Original Investigation

A randomized, controlled trial of bupropion sustained-release for preventing tobacco relapse in recovering alcoholics

J. Taylor Hays, Richard D. Hurt, Paul A. Decker, Ivana T. Croghan, Kenneth P. Offord, & Christi A. Patten

Abstract

Introduction: Studies examining the efficacy of tobacco dependence treatment among recovering alcoholic smokers have produced mixed findings. We set out to investigate this issue further by conducting a randomized, double-blind, placebo-controlled trial of bupropion sustained-release (SR) for smoking relapse prevention among abstinent alcoholic smokers.

Methods: Participants ($N=195$) met *DSM-IV* criteria for a history of alcohol abuse or dependence and had at least 1 year of continuous abstinence from alcohol and drugs. Open-label treatment with nicotine patch therapy was provided to all subjects for 8 weeks. The initial nicotine patch dose was determined by the subject's baseline serum cotinine concentration with an aim to achieve 100% cotinine replacement. All subjects who were confirmed abstinent from smoking throughout the final week of nicotine patch therapy (Week 8) were randomly assigned to receive bupropion SR 300 mg/day or placebo through Week 52.

Results: A total of 110 participants were randomized to the double-blind treatment. No significant difference was observed between the bupropion and placebo groups for rates of continuous smoking abstinence, 41.1% (95% $CI=28.1\%–55.0\%$) versus 40.7% (95% $CI=27.6\%–55.0\%$), respectively, $p=1.0$, or point prevalence abstinence, 39.3% (95% $CI=26.5\%–53.3\%$) versus 40.7% (95% $CI=27.6\%–55.0\%$), respectively, $p=1.0$, at the end of the treatment (Week 52). Relapse to alcohol occurred in 4% of subjects ($n=4$) during the study.

Discussion: Treatment with bupropion SR among abstinent alcoholic smokers did not delay relapse or result in improved long-term smoking abstinence.

Introduction

The cooccurrence of tobacco dependence and alcohol abuse or dependence is well documented (Burling & Ziff, 1988; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Karlamangla, Zhou, Reuben, Greendale, & Moore, 2006). Moreover, it is estimated that alcoholics may constitute up to 26% of all smokers (DiFranza & Guerrera, 1989). Tobacco-dependent individuals with comorbid substance abuse or other psychiatric comorbidity consume more than 34% of all cigarettes smoked, while accounting for only about 7% of the total U.S. population (Grant et al., 2004). Additional evidence suggests that, compared with nonalcoholic smokers, smokers in stable recovery from alcohol abuse are more tobacco dependent, as evidenced by higher serum cotinine concentrations and higher Fagerström scores (Hays et al., 1999; Hughes, 1993, 2002; Hurt et al., 1995). Further, nicotine is more reinforcing among smokers with a history of alcoholism than among those without such a history (Hughes, Rose, & Callas, 2000). A retrospective cohort study of 845 Olmsted County, MN, residents admitted to an inpatient addiction program primarily for alcohol dependence treatment found that tobacco-caused diseases accounted for 50.9% of all deaths while alcohol-related conditions accounted for 34.1% (Hurt et al., 1996). Thus, abstinent alcoholic smokers represent an especially important group for tobacco cessation interventions.

However, studies examining the efficacy of tobacco dependence treatment among abstinent alcoholic smokers have produced mixed findings (Hughes & Kalman, 2006; Hughes, Novy, Hatsukami, Jensen, & Callas, 2003; Hurt et al., 1994; Johnson, Ait-Daoud, Akhtar, & Javors, 2005; Kalman, Kahler, Garvey, & Monti, 2006). In one clinical trial of nicotine patch therapy (21 mg/day) among heavy smokers with a history of alcohol dependence, 6-month smoking abstinence rates (24% in the nicotine

