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Bupropion and cognitive–behavioral treatment for depression in smoking cessation

Richard A. Brown, Raymond Niaura, Elizabeth E. Lloyd-Richardson, David R. Strong, Christopher W. Kahler, Ana M. Abrantes, David Abrams, Ivan W. Miller

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This study is a randomized, double-blind, placebo-controlled clinical trial examining the effects of an intensive cognitive–behavioral mood management treatment (CBTD) and of bupropion, both singularly and in combination, on smoking cessation in adult smokers. As an extension of our previous work, we planned to examine the synergistic effects of CBTD and bupropion on smoking cessation outcomes in general and among smokers with depression vulnerability factors. Participants were 524 smokers (47.5% female, M_{age}=44.27 years) who were randomized to one of four 12-week treatments: (a) standard, cognitive–behavioral smoking cessation treatment (ST) plus bupropion (BUP), (b) ST plus placebo (PLAC), (c) standard cessation treatment combined with cognitive–behavioral treatment for depression (CBTD) plus BUP, and (d) CBTD plus PLAC. Follow-up assessments were conducted 2, 6, and 12 months after treatment, and self-reported abstinence was verified biochemically. Consistent with previous studies, bupropion, in comparison with placebo, resulted in better smoking outcomes in both intensive group treatments. Adding CBTD to standard intensive group treatment did not result in improved smoking cessation outcomes. In addition, neither CBTD nor bupropion, either alone or in combination, was differentially effective for smokers with single-past-episode major depressive disorder (MDD), recurrent MDD, or elevated depressive symptoms. However, findings with regard to recurrent MDD and elevated depressive symptoms should be interpreted with caution given the low rate of recurrent MDD and the low level of depressive symptoms in our sample. An a priori test of treatment effects in smokers with these depression vulnerability factors is warranted in future clinical trials.

Introduction

Major depressive disorder (MDD) is one of the psychiatric disorders most frequently associated with cigarette smoking in adults (Glassman, 1993; Grant, Hasin, Chou, Stinson, & Dawson, 2004) and may impede smoking cessation efforts (Covey, 1999; Glassman, 1993). Although conflicting evidence exists regarding the relationship between having a history of MDD and smoking cessation outcomes (Covey, 2004; Hall, 2004; Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003), depressive symptoms (Niaura et al., 2001) and negative moods (Cinciripini et al., 2003; Ginsberg, Hall, Reus, & Muñoz, 1995; Killen et al., 1996; Kinnunen, Doherty, Militello, & Garvey, 1996) have been consistently associated with poorer smoking outcomes.

Cessation treatments that provide strategies for managing depressive symptoms and negative mood have been developed and examined. Studies by Hall and colleagues examining group cognitive–behavioral mood management treatment, with particular attention to smokers with a history of MDD, have yielded mixed findings (Hall, Muñoz, & Reus, 1994;

Richard A. Brown, Ph.D., Raymond Niaura, Ph.D., David R. Strong, Ph.D., Ana M. Abrantes, Ph.D., Ivan W. Miller, Ph.D., Brown Medical School, Department of Psychiatry and Human Behavior and Butler Hospital, Providence, RI; Elizabeth E. Lloyd-Richardson, Ph.D., Brown Medical School, Department of Psychiatry and Human Behavior and The Miriam Hospital, Providence, RI; Christopher W. Kahler, Ph.D., Brown Medical School, Department of Psychiatry and Human Behavior and Brown University Center for Alcohol and Addiction Studies; David Abrams, Ph.D., Office of Behavioral and Social Sciences Research, National Institutes of Health, Bethesda, MD.

Correspondence: Richard A. Brown, Ph.D., Brown Medical School, Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906, USA. Tel: +1 (401) 455-6254; Fax: +1 (401) 455-6424; E-mail: richard_brown@brown.edu

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Hall et al., 1996; Hall et al., 1998). In all three studies, pharmacotherapy was incorporated into the study designs. In the two studies in which a 10-session mood management treatment was compared with a 5-session control condition, smokers with past MDD had better smoking outcomes with the mood management condition (Hall et al., 1994; Hall et al., 1998). However, in the study in which treatment conditions were equated for contact time (both were 10 sessions), the mood management condition did not outperform the control condition among smokers with past MDD (Hall et al., 1996). These studies suggested that the additional contact time, rather than the specific mood management skills, benefited past MDD smokers. However, in a study of smokers with a history of both MDD and alcohol dependence, a group cognitive–behavioral mood management program was associated with significantly higher rates of smoking abstinence compared with a behavioral skills control group (Patten, Martin, Myers, Calfas, & Williams, 1998).

To examine the efficacy of cognitive–behavioral depression skills treatment, we (Brown et al., 2001) recruited a sample of smokers with past MDD and examined two 8-session group treatments equated for therapist and participant contact time: standard smoking cessation (ST) vs. ST plus cognitive–behavioral treatment for depression (CBTD). Although we did not find a significant main effect of treatment, secondary analyses revealed that smokers with recurrent MDD who received CBTD were significantly more likely to be abstinent than those receiving ST. This finding has since been replicated by pooling the data from the three previously cited studies of Hall and colleagues (Haas, Muñoz, Humfleet, Reus, & Hall, 2004), and these findings together suggest that recurrent MDD may be a marker for smoking cessation failure. Thus rather than any history of MDD, it appears that smokers with two or more lifetime MDD episodes may benefit most from targeted mood management skills in smoking cessation treatment. Interestingly, CBTD has not been shown to significantly improve smoking cessation outcomes for smokers with higher levels of depressive symptoms (Brown et al., 2001) or negative mood (Haas et al., 2004).

