Published in final edited form as:

Nicotine Tob Res. 2007 September ; 9(9): 947–954. doi:10.1080/14622200701540820.

Efficacy of bupropion alone and in combination with nicotine gum

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Abstract

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 one week, end of treatment and six months, but not twelve months post-quit. After the first week post-quit there were no differences in abstinence rates between the AA and AP groups. There were no significant individual difference variables that moderated outcome beyond one week post-quit.

Keywords

bupropion; nicotine gum; smoking cessation

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, 2004, 2005) and approximately 15 million smokers make a quit attempt every year (Centers for Disease Control, 2002, 2004). Of these, fewer than 5% are able to maintain long-lasting abstinence (Centers for Disease

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This research was conducted at the University of Wisconsin, Madison

Control, 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 monotherapies (a single drug by itself; 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 comprising bupropion – which has been shown to be an effective treatment when used by itself. The current study is a randomized clinical trial evaluating the efficacy of a combination of two first-line pharmacotherapies, bupropion SR and 4-mg nicotine gum, compared to bupropion SR alone and a double placebo control condition.

While 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) with an *ad lib* nicotine replacement therapy (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 neuropharmacologic 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, there is evidence that bupropion may eliminate this gender discrepancy (Collins et al., 2004; Smith et al., 2003; Scharf & Shiffman, 2004). This research will examine whether bupropion alone, or the bupropion + gum combination, produces 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 (Fagerstrom & Schneider, 1989). The current 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, there are two main study goals: 1) determine the efficacy of the combination of bupropion and nicotine gum, bupropion alone, and a placebo condition in promoting abstinence from smoking; and 2) identify moderators of treatment effects, such as gender or tobacco dependence, that might be used to develop treatment algorithms.

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 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 parts per million). Participants also completed health-screening questionnaires (i.e., Primary Care Evaluation of Mental Disorders, Spitzer et al., 1994; Center for Epidemiologic Studies Depression Scale, Radloff, 1977) to assess for medical or psychological exclusion criteria including: Center for Epidemiologic Studies Depression Scale scores greater than 16, heavy alcohol use, history of eating disorders, and suicidality. Finally, participants completed the Fagerström Test of Nicotine Dependence (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, b.i.d.) + Active 4-mg nicotine gum (AA, $n = 228$); Active bupropion SR + Placebo nicotine gum (AP, $n = 224$); or Placebo bupropion SR + Placebo gum (PP, $n = 156$). The PP group is considerably smaller than the two active treatments so that there is 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-minute) smoking cessation counseling during which they set a quit date for the following week and 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 nine weeks (eight weeks post-quit) and to begin chewing their study gum on their quit day and continue using the gum for eight weeks. Staff encouraged participants to chew up 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 four weeks and then two more sessions every other week. They received brief counseling at both the Quit Day Session and the first post-quit session (in addition to the Baseline Session) for a total of three 10-minute counseling sessions over three weeks. The counseling, provided by bachelor-degree-level staff, was designed to provide the most effective elements recommended by the Public Health Service Guideline: intra-treatment social support, information and problem-solving, and aid in seeking extra-treatment social support (Fiore et al., 2000). Counseling sessions were periodically audiotaped 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 nine 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 two 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 three days in a row. We used a three-day criterion for relapse based on our previous research (e.g., Zelman, Brandon, Jorenby & Baker, 1992). Subsequently, an workgroup proposed that seven consecutive days should be the definition of treatment failure (Hughes et al., 2003). During follow-up calls participants completed a smoking calendar, similar to the Timeline Followback 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/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 seven days and suicidal ideation.

Follow-up via telephone was attempted at six and 12 months post quit-day, with all participants. During the six- and 12-month follow-up calls all participants answered questions about smoking, suicidality, withdrawal, and affect. Participants who reported 7-day point prevalent abstinence (no smoking, not even a puff, during the seven 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 carbon monoxide analysis (six and twelve 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 analyses with $\alpha=.05$, this study is 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 will be abstinent at 12 months and that only 15% of the participants in the double placebo condition will be abstinent at 12 months (see 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, Kittle, Dramaix, & Bourdous, 1997; Tonnesen et al., 1988).

