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Targeting smokers at increased risk for relapse: treating women and those with a history of depression

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Some studies have shown that female smokers and smokers with a history of depression have an increased risk of relapse following smoking cessation treatment. This study examined the efficacy of bupropion sustained-release (SR) and the nicotine patch for smoking cessation in subgroups of smokers at possible risk for relapse. Data for this study were from a previously published randomized, double-blind, placebo-controlled clinical trial in which 893 smokers were randomized to four treatment conditions: placebo tablet + placebo patch, placebo tablet + 21 mg/24-hr nicotine patch, 300 mg bupropion SR + placebo patch, and 300 mg bupropion SR + 21 mg/24-hr nicotine patch. Study medication continued for 8 weeks after the quit day; brief individual cessation counseling was provided during weekly clinic visits. In comparison to the placebo tablet, bupropion SR approximately tripled 1-year non-smoking rates among women and previously depressed individuals. In contrast, the nicotine patch did not significantly improve cessation rates for any group. We conclude that bupropion SR is a first-line treatment for smoking that has the potential to benefit all smokers, especially women and the previously depressed.

Introduction

Five pharmacotherapies now are approved by the FDA for treating tobacco dependence (Hughes, Goldstein, Hurt, & Shiffman, 1999): nicotine gum, nicotine patch, nicotine inhaler, nicotine nasal spray, and bupropion sustained-release (SR). However, clinicians have been given little guidance on how to select among these medications.

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There is evidence that particular individual differences tend to predict the success of a smoking cessation attempt. Examples of these differences are level of nicotine dependence (Killen, Fortmann, Kraemer, Varady, & Newman, 1992; Pinto, Abrams, Monti, & Jacobus, 1987; Swan, Jack, & Ward, 1997), gender (Bjornson et al., 1995; Hubert, Eaker, Garrison, & Castelli, 1987; Swan, Ward, Carmelli, & Jack, 1993; Wetter, Kenford, Smith, Fiore, Jorenby, & Baker, 1999), and a history of depression (Anda, Williamson, Escobedo, Mast, Giovino, & Remington, 1990; Glassman et al., 1990; Kinnunen, Doherty, Militello, & Garvey, 1996). With regard to the latter two variables, much research suggests that female gender and a positive history of depression predict a reduced likelihood of cessation success, although exceptions exist (Gritz, Thompson, Emmons, Ockene, McLerran, & Nielsen, 1998; Hall, Muñoz, & Reus, 1994; Hall et al., 1998; Sachs, Sawe, & Leischow, 1993; Whitlock, Hollis, Vogt, & Lichtenstein, 1997). The presence of individual differences in cessation outcomes suggests that cessation *processes* in these

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populations may differ substantially. If such process differences do indeed exist as a function of individual differences, then the effectiveness of particular treatments might not generalize well from the general population of smokers to smokers who are either female or previously depressed.

Some researchers have posited that various physiological, psychological, and behavioral factors may mediate observed gender differences in cessation (Gritz, Nielsen, & Brooks, 1996; Perkins, Donny, & Caggiula, 1999). These factors include possible differences between females and males in sensitivity and tolerance to nicotine, withdrawal symptoms, menstrual cycling, concerns about post-cessation weight gain, importance of social support, negative affect, depression, and expectancies about cessation. Too few studies of these factors currently exist to explain the mixed findings on gender differences in abstinence rates. Likewise, few studies have explored mechanisms that might account for a relation between depression history and cessation success.

The purpose of the current investigation is to examine the efficacy of bupropion SR and the nicotine patch in two subgroups of smokers at possibly increased risk for relapse — female smokers and previously depressed smokers. Two large, independent clinical trials have reported that bupropion SR approximately doubles long-term smoking cessation rates compared to placebo (Hurt et al., 1997; Jorenby et al., 1999b) or the nicotine patch (Jorenby et al., 1999b). Only one paper to date has examined bupropion SR efficacy in subgroups reputedly at risk for relapse (Hayford et al., 1999).

As noted previously, evidence suggests that both women and those with a history of depression are less likely than others are to quit smoking successfully (Anda et al., 1990; Bjornson et al., 1995; Glassman et al., 1990; Hubert et al., 1987; Kinnunen et al., 1996; Swan et al., 1993; Wetter et al., 1999). In addition, some research suggests that nicotine replacement therapy (NRT) yields disappointing effects in these populations, either producing no significant impact or not closing the gap in clinical outcomes between the at-risk populations and other smokers (Hall et al., 1996; Killen, Fortmann, Newman, & Varady, 1990; Perkins, 1996; Wetter et al., 1999). Thus, there is evidence in these populations of overall lower rates of cessation success (albeit not entirely consistent; Frederick, Reus, Ginsberg, Hall, Muñoz, & Ellman, 1998) and some evidence that NRT does not compensate for, or redress, this higher level of risk. The apparent higher relapse risk of these subpopulations, plus evidence that NRT is not consistently helpful, led to the intention (prior to conducting the study) to examine bupropion SR effects in subpopulations of smokers from a randomized clinical trial in which bupropion SR was compared with placebo and with the nicotine patch (Jorenby et al., 1999b). While the contrasts involving these subpopulations were planned, these contrasts were of secondary importance to the goal of comparing pharmacotherapy efficacy across all smokers. Therefore, some contrasts in the current analyses were tested under conditions of modest power.

