

Using Mediational Models to Explore the Nature of Tobacco Motivation and Tobacco Treatment Effects

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Various theories have proposed mechanisms for drug motivation and relapse. For instance, negative reinforcement theories focus on the alleviation of withdrawal. However, other theories and some data cast doubt on the importance of withdrawal as a motivator of addictive drug use. Using data from a randomized double-blind placebo-controlled smoking cessation treatment study ($N = 608$), this research examined the impact of withdrawal on drug motivation and the ability to maintain abstinence. Withdrawal was experimentally manipulated by randomly assigning participants to receive active bupropion versus placebo. Mediation analyses revealed that active bupropion reduced the amount of withdrawal and craving that individuals reported in the 1st week post quit; modest support was also found for smaller declines in positive affect. These effects, in turn, were all positively associated with posttreatment abstinence. These results implicate withdrawal as an important factor in motivating persistent tobacco use.

Keywords: withdrawal, smoking cessation, mediation, bupropion

Tobacco dependence is both a chronic and pandemic disease (Fiore et al., 2000) that most commonly takes the form of cigarette smoking. Of the approximately 15 million smokers who make a quit attempt every year (Centers for Disease Control and Prevention, 2002, 2004), fewer than 5% are able to maintain long-lasting abstinence (Centers for Disease Control and Prevention, 2002), and most smokers return to smoking within 2 weeks of making a quit attempt (Kenford et al., 1994; Westman, Behm, Simel, & Rose, 1997).

Multiple theories provide possible explanations for relapse back to addictive drug use. Some venerable theories attribute relapse to negative reinforcement (Jellinek, 1960; Lindesmith, 1947; Wikler, 1948), and this hypothesis continues to be the focus of research and theoretical work (e.g., Baker, Morse, & Sherman, 1987; Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). Research has shown that addictive drugs can produce physical dependence that manifests as aversive withdrawal symptoms when drug levels fall in the

body. This has inspired models that assert that drug use is motivated in part to avoid or escape withdrawal symptoms (Baker et al., 2004; O'Brien, 1976; Solomon, 1977; Solomon & Corbit, 1974; Wikler, 1980).

Other theories of drug motivation emphasize positive reinforcement or incentive mechanisms in drug motivation and argue that withdrawal symptoms are not important determinants of relapse (e.g., Lyvers, 1998; Robinson & Berridge, 1993; Stewart, de Wit, & Eikelboom, 1984; van Ree, Gerrits, & Vanderschuren, 1999). For instance, "many authors have suggested that models of addiction based on the alleviation of withdrawal symptoms (whether 'physical' or 'psychological') are neither necessary nor sufficient to explain to explain compulsive drug-seeking and drug-taking behavior" (Robinson & Berridge, 2000, p. S92). Authors have argued that there is not a strong relation between the addictive potential of a drug and its ability to produce physical dependence and withdrawal symptoms (e.g., van Ree et al., 1999). Furthermore, some theorists have claimed that withdrawal is not a vital determinant of drug motivation based upon claims that there is little correlation between measures of withdrawal severity and drug use or relapse: "the treatment of withdrawal symptoms by themselves has proven to have little effect in the long-term. We suggest that this is because avoidance of withdrawal is not the fundamental motivating force in addiction" (Robinson & Berridge, 2000, p. S106). However, there is now considerable evidence that there is, in fact, a strong relation between severity of tobacco withdrawal symptoms and relapse (McCarthy, Piasecki, Fiore, & Baker, 2006; Piasecki et al., 2000; West, 2005). Previous failures to find a relation between withdrawal and cessation success may

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have been due to a failure to assess withdrawal accurately. For instance, some research has shown that dimensions of the withdrawal syndrome such as initial symptom elevation, variability in symptoms over time, and trajectories of symptoms all can predict likelihood of relapse back to smoking (Piasecki et al., 2000; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003).

Extant research on the relation of withdrawal with cessation success does not, however, permit strong inference regarding the causal role of withdrawal because individuals were not randomly assigned to different levels of withdrawal severity. Thus, it is possible that a third variable (e.g., neuroticism) might independently cause both severe withdrawal as well as heightened cessation failure. Moreover, earlier correlational work did not directly address the issue of whether effective treatments work by suppressing withdrawal symptoms. Several effective treatments, including bupropion, are known to reduce withdrawal symptoms (Durcan et al., 2002; Lerman et al., 2002; Shiffman et al., 2000, 2003; Shiffman, Ferguson, Gwaltney, Balabanais, & Shadel, 2006). Hypothesized mechanisms for the ability of bupropion to reduce withdrawal include decreased activation in the anterior cingulate cortex, which has been linked to craving (Brody et al., 2004); antagonist effects on dopamine reuptake, possibly by occupying dopamine transporters, which may result in alleviation of negative affect associated with withdrawal (Learned-Coughlin et al., 2003; Warner & Shoaib, 2005); and antagonism of nicotinic acetylcholinergic receptors, which might interfere with associative or nonassociative priming of cholinergic systems (Warner & Shoaib, 2005). Despite these findings, there are few published studies of the specific mechanisms that mediate tobacco cessation treatment effects, and those that exist did not impose temporal segregation of treatment and mediational effects (e.g., Lerman et al., 2002) or have long-term relapse data (e.g., Ferguson, Shiffman, & Gwaltney, 2006, which examined outcomes up to 32 days post quit).

Additional research on the mediation of cessation treatments is warranted because the associated statistics test important, tandem hypotheses. The first hypothesis concerns what treatments do, whereas the second hypothesis concerns why smokers succeed or fail in quitting. Thus, in mediation analyses the researcher simultaneously tests and integrates treatment and relapse models. Both models are germane to a withdrawal-based account of relapse. A withdrawal account would not be supported by either of the two outcomes: (a) An effective treatment does not suppress withdrawal symptoms; and (b) a treatment does suppress withdrawal, but the extent of this effect is unrelated to clinical benefit (i.e., higher abstinence likelihood). The implication is that other mechanisms account for treatment effects and abstinence likelihood. Therefore, the analyses of treatment mediation have great potential to reveal the determinants of cessation failure or relapse.

