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RESEARCH REPORT

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Psychological mediators of bupropion sustained-release treatment for smoking cessation

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ABSTRACT

Aim The study aimed to test simultaneously our understanding of the effects of bupropion sustained-release (SR) treatment on putative mediators and our understanding of determinants of post-quit abstinence, including withdrawal distress, cigarette craving, positive affect and subjective reactions to cigarettes smoked during a lapse. The specificity of bupropion SR effects was also tested in exploratory analyses. **Design** Data from a randomized, placebo-controlled clinical trial of bupropion SR were submitted to mediation analyses. **Setting** Center for Tobacco Research and Intervention, Madison, WI, USA. **Participants** A total of 403 adult, daily smokers without contraindications to bupropion SR use. **Intervention** Participants were assigned randomly to receive a 9-week course of bupropion SR or placebo pill and to receive eight brief individual counseling sessions or no counseling. **Measurements** Ecological momentary assessment ratings of smoking behavior and putative mediators were collected pre- and post-quit. **Findings** Results of structural equation and hierarchical linear models did not support the hypothesis that bupropion SR treatment improves short-term abstinence by reducing withdrawal distress or affecting the subjective effects of a lapse cigarette, but provided partial support for mediation by cigarette craving reduction and enhanced positive affect. Bupropion SR effects on point-prevalence abstinence at 1 month post-quit were also mediated partially by enhanced motivation to quit and self-efficacy. **Conclusions** Results provided some support for models of bupropion SR treatment and relapse and suggested that motivational processes may partially account for bupropion SR efficacy.

Keywords Bupropion, cessation, mediation, relapse, smoking, treatment, withdrawal.

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INTRODUCTION

Persuasive evidence has demonstrated the efficacy and effectiveness of bupropion and its sustained-release (SR) formulations (Zyban®, SR® and XL®; GlaxoSmithKline Research Triangle Park, NC, USA) for smoking cessation [1–4], but the mechanism of action remains unclear [5]. Basic research on bupropion has demonstrated that bupropion primarily inhibits norepinephrine and dopamine transporters (reducing re-uptake) [5–7]. Recent research has also demonstrated that bupropion acts as a nicotine antagonist [8] and that this influences nicotine self-administration in animals [9]. Animal research also suggests that bupropion reduces some somatic signs of withdrawal and the inflation of reward thresholds (anhedonia) that occurs in withdrawal [10].

Clinically, bupropion treatment appears to reduce withdrawal symptoms and craving in abstaining smokers [5]. Two laboratory studies examined the effects of bupropion SR on withdrawal and cigarette craving among adult, heavy smokers not intending to quit who abstained from smoking during 2–3-day stays on closed research wards [11,12]. These studies produced mixed results. One study [11] found that 300 mg of bupropion SR reduced abstinence-induced depression, irritability and difficulty concentrating, and reversed abstinence-

related decreases in positive affect, but did not observe any differences in craving between medication groups. Another study [12] found little impact of bupropion on general withdrawal, but found significant bupropion-induced decreases in craving relative to either a placebo or an *ad libitum* smoking condition.

Randomized, placebo-controlled clinical trials of bupropion SR among adults trying to quit smoking have detected typically either short- [13,14] or long-term [15–17] suppression of withdrawal symptoms post-quit. One study that examined treatment effects on multiple dimensions of withdrawal symptoms detected bupropion SR effects on initial levels of withdrawal, but not on symptom growth or volatility [18]. Another trial did not detect differences in withdrawal severity as a function of treatment after controlling statistically for smoking during the post-quit period [19]. Fewer studies have reported on cigarette craving *per se*, but two trials have shown that craving is reduced during initial [20] and prolonged [21] treatment with bupropion SR treatment.

Two mediation analyses of bupropion effects have been published to date [13,22]. In the first [13], the authors reported that change in negative affect from pre- to post-quit partially mediated the effect of bupropion SR treatment on abstinence 8 weeks post-quit. Withdrawal increases were also attenuated significantly in the active bupropion condition, relative to the placebo group, but this change was not related significantly to abstinence at the end of treatment. Positive affect was unaffected by bupropion SR treatment.

More recently, a study [22] reported that bupropion SR treatment decreased total withdrawal and craving (assessed via interactive voice recording system during the first week of the quit attempt) relative to placebo, and that these decreases predicted greater likelihood of abstinence at the end of treatment. Negative and positive affect did not meet criteria for mediation in this study. Tests of these estimated mediated effects were statistically significant. Withdrawal (including increased negative affect and decreased positive affect) and craving have also been implicated in the mediation of nicotine replacement therapy on abstinence [23].

The two previous studies of bupropion SR mediators [13,22] have thus yielded inconsistent results, for reasons that are not yet clear. Failures to demonstrate mediation may arise for methodological reasons (e.g. error in the measurement of the mediator [24]), suboptimal intervals between assessments [25] or substantive reasons (e.g. mistaken understanding about what treatment affects or what predisposes individuals to relapse). Thus, inconsistencies in the findings to date raise questions about the roles of withdrawal, negative affect, positive affect and cigarette craving in mediating bupropion SR efficacy.

The present research is designed to address unresolved questions regarding mediation using structural equation and multi-level models that preserve the temporal ordering of treatment, the mediator and the cessation outcome [25]. Previous studies [13,22] did not control for pre-treatment levels of putative mediators in their mediation models. As such, results of these studies speak to changes from pre-quit to post-quit, but do not control for changes that may have occurred pre-quit as a result of treatment initiation. In addition, an important step in identifying causal pathways involves the sensitive assessment of the time–course of change [25]. The present study compares different ways of assessing putative mediators to explore the influence of assessment methods on results.

Data for the current study came from a double-blind, randomized, placebo-controlled clinical trial comprising adult smokers interested in quitting. Participants were randomized to 9 weeks of active bupropion SR or placebo medication and to either eight brief individual smoking cessation counseling sessions or no counseling. Counseling did not improve abstinence rates and did not interact with bupropion SR to influence abstinence [26]. Given the lack of counseling efficacy, tests of bupropion SR mediators were collapsed across counseling conditions.

