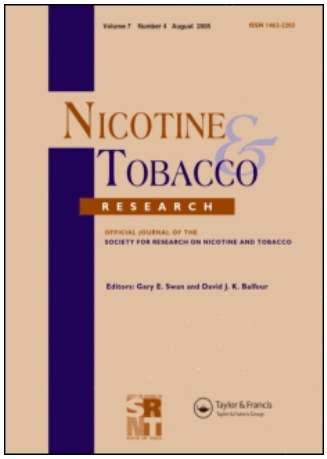

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Efficacy of bupropion alone and in combination with nicotine gum

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Efficacy of bupropion alone and in combination with nicotine gum

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In this double-blind, placebo-controlled smoking cessation treatment study, 608 participants were randomly assigned to receive active bupropion and active 4-mg gum (AA, *n*=228), active bupropion and placebo gum (AP, *n*=224), or placebo bupropion and placebo gum (PP, *n*=156). Relative to the PP group, the AA and AP groups were each significantly more likely to be abstinent at 1 week, end of treatment, and 6 months but not at 12 months postquit. After the first week postquit there were no differences in abstinence rates between the AA and AP groups. We found no significant individual difference variables that moderated outcome beyond 1 week postquit.

Introduction

Tobacco dependence is a chronic and pandemic disease (Fiore et al., 2000) that most commonly takes the form of cigarette smoking. In the United States, more than one-fifth of all adults smoke cigarettes (Centers for Disease Control and Prevention [CDC], 2004, 2005) and approximately 15 million smokers make a quit attempt every year (CDC, 2002, 2004). Of these, fewer than 5% are able to maintain long-lasting abstinence (CDC, 2002). Smokers can increase the odds of quitting successfully by using cessation aids in their quit attempts (e.g., pharmacotherapy, counseling; Fiore et al., 2000), and over time, an increasing percentage of smokers have used such aids (e.g., Pierce & Gilpin, 2002; Solberg et al., 2001; Zhu, Melcer, Sun, Rosbrook, & Pierce, 2000).

Even with effective smoking cessation aids, only about 15%–30% of smokers achieve long-term abstinence in a given quit attempt (Fiore et al., 2000). Therefore, it is vital to develop more effective cessation aids and more effective strategies for using such aids. One promising option for improving tobacco dependence treatment is combination pharmacotherapy. The 2000 Public Health Service guideline (Fiore et al., 2000) recommended combination pharmacotherapies on the basis of a meta-analysis that showed that combinations were more efficacious than single drugs by themselves (monotherapies; see also Richmond & Zwar, 2003). However, the Public Health Service guideline research addressed only combinations of different nicotine replacement therapies (NRTs). Very little research has been done on combination therapies including bupropion, which has been shown to be an effective treatment when used by itself. The present study is a randomized clinical trail evaluating the efficacy of a combination of two first-line pharmacotherapies, bupropion SR and 4-mg nicotine gum, compared with bupropion SR alone and a double placebo-controlled condition.

Although research strongly supports the efficacy of both bupropion and nicotine gum as monotherapies (Fiore et al., 2000), this is the first study to examine the efficacy of combining the two. Previous combination pharmacotherapy research has shown that adding the nicotine patch (a steady-state NRT) to bupropion did not improve cessation rates beyond those found with bupropion alone (Jorenby et al., 1999). In this study, we hypothesized that combining a non-nicotine pharmacotherapy (i.e., bupropion)

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with an ad lib NRT (i.e., nicotine gum) would improve abstinence rates. As an ad lib pharmacotherapy, the nicotine gum allows smokers to respond acutely to stressors or strong temptations by using gum. Moreover, we hypothesized that the two drugs might have additive or synergistic effects because they appear to act via different neuropharmacological mechanisms (Ascher et al., 1995; Ferry & Johnston, 2003; Shiffman et al., 2003). We also wanted to examine the effect of this combination pharmacotherapy on weight gain during smoking cessation.