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patch group) were comparable to results achieved among equally heavy smokers with no past alcohol problems (Hughes et al., 2003). However, many reports indicate that although individuals with active or remitted alcoholism can achieve short-term smoking abstinence, long-term success is not as readily achieved (Hays et al., 1999; Hughes, 1993; Hurt et al., 2005; Prochaska, Delucchi, & Hall, 2004). One explanation for these outcomes may be inadequate treatment with nicotine replacement therapy (NRT). Although NRT is effective in abstinent alcoholic smokers, inadequate nicotine replacement is likely to occur with a standard nicotine patch dose (e.g., 21 mg/day) because of the greater severity of tobacco dependence and the higher cotinine concentrations observed in this group compared with smokers without alcohol problems (Hays et al., 1999). We previously reported the first phase of our study in which 195 abstinent alcoholic smokers received NRT with nicotine patch dose tailored to the baseline serum cotinine concentration (Hurt et al., 2005). The smoking abstinence rate was 51% (7-day point prevalence) at the end of 8 weeks of patch therapy.

The second (relapse prevention) phase of the study was designed to take advantage of the potential for bupropion SR to delay smoking relapse because of its demonstrated effect in delaying relapse to smoking in a general population of smokers (Hays et al., 2001). In addition, bupropion SR was used for relapse prevention because of the adverse effects associated with long-term use of nicotine patch therapy, primarily erythema and pruritus at the patch site often beginning after 4 or 5 weeks of therapy and reducing patient acceptability and adherence to long-term nicotine patch therapy. Bupropion SR, an oral medication, lends itself to long-term use without serious side effects and has little abuse or dependence liability. The overall goal of the study was to determine if long-term use of bupropion SR would reduce the rate of relapse to smoking compared with placebo in abstinent alcoholic smokers who achieve initial abstinence from smoking with tailored nicotine patch therapy.

Methods

Subjects

After we obtained study approval from the Mayo Clinic Institutional Review Board, we recruited potential participants through news releases, advertisements, and notices to local and regional Alcoholics Anonymous (AA) clubs and to alcohol and drug treatment programs. Two members from the local AA community volunteered as study recruiters to assist in our efforts. Subjects were eligible for study inclusion if they were 18 years of age or older, had smoked at least 20 cigarettes/day for the previous year, and were generally in good health. Only one smoker per household was allowed in the study. The history of alcohol dependence was based on *DSM-IV* criteria. Subjects also had at least 1 year of abstinence from alcohol and drugs, corroborated by a significant other and a negative urine drug and alcohol screening test. Exclusion criteria were a personal or family history of seizure disorder, history of severe head trauma, predisposition to seizures, history of or current diagnosis of anorexia nervosa or bulimia, presence of an unstable medical or psychiatric condition, pregnancy, lactation, current use of psychotropic medications, current use (past 30 days) of bupropion, current use of tobacco products other than cigarettes, and current (within the past 3 months) *DSM-IV* diagnosis of a major depressive disorder.

This study focused on subjects with at least 1 year of abstinence from alcohol or other drugs of dependence for several reasons. This approach allowed us to evaluate the effects of tobacco dependence intervention without the confounding factors found in acute detoxification and early sobriety from alcohol. Based on a study in which abstinent alcoholic smokers had a minimum of 3 months of abstinence from alcohol, we anticipated a relapse rate to alcohol or other drugs of 4% or less in our study (Martin et al., 1997).

The 600 individuals who responded to our recruitment efforts were screened by telephone to assess their eligibility with respect to the criteria just described. After initial telephone screening, 213 potential subjects attended an information meeting at which time the study was explained and written informed consent obtained. During the consent process, each subject was informed that multiple corroborative sources would be used to assess for alcohol and drug use during the study period but that this information would be kept confidential. In addition to a respectful interview process, these procedures have been shown to enhance accuracy of self-report of alcohol and drug use in clinical treatment outcome studies with alcoholics (Monti et al., 1993).