Data regarding candidate mediators were assessed in real time using ecological momentary assessment strategies [27] that reduce recall biases and have greater temporal specificity than do typical self-report measures. Different types of reports were collected using varying time-frames (e.g. 'right now', 'last 24 hours') to allow comparison across assessment methods. Data were collected up to nine times per day during the early part of participants' quit attempts. This period was emphasized for three reasons: (a) early symptomatic reactions are predictive of cessation success [22,28], (b) return to smoking often occurs early in a quit attempt [29,30] and (c) treatment effects tend to be largest early in a quit attempt [31]. For these reasons, the current study focused upon relations among treatment, subjective experiences up to 1 week post-quit and biochemically verified 7-day point-prevalence abstinence 1 month post-quit.

Study hypotheses

We predicted that bupropion SR would boost smoking cessation rates by affecting the levels and trajectories of certain withdrawal symptoms, particularly negative affect and craving. This hypothesis was based upon evidence that affective distress and urges to smoke serve as the dominant proximal determinants of drug motivation [13,32–35].

We also predicted that bupropion SR efficacy would be mediated by enhanced positive affect, based on animal

and laboratory research that suggests that bupropion SR reverses abstinence-induced anhedonia [10,11] and acts as an activating agent [7]. This prediction is consistent with negative reinforcement models that identify anhedonia as a component of nicotine withdrawal, with motivational consequences similar to aversive symptoms [32,36].

Given bupropion's antagonism of nicotinic receptors [8,9], we predicted that bupropion would retard or prevent progression from a smoking lapse to a full-blown relapse, defined as smoking at least 7 days in a row [37], as has been documented with nicotine patch therapy [23]. We predicted that bupropion would decrease the subjective effects of smoking during the initial lapse (e.g. reduced 'buzz' from the first cigarette smoked) and thereby inhibit relapse.

In addition to the hypothesis-driven analyses outlined above, we conducted exploratory analyses regarding bupropion effects on quitting motivation and self-efficacy to test the discriminative validity of the relations tested in *a priori* analyses.

METHODS

Participants

Participants were 463 adult daily smokers who volunteered for a randomized, placebo-controlled trial of bupropion SR and individual smoking cessation counseling, as described in a report on the long-term efficacy of the treatments [26]. Participants were recruited via mass media. Inclusion criteria included: being over 18 years of age, smoking at least 10 cigarettes per day, having a baseline expired carbon monoxide (CO) level of greater than 9 parts per million (p.p.m.) and being motivated to quit smoking. Exclusion criteria were: bipolar disorder, psychosis, current depression and contraindications to bupropion SR use (e.g. uncontrolled hypertension, history of seizure disorder, history of eating disorders, current heavy drinking, risk of pregnancy or current breastfeeding). Demographic characteristics of enrollees are shown in Table 1.

Procedures

Study procedures are described in detail elsewhere [26]. Interested volunteers were screened over the telephone and then invited to an orientation at which written informed consent was obtained. Participants were screened at the orientation and a physical examination prior to enrollment. Participants attended a total of 13 office visits over 11 weeks, with the quit day scheduled at the end of the third week, and were followed by telephone monthly to 1-year post-quit. Participants provided breath samples for CO testing at all visits. Maximum remuneration for participation was $200. Participants also completed electronic diary entries several times per day for 2 weeks preceding, and 4 weeks following, the target quit date.

Treatment

Participants were assigned randomly to take bupropion SR or placebo pills for a total of 9 weeks. Participants took one 150-mg pill per day for the first 4 days and two 150-mg pills (one upon waking and one at least 8 hours later) thereafter. Self-reported adherence to the medication regimen, assessed at waking and at bedtime using electronic diaries, exceeded 90% of prescribed doses in both the placebo and active medication groups. Participants were also assigned randomly to receive eight 10-minute individual smoking cessation counseling sessions or no counseling. Counseling followed the Public Health Service Clinical Practice Guideline [1].

Measures

At early screening and office visits, participants provided demographic information and completed the Center for Epidemiologic Studies Depression Scale (CES-D [38] and measures of nicotine dependence, including the Fagerström Test of Nicotine Dependence (FTND [39]).

Electronic diaries (Palm Vx Palmtop Computer, Palm, Inc., Santa Clara, CA, USA) were programmed by invivodata, inc. (Pittsburgh, PA, USA) to administer brief questionnaires. Up to seven momentary reports were programmed to occur at pseudo-random times throughout the waking day (prompts could not occur within 30 minutes of a previous prompt). At participants' regular bedtimes, the electronic diary prompted individuals to complete an evening report regarding the past 24 hours. Both random prompt and evening reports assessed affect (including items derived from the Positive and Negative Affect Schedule (PANAS) [40]), withdrawal symptoms (including items derived from the Wisconsin Smoking Withdrawal Scale [41]) and number of cigarettes smoked. Evening reports assessed motivation to quit, confidence in quitting and medication use. The principal difference between the evening report and random prompt report was the time-frame assessed (past 24 hours versus just before the prompt). In addition, the evening report contained more items regarding withdrawal and craving than did the random report. All continuous ratings were made on an 11-point scale ranging from 1 (No!!) to 11 (Yes!!). Participants were also asked to complete a report following 'slips' the first five times they smoked after the quit date (as tracked by the electronic diary). The slip assessment tapped experiences before, during and after smoking, including the extent to which smoking was

Table 1 Characteristics of the sample included in meditational analyses ($n = 403$).

Variable	*Value*	*Placebo medication* ($n = 201$) *n (%)*	*Active bupropion SR* ($n = 202$) *n (%)*
Sex ($n = 403$)	Female	106 (52.7.0%)	96 (47.5%)
Race/ethnicity ($n = 400$)	Hispanic	0	4 (2.0%)
	White	178 (89.0%)	179 (89.5%)
	African American	11 (5.5%)	14 (7.0%)
	Other	11 (5.5%)	7 (3.5%)
Marital status ($n = 401$)	Married	77 (38.5%)	98 (48.8%)
	Separated or divorced	40 (20.0%)	41 (20.4%)
	Never married	63 (31.5%)	38 (18.9%)
	Cohabitating	15 (7.5%)	21 (10.4%)
	Widowed	4 (2.0%)	3 (1.5%)
Education ($n = 401$)	Less than high school degree	8 (4.0%)	6 (3.0%)
	High school	40 (20.0%)	46 (22.9%)
	Some college	97 (48.5%)	98 (48.8%)
	College degree or greater	55 (27.5%)	51 (25.4%)
Employment status ($n = 397$)	Employed	164 (82.0%)	168 (85.3%)
	Unemployed	11 (5.5%)	8 (4.1%)
	Homemaker	4 (2.0%)	13 (6.6%)
	Student	8 (4.0%)	2 (1.0%)
	Retired	7 (3.5%)	5 (2.5%)
	Disabled	6 (3.0%)	1 (0.5%)
Household income ($n = 393$)	<$25 000	69 (35.2%)	46 (23.4%)
	$25 000–$34 999	30 (15.3%)	31 (15.7%)
	$35 000–$49 999	35 (17.9%)	43 (21.8%)
	>$50 000	62 (31.6%)	77 (39.1%)
		M (SD)	*M (SD)*
Age ($n = 403$)		38.71 (12.10)	39.23 (12.01)
Cigarettes smoked per day ($n = 403$)		21.30 (10.20)	22.02 (10.56)
Baseline CO level ($n = 402$)		23.44 (11.46)	25.24 (11.64)
Baseline FTND score ($n = 403$)		5.01 (2.27)	5.05 (2.38)