Results

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

Participant Characteristics

Six hundred and eight 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., Fagerström Test of Nicotine Dependence, cigarettes smoked per day) or depression symptoms (e.g., Center for Epidemiologic Studies Depression Scale score; data not shown). In addition, during treatment there was 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 amongst treatment conditions ($\chi^2 = 3.69, p = .16$). Participants across the three treatment conditions did not differ in gum use ($M = 4.17$ pieces per 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 three consecutive days of smoking) conducted using 12-month 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 post-quit, 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 post-quit (AA: $Wald = 3.78, OR = 1.71, p = .05$; AP: $Wald = 5.92, OR = 1.88, p = .02$). At 12 months post-quit 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) logistic regression was used to analyze biochemically-confirmed 7-day point prevalence abstinence. The AA condition was coded as the baseline condition. Results revealed that relative to the individuals in the AA condition, those in the AP condition were significantly less likely to be abstinent at 1 week post-quit ($Wald = 3.74, OR = .69, p = .05$). However, there were no statistical differences in abstinence rates between the AA and AP groups at the end of treatment, 6-month post-quit or 12-month post-quit 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 three consecutive days) following a lapse (smoking a cigarette, even one puff).

On average, participants managed to delay relapse for 47.57 ($SD = 105.37$) days 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.

Another outcome of interest is whether particular pharmacotherapies prevent or delay weight gain following a smoking cessation attempt. A univariate ANOVA 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 kilograms ($SD = 2.41$). This was also true when weight was analyzed only in participants who were abstinent at the end of treatment. There was 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 by 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 (Fagerström Test of Nicotine Dependence, 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 by individual difference interactions on smoking status at all four follow-up time points (one week, end of treatment, six months and twelve months). There were significant main effects of gender at all three follow-up time points, after accounting for treatment, such that women were significantly more likely to be smoking than were men (one week: $Wald = 7.97$, $OR = .61$, $p = .01$; end of treatment: $Wald = 5.75$, $OR = .65$, $p = .02$; six months: $Wald = 7.19$, $OR = .59$, $p = .01$). There was a significant gender x treatment interaction, but only at one week post-quit ($Wald = 4.46$, $OR = .61$, $p = .01$). Women who received placebo pharmacotherapy were significantly 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, the Fagerström Test of Nicotine Dependence, the WISDM-68 Automaticity subscale, the WISDM-68 Social/Environmental Goals subscale, and the WISDM-68 Tolerance subscale were all significantly related to outcome, but there were 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 six months following treatment initiation. Individuals who received active bupropion were approximately 1.5 times more likely to be abstinent at one week, the end of treatment, and six months post-quit 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 post-quit, the effect of bupropion had dwindled to non-significance. 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 one week post-quit, 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 this 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 (c.f., Smith et al., 2003), there was some evidence that bupropion neutralizes this gender difference but this interaction between gender and treatment was significant only at the 1-week mark. In addition, while some individual difference variables were related to smoking outcome, including length of previous quit attempts, race, the Fagerström Test of Nicotine Dependence, the WISDM-68 Automaticity subscale, the WISDM-68 Social/Environmental Goads subscale, and the WISDM-68 Tolerance subscale, none of these yielded significant moderation effects. Thus, this research provides little insight into how individual difference variables can be used to develop treatment assignment algorithms.

Limitations

There are limitations to this study. No group received only nicotine gum. Therefore, we were unable to assess the relative efficacy of nicotine gum alone. Although we have a good representation of both Caucasian and African-American participants, we have very little representation of other racial or ethnic groups, which adversely affects our ability to generalize to other racial or 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.

Conclusion

This 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, while there is strong evidence 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.

Acknowledgments

This research was supported by NIH Grants #P50-CA84724-05 and # P50-DA0197-06.

References

- Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, Golden RN, Martin P, Potter WZ, Richelson E, et al. Bupropion: A review of its mechanisms of antidepressant activity. *Journal of Clinical Psychiatry* 1995;56:395–401. [PubMed: 7665537]
- Baker, TB.; Morse, E.; Sherman, JE. The motivation to use drugs: A psychobiological analysis of urges. In: Rivers, C., editor. *Nebraska symposium on motivation*. Lincoln: University of Nebraska Press; 1987. p. 257-323.

- Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: An affective processing model of negative reinforcement. *Psychological Review* 2004;111:33–51. [PubMed: 14756584]
- Bjornson W, Rand C, Connett JE, Lindgren P, Nides M, Pope F, Buist AS, Hoppe-Ryan C, O'Hara P. Gender differences in smoking cessation after three years in the Lung Health Study. *American Journal of Public Health* 1995;85:223–230. [PubMed: 7856782]
- Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Gender differences in quit rates following smoking cessation with combination nicotine therapy: Influence of baseline smoking behavior. *Nicotine & Tobacco Research* 2003;5:111–116. [PubMed: 12745512]
- Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2003. *Morbidity and Mortality Weekly Report* 2005;54:509–513. [PubMed: 15917735]
- Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2002. *Morbidity and Mortality Weekly Report* 2004;53:427–431. [PubMed: 15163928]
- Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2000. *Morbidity and Mortality Weekly Report* 2002;51:642–645. [PubMed: 12186222]
- Collins BN, Wileyto EP, Patterson F, Rukstalis M, Audrain-McGovern J, Kaufmann V, Pinto A, Hawk L, Niaura R, Epstein LH, Lerman C. Gender differences in smoking cessation in a placebo-controlled trial of bupropion with behavioral counseling. *Nicotine & Tobacco Research* 2004;6:27–37. [PubMed: 14982685]
- Community Intervention Trial for Smoking Cessation Research Group. Community intervention trial for smoking cessation (COMMIT): I. Cohort results from a four-year community intervention. *American Journal of Public Health* 1995;85:183–192. [PubMed: 7856777]
- Fagerström KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behaviors* 1978;3:235–241. [PubMed: 735910]
- Fagerström KO, Schneider NG. Measuring nicotine dependence: A review of the Fagerström Tolerance Questionnaire. *Journal of Behavioral Medicine* 1989;12:159–181. [PubMed: 2668531]
- Ferry L, Johnston J. Efficacy and safety of bupropion SR for smoking cessation: Data from clinical trials and five years of postmarketing experience. *International Journal of Clinical Practice* 2003;57:224–230. [PubMed: 12723728]
- Fiore MC.; Bailey, WC.; Cohen, SJ., et al. Treating tobacco use and dependence. Rockville, MD: US Department of Health and Human Services. Public Health Service; 2000.
- Fortmann SP, Killen JD. Nicotine gum and self-help behavioral treatment for smoking relapse prevention: Results from a trial using population-based recruitment. *Journal of Consulting and Clinical Psychology* 1995;63:460–468. [PubMed: 7608359]
- Glover ED, Sachs DPL, Stitzer ML, Rennard SI, Wadland WC, Pomerleau OF, Nowak RT, Daughton DM, Glover PN, Hughes JR, Gross J. Smoking cessation in highly dependent smokers with 4 mg nicotine polacrilex. *American Journal of Health Behavior* 1996;20:319–332.
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction* 1991;86:1119–1127. [PubMed: 1932883]
- Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerstrom KO. Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program. *Chest* 1995;108:447–51. [PubMed: 7634882]
- Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine & Tobacco Research* 2004;5:13–25. [PubMed: 12745503]
- Hurt RD, Sachs DPL, Glover ED, Offord KP, Johnston A, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, Croghan IT, Sullivan PM. A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine* 1997;337:1195–1202. [PubMed: 9337378]
- Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine* 1999;340:685–91. [PubMed: 10053177]