A chief virtue of mediational research is that it does not rely solely on the correlation of withdrawal symptoms with later relapse. Rather, individuals are randomly assigned to treatment conditions that either do or do not reduce withdrawal, and then resultant changes in withdrawal are statistically related to clinical outcomes (Kazdin & Nock, 2003). The use of random assignment to manipulate withdrawal severity permits stronger inferences regarding the causal role of withdrawal than would otherwise be possible.

In this study, we used data from a smoking cessation trial to assess the impact of withdrawal on likelihood of successful tobacco cessation. Withdrawal severity was experimentally manipulated by randomly assigning individuals to pharmacotherapy conditions known to suppress withdrawal (i.e., bupropion alone and bupropion + nicotine gum conditions; see Mooney & Sofuoglu, 2006, for review) or to a placebo control condition. We hypothesized that withdrawal suppression (assessed using real-time assays of withdrawal symptoms, including craving and negative affect) would mediate the effect of pharmacotherapy on abstinence rates. In addition, because withdrawal is associated with anhedonia or loss of ability to experience pleasure (e.g., Cryan, Bruijnzeel, Skjei, & Markou, 2003), we also examined the hypothesis that positive affect would influence relapse vulnerability. The present research has the potential to permit strong inference regarding the role of withdrawal in motivating persistent tobacco use.

Method

The sample used for this study was the same as that found in Piper et al. (in press), which can be referenced for a more detailed account of the methods.

Participants

Participants were recruited through TV, radio, and newspaper advertisements and community flyers. Eligible participants reported smoking 10 or more cigarettes per day and being motivated to quit smoking. Participants denied any physical or mental health issues that would prevent them from participating in or completing the study. Female participants were not pregnant or breastfeeding and took steps to prevent pregnancy during treatment.

Procedure

Participants who passed a phone screen were invited to an orientation session where they provided written informed consent as well as demographic and smoking history information. Participants then attended a baseline session during which they underwent multiple screenings and completed a number of questionnaires, including the Center for Epidemiologic Studies—Depression scale (Radloff, 1977), the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), the Wisconsin Inventory of Smoking Dependence Motives (Piper et al., 2004), and the Tobacco Dependence Screener (Kawakami, Takatsuka, Inaba, & Shimizu, 1999).

Eligible participants were then randomized, in a double-blind fashion using blocked randomization within cohorts, to one of the three treatment groups: active bupropion sustained release (150 mg, b.i.d.) + active 4-mg nicotine gum (AA; $n = 228$); active bupropion sustained release + placebo nicotine gum (AP; $n = 224$); or placebo bupropion sustained release + placebo gum (PP; $n = 156$). There was no placebo bupropion + active nicotine gum arm in this study, so we were not able to examine the efficacy or potential mediators of treatment effects for nicotine replacement per se. After the baseline session, participants attended one session per week for 4 weeks and then two more sessions every other week. They received brief smoking cessation counseling at the 1-week pre-quit visit, the quit day visit, and the first post-quit visit,

Table 1
Participant Demographics

Characteristic	Total (N = 608)		AA (n = 228)		AP (n = 224)		PP (n = 156)	
	n	%	n	%	n	%	n	%
Female	352	57.9	127	55.7	135	60.3	90	57.7
Hispanic	10	1.6	4	1.8	3	1.3	3	1.9
White	449	76.0	170	77.6	165	76.0	114	73.5
African American	130	22.0	43	19.6	50	23.0	37	23.9
Other race	12	2.0	6	2.8	2	0.9	4	2.5
Married	283	46.5	103	45.2	108	48.2	72	46.2
High school education	186	30.7	79	34.8	66	29.5	41	26.6
College degree	98	16.2	35	15.4	32	14.3	31	20.1
Employed for wages	414	69.2	154	69.1	147	66.5	113	73.4
Household income <\$25,000	174	29.2	65	29.1	69	31.2	40	26.5
Household income ≥\$50,000	208	34.9	71	31.9	80	36.2	57	37.7

Note. Percentages are based on the number of individuals who provided data for that question (Ns range from 591–608). AA = active bupropion and active nicotine gum; AP = active bupropion and placebo nicotine gum; PP = placebo bupropion and placebo nicotine gum.

for a total of three 10-min counseling sessions over 3 weeks. Pharmacological treatment concluded at the end of the ninth week, 8 weeks after the quit date.

Data Collection

Data regarding smoking, medication use, affect (Positive and Negative Affect Schedule; Watson, Clark, & Tellegen, 1988), and withdrawal symptoms (Wisconsin Smoking Withdrawal Scale; Welsch et al., 1999) were collected at each study visit. In addition, participants completed a daily diary each day for the 9 weeks of treatment, which assessed number of cigarettes smoked, number of pieces of gum chewed, and the severity of withdrawal symptoms (depressed mood, difficulty sleeping, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, and increased appetite) for that day. Participants also carried cellular phones for 2 weeks, centered around the quit date, to collect real-time data on withdrawal symptoms and life events. They were called four times per day (once when they woke up, once before they went to bed, and at two random times during the day) by an interactive phone-computer system (IVR). They were asked about smoking and stressors since the last call and the occurrence of temptation events, use of study gum, and severity of withdrawal symptoms (e.g., desire to smoke, difficulty concentrating, sadness, irritability) in the past 30 min.¹

Participants were followed up after treatment via telephone monthly until relapse, and an attempt was made to contact all participants, irrespective of smoking status, at 6 and 12 months post quit day. If a participant reported smoking for 3 days in a row, that participant was considered to be relapsed or a cessation failure. We used a 3-day criterion for relapse based on our previous research (e.g., Zelman, Brandon, Jorenby, & Baker, 1992), although a subsequent workgroup proposed that 7 consecutive days should be the definition of treatment failure (Hughes et al., 2003). Participants who reported 7 days of abstinence at their 6- or 12-month follow-ups were scheduled to return to the clinic and provide either a breath sample for carbon monoxide analysis (6 and 12 months) or a blood sample for cotinine analysis (12 months). If individuals could not be reached for a follow-up

assessment, they were coded as smoking at that time point (see Stout, Brown, Longabaugh, & Noel, 1996).