CO: carbon monoxide; FTND: Fagerström Test of Nicotine Dependence; SD: standard deviation; SR: sustained-release.

pleasant, relaxing, affected urges, provided a rush or buzz, tasted good and resulted in feeling sick.

Attrition

Of the 463 individuals enrolled in the study, 403 (87%) were retained through the quit date visit and were considered to have made a quit attempt and retained in mediation analyses because they provided at least some post-quit data. A total of 338 individuals (73% of enrollees) provided data regarding their smoking behavior between weeks 3 and 4 post-quit and 322 (70%) attended the 1-month post-quit visit and provided breath samples for CO testing. All participants lost to follow-up were assumed to be smoking.

Data reduction and psychometric properties

Data reduction techniques were used to construct summary withdrawal distress and cigarette craving variables. Details are provided in the supporting information (see end of paper for details). In brief, factor analyses of random prompt and evening report data yielded two factor solutions, with the first factor reflecting negative affect and cognitive withdrawal symptoms, such as difficulty concentrating (hereafter called withdrawal distress), and the second factor reflecting craving for cigarettes. Cronbach's alpha for withdrawal distress scores and craving scales exceeded 0.80. Two highly correlated positive affect PANAS items ($r = 0.83$) [40] were averaged to yield a positive affect score.

Smoking outcome coding

If any time-stamped electronic diary report on a given day indicated smoking, participants were considered to have smoked that day. Latency to first lapse (smoking at least one puff) and first relapse (smoking at least 7 days in

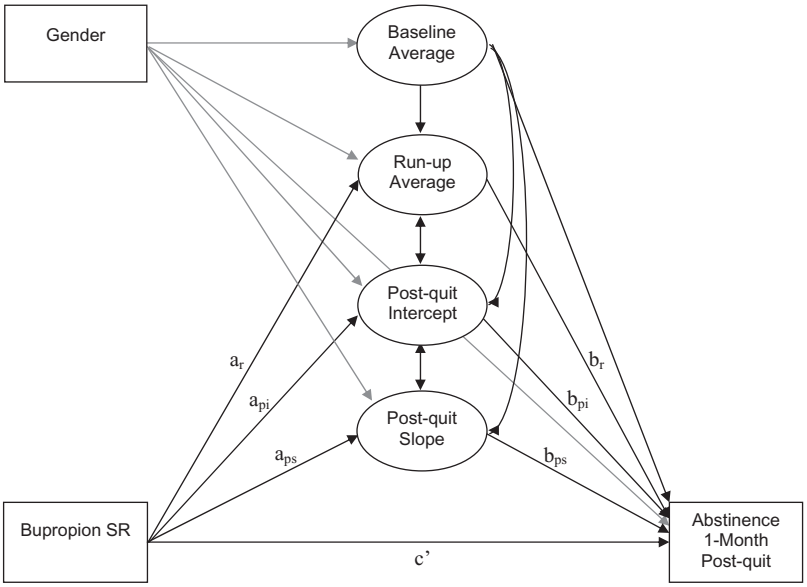

Figure 1 Structural model applied to evening report data. Treatment condition [0 = placebo, 1 = bupropion sustained-release (SR)] was included as a predictor of latent 'run-up average', 'post-quit intercept' (quit-day level) and 'post-quit slope' (change in level over 1 week) variables. Direct (*c′*) and indirect (*a* and *b*) paths linked treatment to the 1-month point-prevalence outcome (1 = abstinent in past 7 days, 0 = any smoking in past 7 days). One baseline covariate (gender) is included for illustration purposes

a row) was determined based on the daily smoking reports collected via electronic diary during treatment and via time-line follow-back interviews during follow-up [26]. Seven-day point-prevalence abstinence confirmed by carbon monoxide testing (average CO less than 10 p.p.m.) 1 month post-quit was the abstinence outcome of interest in this study. In the current sample ($n = 403$) the logistic regression odds ratio (OR) predicting 12-month point-prevalence abstinence from 1 month point-prevalence abstinence was 10.55 [95% confidence interval (CI) = 5.58–19.97]. Of those abstinent at the 1-month point, 38.7% were abstinent at 1 year post-quit compared to 5.7% of those who smoked between weeks 3 and 4 of the quit attempt.

Data analysis

Mediation analyses were conducted using time-stamped electronic diary ratings of withdrawal distress, affect and behavior. In mediation models, scores on the putative mediator collected during the 1-week baseline period and the 1-week pre-quit treatment run-up period were included as control variables [25]. As such, mediation models tested the relations among treatment, change in the candidate mediator from baseline and treatment run-up levels, and outcome. Analyses were conducted both with and without the following time-invariant covariates in each model: gender (0 = male, 1 = female), a dichotomous indicator of racial or ethnic minority status (0 = Caucasian, 1 = minority), a dichotomous indicator of education (0 = some college or less education, 1 = graduated from college or graduate education), years of age, baseline CES-D depression score and baseline FTND nicotine dependence score. Continuous covariates were centered around the grand mean prior to entry in models. Excluding covariates in models did not alter materially the pattern of results in any analysis. To control statistically the effects of smoking during the period of mediator assessment, smoking was treated as a time-varying covariate in all models. The pattern of results was robust across different statistical strategies to control for the effects of smoking during the post-quit period. Multi-level models that controlled for the recency of smoking or smoking in the 48 hours preceding mediator assessment yielded the same results as those that included a simple dichotomous indicator of any smoking since the last report. Controlling for smoking on all post-quit days prior to each symptom or affect rating (i.e. a cumulative time-varying covariate) did not change the pattern of results in mediation models based on evening reports. Smoking and the mediators did not interact significantly in models predicting 1-month abstinence.