Tobacco dependence treatment could be improved if treatments could be assigned to the individuals for whom they would be most effective. Therefore, a second aim of this research was to explore potential moderators of treatment effects, in particular gender and tobacco dependence. Some data suggest that NRT produces differential abstinence rates in men and women, such that women attain lower cessation rates than do men (e.g., Bohadana, Nilsson, Rasmussen, & Martinet, 2003; Wetter et al., 1999). However, evidence indicates that bupropion may eliminate this gender discrepancy (Collins et al., 2004; Scharf & Shiffman, 2004; Smith et al., 2003). The present study examined whether bupropion alone, or the bupropion plus gum combination, produced differential benefit in the two sexes. Tobacco dependence is another important, potential moderator. Measures of tobacco dependence (e.g., Fagerström Tolerance Questionnaire; Fagerström, 1978) have been shown to predict differential response to treatment (Fagerström & Schneider, 1989). The present study comprised several different measures of dependence that were examined for relations with treatment effects. We also explored other potential moderators, such as age, history of depression, race, and length of previous quit attempts.

In sum, this study had two main study goals: (a) to determine the efficacy of the combination of bupropion and nicotine gum, bupropion alone, and a placebo condition in promoting abstinence from smoking and (b) to identify moderators of treatment effects, such as gender or tobacco dependence, that might be used to develop treatment algorithms.

Method

Participants

Participants were recruited through television, 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 breast-feeding and agreed to take 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, including a physical examination and a carbon monoxide (CO) breath test (excluded if CO$<$10 ppm). Participants also completed health-screening questionnaires (i.e., Primary Care Evaluation of Mental Disorders; Spitzer et al., 1994; Center for Epidemiologic Studies Depression Scale [CES-D]; Radloff, 1977) to assess for medical or psychological exclusion criteria, including CES-D scores greater than 16, heavy alcohol use, history of eating disorders, and suicidality. Finally, participants completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), the Nicotine Dependence Syndrome Scale (Shiffman, Waters, & Hickcox, 2004), the Tobacco Dependence Screener (Kawakami, Takatsuka, Inaba, & Shimizu, 1999), and the Wisconsin Inventory of Smoking Dependence Motives (Piper et al., 2004).

At the baseline session, eligible participants were randomized to one of the three treatment conditions: active bupropion SR (150 mg, twice daily) plus active 4-mg nicotine gum (AA, n=228); active bupropion SR plus placebo nicotine gum (AP, n=224); or placebo bupropion SR plus placebo gum (PP, n=156). The PP group was considerably smaller than the two active treatments so that there would be more power to detect a difference between the active groups, which was hypothesized to be a smaller effect than an active versus placebo comparison. Randomization was conducted in double-blind fashion using blocked randomization within each of the 10 cohorts. Participants received brief (10-min) smoking cessation counseling during which they set a quit date for the following week and received their study medications, which they were instructed to use in a manner consistent with the package inserts. Specifically, participants were instructed to begin taking their study pills a week before their target quit date and continue taking the pills for 9 weeks (8 weeks postquit) and to begin chewing their study gum on their quit date and continue using the gum for 8 weeks. Staff encouraged participants to chew as many as to 12 pieces of gum per day to cope with withdrawal symptoms and aid their quit attempt. Finally, participants provided a blood sample for cotinine analysis.

After the baseline session, participants attended one session per week for 4 weeks and then two more sessions every other week. They received brief counseling at both the quit date session and the first postquit session (in addition to the baseline session) for a total of three 10-min counseling sessions over 3 weeks. The counseling, provided by bachelor-degree-level staff, was designed to provide the most effective elements recommended by the Public Health Service guideline: intratreatment social support, information and problem solving, and aid in seeking extratreatment social support (Fiore et al., 2000). Counseling sessions were audiotaped periodically so that a licensed clinical psychologist could assess adherence to the counseling protocol. At the remaining sessions, participants completed questionnaires, had their vital signs assessed, and received study medications.