There is some basis for assuming that bupropion might aid the two targeted subpopulations (women and those with a history of depression). First, evidence indicates that both populations experience especially elevated or prolonged withdrawal or affective symptoms after cessation (Ginsberg, Hall, Reus, & Muñoz, 1995; Gritz et al., 1996; Piasecki, Kenford, Smith, Fiore, & Baker, 1997) (although not all studies report especially high post-cessation withdrawal or affective symptoms in these populations; Hall et al., 1998). If both subpopulations experience heightened affective symptoms following cessation, then an antidepressant might be efficacious in enhancing cessation rates. This hypothesis is based on evidence that affective symptoms can precipitate relapse (Covey, Glassman, & Stetner, 1990; Hall et al., 1996) and that antidepressants such as nortriptyline (Hall et al., 1998), fluoxetine (Borrelli et al., 1996), and bupropion (Shiffman et al., 2000) can alleviate such symptoms.

The evidence regarding the efficacy of antidepressants in the treatment of smoking is not uniformly consistent or positive. For instance, the evidence that imipramine hydrochloride or fluoxetine is efficacious for smoking cessation is either difficult to interpret or weak.

However, failures to demonstrate convincingly the efficacy of the antidepressants listed above should not discourage an examination of the impact of bupropion SR on subpopulations. This is because bupropion may exert its effects through different mechanisms than do either tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs; Feighner, 1999; Fyer & Lukas 1999; Horst & Preskorn, 1998). Thus it is possible that bupropion might be effective in affecting cessation-related affective processing, whereas other antidepressants are not. Moreover, there is suggestive evidence that even among antidepressants that exert weak or inconsistent effects among a general population of smokers, some antidepressants do benefit subpopulations of smokers. For instance, although fluoxetine has failed to earn recognition as an efficacious smoking cessation pharmacotherapy in recent evidence-based smoking cessation treatment guidelines (Fiore et al., 2000), there *is* evidence that it may be beneficial to subpopulations of smokers, namely those with mild depression or with a history of depression (Blondal et al., 1999; Borrelli et al., 1996; Hitsman et al., 1999). Interestingly, these reports are paralleled by a recent study (Hayford et al., 1999) reporting a short-term benefit of bupropion SR for smokers with a history of depression. Thus, a variety of findings argue for an examination of bupropion SR

efficacy among women and the previously depressed. The following observations constitute supportive evidence:

1. These subpopulations tend to show poorer cessation outcomes than do other smokers.
2. NRT has not been consistently or strongly efficacious in these subpopulations.
3. Both subpopulations may experience greater negative affect or withdrawal symptoms upon smoking abstinence than do other smokers.
4. Bupropion has been shown to be efficacious in ameliorating negative affect.
5. Recent evidence suggests that at least two antidepressants *may* be especially efficacious among individuals high in negative affect symptomatology.

Support for the above evidence statements is not uniformly consistent, and it tends to address the subpopulation with depression history more than it addresses women. However, given the overlap between female gender and depression among smokers, it has been difficult in many studies to attribute effects to either factor alone (Salive & Blazer, 1993). In light of the difficulties in disentangling the two factors and the potential for clinical benefit among women, it seems important to determine the efficacy of bupropion SR in both populations.

We utilized data from Jorenby et al. (1999) in a set of secondary analyses to examine biochemically confirmed abstinence rates at end of treatment and at 1-year follow-up as a function of both gender and depression history status. We tested the prediction that subpopulation status would make a difference only if the smoker did *not* receive bupropion SR. That is, females and the previously depressed would have lower abstinence rates than would other smokers only if they received placebo tablets instead of bupropion SR. Thus, we predicted that bupropion SR would neutralize the negative impact of gender and depression history on long-term abstinence from smoking.

Method

Participants

A total of 893 smokers (467 females and 426 males) were recruited at four study sites and were randomized to treatment. All participants were at least 18 years of age, had smoked at least 15 cigarettes per day for the previous year, and were motivated to quit smoking. Participants received free smoking cessation treatment (including behavioral treatment and medications) in exchange for their participation. No monetary compensation was provided to participants. This study was approved by the institutional review boards (IRBs) at all study sites, and all participants signed an informed consent form approved by the IRB.

Procedures

Complete descriptions of study procedures are reported in Jorenby et al. (1999). Briefly, smokers at each of four sites (Arizona, California, Nebraska, and Wisconsin) were recruited for the study via media advertisements. Potential participants were excluded for any of the following reasons: serious medical or psychiatric conditions (e.g., current depression); use of exclusionary medications (antidepressants, neuroleptics, medications contraindicated for use with bupropion SR, investigational drugs, etc.); psychoactive substance use in the prior week, or substance abuse in the prior year; pregnancy or lactation; prior use of bupropion SR; use within the prior 6 months of NRT; current smoking cessation treatment; and regular use of non-cigarette tobacco products. Smokers with a history of depression were eligible for participation.

Smokers who met eligibility criteria, including medical, psychiatric, and other exclusion and inclusion criteria, were randomized to one of four treatments: placebo tablet + placebo patch ($n = 160$), placebo tablet + nicotine patch ($n = 244$), 300 mg bupropion SR + placebo patch ($n = 244$), and 300 mg bupropion SR + nicotine patch ($n = 245$). Tablets (bupropion SR or placebo) were taken starting 1 week prior to the quit day; patches (active nicotine or placebo) were applied on the quit day. Both tablets and patches were used for 8 weeks after the quit day. Participants in the two bupropion SR conditions received 150 mg bupropion SR daily for the first 3 days and 150 mg bupropion SR twice daily for days 4–63. Participants using active nicotine patches (Habitrol, Novartis Consumer Health) applied one 21-mg patch/24-hr daily during weeks 2–7, one 14-mg patch/24-hr daily during week 8, and one 7-mg patch/24-hr daily during week 9. Participants were instructed to wear the patch for 24 h each day and to apply a new patch daily.