Consistent with current recommendations for mediation tests [42], mediational hypotheses were rejected if: (i) path *a* linking bupropion SR treatment to the putative mediator (see Fig. 1; each path linking treatment to a mediator has a subscript identifying the mediator) was not significant; (ii) the putative mediator was not related to 1-month abstinence (*b* paths in Fig. 1) when controlling for treatment, concurrent post-quit smoking and baseline mediator level; (iii) the direct relation between bupropion SR treatment and abstinence (path *c′* in Fig. 1) was not at least reduced by the inclusion of the putative mediators in the model; (iv) the CI for the estimate of the mediated effect (the products of Fig. 1 paths *a* and *b* with corresponding subscripts) contained zero (computed using the Prodclin program developed by MacKinnon and colleagues [43]); or (v) the mediated effect was not

significant using the Sobel [44] equation for the standard error (SE) of the mediated effect tested against a corrected Z′ distribution derived empirically to test the product of coefficients [42].

Modeling methods differed for evening report and random report data due to the differences in the sampling schedule and data structure across these assessments. Evening report data collected at equal (i.e. daily) intervals were analyzed using structural equation modeling with Mplus software [45] (Muthén & Muthén, Los Angeles, CA, USA). Weighted least squares with mean- and variance-adjustment (WLSMV) estimation was used, as this permits missing data and a dichotomous outcome. Random prompt withdrawal distress, craving and positive affect data collected at unequal, variable intervals not amenable to latent growth curve modeling were analyzed using multi-level models with hierarchical linear modeling (HLM5) software [46] (Scientific Software International, Lincolnwood, IL, USA). Treatment was included as a predictor of individual subjects' growth coefficients within HLM and empirical Bayes' estimates of individual mediator growth coefficients derived from these models were used as predictors of 1-month abstinence in logistic regression analyses in SPSS version 15.0 (SPSS for Windows, release 15.0, 2006; SPSS, Inc., Chicago, IL, USA). All models reported here converged readily.

RESULTS

Treatment effects

One-third (33.3%, 95% CI = 24.6–42.0%) of the 201 quit-day visit attendees who received placebo medication reported no smoking between weeks 3 and 4 of the quit attempt and provided a CO sample below 10 p.p.m. In contrast, 52.5% (95% CI = 43.6–31.4%) of the 202 participants receiving active medication had CO-confirmed abstinence 1 month post-quit. Logistic regression analysis showed a significant medication effect promoting abstinence (OR = 2.16, 95% CI = 1.21–3.87) but no significant counseling effect (OR = 1.52, 95% CI = 0.84–2.75) and no significant interaction between counseling and medication (OR = 1.06, 95% CI = 0.47–2.39). In addition, survival analysis revealed that participants receiving active bupropion SR had significantly longer latencies to relapse (smoking 7 days in a row) following a first slip (median survival = 39.00 days, 95% CI = 24.00–54.00) than did those receiving placebo medication (median survival = 13.00, 95% CI = 4.15–21.85). We followed these analyses with mediation analyses in an effort to explain the observed medication effect on 1-month abstinence and latency to relapse following an initial lapse. One-year post-quit abstinence rates indicated no significant bupropion SR effect in the sample of 403 quit-day attendees. In the active bupropion SR group, 23.8% of people achieved CO-confirmed 7-day point-prevalence abstinence at 1 year, compared to 15.9% in the placebo group (OR = 1.58, 95% CI = 0.78–3.23 with covariates in the model).

Evening reports

The general form of the measurement model used to construct latent mediator variables from repeated evening reports in MPlus is shown in Fig. S1 in the supporting information. The latent variables constructed included a latent 'baseline average' variable that captured the mean level of the target variable in the week before the beginning of treatment, a 'run-up average' variable reflecting the mean level of the target variable over the 7 days between the beginning of treatment and the target quit day, a 'post-quit intercept' variable reflecting the level of the variable on the first day of the quit attempt and a 'post-quit slope' latent variable reflecting the rate of change in symptoms over the first week of the quit attempt. Correlations among the residual variances for the repeated measures of the mediator were constrained to be equal within each assessment period (baseline, treatment run-up and post-quit) and an auto-regressive process of order 1 [AR(1)] autocorrelation structure was specified. The first week of the quit attempt was emphasized because this is a critical period in terms of treatment effects, peak withdrawal distress and abstinence [30,31], in which 69% of participants in the current study lapsed. Linear rather than quadratic growth was modeled because models with higher-order growth components failed to converge or fitted the data poorly.

The general form of the structural model fit to the data is shown in Fig. 1. Only one time-invariant covariate (gender) is shown for simplicity. Mediation paths in Fig. 1 are identified by a letter and subscript that correspond to the MPlus results shown in Table 2. Paths labeled *a* represent treatment effects on mediators (e.g. a_{pi} is the treatment effect on the quit-day mediator, or post-quit intercept, rating). Paths labeled *b* represent the relation between the mediator and 1-month outcome (e.g. b_{pi} is the relation between the quit-day mediator rating and abstinence). Model fit was evaluated with the root mean square error of approximation (RMSEA values < 0.08), Tucker-Lewis Index (TLI values > 0.95) and weighted root mean square residual (WRMR values < 0.90) [45,47–49]. Models achieved adequate-to-good fit.

Results did not support the hypothesis that bupropion SR treatment would reduce withdrawal distress or craving for cigarettes. Indeed, withdrawal distress and craving were significantly higher among those receiving active bupropion SR during treatment run-up than

Table 2 Evening report mediation model estimates.