At the information meeting, subjects completed a self-administered demographic and tobacco use history form and the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The Alcohol Dependence Scale (ADS; Skinner & Allen, 1982) was used to measure severity of alcohol dependence. The ADS is a 25-item self-report measure that incorporates physiological, psychological, and social components of alcohol dependence, including a range of drinking behaviors, increased tolerance to alcohol, and alcohol withdrawal symptoms. The ADS has demonstrated reliability and validity. Given that subjects were currently abstinent from alcohol, they were instructed to answer the questions in reference to the last 12-month period in which they were drinking. A score of 14–21 indicates moderate levels of alcohol dependence, and a score of 22 or more indicates severe levels of dependence (Skinner & Horn, 1984). The National Institute of Mental Health Diagnostic Interview Schedule–Revised (DIS; Robins et al., 1999) also was administered by a trained study assistant to assess the current and lifetime occurrence of alcohol dependence, major depressive disorder, and bipolar disorder as defined by *DSM-IV* (American Psychiatric Association, 1994). The alcohol dependence, depression, and mania sections of the DIS were administered; no other psychiatric disorders were assessed.

At the information meeting, a blood sample was obtained for baseline serum cotinine concentration. A urine sample was collected to screen for alcohol and drugs of abuse and to test for pregnancy in female subjects. Each subject was asked to provide the names of three significant others (e.g., spouse, relative, and AA sponsor) to confirm their current abstinence from alcohol and drugs and to assist in the follow-up data collection of the subject's smoking, alcohol, and drug use. Letters were then sent to these significant others inviting their participation. Prior to the next visit, the subject was required to have signed letters from three significant others willing to participate. One of these informants was contacted prior to the subject's enrollment in the study to verify the subject's abstinence from alcohol and drugs during the past 12 months.

Subjects meeting the initial study criteria were then scheduled for a baseline visit and physical examination. Subjects were instructed on completing daily diaries in which they were to record smoking rates and nicotine withdrawal symptoms based on the Minnesota Nicotine Withdrawal Scale, a validated, self-administered instrument that asks the smoker to rate each of eight withdrawal symptoms on a 5-point scale (Hughes & Hatsukami, 1998). Of the 213 subjects attending the information meeting, 203 returned for the baseline visit. At that time, vital signs were taken, daily diaries with self-reported smoking rates and withdrawal symptoms since the information meeting were collected, and the physician investigator performed a medical history and a brief examination. Moreover, the 24-item Hamilton Depression Rating Scale (HDRS; Garside, 1976; Hamilton, 1967) was administered to measure severity of current depressive symptoms. This structured interview was conducted by trained interviewers with a mean interrater reliability coefficient of .92. HDRS scores can take on possible values from 0 to 74; a cutoff score of 20 or more is indicative of clinical depression, and scores of 10 or below are considered within the normal range (Cleary & Guy, 1987). Of the 203 attending the baseline visit, 195 individuals met all the study inclusion and exclusion criteria, including confirmation of alcohol and drug abstinence by a significant other and a negative urine alcohol and drug screen, and were willing to participate.

Procedure

Open-label phase. Study procedures have been described in detail elsewhere (Hurt et al., 2005); only a brief description follows. At the end of the baseline visit, the study physician provided a strong message to stop smoking and assigned the target quit date 1 day after the baseline visit. Tailored nicotine patch therapy was provided in an open-label fashion based on a previously developed algorithm (Dale et al., 1995). At baseline and at each subsequent visit, the study assistant provided brief, individualized office counseling covering topics such as ways to avoid high-risk situations, how to seek out social support, how to manage cravings, and other cognitive and behavioral strategies. All subjects were encouraged to complete 8 weeks of tailored nicotine patch therapy and were asked to return to the clinic on a weekly basis during the 8 weeks of treatment for brief behavioral counseling. At each visit, the study assistant reviewed the treatment plan, provided self-help material, and reviewed individual homework assignments.

Expired-air carbon monoxide (CO) concentrations of less than 8 parts per million (ppm) were used to biochemically confirm self-reported abstinence from smoking tobacco at each visit. At Week 8, irrespective of the subject's self-reported tobacco use status, we contacted a significant other by telephone to verify the subject's abstinence from alcohol and drugs for the period since baseline. We attempted to contact the same significant other at baseline and at Week 8. Moreover, a urine and alcohol drug screen was used to confirm self-reported abstinence from alcohol and other drugs.