Results

Study enrollment began in 2001 and was completed in October 2002. Data collection was completed in January 2004. All analyses were conducted using SPSS 11.5 software unless otherwise noted.

Participant Characteristics

A total of 608 smokers (57.9% women) participated in this study (see Tables 1 and 2 for demographic and tobacco dependence information).

Treatment Effects

We combined the two groups that received active bupropion (AA and AP groups) and compared them to the individuals who received only placebo medication (PP group). We examined smoking rates at four follow-up time points (1 week post quit, end of treatment, 6 months, and 12 months; see Table 3). Logistic regression results, using carbon monoxide-confirmed 7-day point-prevalence abstinence for the four different time points as dependent variables, revealed significant treatment effects at all time points except 12 months (see Table 3). Even though the AA group was 1.45 times less likely to be smoking by the end of the first week relative to the AP group (Wald $Z = 3.74$, $p = .05$), there were no significant differences between the two groups (AA vs. AP) at the end of treatment, 6 months, or 12 months (see Figures 1 and 2 for survival curves for first day to lapse and first day to relapse). Given the lack of treatment differences in outcome beyond 1 week and that, on average, participants only used 4 pieces

¹ It should be noted that daily diary and IVR assessments were highly correlated. For example, average daily withdrawal, $r = .64$, $p < .01$; average sadness/depressed mood, $r = .54$, $p < .01$.

Table 2
Participant Age, Dependence, and Depression Scores, *M* (*SD*)

Dependence measure	Total (<i>N</i> = 608)	AA (<i>n</i> = 228)	AP (<i>n</i> = 224)	PP (<i>n</i> = 156)
Age, in years	41.78 (11.34)	41.14 (11.30)	42.26 (11.41)	42.03 (11.31)
Fagerström Test for Nicotine Dependence	5.64 (2.13)	5.69 (2.20)	5.70 (2.04)	5.48 (2.16)
Tobacco Dependence Screener	6.43 (2.03)	6.44 (1.93)	6.44 (2.06)	6.42 (2.12)
Cigarettes per day	22.44 (9.87)	22.09 (8.89)	23.39 (10.81)	21.57 (9.75)
Wisconsin Inventory of Smoking Dependence Motives	52.33 (12.92)	51.71 (12.07)	52.36 (13.36)	53.17 (13.51)
Center for Epidemiologic Studies-Depression scale	6.06 (4.52)	5.88 (4.22)	6.03 (4.47)	6.35 (5.00)

Note. AA = active bupropion and active nicotine gum; AP = active bupropion and placebo nicotine gum; PP = placebo bupropion and placebo nicotine gum.

of gum per day,² a rate that is well below the recommended dose for clinical effectiveness, we felt that it was appropriate to combine the AA and AP groups into one group for mediation analyses. See Piper et al. (in press) for a more detailed account of the treatment effects.

Mediation of Treatment Effects

The first step in our mediation analyses was to identify potential withdrawal and affect mediators. Data on withdrawal were collected using cell phones and questionnaires completed at every study visit (i.e., once prior to the quit day, on the quit day, and four times post quit). Of the 30,968 IVR calls attempted, 23,786 (76.8%) were completed. This was comparable to compliance rates reported in McCarthy, Piasecki, Fiore, and Baker (2006), in which 80.3% of the assessments were completed; and Shiffman and Paty (2006), in which more than half of the participants responded to at least 89% of the assessments. However, the compliance for the current study was below the 80% cutoff recommended by Stone and Shiffman (2002). Using the ecological momentary assessment data collected 1 week pre quit and 1 week post quit, we examined growth patterns for four withdrawal variables (total withdrawal, negative affect/concentration, craving, and food/hunger)³ with maximum likelihood estimation using hierarchical linear modeling software (HLM 5.04; Raudenbush, Bryk, & Congdon, 2001). A discontinuous piecewise linear model was fit to each potential mediator with the quit date defining a node point. Specifically, each potential mediator was modeled as follows:

$$M = \beta_0 + \beta_1(\text{pre-post}) + \beta_2(\text{days pre quit}) + \beta_3(\text{days post quit}) + e, \quad (1)$$

where each potential mediator (*M*) was a function of the time at which the measure was observed. The pre-post variable was a dummy variable coded as 0 if the data were collected before 12:01 a.m. on the quit day and as 1 if the data were collected on or following the quit day. The days pre quit variable indicated the number of days prior to the quit day coded negatively (i.e., -7, -6, -5, etc., to 0 at the quit date and all days post quit), and the days post quit variable indicated days since the quit day coded positively (i.e., 0 for all days prior to the quit date, and ranging from 0 on the quit date up to 7 for 1-week post quit). In this way, the model represented individual differences in mediator change with respect to four parameters: β_0 = the pre-quit intercept, or the level of the potential mediator immediately prior to the quit attempt

(when all time variables were coded as 0); β_1 = the jump in the potential mediator that occurred on the quit day (when pre-post = 1 and all other time variables were 0); β_2 = the pre-quit slope (the expected change in potential mediator per day change pre quit); and β_3 = the post-quit slope (the expected change in potential mediator per day change post quit). Using a forward model-building approach, we allowed one parameter at a time to vary randomly among individuals until we achieved maximum model fit. For each potential mediator, the best model fit resulted from allowing all parameters to vary across participants.