Variable	*Path*	*Est*	*SE*	*Est/SE*	*Std XY*	χ^2	χ^2 *df*	*RMSEA*	*TLI*	*WRMR*
Withdrawal†	Run-up average on bupropion SR (a_r)	0.30	0.14	2.05*	0.12	117.51*	65	0.05	0.96	0.97
	Post-intercept on bupropion SR (a_{pi})	0.08	0.17	0.45	0.03					
	Post-slope on bupropion SR (a_{ps})	–0.01	0.03	–0.38	–0.04					
	Abstinence on run-up average (b_r)	–0.24	0.18	–1.33	–0.29					
	Abstinence on post-intercept (b_{pi})	0.37	0.10	3.87*	0.52					
	Abstinence on post-slope (b_{ps})	–0.88	1.21	–0.73	–0.11					
Craving‡	Run-up average on bupropion SR (a_r)	0.58	0.26	2.21*	0.13	130.25*	74	0.04	0.93	0.95
	Post-intercept on bupropion SR (a_{pi})	–0.09	0.31	–0.28	–0.02					
	Post-slope on bupropion SR (a_{ps})	0.05	0.05	1.14	0.16					
	Abstinence on run-up average (b_r)	–0.13	0.19	–0.72	–0.29					
	Abstinence on post-intercept (b_{pi})	0.12	0.04	3.29*	0.32					
	Abstinence on post-slope (b_{ps})	–3.79	4.85	–0.78	–0.57					
Positive affect	Run-up average on bupropion SR (a_r)	0.21	0.56	0.39	0.02	113.61*	66	0.04	0.94	0.93
	Post-intercept on bupropion SR (a_{pi})	1.53	0.63	2.43*	0.12					
	Post-slope on bupropion SR (a_{ps})	–0.09	0.07	–1.25	–0.16					
	Abstinence on run-up average (b_r)	–0.02	0.03	–0.53	–0.08					
	Abstinence on post-intercept (b_{pi})	0.06	0.02	3.31*	0.38					
	Abstinence on post-slope (b_{ps})	0.07	0.59	0.12	0.02					
Motivation	Run-up average on bupropion SR (a_r)	–0.01	0.30	–0.04	–0.00	95.17*	67	0.03	0.95	0.85
	Post-intercept on bupropion SR (a_{pi})	0.42	0.34	1.25	0.07					
	Post-slope on bupropion SR (a_{ps})	0.18	0.06	2.99**	0.33					
	Abstinence on run-up average (b_r)	–0.01	0.05	–0.13	–0.02					
	Abstinence on post-intercept (b_{pi})	0.12	0.03	4.34**	0.36					
	Abstinence on post-slope (b_{ps})	0.66	0.49	1.35	0.18					
Confidence§	Run-up average on bupropion SR (a_r)	0.02	0.29	0.06	0.00	108.43*	72	0.04	0.94	0.89
	Post-average on bupropion SR (a_{pa})	1.01	0.31	3.29**	0.16					
	Abstinence on run-up average (b_r)	–0.00	0.05	–0.03	–0.00					
	Abstinence on post-average (b_{pa})	0.13	0.03	4.49**	0.38					
Willing to work§	Run-up average on bupropion SR (a_r)	–0.01	0.30	–0.02	–0.00	97.02*	71	0.03	0.96	0.84
	Post-average on bupropion SR (a_a)	0.96	0.31	3.06**	0.15					
	Abstinence on run-up average (b_r)	–0.01	0.05	–0.27	–0.03					
	Abstinence on post-average (b_{pa})	0.12	0.03	4.60**	0.37					

*$P < 0.05$, **$P < 0.0035$. †A path from baseline withdrawal to the post-quit intercept and the correlation between the post-quit intercept and slope were dropped to facilitate convergence. ‡Improper solutions resulted when post was correlated with post-slope, so this correlation was deleted from the model. §Improper model solutions resulted when the post-quit slope latent variable was included. The post-average latent variable reflects the average level of the variable across the first week post-quit (noted by the subscript $_{pa}$). Est: estimate; SR: sustained-release; std: fully standardized; RMSEA: root mean square error of approximation; TLI: Tucker–Lewis Index; WRMR: weighted root mean square residual.

among those receiving placebo, but this was not related significantly to abstinence. Withdrawal distress on the quit day was related positively to the likelihood of achieving abstinence, but was not affected by bupropion SR. Our hypothesis regarding the mediating effects of positive affect received greater support. People receiving active bupropion SR had higher positive affect ratings on the quit day (a_{pi}), and these ratings were significantly predictive of abstinence (b_{pi}). The mediated effect for post-quit positive affect was significant ($ab_{pi} = 0.09$, SE = 0.05, 95% CI = 0.01–0.20, $Z' = 1.89$, $P < 0.05$). Deleting the direct path between bupropion SR and abstinence (c') did not affect model fit ($\Delta\chi^2 = -0.9$), whereas deleting the indirect paths resulted in a greater, but still modest, change in model fit (when a paths deleted $\Delta\chi^2 = 1.42$, when b paths deleted $\Delta\chi^2 = 2.05$, $\Delta df = 1$). The significance of change in model fit is not reported because the difference between χ^2 statistics is not distributed on a χ^2 distribution when WLSMV estimation is used.

Exploratory analyses with general motivational mediators of treatment (i.e. motivation to quit, willingness to work hard at quitting) and confidence in one's ability to quit indicated that the average level of confidence in quitting and of willingness to work at quitting in the first week of the quit attempt mediated bupropion SR effects on abstinence. Given the exploratory nature of these analyses, a conservative alpha level corrected for the 14 tests presented in Table 2 ($\alpha = 0.0035$) was used. Although bupropion SR treatment was associated with greater increases in motivation over the first week of the quit attempt, only the initial level of post-quit motivation to stop smoking, not rate of change, was predictive of

abstinence. The average levels of both confidence in one's ability to stay smoke-free and willingness to work hard at quitting were significantly higher in the first week of the quit attempt for those receiving active medication versus placebo and this, in turn, was predictive of abstinence 1 month post-quit. Separate intercepts and slopes could not be estimated for these variables due to convergence problems. Deleting the direct path between treatment variables and smoking outcome (c') cost little in terms of model fit (confidence $\Delta\chi^2 = 0.21$, willingness $\Delta\chi^2 = 0.17$), whereas deleting the indirect paths resulted in a more substantial change in model fit (confidence: when a paths deleted $\Delta\chi^2 = 6.75$, when b paths deleted $\Delta\chi^2 = 1.28$, $\Delta df = 1$; willingness: when a paths deleted $\Delta\chi^2 = 5.54$, when b paths deleted $\Delta\chi^2 = 0.58$, $\Delta df = 1$). The estimated mediated effects for both confidence ($ab_{p\ average} = 0.13$, SE = 0.05, 95% CI = 0.05–0.24; $Z' = 2.60$, $P < 0.05$) and willingness to work at quitting ($ab_{p\ average} = 0.12$, SE = 0.05, 95% CI = 0.04–0.22; $Z' = 2.45$, $P < 0.05$) were significantly different than zero.