Randomized treatment phase. Subjects who were (a) biochemically confirmed abstinent from smoking during the eighth week of the nicotine patch phase and (b) abstinent from alcohol and drugs, indicated by a negative urine alcohol and drug screen and no self or significant other reports of alcohol or drug use, were randomized to receive bupropion SR 150 mg/day (or an identical placebo) for 3 days followed by 150 mg twice daily. Each

subject was provided brief (10 min or less) individualized behavioral counseling at each study visit (weekly during Weeks 9–12; monthly during Weeks 13–24; and at Weeks 52 [end of randomized treatment], 53, 64, and 76). Continuous smoking abstinence was determined at each visit by self-report of no smoking since the previous visit and confirmed by expired-air CO of less than 8 ppm. Relapse to smoking was defined as seven consecutive days of smoking one or more cigarettes or two consecutive weeks with one or more days of smoking. A urine screen for alcohol and other drugs of dependence was obtained at Week 52, and the subject's significant other (informant) was contacted to verify self-reported abstinence from alcohol and drugs at Weeks 24 and 52.

Data analyses

The 7-day point prevalence smoking status at the end of the open-label patch phase was used to determine eligibility to enter the randomized portion of the trial. Baseline characteristics of the placebo and bupropion groups were compared using the two-sample rank-sum test for continuous variables and the chi-square test for categorical variables.

The efficacy of bupropion for preventing smoking relapse during the randomized, double-blind medication phase and follow-up phase was assessed by analyzing time to smoking relapse. Relapse to smoking was defined as seven consecutive days of smoking one or more cigarettes or two consecutive weeks with one or more days of smoking (Hughes et al., 2003). The relapse date was defined as the first day of smoking during the period in which the relapse criteria were met. If subjects dropped out of the study, they were considered to have relapsed to smoking with their date of relapse being the day following their last known date of abstinence. Kaplan–Meier survival estimates and proportional hazards regression models were used to analyze time from randomization to first smoking relapse. For participants who remained continuously abstinent, time to first relapse was censored by using the date of their final study visit (Week 76). For the proportional hazards regression analyses, the dependent variable was time to first smoking relapse, and the independent variable was medication assignment (bupropion or placebo). Point prevalence and continuous smoking abstinence rates were calculated, along with 95% CIs, and compared between treatment groups using the Fisher's exact test.

Nicotine withdrawal was summarized using weekly mean withdrawal scores for the week prior to randomization and the first 4 weeks following randomization. Postrandomization nicotine withdrawal scores were analyzed as change from baseline, with baseline defined as the week prior to randomization. Change in nicotine withdrawal was assessed using repeated measures analysis of variance (ANOVA). To supplement this analysis, the mean change in nicotine withdrawal for each group was compared with 0 at each timepoint using the signed-rank test and compared between groups using the two-sample rank-sum test. In addition, weekly means for nicotine withdrawal were computed at Weeks 52 and 53. The change in nicotine withdrawal from Week 52 (end of medication) to Week 53 was compared between treatment groups using the two-sample rank-sum test to assess whether discontinuation of bupropion had an effect on nicotine withdrawal.

The HDRS was completed at randomization and at Weeks 10, 12, 16, 20, 24, 52, 53, and 76. For each case, we examined

changes in total HDRS scores. HDRS scores were analyzed using repeated measures ANOVA. To supplement this analysis, the mean change in total HDRS scores for each group was compared with 0 at each timepoint using the signed-rank test and compared between groups using the two-sample rank-sum test. To test the hypothesis that discontinuing use of bupropion is associated with changes in depression, the two-sample rank-sum test was used to compare groups with respect to the change in total HDRS scores from Weeks 52 to 53 and from Weeks 52 to 76.

The participant's weight was recorded at each visit throughout the randomized, double-blind medication phase. Change in body weight from randomization was analyzed for all subjects using repeated measures ANOVA. If subjects relapsed to tobacco, their data were excluded from the analysis following their date of relapse. In addition, change in body weight was analyzed among participants who remained abstinent through the end of the randomized, double-blind medication phase (Week 52) and through the follow-up phase (Week 76) using the two-sample rank-sum test.