Data collection

Data regarding smoking, vital signs (e.g., weight, blood pressure), 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 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. Participants also carried cellular phones for 2 weeks, centered around the quit date, to collect real-time data on symptoms and events.

Follow-up

Participants were followed-up monthly after treatment via telephone until relapse. Relapse was defined as smoking for 3 days in a row. We used a 3-day criterion for relapse based on our previous research (e.g., Zelman, Brandon, Jorenby, & Baker, 1992). Subsequently, a workgroup proposed that 7 consecutive days should be the definition of treatment failure (Hughes et al., 2004). During follow-up calls participants completed a smoking calendar, similar to the timeline follow-back method for alcohol use (Sobell & Sobell, 1992), in which they reported all smoking during the previous month (or since previous contact) as well as use of other smoking cessation aids. Follow-up calls also solicited ratings of withdrawal symptoms, feeling fatigued or tired of trying to quit, confidence in ability to smoke and not return to smoking, motivation to stay quit based on the individual's experiences during the previous 7 days, and suicidal ideation.

Follow-up via telephone was attempted with all participants at 6 and 12 months postquit. During the 6- and 12-month follow-up calls all participants answered questions about smoking, suicidality, withdrawal, and affect. Participants who reported 7-day point-prevalence abstinence (no smoking, not even a puff, during the 7 days prior to the follow-up call) at their 6- or 12-month follow-up calls were scheduled to return to the clinic and provide either a breath sample for CO analysis (6 and 12 months) or a blood sample for cotinine analysis (12 months). Participants who could not be reached at follow-up were considered to be smoking for the purposes of follow-up analyses. Both 7-day point-prevalence abstinence and continuous abstinence were used as outcome measures.

Power

Using a two-tailed power analysis with alpha equal to .05, this study was adequately powered to detect approximately a 12% difference in abstinence rates among the three treatment conditions (AA, AP, PP). Power calculations were based on the assumption that approximately 30% of participants receiving active bupropion alone would be abstinent at 12 months and that only 15% of the participants in the double placebo condition would be abstinent at 12 months (Hurt et al., 1997; Jorenby et al., 1999). We assumed that using 4-mg nicotine gum would result in abstinence rates of approximately 40% at 12 months (Herrera et al., 1995; Kornitzer, Kittel, Dramaix, & Bourdoux, 1997; Tonnesen et al., 1988).

Results

Study enrollment began in 2001 and was completed in October 2002 (Figure 1). Data collection was completed in January 2004. All analyses were conducted using SPSS version 14.0. All analyses were intent-to-treat unless otherwise noted.

Participant characteristics

A total of 608 smokers (57.9% women) participated in this study (see Table 1 for demographic information). Treatment conditions did not differ significantly ($p>.05$) on any demographic variables or tobacco dependence indicators (e.g., FTND, cigarettes smoked per day) or depression symptoms (e.g., CES-D score; data not shown). In addition, during treatment we found no differential attrition across treatment conditions ($\chi^2=2.86$, $p=.24$). At 73.1% of study visits it was judged that participants were taking their pills as directed by study staff (i.e., they returned the correct number of pills plus or minus two) and compliance did not differ among treatment conditions ($\chi^2=3.69$, $p=.16$). Participants across the