Random prompt data

In multi-level analyses used to analyze the variable occasion random prompt data, piecewise models were used to assess the rate of change and final level of the mediator during the baseline period, rate of change and final level (just before the quit attempt) of the mediator during the treatment run-up period, and the initial level (just after the quit attempt started) and rate of change in the mediator in the first week of the quit attempt, controlling for any smoking since the last report and for baseline covariates. In other words, intercepts and linear slopes were estimated separately in each of the baseline, run-up and post-quit assessment epochs. In HLM analyses, random effects equations were used so that estimates of observation-level (level 1) coefficients were allowed to vary across participants (level 2). Specifying random effects improved model fit significantly without leading to problems with convergence. Plots derived from HLM analyses of random prompt scores as a function of treatment condition (entered as a level 2 predictor) are shown in Fig. 2.

Empirical Bayes' estimates of individual intercept and slope variables estimated in HLM models were used as predictors of 7-day point-prevalence abstinence 1 month post-quit (achieved by 42.5% of subjects) in logistic regression analyses. ORs and CIs from these analyses are displayed in Table 3, along with the mean and standard deviation for each estimated parameter. Interaction terms between bupropion SR condition and empirical Bayes' estimates of mediators were non-significant in the final models and are not shown.

Table 3 Results of logistic regression analyses ($n = 400$) predicting carbon monoxide (CO)-confirmed 7-day point-prevalence abstinence 1 month post-quit (42.5% abstinent) from random prompt estimates.

		Without covariates				*With covariates*			
	Predictor	*Mean*	*SD*	*OR*	*95% CI*	*Mean*	*SD*	*OR*	*95% CI*
Withdrawal	Bupropion SR			2.19**	1.45–3.30			2.21**	1.45–3.38
	Baseline intercept	1.99	1.41	1.16	0.72–1.89	1.90	1.38	1.19	0.72–1.98
	Baseline slope	–0.03	0.13	0.68	0.10–4.46	–0.05	0.12	0.32	0.04–2.30
	Run-up intercept	2.06	1.44	0.80	0.49–1.29	2.01	1.43	0.74	0.45–1.23
	Run-up slope	0.02	0.12	8.68	0.33–228.22	0.02	0.12	14.57	0.48–444.94
	Post-quit intercept	3.51	1.73	1.05	0.88–1.24	3.47	1.66	1.16	0.96–1.41
	Post-quit slope	–0.06	0.16	2.99	0.70–12.80	–0.06	0.16	4.36*	0.95–19.90
Craving	Bupropion SR			2.07**	1.37–3.13			2.09**	1.37–3.20
	Baseline intercept	4.29	2.29	1.03	0.69–1.54	4.27	2.31	1.20	0.79–1.84
	Baseline slope	0.06	0.14	0.61	0.06–5.75	0.06	0.14	0.41	0.04–4.25
	Run-up intercept	4.28	2.43	1.03	0.70–1.51	4.35	2.45	0.88	0.59–1.32
	Run-up slope	0.05	0.18	1.83	0.09–37.37	0.05	0.18	4.53	0.20–104.38
	Post-quit intercept	6.98	2.22	0.91*	0.81–1.02	7.04	2.09	0.96	0.85–1.08
	Post-quit slope	–0.17	0.26	0.22**	0.09–0.53	–0.18	0.25	0.27**	0.11–0.66
Positive affect†	Bupropion SR			2.13**	1.41–3.23			2.15**	1.41–3.28
	Baseline intercept	5.21	2.66	0.83**	0.69–0.99	5.24	2.59	0.84*	0.70–1.02
	Baseline slope	–0.02	0.14	1.34	0.22–8.33	–0.03	0.14	1.51	0.23–9.96
	Run-up	5.34	2.79	1.19*	0.98–1.44	5.36	2.71	0.43	0.12–1.53
	Post-quit intercept	7.16	2.16	1.07	0.93–1.24	7.13	2.06	1.08	0.93–1.25
	Post-quit slope	–0.05	0.14	5.46**	1.09–27.38	–0.05	0.14	4.79*	0.93–24.78

*$P < 0.10$, **$P < 0.05$. †Run-up slope was not included in the logistic regression model because including this predictor yielded extremely broad confidence intervals. CI: confidence interval; OR: odds ratio; SD: standard deviation; SR: sustained-release.