Additionally, medication and study visit schedule adherence were compared between groups using the two-sample rank-sum test and the chi-square test as appropriate. In all cases, two-sided p values of .050 or less were considered statistically significant.

Results

Patch phase

A total of 195 participants were enrolled in the open-label patch phase of this study. The participants were on average 43.8 years old ($SD=9.4$, range = 20–75) and 23% were female. Participants smoked an average of 29.9 cigarettes/day ($SD=11.8$, range = 10–80). Among study participants, 74% had FTND scores of 7 or higher. Participants had a mean ADS score of 21.7 ($SD = 7.7$), indicating relatively severe levels of prior alcohol dependence. Overall, 12% met *DSM-IV* criteria for a history of major depressive disorder. The mean HDRS score was within the normal range; 95.3% of participants had a score of 10 or less, whereas 4.7% had a score of 11–19. At baseline, participants had mean serum cotinine concentrations of 299.5 ng/ml ($SD = 112.6$, range = 96–806). Baseline cotinine concentrations were used to assign each participant's initial patch dose: 41 participants (21%) were assigned to the 22-mg patch group (baseline cotinine ≤ 200 ng/ml), 65 participants (33%) were assigned to the 33-mg patch group ($200 \text{ ng/ml} < \text{baseline cotinine} \leq 300 \text{ ng/ml}$), and 89 participants (46%) were assigned to the 44-mg patch group (baseline cotinine $> 300 \text{ ng/ml}$). A detailed description of the outcomes of the open-label patch phase has been reported previously (Hurt et al., 2005).

Table 1 presents the baseline characteristics of the 110 participants who were randomized to the double-blind relapse prevention phase of the trial. Baseline demographics did not differ significantly between the two treatment groups. A total of 71 participants remained in the study through completion of the Week 76 follow-up assessment; 37 (66%) in the bupropion group versus 34 (63%) in the placebo group, $p = .842$. A total of 53 participants discontinued medication use prematurely; 25

(45%) in the bupropion group versus 28 (52%) in the placebo group, $p = .567$. The primary reasons for discontinuing medication use included withdrawn consent ($n = 31$; 14 bupropion and 17 placebo) and lost to follow-up ($n = 12$; 7 bupropion and 5 placebo).

Relapse to smoking

The median time to relapse to smoking from randomization was 165 days for the placebo group and 141.5 days for the bupropion group (*hazard ratio* = 1.01, 95% *CI* = 0.63–1.63, $p = .965$, proportional hazards regression). Figure 1 displays the Kaplan-Meier estimates of smoking relapse by treatment group. No significant difference was seen between the bupropion and placebo groups for the continuous smoking abstinence rates at the end of the medication, Week 52, 41.1% ($n = 23$, 95% *CI* = 28.1%–55.0%) for the bupropion group versus 40.7% ($n = 22$, 95% *CI* = 27.6%–55.0%) for the placebo group ($p = 1.0$), or through the completion of follow-up, Week 76, 37.5% ($n = 21$, 95% *CI* = 24.9%–51.5%) for the bupropion group versus 38.9% ($n = 21$, 95% *CI* = 25.9%–53.1%) for the placebo group ($p = 1.0$).

7-Day point prevalence smoking abstinence

At the end of the medication phase, Week 52, the 7-day point prevalence smoking abstinence rates were 39.3% ($n = 22$, 95% *CI* = 26.5%–53.3%) in the bupropion group versus 40.7% ($n = 22$, 95% *CI* = 27.6%–55.0%) in the placebo group ($p = 1.0$). The 7-day point prevalence smoking abstinence rates at the end of the study, Week 76, were 35.7% ($n = 20$, 95% *CI* = 23.4%–49.6%) in the bupropion group versus 37.0% ($n = 20$, 95% *CI* = 24.3%–51.3%) in the placebo group ($p = 1.0$). There were no significant differences for 7-day point prevalence smoking abstinence rates at any visit throughout the study.