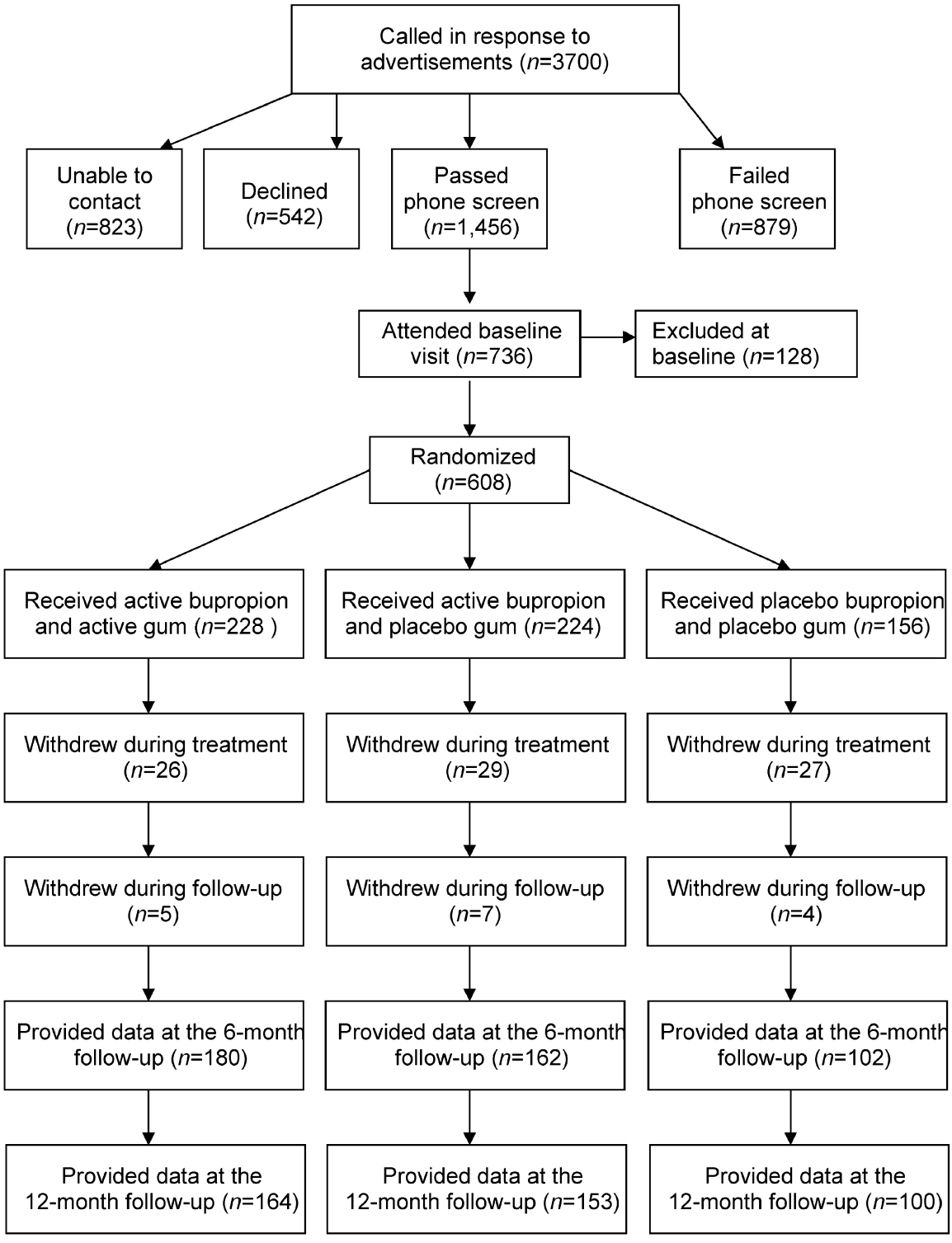

Figure 1. CONSORT figure of participant flow through the study.

three treatment conditions did not differ in gum use: $M=4.17$ pieces/day ($SD=3.4$), $F(2, 412)=.26$, $p=.77$. A total of 781 adverse events were reported in this study. The most common adverse events were insomnia (4.73% of all adverse events), headache (2.59% of all adverse events), and cold symptoms (2.57% of all adverse events).

Efficacy

The first hypothesis was that active pharmacotherapy (AA and AP groups) would improve cessation rates over placebo. A Cox regression analysis of latency to relapse (defined as number of days to 3 consecutive days of smoking) conducted using 12-month

Table 1. Participant demographics.