Prior to the point at which participants quit smoking, baseline measures were collected, including serum cotinine, vital signs, expired air carbon monoxide (CO), smoking history, the Beck Depression Inventory (BDI; Beck & Steer, 1978), the Self-Administered Alcoholism Screening Test (SAAST; Swenson & Morse, 1975), the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988); and the Fagerström Tolerance Questionnaire (FTQ; Fagerström, 1978). In addition, the mood disorders section of the Structured Clinical Interview for the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) (SCID; First, Spitzer, Williams, & Gibbon, 1995) was administered.

Participants returned for weekly clinic visits during the treatment period for completion of various assessments and for brief individual counseling. Intra-treatment assessments included measurement of CO, vital signs, and the PANAS. In addition, all

participants kept a daily diary during the first 12 weeks of the study with measures of smoking status, craving, and withdrawal symptoms. Post-treatment follow-up clinic visits occurred at 10, 12, 26, and 52 weeks and included assessment (CO, vital signs, and BDI) and relapse prevention counseling.

Measures

The primary outcome variable was biochemically confirmed (via CO) smoking status at end of treatment (week 9) and 1 year post-cessation. Smoking status was measured as 1-week point prevalence abstinence, based on self-report of no smoking for the 7 days prior to assessment and on CO of 10 ppm or less at the corresponding clinic visit. A secondary outcome variable was the negative affect subscale of the PANAS (Watson et al., 1988). The PANAS consists of 20 Likert-type items rated on a five-point rating scale (1 = *very slightly or not at all*; 5 = *extremely*) that measure positive affect (10 items) and negative affect (10 items) during the past week.

The two risk factors examined in the current study are female gender and history of depression. History of depression was ascertained at baseline by means of the mood disorders section of the SCID (First et al., 1995) using criteria for major depression from DSM-IV (American Psychiatric Association, 1994).

The following measures were used as control variables in logistic regression analyses described below: age (in years), severity of nicotine dependence as measured by the FTQ (Fagerström, 1978), and number of symptoms associated with alcohol abuse or dependence as measured by the SAAST (Swenson & Morse, 1975). The FTQ is a self-report questionnaire consisting of eight questions about smoking that yield a total score ranging from 0 to 11. Higher scores on the FTQ are indicative of greater severity of nicotine dependence. The SAAST is a 37-item self-report questionnaire that yields a total score ranging from 0 to 30 (only 30 of the 37 items are used in the scoring). Higher scores on the SAAST are associated with an increased likelihood of problem drinking. These measures were included as covariates in the abstinence analyses because each has been shown to be associated with smoking cessation outcomes (e.g., older age, higher levels of nicotine dependence, and alcohol problems are all associated with lower abstinence rates).

Data analyses. In this study, each active medication (bupropion SR and nicotine patch) had a corresponding placebo (tablet or patch) such that there were four conditions: placebo tablet + placebo patch, placebo tablet + nicotine patch, bupropion SR + placebo patch, and bupropion SR + nicotine patch. Thus, the basic study design consisted of two between-groups factors – a bupropion SR factor and a patch factor – fully crossed, yielding two main effects and a two-way interaction effect (bupropion SR × patch). Contrast coding was used to represent the bupropion SR and patch main effects and the bupropion SR × patch interaction (Cohen & Cohen, 1983). Because the dependent variable is dichotomous (abstinent vs. smoking), hierarchical logistic regression (Hosmer & Lemeshow, 1989) was used to test predictions about interactions between treatment factors (bupropion SR and patch) and relapse risk factors (gender and depression history) as well as for computing adjusted odds ratios (*OR*), a measure of the odds of abstinence in one group relative to another group. For example, an *OR* of 2 for males vs. females would indicate that males are twice as likely to abstain from smoking as females. Age, FTQ score, and SAAST score were included as control variables in the first step of model testing.

We predicted that bupropion SR status would interact statistically with both gender and depression history. In the case of gender, we predicted that females, when treated with only placebos or the nicotine patch + placebo pill, would achieve lower abstinence rates than would males. However, we predicted that females given bupropion SR would achieve abstinence rates comparable to those of males. Similarly, with respect to depression history, we expected that the previously depressed would be less likely to be abstinent than never-depressed participants, but only when not taking bupropion SR (i.e., when given only placebos, or when given the nicotine patch + placebo pill).

Analyses proceeded as follows: (a) to ensure that smoking status did not differ as a function of the *joint* effects of bupropion SR and patch, (not predicted, but possible), two separate logistic regression models were tested that entered control variables, main effects, and relevant two-way interactions on step 1 followed by a three-way interaction on step 2 (bupropion SR × patch × gender in one analysis; bupropion SR × patch × depression history in a second analysis). The change in −2 log-likelihood from step 1 to step 2 yields a 1-*df* chi-square statistic that evaluates the statistical significance of adding the three-way interaction to the model. Neither analysis yielded a significant three-way interaction; therefore, model testing was undertaken to assess the specific predictions stated above. (b) The predicted two-way interactions of interest, bupropion SR × gender and bupropion SR × depression history, were examined in separate hierarchical logistic regression analyses. In these models, control variables and main effects were entered on step 1, and the relevant two-way interaction was entered on step 2. (c) Significant two-way interactions were then examined by means of follow-up focused comparisons, via additional logistic

regression analyses. Follow-up logistic regressions were computed at single levels of the bupropion SR factor (e.g., for placebo only) to discover the nature of significant interactions; they included age, FTQ score, and SAAST score. These regressions yielded Wald statistics for each effect in the model as well as adjusted ORs (adjusted for age, FTQ, and SAAST) and 95% confidence intervals (*CI*s) for the *OR*s.