Relapse to alcohol or other drugs

Two subjects in the placebo group and two subjects in the bupropion group relapsed to alcohol, but there was no relapse to any other drug use. The timing of the alcohol relapse was at Week 76 (two subjects) and one subject each at Weeks 32 and 24. The average time in stable alcohol recovery prior to relapse was 5.1 years. In the 7 days prior to the alcohol relapse, two subjects were smoking and two subjects were abstinent from smoking. The alcohol relapse episodes for these subjects were prolonged or continuous for two subjects and brief “slips” with immediate return to alcohol abstinence, which was maintained through the final follow-up visit, for the other two. Additionally, two of the four subjects were abstinent from smoking at the final follow-up visit (7-day point prevalence), whereas only one of the four was continuously abstinent from smoking from randomization through Week 76 (subject assigned to active bupropion treatment). All four subjects reported that they did not believe their alcohol relapse was related to stopping smoking.

Nicotine withdrawal

The mean nicotine withdrawal change from randomization (Week 8) was assessed for each week during the first 4 weeks of the randomized, double-blind medication phase. From repeated measures ANOVA, participants' change in nicotine withdrawal was found to significantly ($p < .001$) increase over time for each

Table 1. Baseline participant demographics

Characteristics	Placebo (<i>n</i> = 54)				Bupropion (<i>n</i> = 56)			
	Number of subjects (%)	<i>M</i> (<i>SD</i>)	Median	Range	Number of subjects (%)	<i>M</i> (<i>SD</i>)	Median	Range
Age, years		44.0 (9.3)	44	24–61		43.9 (10.7)	45	20–75
Male	42 (78)				44 (79)			
Married	29 (54)				31 (55)			
Cigarettes per day		27.8 (11.0)	25	10–70		28.3 (10.9)	26.5	10–80
Years of regular smoking		25.2 (10.4)	24.5	7–51		25.7 (10.5)	28	3–52
Number of previous stop attempts ^a								
0	5 (9)				10 (18)			
1	14 (26)				10 (18)			
2	9 (17)				14 (25)			
3	13 (25)				11 (20)			
4 or more	12 (23)				11 (20)			
Longest previous smoking abstinence								
<24 hr or not at all	3 (6)				6 (11)			
1–6 days	9 (17)				13 (23)			
1–4 weeks	10 (19)				12 (21)			
5 Weeks and 6 months	15 (28)				8 (14)			
7 Months and 1 year	9 (17)				8 (14)			
>1 year	8 (15)				9 (16)			
Other cigarette smokers in the home	20 (37)				25 (45)			
Years abstinent from alcohol								
1–4.9	15 (28)				24 (43)			
5–9.9	17 (31)				14 (25)			
10 or more	22 (41)				18 (32)			
Recovering from other drug problems	19 (35)				17 (30)			
Years abstinent from drugs ^b								
1–4.9	3 (16)				8 (47)			
5–9.9	7 (37)				7 (41)			
10 or more	9 (47)				2 (12)			
AA/12-step sponsor	28 (52)				28 (50)			
AA/12-step sponsor smokes	13 (46)				14 (50)			
Fagerström Test for Nicotine Dependence score								
<7	18 (33)				15 (27)			
≥7	36 (67)				41 (73)			
Alcohol Dependence Scale ^c								
No DSM diagnosis (0–8)	1 (2)				2 (4)			
Low dependence (9–13)	9 (18)				7 (13)			
Moderate dependence (14–21)	19 (39)				23 (43)			
Substantial dependence (22–30)	14 (29)				16 (30)			
Severe dependence (≥31)	6 (12)				6 (11)			
Age at onset of alcohol problems ^a		19.0 (4.9)	18	10–35		19.9 (7.6)	18	12–45
Hamilton Depression Rating Scale ^d								
≤10	52 (96)				52 (95)			
>10	2 (4)				3 (5)			
Lifetime history of MDD ^e	6 (12)				4 (7)			

Note. AA, Alcoholics Anonymous; MDD, major depressive disorder.

^aData are missing for one subject who received placebo.

^bYears abstinent from drugs differed between groups when treated categorically ($p = .036$). When years are treated continuously, the p value is .057. No other variables differed between groups.