Using IVR data and daily diary data, HLM model results revealed statistically significant increases in the ratings of withdrawal, negative affect/concentration, craving, and food/hunger symptoms and decreases in positive affect on the quit day (see change on quit day estimates in Table 4). The symptoms that increased on the quit day (e.g., craving) then significantly decreased over the course of the first week post quit, with the exception of food/hunger symptoms, which increased slightly over the first week post quit. Positive affect continued to decrease over the first week post quit (see post-quit slope estimates in Table 4). Including cigarette smoking as a time-varying covariate in the models revealed that cigarette smoking had a very modest relation with a subsequent rating of withdrawal, a $B = .009$ increment in withdrawal rating magnitude. Entry of the time-varying covariate did not affect estimation of treatment effects on withdrawal symptomatology. Recent gum use, within the past 30 min, was also analyzed as a time-varying covariate with similar results such that

² There was not a relation between abstinence outcome and the amount of gum used in the AA condition. On average, participants in this condition used 4.09 ($SD = 3.44$) pieces of gum per day (20.3% of participants didn't chew any gum, 34.8% chewed 1-4 pieces per day, 27.2% chewed 5-8 pieces per day, and 17.7% chewed more than 8 pieces per day).

³ These symptom categories were based upon an exploratory factor analysis that was conducted on symptom scores averaged across all data collection occurrences. The withdrawal items included negative affect/concentration items (felt hopeless, felt impatient, felt sad, been tense or anxious, been irritable, had trouble concentrating), craving items (desire to smoke, had cigarettes on my mind), and food/hunger items (eating a lot, thought about food).

Table 3
7-Day Point-Prevalence Smoking Follow-Up Rates (%) and Logistic Regression for Active Versus Placebo Medication

Time point	Abstinence rates				Statistical results		
	AA	AP	Active medication (AA + AP)	Placebo (PP)	Wald Z	<i>p</i>	OR
1 week	53.5	62.5	58.0	78.2	19.59	<.01	.38
End of treatment	61.8	68.8	65.3	82.7	15.97	<.01	.39
6 months	77.2	75.4	76.3	85.3	5.40	.02	.56
12 months	79.4	81.3	80.3	86.5	3.00	.08	.63

Note. AA = active bupropion and active nicotine gum; AP = active bupropion and placebo nicotine gum; PP = placebo bupropion and placebo nicotine gum; OR = odds ratio.

it did not affect estimation of treatment effects on withdrawal symptomatology.⁴

As all five potential mediators considered above (withdrawal, craving, negative affect/concentration, food/hunger, and positive affect) displayed statistically significant change of some form over the studied 2-week time period, all five continued to be considered as potential mediators. The set of potential mediators was further refined by studying the predictive effects of treatment on change. The relations of treatment with (a) the quit-day jump and (b) the post-quit slope were evaluated for all five outcomes via HLM analyses.

Statistically significant effects of treatment (AA and AP vs. PP; $p < .05$) were attained for three potential mediators with respect to either tested effect: withdrawal (jump: estimate = $-.09$, $SE = .04$, $p = .02$; slope: estimate = $-.11$, $SE = .05$, $p = .03$), craving (jump: estimate = $-.16$, $SE = .09$, $p = .056$; slope: estimate = $-.35$, $SE = .10$, $p < .01$), and positive affect (jump: estimate = $.87$, $SE = .45$, $p = .05$; slope: estimate = $.14$, $SE = .09$, $p = .12$). Significant treatment effects were not observed for either tested effect for negative affect/concentration or food/hunger. Unfortunately, HLM does not accommodate full mediational modeling. Thus, to explore the effects of withdrawal, craving, and positive affect as mediators in the predictive effects of treatment on relapse, we specified mediational models using Mplus software (Muthén & Muthén, 2004).

To accommodate the availability of only one pre-quit measure of positive affect, we fit different mediational models for craving and withdrawal versus positive affect. HLM analyses had used four variables to model the growth trajectories for craving and withdrawal (pre-quit intercept, pre-quit slope, change on quit day, and post-quit slope). As both change on quit day and post-quit slope may be affected by treatment, each could theoretically be studied as distinct mediators. However, a composite of these two effects was created in Mplus and studied as a mediator in the current analyses. The composite was used for several reasons: (a) The central hypothesis concerned overall aversiveness of withdrawal, not a specific trajectory element; and (b) statistical power is enhanced when combining the effects of change on quit day and post-quit slope. The composite mediator latent variable was defined as the sum of the change in symptoms on the quit day and 6 times the post-quit slope by fixing the path coefficients from the change on quit day and post-quit slope to 1 and 6, respectively. These coefficients were chosen so as to allow the composite latent variable to reflect total change in the potential mediator from just before the quit attempt to 1 week post quit. (Note that the post-quit

slope latent variable represents change in each potential mediator per day, and thus must be multiplied by 6 to indicate change over 1 week.) Predictive effects of treatment were then introduced only on the composite latent variable, which, in turn, was assumed to predict abstinence status (see Figure 3 for a path diagram of the model).

The mediation model for positive affect included latent variables corresponding to the level of positive affect before quitting (the pre-quit intercept), change in positive affect on the quit day, and post-quit slope of positive affect; thus the composite latent variable could be calculated and studied in the same way as for the other hypothesized mediators. Separate models were fit for the relapse measures at all three time points when there were significant treatment effects. In Mplus, a weighted least squares estimator is used to accommodate the dichotomous outcome (relapse). Model fit indexes indicated good model fit for the craving and withdrawal models for all three time points (root mean square errors of approximation [RMSEAs] = $.04-.07$, weighted root mean square residuals [WRMRs] = $.70-.96$, Tucker-Lewis Indexes [TLIs] = $.98-.99$, comparative fit indexes [CFIs] = $.95-.97$) and positive affect model for both follow-up time points (RMSEAs = $.00$, WRMRs = $.36-.37$, TLIs = 1.00 , and CFIs = 1.00).⁵

A common approach to testing mediational effects involves testing whether the product of paths (i.e., the indirect effect) from treatment to mediator and mediator to outcome differs from zero. However, statistical tests of this null hypothesis are complicated by the fact that the hypothesis of a null indirect effect is a compound hypothesis, and the consequential finding that there is no single

⁴ It might seem surprising that gum use was unrelated to withdrawal symptoms. However, there is evidence that participants are more likely to smoke when their withdrawal symptoms are particularly high (Piasecki et al., 2003). Thus, any effect of nicotine use is superimposed on a higher than normal craving or withdrawal level. Also, there is evidence that urges and other symptoms may rebound quickly after smoking (Hendricks, Ditre, Drobes, & Brandon, 2006; Jarvik et al., 2000), suggesting that any suppressant effect would be lost if there were much of a delay between use and assessment. Finally, as noted earlier, relatively little gum was used, and most individuals did not smoke during the post-quit ecological momentary assessment period.