For all of the above analyses, two sets of models were tested: one set tested end-of-treatment smoking status as the dependent variable, and the other set tested 1-year smoking status as the dependent variable. Finally, patch × gender and patch × depression history interactions also were tested to examine possible (though not predicted) differential efficacy of the nicotine patch relative to the placebo patch for the two relapse risk factors.

Predictions concerning change in negative affect from baseline to 1 week post-cessation paralleled the predictions for smoking status outcomes, namely that without bupropion SR, females would have higher post-cessation negative affect than males, whereas no group differences would be observed among individuals using bupropion SR. (A similar prediction was made for depression history, but testing of the prediction was not feasible due to small sample sizes for depression history positive individuals, especially males. Sample sizes were further reduced because of missing data for the dependent measure.) These predictions were examined in a two-factor (gender × bupropion SR) analysis of covariance (ANCOVA; Huitema, 1980) in which NPANAS at 1 week post-cessation was the dependent variable and NPANAS at baseline was the covariate. Individuals with a positive history of depression were excluded from the gender × bupropion SR ANCOVA to test the prediction concerning gender without the possible confound of a higher rate of depression history in females.

Results

Table 1 presents descriptive characteristics relevant to the current study for the four treatment groups. More detailed descriptive statistics on baseline characteristics of participants in each of the four treatment groups were reported by Jorenby et al. (1999), who also reported that there were no interactions between study site and treatment for the abstinence outcomes. We conducted additional analyses to address possible site differences in the subgroup analyses (examining homogeneity of ORs across sites) and found no significant site differences. Table 2 presents overall confirmed point prevalence abstinence rates for the treatment groups at end of treatment (study week 9; 8 weeks post-cessation) and at 1-year follow-up, as well as rates for relapse risk subgroups (males vs. females; negative vs. positive history of depression).

As noted above, preliminary hierarchical logistic regression analyses revealed no statistically significant three-way interactions (bupropion SR × patch × gender; bupropion SR × patch × depression history) at end of treatment or 1-year follow-up. Direct testing of the predicted two-way interaction between bupropion SR and gender revealed a significant interaction at 1 year, $\chi^2(1, n=890)=6.7$, $p<.01$, but not at end of treatment, $\chi^2(1, n=890)=1.9$, $p=.17$. The predicted interaction between bupropion SR and depression history was significant at both the end of treatment, $\chi^2(1, n=890)=4.5$, $p<.05$, and at the 1-year follow-up, $\chi^2(1, n=890)=5.5$, $p<.05$. Subsequent testing of two-way interactions between patch and each of the two relapse risk factors failed to reveal significant effects at either the end of treatment or the 1-year follow-up. Figures 1 and 2 show point prevalence abstinence at 1 year for the four treatment groups by gender and depression history, respectively.

Table 3 presents results for logistic regressions as well as confirmed point prevalence abstinence rates such that abstinence rates correspond to the bupropion SR main effect analyzed in the main logistic regression analyses above. Thus, the original four treatment groups are combined and compared as follows: (a) no bupropion SR, consisting of the combination of placebo tablet + placebo patch, and placebo tablet + active nicotine patch; vs. (b) bupropion SR, consisting of the combination of bupropion SR + placebo patch, and bupropion SR + active

Table 1. Characteristics of the treatment groups

Characteristic	Treatment groups			
	Placebo	Nicotine patch	Bupropion SR	Bupropion SR + patch
Sample size	$n=160$	$n=244$	$n=244$	$n=245$
% Female	58.8%	51.6%	51.6%	49.4%
% Positive history of depression	15.6%	18.0%	20.9%	17.6%
Mean age (in years)	42.7 (10.2)	44.0 (10.9)	42.3 (10.2)	43.9 (11.6)
Mean FTQ score	7.5 (1.8)	7.4 (1.7)	7.4 (1.6)	7.3 (1.8)
Mean SAAST score	2.6 (5.0)	2.3 (4.3)	2.0 (4.1)	2.0 (3.3)

Standard deviations are in parentheses.
FTQ, Fagerström Tolerance Questionnaire (Fagerström, 1978); SAAST, Self-Administered Alcohol Screening Test (Swenson & Morse, 1975).