^cData were missing for five placebo and two bupropion subjects (five subjects, four placebo and one bupropion, did not complete it, and two subjects, one placebo and one bupropion, have a missing score due to missing items).

^dData are missing for one bupropion subject who have a missing score due to missing items.

^eData are missing for two placebo subjects and one bupropion subject.

Figure 1. Display of the Kaplan–Meier estimates of smoking relapse by treatment group from randomization through Week 76. The dashed line represents the bupropion SR group, the solid line the placebo. $p=.965$.

group, but there was no differential effect between groups. For the bupropion group, the average nicotine withdrawal scores over Weeks 10 and 11 were significantly higher than the baseline assessment ($p=.006$ and $p=.002$, respectively). For the placebo group, the average nicotine withdrawal score over Week 10 was significantly higher than the baseline assessment ($p=.03$). There was neither significant difference between treatment groups for the change in nicotine withdrawal from Weeks 52 to 53 nor any significant change within groups.

Hamilton Depression Rating Scale scores

From repeated measures ANOVA, there was neither a treatment nor a time effect when examining change in total HDRS scores over Weeks 10, 12, 16, 20, and 24. We found no difference between treatment groups at any timepoint for the change in total HDRS scores from randomization. In addition, we found no difference between treatment groups when comparing the change in total HDRS scores from Weeks 52 to 53 and from Weeks 52 to 76. At Week 10, HDRS scores were significantly higher in the placebo group ($p=.046$) and in the bupropion group ($p=.018$), compared with Week 8. At Week 76, subjects within the placebo group had significantly lower total HDRS scores, compared with Week 52 ($p=.037$).

Weight change

Figure 2a displays the mean weight change from randomization (Week 8) for the 110 participants randomized in the double-blind medication phase. At Weeks 9, 10, 11, and 12, subjects in the placebo group gained significantly more weight than those in the bupropion group ($p<.002$ in each case, two-sample rank-sum test). At the end of the randomized, double-blind medication phase (Week 52), the mean weight gain was 1.7 kg in the bupropion group compared with 2.1 kg in the placebo group ($p=.995$). At the end of the follow-up phase (Week 76), the mean weight gain in the bupropion group was 1.6 kg compared with 2.4 kg in the placebo group ($p=.644$). Figure 2b displays mean weight change for the 45 subjects continuously abstinent from smoking at Week 52, the end of the randomized, double-blind medication phase. The mean weight change was 3.1 kg for the bupropion group ($n=22$ with data available) and 4.1 kg for the placebo group ($n=20$ with data available; $p=.696$). For the

Figure 2. (a) Mean weight change from randomization (Week 8) for all 110 randomized subjects. At Weeks 9, 10, 11, and 12, subjects in the placebo group (solid line) gained significantly more weight than those in the bupropion SR group (dashed line). (b) Mean weight gain for the 42 subjects who were continuously abstinent from smoking through the end of the follow-up phase (Week 76). There were no differences between the bupropion SR (dashed line) and placebo (solid line) groups at any point.

42 subjects continuously abstinent from smoking through the end of the follow-up phase (Week 76), the mean weight change was 3.4 kg for the bupropion group ($n=20$ with data available) and 4.3 kg for the placebo group ($n=18$ with data available; $p=.630$).

Safety

The most common adverse events reported were upper respiratory infection/upper respiratory symptoms (24/56 [43%] on bupropion; 33/54 [61%] on placebo), headache (18/56 [32%] on bupropion; 27/54 [50%] on placebo), nausea/vomiting (13/56 [32%] on bupropion; 13/54 [24%] on placebo), insomnia (9/56 [16%] on bupropion; 13/54 [24%] on placebo), and dyspepsia (9/56 [16%] on bupropion; 13/24 [24%] on placebo). We found no significant differences between bupropion and placebo-treated subjects in the rates of any adverse events. The vast majority of adverse events were rated as mild. No serious adverse events and no deaths occurred during the randomized phase of the trial. Four participants dropped out of the study due to adverse events (all assigned to bupropion).