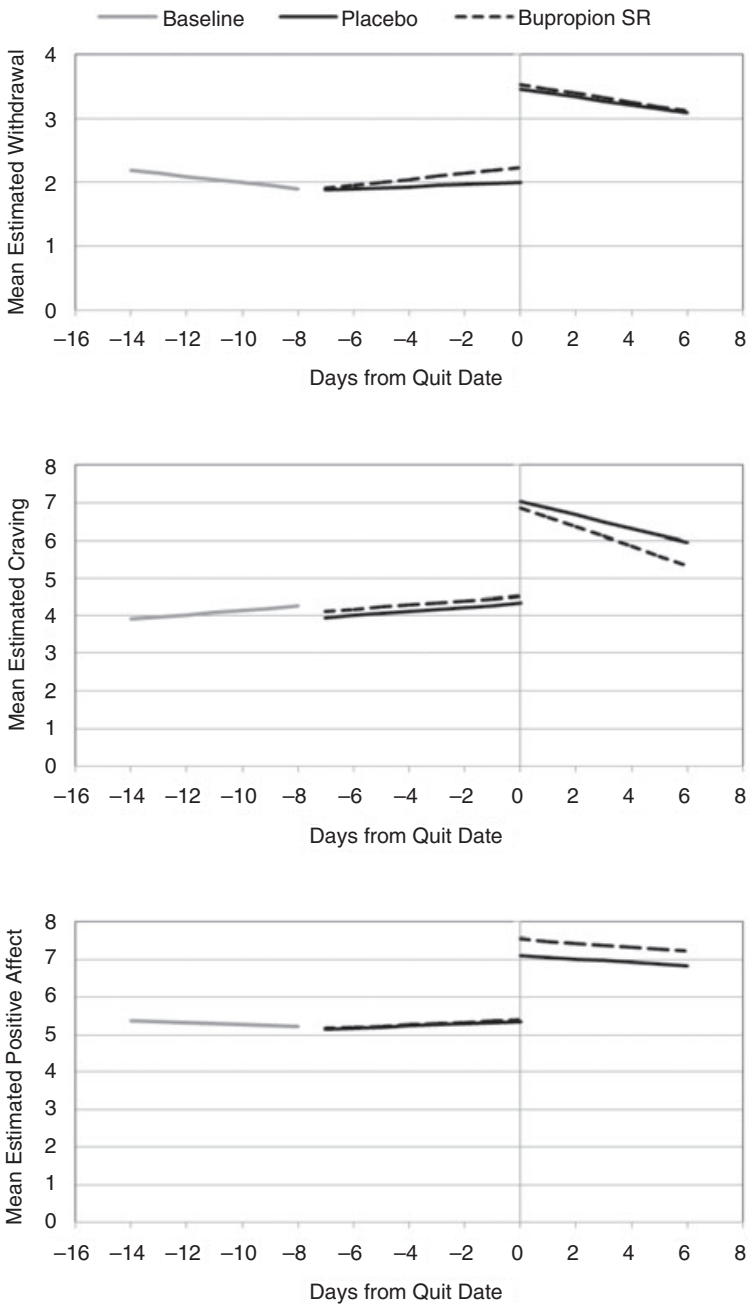

Figure 2 Estimated growth in candidate mediators of bupropion sustained-release (SR) effects derived from hierarchical linear modeling (HLM) multilevel models of withdrawal distress, cigarette craving and positive affect. Intercept and linear slope variables were estimated separately in each assessment epoch. The baseline intercept was set to 11:59 p.m. on day –8 and the slope was estimated between days –14 and –8. The treatment run-up intercept was set to 11:59 p.m. on day –1 and the run-up slope was estimated between days –7 and –1. The post-quit intercept was set to 12:00 a.m. on the quit day (day 0) and the post-quit slope was estimated between days 0 and 6

Withdrawal distress summary scores declined modestly during the baseline period ($t_{393} = -3.41$, $P = 0.001$), and were stable during the treatment run-up period ($t_{392} = 1.46$, $P = 0.15$). As in the evening report data, participants receiving active medication had significantly higher withdrawal distress ($t_{392} = 2.04$, $P = 0.04$) just before the quit attempt than did those receiving placebo. The groups did not differ in symptom severity upon quitting, however ($t_{392} = 0.48$, $P = 0.63$); both experienced a jump in withdrawal distress on the quit date. Withdrawal distress declined post-quit ($t_{392} = -3.13$, $P = 0.002$) for both treatment groups ($t_{392} = -0.32$, $P = 0.75$). In logistic regression analyses (Table 3), a marginal relation between the rate of decline in withdrawal distress and 1-month point-prevalence abstinence was observed, such that higher slopes were marginally predictive of abstinence.

In cigarette craving models, significant positive growth occurred in both the baseline ($t_{393} = 2.88$, $P = 0.004$) and treatment run-up periods ($t_{392} = 2.14$, $P = 0.03$), followed by a jump on the quit day and then a significant decline in craving in the first week of the quit attempt ($t_{392} = -5.42$, $P < 0.001$). Treatment was not related to craving just before or just after the

quit date ($t_{392} < 0.92$, $P > 0.05$). The rate of decline post-quit was significantly faster (–0.26 points per day) among those receiving active medication than among those receiving placebo (–0.18 points per day, $t_{393} = 1.95$, $P = 0.05$). Models predicting abstinence from craving dimensions (Table 3) indicated that higher quit-day craving levels were marginally, inversely predictive of abstinence between weeks 3 and 4 post-quit, while lower post-quit slopes (faster declines) were significantly predictive of abstinence. The estimate of the mediated effect for post-quit slope in craving was significant ($ab_{ps} = 0.10$, SE = 0.06, 95% CI = 0.002–0.24; $Z' = 1.61$, $P < 0.05$). Bupropion SR remained a significant predictor of abstinence 1-month post-quit in models containing post-quit craving slope and the other dimensions of craving.

Positive affect did not change significantly prior to the quit date ($t_{393} < 1.30$, $P > 0.20$ for both baseline and run-up periods) but did increase at the start of the quit attempt and declined significantly thereafter ($t_{392} = -2.16$, $P = 0.03$), regardless of medication condition ($t_{392} = -0.12$, $P = 0.91$). Positive affect level just before the quit attempt was unrelated to treatment ($t_{392} = 0.30$, $P = 0.76$) but, just after the quit date, positive affect was significantly higher among those receiving active versus placebo medication ($t_{392} = 2.63$, $P = 0.01$). Positive affect at the start of the quit date was not related significantly to outcome, but greater maintenance in positive affect over the first week of the quit attempt was marginally predictive of 1-month abstinence (Table 3).

Lapse to relapse latency

We conducted regression analyses to determine whether self-reported reactions to the initial slip mediated the observed medication effect on latency to relapse. The 277 people who completed slip reports were significantly older (M = 40.00, SD = 12.37 years) than the 40 people (26.5%) who slipped but did not complete a report (M = 35.08, SD = 10.93 years; $t_{315} = 2.30$, $P = 0.02$), but did not differ from non-reporters in terms of treatment condition, demographics or baseline characteristics (all P values > 0.05). Active and placebo medication groups did not differ significantly on any of the slip reactions analyzed (all $R^2 < 0.01$, all $P > 0.05$). As such, the mediation hypothesis regarding slip reactions was rejected due to the lack of treatment effects on the putative mediator.

DISCUSSION

The current study tested specific hypotheses regarding psychological mediators of bupropion SR effects on early abstinence from smoking. In addition, we tested the specificity of our model of bupropion SR effects by exploring general motivational mediators, such as confidence in one's ability to quit smoking, that we did not expect to be influenced by bupropion SR. Results from this study inform our current model of bupropion SR effects and the psychological processes that account for its efficacy.

Our central hypotheses, that bupropion SR works, in part, by reducing withdrawal distress and cravings for cigarettes, by enhancing positive affect and by altering reactions to smoking post-quit received mixed support. As in previous research [22], summary scores capturing withdrawal distress over the first week post-quit were not improved significantly by bupropion SR treatment. Bupropion SR has produced inconsistent effects on withdrawal during the first week of a quit attempt across randomized, placebo-controlled trials [13–15,22] and laboratory studies [11,12]. Surprisingly, greater or escalating withdrawal distress was not predictive of greater difficulty quitting in this sample, as it has been in previous research (e.g. [32,34]. Such inconsistency may reflect our focus on withdrawal during the first week of the quit attempt rather than a longer period of time, our decision to model craving and non-craving withdrawal distress separately or our use of electronic diaries rather than paper diaries [34].