	Total (N=608)		Active bupropion, active gum (n=228)		Active bupropion, placebo gum (n=224)		Placebo bupropion, placebo gum (n=156)	
Characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Women	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
Black	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: < US$25,000	174	29.2	65	29.1	69	31.2	40	26.5
Household income: US$50,000 or greater	208	34.9	71	31.9	80	36.2	57	37.7
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age, years	41.78	11.34	41.14	11.30	42.26	11.41	42.03	11.31
Age at first cigarette, years	13.83	3.95	13.71	4.10	13.69	3.83	14.21	3.88
Cigarettes smoked per day	22.44	9.87	22.09	8.89	23.39	10.81	21.57	9.75
Number of previous quit attempts	6.06	13.28	6.03	13.55	5.61	10.56	6.70	15.98
FTND score	5.64	2.13	5.69	2.20	5.70	2.04	5.48	2.16
Baseline carbon monoxide level, ppm	27.11	11.68	26.26	11.62	27.25	11.16	28.15	12.48

Note. FTND, Fagerström Test for Nicotine Dependence; *SD*, standard deviation.

follow-up data indicated that individuals who received active pharmacotherapy were statistically more likely to be abstinent than were individuals who received only placebo pharmacotherapy (AA: $Wald$=11.64, OR=.64, p<.01; AP: $Wald$=7.44, OR=.70, p<.01; see Figure 2 for survival curves). Logistic regression was used to predict CO-confirmed 7-day point-prevalence abstinence for the four different time points with the double placebo condition (PP) coded as the baseline condition. See Table 2 for abstinence rates. Analyses revealed that at 1 week postquit both the AA ($Wald$=23.41, OR=3.12, p<.01) and AP ($Wald$=10.38, OR=2.15, p<.01) groups were significantly more likely to be abstinent than the PP group. These results also were true at the end of treatment (AA: $Wald$=18.44, OR=2.95, p<.01; AP: $Wald$=9.17, OR=2.17, p<.01) and at 6 months postquit (AA: $Wald$=3.78, OR=1.71, p=.05; AP: $Wald$=5.92, OR=1.88, p=.02). At 12 months postquit the active treatment conditions no longer differed statistically from the double placebo condition (AA: $Wald$=3.21, OR=1.67, p=.07; AP: $Wald$=1.85, OR=1.48, p=.17).

To determine whether combining 4-mg nicotine gum with active bupropion (AA) improved cessation rates above those produced by active bupropion alone (AP), we used logistic regression to analyze biochemically confirmed 7-day point-prevalence abstinence. The AA condition was coded as the baseline condition. Relative to the individuals in the AA condition, those in the AP condition were significantly less likely to be abstinent at 1 week postquit ($Wald$=3.74, OR=.69, p=.05). However, we found no statistical differences in abstinence rates between the AA and AP groups at the end-of-treatment, 6-month postquit, or 12-month postquit time points. The lack of significant differences between the two groups beyond the first week was confirmed in survival analyses.

In addition to analyzing relapse data, we examined latency to relapse (smoking at least one cigarette on 3 consecutive days) following a lapse (smoking a cigarette, even one puff). On average, participants managed to delay relapse for 47.57 days (SD=105.37) after having their first cigarette following their quit attempt. We found that 65.7% of individuals who relapsed by the end of the study returned to daily smoking the same day they lapsed. Results of a linear regression indicated that treatment condition did not predict latency to relapse after a lapse nor did gender, depressive symptoms, or nicotine dependence.