Discussion

The present study is one of the first to assess the efficacy of bupropion SR for relapse prevention among a group of nondepressed smokers with alcohol dependence in sustained full remission. The major finding is that bupropion SR did not reduce or delay relapse to smoking in this population. Tailored nicotine patch therapy did result in excellent end-of-treatment abstinence (Hurt et al., 2005), but this did not translate into higher rates of prolonged smoking abstinence among the bupropion-treated subjects. These results are in contrast to a previous study of bupropion SR used for smoking relapse prevention (Hays et al., 2001) but are consistent with a study of tailored NRT followed by bupropion for smoking relapse prevention in a multicenter trial, both conducted among general population samples of smokers (Hurt et al., 2003). Our findings are also consistent with a recent meta-analysis that concluded that smokers with a history of alcohol dependence respond equally well to tobacco dependence treatment but are less likely to achieve permanent abstinence during their lifetime (Hughes & Kalman, 2006).

Our approach using tailored nicotine patch therapy plus bupropion SR was thought to be potentially beneficial for recovering alcoholics because it is consistent with a method of alcohol dependence treatment and relapse prevention using medications such as naltrexone or acamprosate to promote cessation and support long-term abstinence. However, our study does not support the use of bupropion SR for smoking relapse prevention among smokers in stable recovery from alcohol problems.

Our findings add to the literature on the pharmacological treatment of tobacco dependence among recovering alcoholics. We used tailored nicotine patch therapy as the initial treatment to achieve smoking abstinence, whereas a previously reported study (Hays et al., 2001) used open-label bupropion as the initial treatment. Using the same drug for initial treatment of tobacco dependence and continuing it for relapse prevention may be the preferred approach. Additional studies in the population of recovering alcoholic smokers will be necessary to test this approach.

The strengths of our study include its randomized, double-blind design in a large number of subjects in stable recovery from alcohol dependence. Our interventions and assessments were comprehensive and detailed. Our study subjects were mostly male and White and were less likely than expected to endorse a history of major depression. These factors may limit the generalizability of our findings.

We found no increase in depressive symptoms over time or between the bupropion SR and placebo groups. Depression is common among recovering alcoholics, and depressive symptoms may be associated with an increased risk of relapse (Strowig, 2000). In contrast, we found evidence of increased nicotine withdrawal symptoms during the weeks shortly after randomization. It is difficult to ascribe these increases in nicotine withdrawal scores to the discontinuation of nicotine patch since the increases occurred at 2–3 weeks following the end of nicotine patch therapy. Regardless, most smoking relapse activity occurred after Weeks 10–11, the period when nicotine withdrawal symptom scores increased over baseline levels. Thus,

neither depressive symptoms nor possible nicotine withdrawal appear to explain the smoking relapse activity we observed among all randomized subjects.

A previous study of bupropion SR for smoking relapse prevention found a significant effect for reducing weight gain in bupropion-treated subjects (Hays et al., 2001). The present study found a modest effect for reduced weight gain among the bupropion group in the first weeks of randomized therapy that waned thereafter. Although the bupropion-treated subjects experienced less actual weight gain, both in the overall analysis and among subjects who were continuously abstinent from smoking (greater than 1 kg less weight gain among smoking abstinent subjects on bupropion compared with those on placebo), these differences were not significant due to the small numbers of participants in each group. The effects of bupropion on ameliorating postcessation weight gain may not be as robust in this select population of smokers as one might expect among the general population.

In summary, we found that bupropion SR compared with placebo was not effective for smoking relapse prevention when provided following tailored NRT in a group of smokers in stable recovery from alcohol dependence. Bupropion SR was well tolerated, however. In addition, relapse to alcohol or drug use during smoking cessation occurred in a small minority of participants and was similar to the rate found in a prior study of recovering alcoholic smokers treated for tobacco dependence (Martin et al., 1997). Additional research in smokers with a history of alcohol dependence is warranted to determine the most effective pharmacological and behavioral approaches to treatment for these smokers who are at high risk of tobacco-caused morbidity and mortality.

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Declaration of Interests

None declared.

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