Table 2. Confirmed point prevalence abstinence rates for the four treatment groups at end of treatment (week 9) and 1 year, overall, by gender, and by history of depression

Risk group/time	Treatment group			
	Placebo	Nicotine patch	Bupropion SR	Bupropion SR + patch
Overall				
Week 9	32.5% (52/160)	41.4% (101/244)	57.8% (141/244)	66.1% (162/245)
Week 52	15.6% (25/160)	16.4% (40/244)	30.3% (74/244)	35.5% (87/245)
Males				
Week 9	37.9% (25/66)	43.2% (51/118)	55.1% (65/118)	67.7% (84/124)
Week 52	25.8% (17/66)	22.0% (26/118)	34.7% (41/118)	35.5% (44/124)
Females				
Week 9	28.7% (27/94)	39.7% (50/126)	60.3% (76/126)	64.5% (78/121)
Week 52	8.5% (8/94)	11.1% (14/126)	26.2% (33/126)	35.5% (43/121)
No history of depression				
Week 9	34.8% (47/135)	44.0% (88/200)	59.1% (114/193)	64.9% (131/202)
Week 52	17.0% (23/135)	18.5% (37/200)	30.6% (59/193)	35.1% (71/202)
History of depression				
Week 9	20.0% (5/25)	29.5% (13/44)	52.9% (27/51)	72.1% (31/43)
Week 52	8.0% (2/25)	6.8% (3/44)	29.4% (15/51)	37.2% (16/43)

nicotine patch. The table presents overall abstinence rates as well as rates for males only, females only, smokers with no history of depression, and smokers with a positive history of depression. In addition, Wald statistics and *OR*s with 95% *CI*s are presented.

Follow-up logistic regressions were computed to examine the nature of the significant interactions between bupropion SR and gender (at 1 year) and between bupropion SR and depression history (end of treatment and 1 year). Separate tests of the gender effect at each level of bupropion SR (placebo tablet; active bupropion SR) at 1 year were computed. Control variables (age, FTQ score, and SAAST score) and patch status were entered at step 1 of the logistic regression, and gender was entered at step 2. The statistical significance (evaluated via a chi-square test) of the change in −2 log-likelihood associated with adding the gender effect (females vs. males) provided the focused comparison. These analyses revealed a significant difference in abstinence rates at 1 year between females (10.0%) and males (23.4%) when the placebo tablet was used, $\chi^2(1, n=403)=16.2$, $p<.001$. In contrast, for participants using bupropion SR, no difference between females (30.8%) and males (35.1%) was found, $\chi^2(1, n=487)=1.0$, $p=.32$; see Table 3. Controlling for depression history in these analyses yielded the same results.

Separate tests of the depression history effect at each level of bupropion SR were computed to identify the significant bupropion SR × depression history

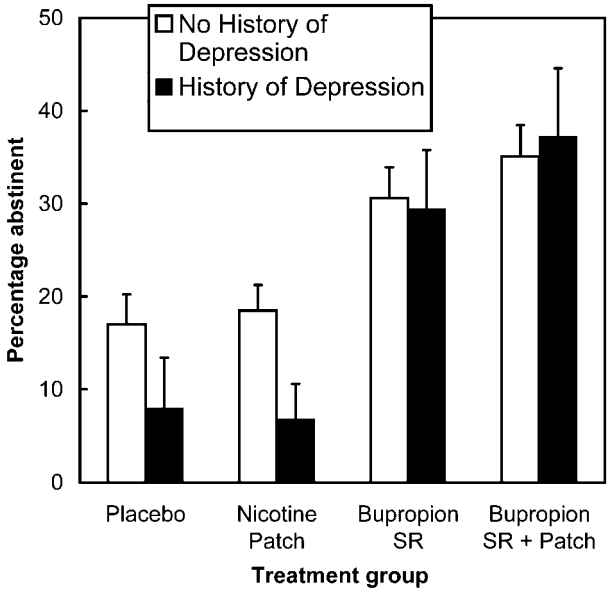

Figure 1. Confirmed point prevalence abstinence rates at 1 year by treatment group and gender. *Placebo*=placebo tablet+placebo patch; *Nicotine Patch*=placebo tablet+nicotine patch; *Bup SR*=bupropion SR+placebo patch; *Bup SR plus Nicotine Patch*=bupropion SR+nicotine patch. Error bars represent standard errors.

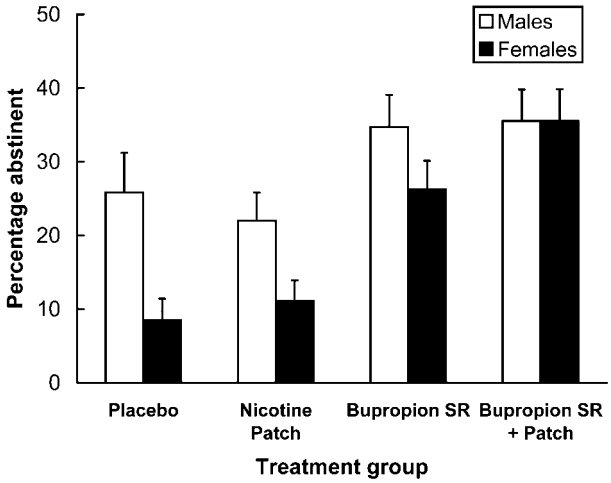

Figure 2. Confirmed point prevalence abstinence rates at 1 year by treatment group and history of depression. *Placebo*=placebo tablet+placebo patch; *Nicotine Patch*=placebo tablet+nicotine patch; *Bup SR*=bupropion SR+placebo patch; *Bup SR plus Nicotine Patch*=bupropion SR+nicotine patch. Error bars represent standard errors.