Cigarette craving received greater support as a candidate mediator in the current sample than did withdrawal distress, but the results differed across the two types of reports analyzed. Whereas craving levels assessed by random time-sampling throughout the day suggested that rate of decline in craving post-quit partially mediated bupropion SR effects, evening reports summarizing craving over the preceding 24 hours did not reveal a beneficial bupropion SR effect. As such, our results support findings that post-quit craving assessed in a momentary fashion mediates bupropion SR effects [22], but suggests that these results are not robust across different assessment time-frames. Craving tends to be episodic and individuals may have difficulty integrating craving experiences over longer periods, which may account for the discrepancy across the two craving measures assessed in this study. Indeed, research regarding physical pain suggests that ratings of pain tend to be influenced by peak and final levels, rather than average level or duration [50]. Craving ratings at the end of the day may be influenced similarly by peak or recent experiences.

Conversely, the mediating role of positive affect received greater support in the evening report than in the random prompt data. Bedtime ratings of positive affect over the past day were significantly higher, on average, post-quit among those receiving active bupropion SR than among those receiving placebo, and elevated post-quit positive affect was predictive of greater likelihood of abstinence at the 1-month follow-up. The pattern of results was similar for random prompt data capturing

momentary positive affect, such that active medication enhanced positive affect at the outset of the quit attempt, but we did not detect a significant relation between momentary ratings of quit-day positive affect and later abstinence. Instead, we found that the trajectory of positive affect over the first week post-quit predicted later abstinence positively, but was not influenced by bupropion SR.

Our fourth hypothesis, that active medication would alter the experience of the first cigarette smoked post-quit, was not supported. We failed to find any treatment-related differences in ratings of the pleasure, urge reduction, relaxation, buzz, taste or sickness conferred by the first cigarette. As such, initial slip reactions could not mediate the delay in relapse following a lapse due to bupropion SR medication observed in this sample. Reports of slip reactions were user-initiated in this study and were not recorded by 40 of the 317 smokers whose other data indicated that a slip had occurred. As such, non-adherence to assessment instructions may have colored the results (e.g. if the slips that were recorded differed systematically from those that were not).

Exploratory analyses provided support for the mediating role of motivation and self-efficacy items that we did not expect to be activated differentially in the active and placebo medication conditions in this study. Although it is not surprising that motivation to stop smoking and quitting self-efficacy predicted behavior change [51,52], we have little understanding of the reasons bupropion SR improved participants' willingness to work hard at quitting and confidence. It may be that these are composite variables that reflect a host of small, specific effects of bupropion that may differ across individuals. Individuals may differ in sensitivity to small effects (i.e. some people may be highly attuned to changes in craving, whereas others may be more attentive to changes in anxiety) and may make appraisals of such effects that influence motivation and self-efficacy. Alternatively, it may be that the higher rate of side effects (e.g. dry mouth) reported in the active medication condition [26], and the absence of an active placebo to mimic such effects may have compromised blinding and led to differences in expectancies, confidence and motivation in the two conditions [53]. It will be important to explore and explain the mediating role of motivation and self-efficacy in future bupropion research.

The current study yielded new information about the psychological effects and mediators of bupropion SR. Taken together, past and current data [13,22] suggest that negative affect is not improved consistently by bupropion SR treatment. The reasons for this inconsistency are unclear, and may reflect the influence of: the timing, timeframe, mode or content of assessment; analytical strategy; or some combination of these or other methodological factors. The lack of consistency across studies appears to challenge our current models of both bupropion SR action and relapse. However, the diversity of the measures and methods used across studies makes it difficult to discern whether it is our models or methods that require revision.

In addition, our current results, along with other recent findings from our laboratory [28], suggest that cigarette craving may play a central role in relapse and may mediate bupropion SR effects on abstinence. Results also suggest that momentary assessments of craving may be more sensitive indicators of relapse vulnerability than are daily recall summaries, and that change in craving may be especially important and improved by bupropion SR treatment. Our results also highlight the relapse risk associated with anhedonia and the importance of assessing positive affect in addition to withdrawal distress. The current results add to the research suggesting that people low in positive affect may be particularly vulnerable to relapse and likely to benefit from treatments that promote positive affect [54]. Overall, the results also highlight the modest impact of treatment on quit-induced increases in withdrawal distress and craving.

Limitations

The interpretation of both significant and null results in this study should be tempered by the following concerns. First, the generalizability of the results to the broader population of smokers may be limited, particularly given the high level of motivation to quit and willingness to participate in an intensive treatment study among our enrollees. In addition, assessment reactivity and attrition may have reduced the generalizability or validity of our results. We observed high rates of attrition and heard many complaints about the assessment burden in this study. Thirdly, some of the mediational analyses may not have been optimally sensitive. For instance, data collected with a variable occasion design (i.e. random prompt data) could not be treated as latent variables without loss of temporal resolution (i.e. by aggregating multiple reports within a single day to a single variable), and this prevented effective isolation of error and reduced our ability to detect mediator–outcome relations due to the shrinkage in variance in empirical Bayes' estimates. In addition, problems with reliability of these estimates may account for the broad confidence intervals observed in logistic regression analyses (e.g. for run-up variables).

CONCLUSION

In general, the results of this study suggest that our model of how bupropion SR promotes smoking abstinence needs revision. Current understanding of the pharmacological mechanisms of bupropion SR action suggested mediation hypotheses that received partial support, but cannot account easily for the meditational

pathways through motivation and self-efficacy. As such, additional research on the psychological mechanisms of bupropion SR action may provide a useful adjunct to tests of pharmacological mechanisms. The current study illustrates one way to enhance the yield of clinical trials by including measures of putative mediators and conducting multivariate analyses.

Declarations of interest

Douglas E. Jorenby has received research support from Nabi Biopharmaceutical and Pfizer, Inc. and consulting fees from Nabi Biopharmaceutical. Saul Shiffman serves as consultant to GlaxoSmithKline Consumer Healthcare on an exclusive basis regarding over-the-counter (OTC) smoking cessation products and is also a partner in a company that is developing a new nicotine medication. He is a co-founder of invivodata, inc., which provides electronic diary services for clinical research. Timothy B. Baker has served as a consultant, given lectures sponsored by, or has conducted research sponsored by GlaxoSmithKline, Nabi Biopharmaceuticals, Pfizer and Sanofi-Synthelabo. GlaxoSmithKline provided complimentary active and placebo medication used in this study. GlaxoSmithKline was not involved in the design, data collection, analysis or reporting of this study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix A
Figure A1

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