participants. Although the demographic characteristics of this sample were similar to those of the region, we cannot generalize these findings to non-White populations. We also used a design that did not allow proximal assessment of event–relapse relationships. Methodologically, we relied on self-reports of global positive and negative affect assessed at treatment contacts; as a result, we may have missed the more rapid moment-to-moment changes in affect that have been associated with lapse risk (Shiffman et al., 2007). Further, we were unable to verify biochemically the specific point at which smoking lapse occurred and relied on self-reports, which may lead to increased error in our estimates of lapse risks. Finally, we did not evaluate blood levels to assess more explicitly the causal relationship between the bupropion levels and the hypothesized mediators. Thus, we cannot make a more specific causal inference with regard to these findings.

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Declaration of Interests

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