Table 3. Confirmed point prevalence abstinence rates and adjusted odds ratios for no bupropion SR vs. bupropion SR at end of treatment (week 9) and 1 year, overall, by gender, and by history of depression

Risk group/time	No bupropion SR	Bupropion SR	Wald	*p*	Adjusted odds ratio (95% CI)
Overall					
Week 9	37.9% (153/404)	62.0% (303/489)	53.1	.000	2.9 (2.2–3.8)
Week 52	16.1% (65/404)	32.9% (161/489)	30.7	.000	2.6 (1.8–3.6)
Males					
Week 9	41.3% (76/184)	61.6% (149/242)	16.4	.000	2.3 (1.6–3.5)
Week 52	23.4% (43/184)	35.1% (85/242)	5.1	.025	1.7 (1.1–2.6)
Females					
Week 9	35.0% (77/220)	62.3% (154/247)	37.6	.000	3.5 (2.3–5.2)
Week 52	10.0% (22/220)	30.8% (76/247)	30.4	.000	4.6 (2.7–8.0)
No history of depression					
Week 9	40.3% (135/335)	62.0% (245/395)	32.6	.000	2.5 (1.8–3.4)
Week 52	17.9% (60/335)	32.9% (130/395)	17.7	.000	2.2 (1.5–3.1)
History of depression					
Week 9	26.1% (18/69)	61.7% (58/94)	22.5	.000	6.3 (2.9–13.3)
Week 52	7.2% (5/69)	33.0% (31/94)	13.5	.000	7.0 (2.5–19.8)

No bupropion SR, combination of placebo tablet + placebo patch, and placebo tablet + active nicotine patch; bupropion SR, combination of bupropion SR + placebo patch, and bupropion SR + active nicotine patch; Wald, Wald statistic (1 df) from logistic regression analysis. Bupropion SR effect while controlling for age, FTQ score (Fagerström, 1978), and SAAST score (Swenson & Morse, 1975). All odds ratios are adjusted for age, FTQ score, SAAST score, and patch status (placebo vs. active); overall analyses also adjusted for sex and depression history; gender analyses also adjusted for depression history; depression history analyses also adjusted for gender.

interactions at week 9 and 1 year. Control variables (age, FTQ score, and SAAST score) and patch status were entered at step 1 of the logistic regression, and depression history was entered at step 2. Of participants who received the placebo tablet, those with a history of depression had a significantly lower abstinence rate, $\chi^2(1,\ n=403)=4.9,\ p<.05$, at week 9 (26.1%) than participants not previously depressed (40.3%). The placebo tablet group comparison at 1-year follow-up (7.2% for previously depressed vs. 17.9% for never depressed) also was statistically significant, $\chi^2(1,\ n=403)=5.3,\ p<.05$. Subsequent modeling that included gender as an additional control variable in the placebo pill comparisons revealed a marginally significant depression history effect, $\chi^2(1,\ n=403)=4.9,\ p=.05$, at week 9 and a non-significant effect at 1 year, $\chi^2(1,\ n=403)=2.9,\ p=.09$. There thus appears to be overlap between gender and depression history in terms of accounting for variability in smoking status at 1 year. For participants taking bupropion SR, no difference between previously depressed participants and never-depressed participants was found at week 9 (61.7% vs. 62.0%, respectively), $\chi^2(1,\ n=487)=0.3,\ p=.61$, or at 1 year (33.0% vs. 32.9%, respectively), $\chi^2(1,\ n=487)=0.6,\ p=.43$. Controlling for gender in these bupropion SR comparisons yielded the same pattern of results.

As shown in Table 3, all bupropion SR comparisons (no bupropion SR vs. bupropion SR) are statistically significant, indicating that bupropion SR is efficacious both overall and for each of the of smoker subpopulations. Of particular interest are the *OR*s that show that bupropion SR is especially efficacious for females (*OR*s = 3.5 and 4.6 at end of treatment and 1 year follow-up, respectively) compared with males (*OR*s = 2.3 and 1.7). At 1 year, 95% *CI*s for *OR*s for females (*CI* = 2.7 to 8.0) and males (*CI* = 1.1 to 2.6) were non-overlapping, indicating that the *OR*s for females were significantly higher. *OR*s for smokers with a history of depression (*OR*s = 6.3 and 7.0 at end of treatment and 1-year follow-up, respectively) were higher than the *OR*s for smokers with no history of depression (*OR*s = 2.5 and 2.2, respectively), but 95% *CI*s were overlapping (the broad CIs reflect the relatively smaller number of participants with a prior history of depression).

Because Hall et al. (1996) found a gender × depression history interaction effect when analyzing nortripyline's impact on smoking abstinence, a similar post hoc analysis was conducted for the current study. After we entered control variables, treatment main effects, gender, and depression history, we entered the gender × depression history interaction into models predicting smoking status at week 9 and at 1 year. No significant two-way interaction between gender and depression history was found at week 9, $\chi^2(1,\ n=890)=0.7,\ p=.42$, or at 1-year follow-up, $\chi^2(1,\ n=890)=0.2,\ p=.67$.

Tests of predictions concerning gender differences in change in negative affect from baseline to 1 week post-cessation were assessed via two-factor ANCOVAs on NPANAS. The current data were found to meet the assumptions of ANCOVA (e.g., homogeneity of within-cell regressions), and analyses were conducted to test specific predictions. As predicted, a significant gender × bupropion SR interaction was found, $F(1,655)=5.48,\ p<.02$. Follow-up comparisons revealed that females and males using the placebo tablet differed in post-cessation negative

affect (least-squares means: 2.04 vs. 1.86, respectively; $p < .02$), whereas no difference was observed for those using bupropion SR (1.79 vs. 1.85, respectively).