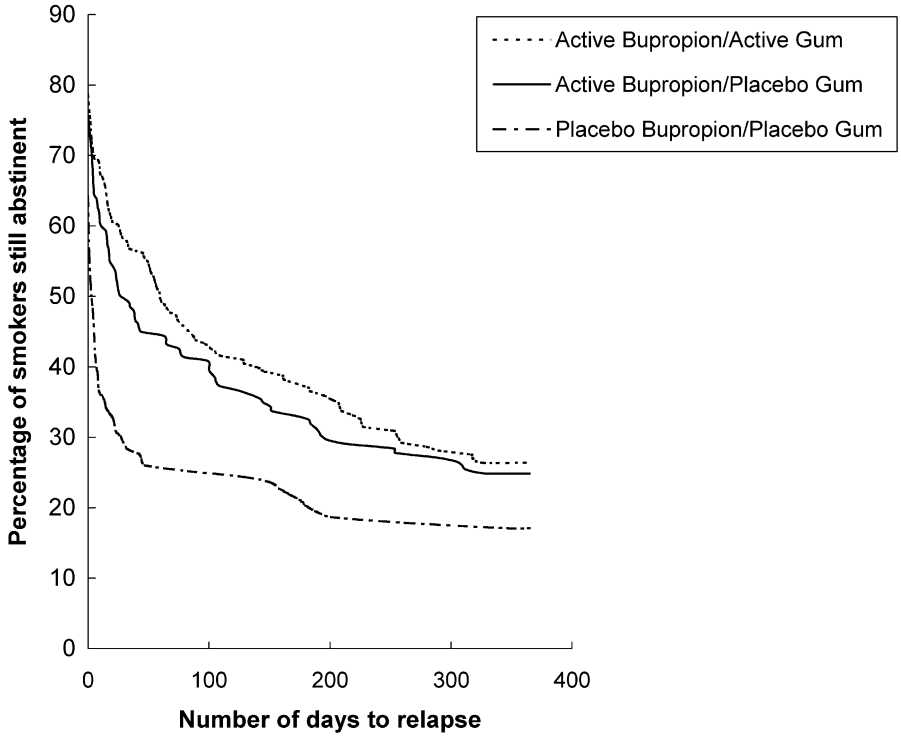

Figure 2. Survival curves for the three treatment conditions.

Another outcome of interest was whether particular pharmacotherapies prevent or delay weight gain following a smoking cessation attempt. A univariate analysis of variance revealed no significant effects of treatment condition on weight gain between baseline and the end of treatment, with participants gaining an average of 1.53 kg (SD=2.41). This also was true when weight was analyzed only in participants who were abstinent at the end of treatment. We found a main effect of gender such that women gained fewer kilograms by the end of treatment (M=1.23, SD=2.38) than did men (M=1.90, SD=2.41), t (417)=2.85, $p<.05$; however, the gender × treatment interaction was not statistically significant.

Moderation of treatment effects

Gender, age, race, number of cigarettes smoked per day, length of longest previous quit attempt, number of quit attempts, history of depression, and dependence measures (FTND, Wisconsin Inventory of Smoking Dependence Motives-68 scales [WISDM-68], and Tobacco Dependence Screener) were tested as moderators using logistic regression. We modeled the main effects of treatment and the individual difference variables and the treatment × individual difference interactions on smoking status at all four follow-up time points (1 week, end of treatment, 6 months, and 12 months). We found significant main effects of gender at three follow-up time points, after accounting for treatment, such that women were significantly more likely to be smoking than were men (1 week: $Wald$=7.97, OR=.61, p=.01; end of treatment: $Wald$=5.75, OR=.65, p=.02; 6 months: $Wald$=7.19, OR=.59, p=.01). There was a significant gender × treatment interaction, but only at 1 week postquit ($Wald$=4.46, OR=.61, p=.01). Women who received placebo pharmacotherapy were significantly

Table 2. Seven-day point-prevalence abstinence rates (percent) at various follow-up time points for each experimental condition.