- Kawakami N, Takatsuka N, Inaba S, Shimizu H. Development of a screening questionnaire for tobacco/nicotine dependence according to ICD-10, DSM-III-R, and DSM-IV. *Addictive Behaviors* 1999;24:155–166. [PubMed: 10336098]
- Kornitzer M, Kittel F, Dramaix M, Bourdoux P. A double blind study of 2 mg versus 4 mg nicotine-gum in an industrial setting. *Journal of Psychosomatic Research* 1987;31:171–6. [PubMed: 3295212]
- MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods* 2002;7:83–104. [PubMed: 11928892]
- Mooney M, Babb D, Jensen J, Hatsukami D. Interventions to increase use of nicotine gum: A randomized, controlled, single-blind trial. *Nicotine & Tobacco Research* 2005;7:565–579. [PubMed: 16085528]
- Niaura RS, Rohsenow DJ, Binkoff JA. Relevance of cue reactivity to understanding alcohol and smoking relapse. *Journal of Abnormal Psychology* 1988;97:133–152. [PubMed: 3290304]
- Pierce JP, Gilpin EA. Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. *JAMA* 2002;288:1260–1264. [PubMed: 12215133]
- Piper ME, Federman EB, Piasecki TM, Bolt DM, Smith SS, Fiore MC, Baker TB. A multiple motives approach to tobacco dependence: The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). *Journal of Consulting and Clinical Psychology* 2004;72:139–154. [PubMed: 15065950]
- Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1:385–401.
- Richmond R, Zwar N. Review of bupropion for smoking cessation. *Drug & Alcohol Review* 2003;22:203–20. [PubMed: 12850907]
- Scharf D, Shiffman S. Are there gender differences in smoking cessation, with and without bupropion? Pooled- and meta-analyses of clinical trials of bupropion SR. *Addiction* 2004;99:1462–1469. [PubMed: 15500599]
- Shiffman S, Johnston AJ, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA, Gnys M, Evoniuk G, DeVeugh-Geiss J. The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacology* 2000;148:33–40. [PubMed: 10663415]
- Shiffman S, Shadel WG, Niaura R, Khayrallah MA, Jorenby DE, Ryan CF, Ferguson CL. Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. *Psychopharmacology* 2003;166:343–350. [PubMed: 12601502]
- Shiffman S, Waters AJ, Hickcox M. The Nicotine Dependence Syndrome Scale: A multidimensional measure of nicotine dependence. *Nicotine & Tobacco Research* 2004;6:327–349. [PubMed: 15203807]
- Smith SS, Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Jamerson B, Fiore MC, Baker TB. Targeting smokers at increased risk for relapse: Treating women and those with a history of depression. *Nicotine & Tobacco Research* 2003;5:99–109. [PubMed: 12745511]
- Sobell, LC.; Sobell, MB. Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In: Litten, RZ.; Allen, J., editors. *Measuring alcohol consumption: Psychosocial and biological methods*. Totowa, NJ: Humana Press; 1992. p. 41-72.
- Solberg LI, Boyle RG, Davidson G, Magnan S, Link Carlson C, Alesci NL. Aids to quitting tobacco use: How important are they outside controlled trials? *Preventive Medicine* 2001;33:53–58. [PubMed: 11482996]
- Spitzer RL, Williams JBW, Kroenke K, Linzer M, deGruy FV, Hahn S, Brody D, Johnson JG. Utility of a new procedure for diagnosing mental disorders in primary care: The PRIME-MD 1000 study. *JAMA* 1994;272:1749–1456. [PubMed: 7966923]
- Stone AA, Shiffman S. Ecological momentary assessment (EMA) in behavioral medicine. *Annals of Behavioral Medicine* 1994;16:199–202.
- Tonnesen P, Fryd V, Hansen M, Helsted J, Gunnarsen AB, Forchhammer H, Stockner M. Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. *New England Journal of Medicine* 1988;318:15–18. [PubMed: 3336380]

- Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology* 1988;54:1063–1070. [PubMed: 3397865]
- Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Development and validation of the Wisconsin Smoking Withdrawal Scale. *Experimental and Clinical Psychopharmacology* 1999;7:354–361. [PubMed: 10609970]
- Wetter DW, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Baker TB. Gender differences in smoking cessation. *Journal of Consulting and Clinical Psychology* 1999;67:555–562. [PubMed: 10450626]
- Zelman DC, Brandon TH, Jorenby DE, Baker TB. Measures of affect and nicotine dependence predict differential response to smoking cessation treatments. *Journal of Consulting & Clinical Psychology* 1992;60:943–52. [PubMed: 1460156]
- Zhu SH, Melcer T, Sun J, Rosbrook B, Pierce JP. Smoking cessation with and without assistance: A population-based analysis. *American Journal of Preventive Medicine* 2000;18:305–311. [PubMed: 10788733]

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

Figure 2.
Survival curves for the three treatment conditions

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)	
	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
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 or greater	208	34.9	71	31.9	80	36.2	57	37.7
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	41.78	11.34	41.14	11.30	42.26	11.41	42.03	11.31
Age at first cigarette	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
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 CO level	27.11	11.68	26.26	11.62	27.25	11.16	28.15	12.48

Table 2

7-day point prevalence abstinence rates (%) at various follow-up time points for each experimental condition

	Active Bupropion, Active Gum					Active Bupropion, Placebo Gum (n = 224)					Placebo Bupropion, Placebo Gum (n = 156)				
Time point	Total (228)	Male (101)	Female (127)	Csn (173)	Af-Am (46)	Total (224)	Male (89)	Female (135)	Csn (165)	Af-Am (50)	Total (156)	Male (66)	Female (90)	Csn (114)	Af-Am (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

Csn = Caucasian; Af-Am = African America