Discussion

In this study, bupropion SR was found to be efficacious for smokers of both genders as well as for smokers with and without a history of depression (Table 3) at both end of treatment and 1-year follow-up. However, our specific prediction that gender (female vs. male) would interact with bupropion SR status (placebo vs. active) was supported at 1-year follow-up but not at end of treatment. More specifically, bupropion SR was found to be especially efficacious for female smokers ($OR = 4.6$ at 1 year) compared with male smokers ($OR = 1.7$). At 1-year follow-up, females using the placebo tablet had an abstinence rate of 10.0% (compared with 23.4% for males), whereas females using bupropion SR had an abstinence rate of 30.8%, nearly reaching the levels observed for males using bupropion SR (35.1%). In addition, a significant gender × bupropion SR interaction was observed in an analysis of post-cessation negative affect: Females using the placebo tablet reported greater negative affect than males using the placebo tablet, whereas no gender differences were observed for smokers using bupropion SR.

Our prediction that history of depression would interact with bupropion SR was supported both at the end of treatment and at 1-year follow-up. As predicted, among participants taking the placebo tablet, previously depressed smokers had a significantly lower abstinence rate (26.1%) at end of treatment than did never-depressed smokers (40.3%). Also, as predicted, abstinence rates did not differ between the two depression history groups (positive vs. negative history) of participants taking bupropion SR (both approximately 62%). A similar pattern of results was found at 1-year follow-up; the comparison of abstinence rates at 1 year for placebo tablet participants (7.2% for previously depressed vs. 17.9% for never depressed) was statistically significant ($p < .05$). However, it is important to note that when gender was included as a control variable (along with age, FTQ score, SAAST score, and patch status), this difference was no longer significant ($p = .08$). This suggests that the relation between depression history and cessation success is somewhat dependent on gender. In addition, a greater percentage of females in the study had a history of depression (24.6%) than did males (11.3%), and this difference may have reduced power for testing the moderating effects of depression history per se.

Unlike what was shown by the robust findings for bupropion SR, the nicotine patch alone did not significantly improve abstinence rates either for smokers as a group or for either subpopulation at either endpoint (9 weeks or 1 year) when compared with the placebo condition. Although the original study was adequately powered to detect significant patch effects overall, the subgroup analyses in the current study may have been underpowered to detect significant patch effects, due to small sample sizes. Thus, although the patch produced higher 9-week abstinence rates than the placebo among females (39.7% vs. 28.7%) and among those with a history of depression (29.5% vs. 20.0%), these differences were not statistically significant. Similarly, among all subjects, abstinence rates for the combined bupropion SR + patch group were not significantly higher than rates produced by bupropion SR alone. However, rates in the bupropion SR + patch group were non-significantly higher for the two subpopulations at both endpoints. Because the nicotine patch boosted 1-year abstinence rates for subpopulation participants by almost 10% when it was combined with bupropion SR (see Table 2), further investigation of combined bupropion SR + patch treatment is warranted.

In summary, these results suggest that bupropion SR is especially effective for female smokers and for smokers with a history of depression, two subpopulations that appear to be at increased risk for relapse. Females with and without a history of depression benefited from bupropion SR. However, it was unclear whether bupropion benefited those with a depression history when gender was taken into account. This ambiguous outcome may be due, in part, to the overlap in female gender and depression (Kessler et al., 1994), making it difficult to ascertain the unique effects of these individual differences. Finally, there was evidence that the combination of the nicotine patch and bupropion SR could benefit both targeted subpopulations of smokers relative to either medication alone. Although this benefit was not statistically significant in the present research, its magnitude was sufficient to warrant further research on this combined treatment.

This study constitutes one more test of the notion that female gender and a history of depression are risk factors for smoking cessation failure. As noted earlier, many studies have reported poorer outcomes among these groups (Glassman & Covey, 1996; Perkins, 1996; Wetter et al., 1999), but individual differences have not consistently predicted cessation failure (Cummings, Jaen, & Giovino, 1985; Frederick et al., 1998). The present study supports the notion that female gender and depression history constitute risk factors for cessation failure or relapse, at least among smokers who volunteer for a formal cessation program and who do not receive buproprion SR. Among participants not taking bupropion, males were more than twice as likely to be abstinent at 12 months

post-treatment than were females, and those with no history of depression were similarly advantaged with respect to the previously depressed.

One limitation of this study is that subjects with a history of depression were not oversampled and stratified across groups. Thus, only 18.3% ($n=163$) of smokers in the study had a history of depression; this resulted in lower power to detect effects involving this variable (e.g., a gender × depression history interaction; Hall et al., 1998).

Another limitation of the current study concerns the apparent lack of efficacy of the nicotine patch. Jorenby et al. (1999) failed to find efficacy for the nicotine patch in analyses of point prevalence abstinence but did find a significant patch effect using continuous abstinence. (Jorenby et al. reported an incorrect OR of 1.1 for the comparison between the nicotine patch + placebo tablet condition and the double placebo condition, using 1-year continuous abstinence as the outcome. The correct *OR* is 1.8; see Hughes, 1999, and Jorenby, Fiore, & Baker, 1999a.) The majority of nicotine patch clinical trials have reported higher abstinence rates for users of the active nicotine patch vs. users of the placebo patch (Fiore, Smith, Jorenby, & Baker, 1994).