⁵ Model evaluation involved an examination of the WRMR, RMSEA, TLI, and CFI. We considered the following to indicate adequate fit: WRMR $<.90$, RMSEA $\leq .08$, TFI $>.95$, and CFI $>.90$ (Browne & Cudeck, 1993; Newcomb, 1994; Yu & Muthén, 2001).

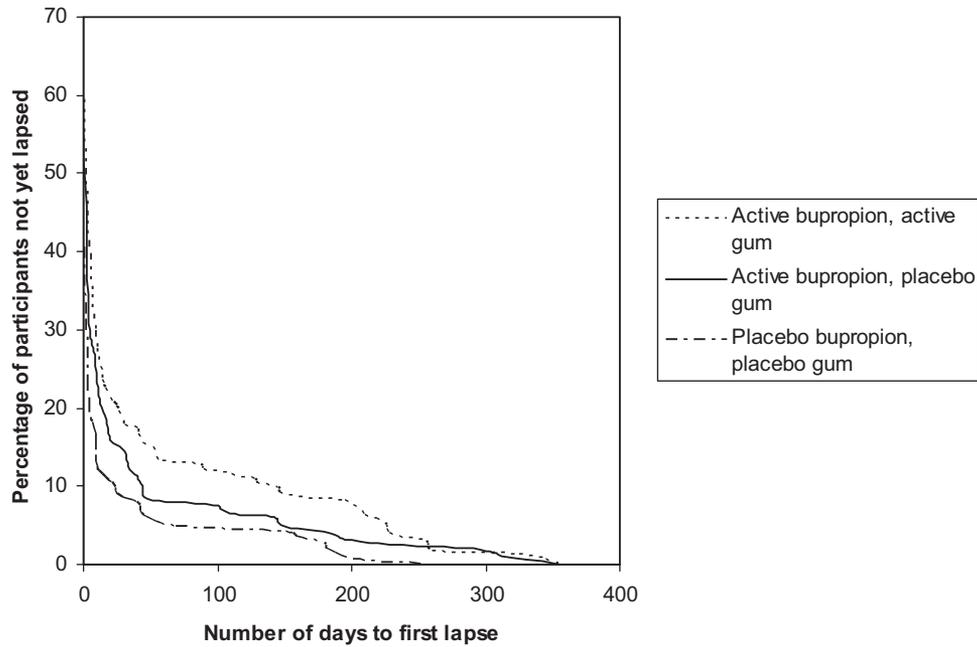


Figure 1. Survival curves for number of days to lapse (i.e., until participants smoked their first cigarette) for the three treatment conditions.

test that is optimal in terms of Type I error control and maximization of power across all conditions represented by the null hypothesis (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). As a result, we tested the mediation effect for each hypothesized mediator using three different approaches: (a) the joint significance test, (b) asymmetric confidence intervals of the prod-

uct of the indirect paths (MacKinnon & Lockwood, 2001), and (c) the z' test of the product of the indirect paths (MacKinnon et al., 2002). Taken together, these tests can help in determining which components of the null hypothesis can be confidently rejected.

The joint significance test is based on individual testing of the two paths in the indirect effect. The indirect effect is assumed to be

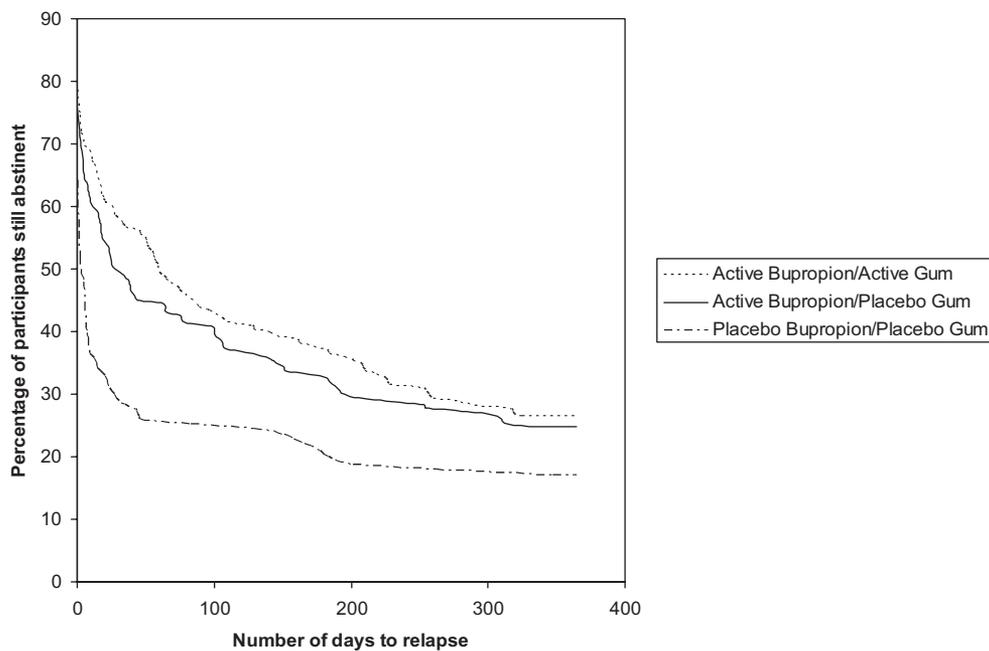


Figure 2. Survival curves for number of days to relapse for the three treatment conditions. A relapse was defined as any smoking for 3 days in a row.