	Active bupropion, active gum (n=228)					Active bupropion, placebo gum (n=224)					Placebo bupropion, placebo gum (n=156)				
Time point	Total (228)	Male (101)	Female (127)	White (173)	Black (46)	Total (224)	Male (89)	Female (135)	White (165)	Black (50)	Total (156)	Male (66)	Female (90)	White (114)	Black (36)
1 week	46.5	50.5	43.3	50.3	32.6	37.5	40.4	35.6	39.4	32.0	21.8	36.4	11.1	21.9	16.7
End of treatment	38.2	41.6	35.4	41.6	23.9	31.3	38.2	26.7	32.1	30.0	17.3	22.7	13.3	17.5	19.4
6 months	22.8	24.8	21.3	26.0	10.9	24.6	33.7	18.5	27.9	16.0	14.7	19.7	11.1	15.8	13.9
12 months	20.6	22.8	18.9	23.1	8.7	18.8	25.8	14.1	20.0	16.0	13.5	19.7	8.9	14.9	8.3

more likely to be smoking (88.9%) than were men who received active (54.2%) or placebo (63.6%) pharmacotherapy or women who received active pharmacotherapy (60.7%). Length of previous quit attempts, race, FTND, the WISDM-68 automaticity subscale, the WISDM-68 social/environmental goads subscale, and the WISDM-68 tolerance subscale were all significantly related to outcome, but we found no significant interactions between these variables and treatment. There were no moderating effects for any individual difference variables.

Discussion

Data from this large clinical trial constitute additional evidence that bupropion enhances smoking cessation rates for at least 6 months following treatment initiation. Individuals who received active bupropion were approximately 1.5 times more likely to be abstinent at 1 week, end of treatment, and 6 months postquit than were those who received placebo. However, by the end of the first week, fewer than half of the individuals receiving active medication were abstinent. Moreover, by 1-year postquit, the effect of bupropion had dwindled to nonsignificance. Therefore, these results underscore the need to develop interventions for tobacco use and dependence that yield larger and more durable effects.

Our hypothesis that nicotine gum would augment the efficacy of bupropion was not supported when long-term outcomes were examined. Although gum was associated with a 10% boost in abstinence rates at 1 week postquit, no significant effect of gum was detected at later time points. On average, participants in all three treatment groups reported chewing four pieces of gum per day, which is at the low end of the recommended dose. If withdrawal amelioration is a mechanism via which nicotine gum exerts its effects, it is possible that participants would have achieved better clinical success if they had used more gum. However, great efforts were made to encourage high levels of gum use in the present study. As other researchers have found, it may be difficult to foster high levels of gum use among quitting smokers (e.g., Fortmann & Killen, 1995; Glover et al., 1996; Mooney, Babb, Jensen, & Hatsukami, 2005).

As many previous studies have shown, women were less likely to stop smoking than were men (Bjornson et al., 1995; Community Intervention Trial for Smoking Cessation Research Group, 1995; Wetter et al., 1999). As in past research (cf., Smith et al., 2003), some evidence indicated that bupropion neutralizes this gender difference but this interaction between gender and treatment was significant only at the 1-week mark. In addition, although some individual difference variables were related to smoking outcome, including length of previous quit attempts, race, FTND, the WISDM-68 automaticity subscale, the WISDM-68 social/environmental goads subscale, and the WISDM-68 tolerance subscale, none of these variables yielded significant moderation effects. Thus the present research provides little insight into how individual difference variables can be used to develop treatment assignment algorithms.

Limitations

Limitations to this study should be considered. No group received only nicotine gum. Therefore, we were unable to assess the relative efficacy of nicotine gum alone. Although White and Black populations were well represented, other racial or ethnic groups were not, which adversely affects our ability to generalize to these other populations. Also, 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.

Conclusion

The present study supports the efficacy of bupropion as a smoking cessation pharmacotherapy, but it does not support the use of nicotine gum as a bupropion adjuvant. Thus, although strong evidence indicates that combinations of NRT drugs enhance smoking cessation rates (Fiore et al., 2000; Richmond & Zwar, 2003), there is increasing evidence that NRT does not boost the efficacy of bupropion treatment. Unfortunately, this research also demonstrates the pressing need for continued research aimed at developing new pharmacotherapies for smoking cessation; most smokers receiving active treatments had begun to smoke by the first week post-treatment. Women, in particular, were at heightened risk for cessation failure.

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