Jorenby et al. (1999) addressed this issue and noted that abstinence rates in double placebo conditions may be higher than in single placebo conditions (Fagerström, 1994). Inspection of Table 2 shows that, at 1-year follow-up, male smokers in the double placebo condition had a slightly *higher* abstinence rate (25.8%) than male smokers in the active patch only condition (22.0%). Corresponding percentages for females were 8.5% and 11.1%, respectively. Thus, females in the two non-bupropion SR conditions (double placebo, and active patch + placebo tablet) had very low abstinence rates, and male smokers in the double placebo condition had a 12-month abstinence rate that was more than double the pooled 6-month abstinence rate of 9.4% for 13 patch clinical trials examined in a meta-analysis by Fiore et al. (2000). It is possible that because of some unknown factor(s), this study constituted a relatively insensitive crucible for detecting nicotine patch efficacy. Having said that, though, it is important to note that a substantial amount of previous research attests to the inability of NRT to produce equivalent outcomes in men and women, and in the depressed and non-depressed (Hall et al., 1996; Killen et al., 1990; Kinnunen et al., 1996; Wetter et al., 1999). More research is clearly needed before it is possible to draw firm conclusions about the relative efficacy of the nicotine patch and bupropion SR, both among smokers in general and among subpopulations of smokers. However, the current results agree with earlier findings suggesting that bupropion is especially effective with certain high-risk populations (Hayford et al., 1999; Hitsman et al., 1999).

The present results must be replicated before one can have confidence that bupropion SR is especially efficacious for the previously depressed or for women. However, even if it is found to be particularly efficacious in these subpopulations, vital questions remain. For instance, it is unclear whether bupropion SR is more efficacious in these groups than are other antidepressants, such as nortriptyline (Hall et al., 1998) or fluoxetine (Hitsman et al., 1999). In addition, much remains to be discovered concerning the possible mechanisms of action that might account for bupropion SR's effects. For instance, at the level of motivational mechanisms or mediators, it is unknown whether bupropion exerts its effects on cessation because it reduces negative affectivity. It certainly appears to reduce post-cessation negative affect (Shiffman et al., 2000), and the present results suggest that it may be especially effective at reducing negative affect among women. However, it is unclear whether this, indeed, accounts for its impact on abstinence rates — either among smokers in general or in subpopulations of smokers. For instance, although the evidence is strong that bupropion SR does reduce symptoms of negative affect, it is unclear that it is superior to the nicotine patch in this regard (Jorenby et al., 1999b). Other possible motivational mechanisms might be that buproprion SR allows individuals to experience greater pleasure during withdrawal (Shiffman et al., 2000) or that it enhances the incentive salience of non-pharmacological stimuli (either of these effects might be due to its dopaminergic actions). Alternatively, bupropion SR might enhance cognitive/behavioral performance (Shiffman et al., 2000), and this might enhance cessation success.

There is also uncertainty regarding which of bupropion's neuropharmacological actions might be beneficial clinically. For instance, although its antidepressant effects have often been attributed to its noradrenergic and dopaminergic actions (Horst & Preskorn, 1998), it is also possible that its functional inhibition of specific cholinergic receptor sites mediates its clinical impact on smoking outcomes (Fyer & Lukas, 1999; Slemmer, Martin, & Dama, 2000). In addition, recent research featuring chronic infusion of bupropion in rats revealed dose-related decreases in spontaneous neuronal firing in norephinephrine neurons in the locus coeruleus, and dose-related increases in firing rates of 5-HT neurons in the dorsal raphe nucleus (Dong & Blier, 2001). However, this research produced no evidence of altered firing rates in dopaminergic neurons in the ventral tegmentum (although rats were not tested in the presence of incentive stimuli). In sum, little is known at present about the motivational or neuropharmacological processes that mediate bupropion's impact on smoking cessation. This level of ignorance should not be a surprise, because there is still considerable debate about how bupropion and other antidepressants

produce clinical benefit in depression (Feighner, 1999; Horst & Preskorn, 1998). Perhaps the exploration of bupropion SR's effects in reputed high-risk smokers may help reveal those of its actions that are beneficial to smokers in general.

One feature of bupropion SR's impact that should be noted is that the differences between the bupropion SR and non-bupropion SR conditions actually grew over the *post-treatment* period. Among men and the never-depressed, abstinence rates fell about 40–50% from week 9 to week 52. By contrast, among the targeted subpopulations, abstinence rates fell about 70% during this period. However, if women or the previously depressed had received bupropion SR up to week 9, abstinence rates fell only 50% and 47%, respectively, during weeks 9 to 52. Thus, bupropion had the effect of normalizing the likelihood of long-term relapse in the target subpopulations. This suggests either that bupropion aided these subjects so substantially during treatment that they were better able to weather future storms or that it exerted durable effects on relevant neurophysiological/motivational processes — effects that persisted once the drug was withdrawn. Future research should attempt to replicate this finding, as it is rare to detect a treatment that affects the likelihood of smoking relapse once the treatment is withdrawn.

Overall, the current study provides support for the use of bupropion SR in smokers regardless of gender and history of depression. The results also replicate findings (Wetter et al., 1999) that female gender and history of depression predict worse outcomes in formal cessation programs. However, these two risk factors predicted poor outcomes only when smokers did not receive bupropion SR. When females and previously depressed smokers received bupropion SR, their success was similar to that of other smokers. This suggests that members of these risk groups should be especially encouraged to take bupropion SR (if not medically contraindicated) in smoking cessation attempts.

Further research is needed to address study limitations and to replicate the findings presented here before such a recommendation can be fully embraced. In addition, new research is needed that investigates optimal combinations of bupropion SR and other interventions such as psychosocial support (e.g., individual or group counseling), clinician monitoring of intra-treatment response to bupropion SR, scheduled or ad libitum NRT, and post-treatment relapse prevention.

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