Table 4
Fixed Estimates of Growth Parameters for Withdrawal Variables With Robust Standard Errors

Variable	Pre-quit intercept (SE, <i>p</i>)	Change on quit day (SE, <i>p</i>)	Pre-quit slope (SE, <i>p</i>)	Post-quit slope (SE, <i>p</i>)
Total withdrawal	1.47 (.03, <.01)	0.26 (.02, <.01)	.00 (.00, .93)	-.03 (.00, <.01)
Craving	2.11 (.05, <.01)	0.54 (.05, <.01)	.01 (.01, .16)	-.08 (.01, <.01)
Negative affect/concentration	1.33 (.02, <.01)	0.21 (.02, <.01)	.00 (.02, .33)	-.02 (.00, <.01)
Food/hunger	1.34 (.02, <.01)	0.15 (.02, <.01)	.00 (.00, .85)	.01 (.00, .03)
Positive affect	35.53 (.28, <.01)	-3.49 (.24, <.01)		-.15 (.05, <.01)

statistically significant only when the null hypothesis of no effect is rejected for both paths in the mediational pathway. In our analyses, each individual path was evaluated using a *t* statistic computed as the path estimate divided by its standard error; due to the large sample size, the statistics were approximately normal under a null hypothesis of no effect and could therefore be evaluated using ± 1.96 cutoffs at an $\alpha = .05$ significance level. The asymmetric confidence interval for the distribution of the indirect effect is constructed according to the distribution of a product of normally distributed random variables, and in this way it accommodates the nonnormal distribution of the random effect. The confidence limits can be estimated using the program PRODCLIN (MacKinnon, Fritz, Williams, & Lockwood, in press) based on the parameter estimates, standard errors, and correlation estimates across effects in the mediational pathway. The null hypothesis of no mediated effect is rejected when the confidence interval excludes zero.

Finally, the z' statistic is computed as the product of the coefficient estimates for each path in the indirect effect divided by their standard error, a test statistic that is equivalent to that used in the Sobel (1982) test. As in Mplus, we computed the standard error of the product of coefficients using the delta method (details also provided in MacKinnon et al., 2002) based on the estimates of the paths and their standard errors. The critical values for the z' test were evaluated using empirical cutoffs for the z' test statistic derived by MacKinnon et al. (2002) for conditions in which both paths in the indirect effect are zero; for our sample size, the empirical cutoffs for this statistic were approximately $\pm .97$ at an $\alpha = .05$ significance level. Although these empirical cutoffs were derived using simulations that involved continuous as opposed to binary outcomes, recent work (MacKinnon, Yoon, Lockwood, & Taylor, 2005) has suggested the distribution of the test statistic looks essentially the same with binary outcomes (assuming logistic regression is applied), implying that the same critical values should provide a good approximation even when using binary outcomes.

The joint significance, asymmetric confidence interval, and the z' tests all evaluate a null hypothesis that the indirect path is equal to zero. The z' test displays maximal power but only controls Type I error at the nominal level for null conditions in which both paths in the indirect effect are zero. By contrast, the joint significance and asymmetric confidence interval tests provide overly conservative Type I error control for certain null conditions (and consequently, reduced power), but unlike z' show no inflation of Type I error across null conditions in which only one path (but not both) equals zero (MacKinnon et al., 2002). Consequently, one can view the z' test as a liberal test for mediational effects (i.e., prone to

Type I error inflation under certain null conditions), whereas the joint significance and asymmetric confidence interval tests are somewhat conservative tests (i.e., prone to deflation of power under certain null conditions). Consistent with MacKinnon et al.'s (2002) recommendations, we consider all three tests in examining mediational effects, noting that the joint significance and asymmetric confidence interval tests may ultimately provide the most convincing evidence that both paths in the mediational pathway differ from zero.

The resulting models thus portrayed effects of treatment on relapse through two pathways—one direct and the other indirect through the mediator. In order to quantify the amount of mediation related to the indirect effect, we calculated the percentage of mediation by dividing the proportion of variance attributable to the indirect effect (the mediation effect) by the proportion of variance due to the total effect related to treatment.

Figure 3 illustrates the various paths among the composite mediator, treatment condition, and outcome. The effects of pre-quit intercept and pre-quit slope controlled for individual differences unrelated to treatment that were anticipated to influence relapse. The results in Table 5 indicate the size, direction, and significance of each individual path depicted in Figure 3 for craving, withdrawal, and positive affect, as well as the indirect effects and percentage of the total effect due to mediation. The results were consistent with the hypothesis that total withdrawal and craving during the initial week of quitting during treatment are mechanisms via which bupropion, alone or in combination with nicotine gum, exerts its effects. Each of these hypothesized mediators was supported by all three mediation tests across all three follow-up time points. Positive affect was supported as a mediator under the z' test but not the joint significance test or the asymmetric confidence interval test. Although a significant effect was detected between mediator and relapse, a significant effect from treatment to mediator was not supported under the joint significance test. Overall, the data suggested that increased levels of withdrawal and craving were both related to cessation failure and that decreased levels of positive affect may have been linked as well. However, linkages between treatment and mediator were only confirmed for withdrawal and craving. These findings were also consistent with the quantification of mediational effects. Specifically, withdrawal and craving each accounted for a significant proportion of treatment effects (33%–57% and 12%–23%, respectively); the estimated proportion accounted for due to positive affect was approximately 1%.

To further illustrate these effects, we used a stage-sequential approach to portray the mediation effect as it was synthesized over the three mediators (Collins, Graham, & Flaherty, 1998; Mc-

Table 5
Path Coefficients in the Mediation Models, Estimate (Estimate/SE)

Mediator	Follow-up occasion	Direct effect	Treatment on mediator	Mediator on outcome	Indirect effect	Total effects	Mediation percentage	Joint significance test	Asymmetric CI test (95% CI)	z' test
Craving	1 week	-.31 (-3.72) ^a	-.17 (-2.40) ^a	.34 (4.37) ^a	-.06 (-1.98) ^b	-.37	15.72	Reject null	Reject null (-.12, -.01)	Reject null
	End of treatment	-.29 (-3.53) ^a	-.17 (-2.40) ^a	.25 (3.24) ^a	-.04 (-1.68) ^b	-.33	12.78	Reject null	Reject null (-.09, -.01)	Reject null
	6 months	-.15 (-1.82)	-.17 (-2.40) ^a	.27 (3.29) ^a	-.05 (-1.85) ^b	.20	23.43	Reject null	Reject null (-.10, -.01)	Reject null
Total withdrawal	1 week	-.30 (-3.69) ^a	-.38 (-2.41) ^a	.57 (3.49) ^a	-.22 (-2.11) ^b	-.52	41.93	Reject null	Reject null (-.46, -.04)	Reject null
	End of treatment	-.29 (-3.54) ^a	-.38 (-2.41) ^a	.38 (2.31) ^a	-.14 (-1.92) ^b	-.43	33.24	Reject null	Reject null (-.34, -.01)	Reject null
	6 months	-.15 (-1.76)	-.38 (-2.41) ^a	.53 (3.00) ^a	-.20 (-1.97) ^b	-.35	57.31	Reject null	Reject null (-.45, -.03)	Reject null
Positive affect	End of treatment	-.28 (-2.74) ^a	.03 (1.46)	-.10 (-3.20) ^a	-.003 (-1.37) ^b	-.28	1.06	Retain null	Retain null (-.01, .00)	Reject null
	6 months	-.14 (-1.59)	.03 (1.46)	-.07 (-2.44) ^a	-.002 (-1.26) ^b	-.14	1.48	Retain null	Retain null (-.01, .00)	Reject null

Note. CI = confidence interval.

^a Statistically significant using z -value cutoff of ± 1.96 . ^b Statistically significant using the MacKinnon z' distribution cutoff of $\pm .97$ for a significant indirect effect (MacKinnon et al., 2002, p. 90).

to a limited degree, levels of positive affect during treatment, predicted ability to remain abstinent at multiple follow-up time points. It appears that the reason that the mediational test of positive affect failed the joint significance criterion was the relatively weak relation between treatment and the mediator (positive affect during treatment), despite the previous finding of a significant enhancement of positive affect by pharmacotherapy in HLM growth-curve modeling. Taken together, these findings suggest

that bupropion treatment affects withdrawal, craving, and, to a limited degree, positive affect early in the quit attempt, and that such effects are protective factors in the successful attainment and maintenance of abstinence up to 6 months post quit. Active pharmacotherapy reduced overall withdrawal distress, including craving, and mitigated declines in positive affect: Each of these effects appears to account for the suggested clinical benefit of pharmacotherapy (craving: 13%–23%, withdrawal: 33%–57%), but the effect due to positive affect is relatively weak (1%).

These results provide some insight into forces driving addictive tobacco use—specifically, they support a causal role of craving and withdrawal distress in motivating a return to tobacco use. This interpretation dovetails nicely with theoretical models of dependence in which negative reinforcement is a key motivator for drug use (e.g., Baker et al., 2004). These findings suggest that previous research showing a correlation between withdrawal severity and drug use outcomes (e.g., Piasecki et al., 2000, 2003) cannot be attributed to an individual difference (third) variable that produces both severe withdrawal and heightened relapse likelihood. In the present research, reduced withdrawal severity was achieved through random assignment, and nevertheless, it continued to be associated with increased ability to quit and stay quit. Moreover, the temporal ordering of the treatment, mediator, and outcome variables, as well as the use of latent mediator variables, support causal inferences regarding the role of withdrawal in precipitating smoking (Cole & Maxwell, 2003).

One could argue that the present findings do not accord strictly with a withdrawal-based account of smoking motivation because both the craving and positive affect variables might be viewed as distinct from withdrawal per se. After all, craving is not included as a tobacco withdrawal syndrome in the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*, and no formal withdrawal classification comprises anhedonia. At present there is no consensus on the constituents of the tobacco withdrawal syn-

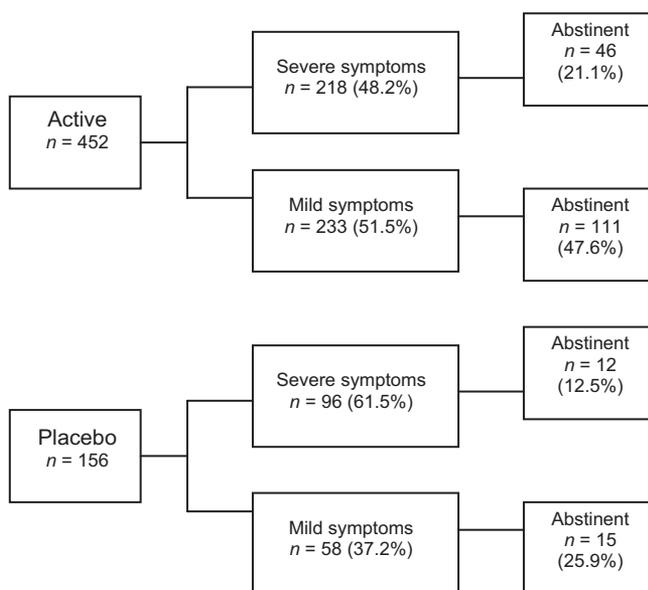


Figure 4. Stage-sequential approach to depicting the mediation of treatment effects at the end of treatment by a composite mediator. In this approach, individuals are assigned to various groups based on their status on the mediator, and then the outcome is compared among the groups.

drome. Furthermore, incentive theorists maintain that craving is part of the incentive system, not the withdrawal system (e.g., Robinson & Berridge, 1993). However, the most commonly used assessments of withdrawal feature craving/urge as a component (Hughes & Hatsukami, 1986; Welsch et al., 1999). In addition, there is clear evidence that craving increases as a function of deprivation and is correlated with other withdrawal measures (Piasecki et al., 2000; Sayette, Martin, Hull, Wertz, & Perrott, 2003). The role of anhedonia as a component of withdrawal is supported by a considerable body of research that indicates that drug deprivation in dependent animals is associated with increased thresholds for reward (Epping-Jordan, Watkins, Koob, & Markou, 1998; Watkins, Koob, & Markou, 2000). In the present research, all of the variables that were associated with significant mediational effects (e.g., craving, total withdrawal, and positive affect) also showed significant changes as a function of tobacco cessation, suggesting that they are indeed elements of the nicotine withdrawal syndrome. Thus, mediational research has the potential to reveal not only factors that are consistently affected by deprivation, but also those that share a similar or functionally congruent (homologous) relation with drug motivation. For example, craving is not only augmented by cessation, it is also a significant motivational prod to return to drug use. In sum, mediational research has the potential to elucidate the nature of withdrawal and its motivational significance.

Two of the three mediators (craving and withdrawal) identified in this study account for clinically significant portions of variance in treatment effects on outcome. The results suggest that each of the mediators accounts for some unique portion of the pharmacotherapeutic effect. The latter inference is supported by the consistent increase in treatment-symptom association as each mediator was added to a symptom composite (see Figure 4). However, the existence of significant treatment effects, after controlling for the mediation of withdrawal symptoms, indicates that other mechanisms also play a role in mediating outcomes. Thus, the current results provide some support for withdrawal and negative reinforcement models but do not show that these models suffice to explain outcomes. Other potential treatment mechanisms include a reduction in reward expectation (i.e., decreased incentive value; Robinson & Berridge, 1993), reduced stress reactivity (e.g., McCarthy et al., 2006; Shiffman & Waters, 2004), cessation fatigue (Piasecki, Fiore, McCarthy, & Baker, 2002), reduced import of smoking cues (Niaura, Rohsenow, & Binkoff, 1988; Waters et al., 2004), or withdrawal and affective dynamics that play out over a longer period of time than just 1 week post quit (Piasecki et al., 2000). How these potential mechanisms might be related to underlying neuropharmacologic effects of bupropion is currently unknown.

The stability of the mediational effects over the 6-month follow-up interval suggests that the same sorts of factors influence success and failure across the posttreatment period. This may not be due to persistence of treatment effects on the mediators, but instead due to the fact that the mediators affect smoking early in the follow-up period, and early smoking is a strong predictor of later smoking (e.g., Kenford et al., 1994).

Close inspection of the indirect paths of the mediation models (treatment to mediator and mediator to outcome) provides further insight into bupropion's effects on outcome (see Table 5). The indirect paths indicate that whereas the mediators appear to have a

strong influence on outcome, treatment exerts only modest effects on the mediators. This indicates a need to develop new treatments or use existing treatments in such a way so that they have stronger effects on these three proximal targets of treatment: craving, total withdrawal symptoms, and positive affect.

It is important to engage in a thorough evaluation of how treatment affects all of the principal determinants of abstinence outcomes, and it is equally important to identify which determinants of abstinence are not affected by treatment. These data may provide valuable proximal targets for the development of new and improved interventions. Thus, the mediational analysis framework has the potential to reveal (a) how well treatments work, (b) processes that affect clinical outcomes, (c) which of these processes are and are not affected by treatment, and (d) the degree to which these processes are affected (McCarthy et al., 2007). In addition to this yield of information, mediational analysis may be used to characterize how time courses or treatment dosages affect causal relations. For instance, the mediational framework might be used to examine how much treatment is needed to obtain an effect on a mediator, and how long such an effect provides protection against relapse. In short, this research strategy constitutes a bootstrapping approach to psychopathology as it simultaneously provides information on the nature of the disorder as well as a rational approach to treatment evaluation and development.

Limitations

In order to maximize the power of our mediation analyses and obtain solution convergence, we combined the AA and AP groups. Therefore, we did not use a pure bupropion condition for mediational analyses. However, the fact that nicotine gum had no effect on abstinence after 1 week post quit suggests that the treatment effect being mediated could be attributed to bupropion. In addition, an inspection of path coefficients in a between-groups analysis suggested similar mediational effects in the two treatment conditions. Another limitation to our mediation analyses is that we collected real-time assessment data only during the week before and the week after the quit attempt, a relatively narrow temporal window. In addition, we did not have real-time data for all of our mediators. Positive affect had the weakest mediation effect, and that may have been due to the fact that the data were collected via daily diaries versus real-time recording. Another limitation of this research is that we did not examine blood levels of bupropion or its major metabolites (hydroxybupropion, therohydrobupropion, and erythrohydrobupropion). Thus, we could not determine whether blood levels of bupropion mediated the effects of treatment condition on withdrawal suppression, which would provide more specific information on causal mechanisms.

Although we had a good representation of both White and African American participants, we had very little representation of other ethnic groups, which adversely affects our ability to generalize to other ethnic populations. It should also be noted that the results of this study may not generalize to the population of smokers at large, given that these results were obtained from smokers who were highly motivated to quit and underwent a relatively intensive research experience. Despite these limitations, we feel that this study provides important insight into the mechanisms of tobacco motivation.

Conclusion

Those individuals who were randomly assigned to bupropion treatment showed reduced overall withdrawal and craving in the first week post quit and marginally higher levels of positive affect, relative to individuals receiving placebo treatment. These effects were associated with greater ability to quit smoking and stay quit, providing support for theories that stress the role of withdrawal as motivating tobacco use and relapse in addicted smokers.

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