In addition to the development of cognitive–behavioral mood management treatments for depressed smokers, the efficacy of antidepressant pharmacotherapy has been examined, with the majority of the focus on bupropion hydrochloride. Bupropion is a selective inhibitor of noradrenalin and dopamine. It has been hypothesized that bupropion's effect on reducing the reuptake of dopamine in the mesolimbic system may result in reduced cravings while reduced reuptake of noradrenalin in the locus coeruleus may reduce nicotine withdrawal symptoms (Hays & Ebbert, 2003). Bupropion has consistently outperformed placebo in acute smoking cessation studies (Gonzales et al., 2001; Hall et al., 2002; Hurt et al., 1997; Jorenby et al., 1999; Simon, Duncan, Carmody, & Hudes, 2004; Tonnesen et al., 2003); in relapse prevention studies (Cox et al., 2004; Hays et al., 2001); and across varied subpopulations of smokers such as those with cardiovascular disease (Tonstad et al., 2003), those with post-traumatic stress disorder (Hertzberg, Moore, Feldman, & Beckham, 2001), those with schizophrenia (Evins et al., 2001; George et al., 2002), hospital employees (Dalsgaro et al., 2004), African Americans (Ahluwalia, Harris, Catley, Okuyemi, & Mayo, 2002), veterans with dual diagnoses (Saxon et al., 2003), and adolescents with attention-deficit/hyperactivity disorder (Upadhyaya, Brady, & Wang, 2004).

Given that bupropion is an antidepressant, several studies have examined whether it has differential impact on depressive symptoms during smoking cessation. Depressive symptoms, as measured by the Beck Depression Inventory, have not been found to change following smoking cessation treatment with bupropion lasting either 7 weeks (Hurt et al., 1997) or 9 weeks (Jorenby et al., 1999). However, findings are less consistent when the efficacy of bupropion is examined for cessation among smokers with a history of MDD, with some studies finding bupropion to be more efficacious for past-MDD smokers (Hall et al., 2002; Smith et al., 2003) and some studies finding no such differential efficacy (Cox et al., 2004; Hayford et al., 1999).

A few important questions remain about the efficacy of cognitive–behavioral mood management treatments and bupropion for smokers with depressive vulnerabilities. First, it is unclear whether a more intensive cognitive–behavioral mood management treatment will have robust effects even among those with less severe vulnerabilities. Second, mood management treatments and bupropion have primarily been studied independently as smoking cessation efforts. Previous studies have not explored these two therapeutic approaches in concert for improving smoking cessation outcomes. It is possible that the combination of these two approaches could synergistically influence both mood and smoking outcomes among depressed smokers. Reviews (Conte, Plutchik, Wild, & Karasu, 1986; Friedman et al., 2004b) and studies (Keller et al., 2000; Miller et al., 2005) suggest that combined psychotherapy plus pharmacotherapy can be more effective than either treatment alone for MDD. Similarly, the clinical practice guideline for the treatment of tobacco use and dependence recommends pharmacotherapy in combination with more intensive treatments (Fiore et al., 2000).

The present study examined the effects of an intensive cognitive–behavioral mood management treatment and of bupropion, both singularly and in combination, on the achievement and maintenance of smoking cessation in adult smokers within a randomized placebo-controlled clinical trial. This study builds on our previous work (Brown et al., 2001) by increasing the intensity of CBTD from 8 sessions to 12 sessions and by incorporating a test for the efficacy of bupropion. These changes were made after looking to the depression treatment literature, which indicates that the typical course of cognitive–behavioral treatment for MDD is 16–20 sessions (DeRubeis et al., 2005; Hollon et al., 1992) and that the benefits of combined psychotherapy and pharmacotherapy have been demonstrated (Friedman et al., 2004a; Hollon et al., 2005). We were particularly interested in studying the synergistic effect of CBTD plus bupropion on smoking cessation outcomes in general and in an at-risk smoking subpopulation based on depression vulnerability factors for smoking cessation failure that are both historical (i.e., smokers with single-past-episode and recurrent MDD) and current (i.e., elevated depressive symptoms).

Method

Participants

Participants were 524 smokers recruited via newspaper, radio, and television advertisements to participate in a randomized, double-blind, placebo-controlled 2×2 clinical trial comparing (a) standard, cognitive–behavioral smoking cessation treatment plus bupropion SR (ST+BUP), (b) standard, cognitive–behavioral smoking cessation treatment plus placebo (ST+PLAC), (c) standard cessation treatment combined with cognitive–behavioral treatment for depression plus bupropion SR (CBTD+BUP), and (d) standard cessation treatment combined with cognitive–behavioral treatment for depression plus placebo (CBTD+PLAC). Phone calls from potential participants went to a general, hospital-based health and wellness referral phone line staffed by hospital volunteers. At this time, potential participants were informed about the nature of the study, requirements for participation, and study exclusion criteria of concurrent psychological or psychiatric treatment and unstable medical conditions (e.g., hypertension, seizure disorder). They were then invited to attend an informational meeting prior to study participation. Because of the extensive and diverse demands placed on the health and wellness volunteer staff, we were unable to systematically collect information about the participants who did not attend the informational meetings. At this meeting, potential participants were informed about all study procedures, were randomized to one of two hospital study sites, and were scheduled for an intake interview at their assigned site to confirm eligibility. At the intake interview, participants signed statements of informed consent approved by the Butler Hospital or the Miriam Hospital institutional review board.

All participants in this study were smoking 10 or more cigarettes per day over the past year. Exclusion criteria were (a) current Axis I disorder according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition; *DSM*-IV; American Psychiatric Association, 1994), (b) *DSM*-IV diagnosis of past-year psychoactive substance abuse or dependence (other than nicotine), (c) current use of psychotropic medication or medication that may interact adversely with bupropion, (d) current weekly (or more frequent) psychotherapy, or (e) use of other tobacco products. Participants also were screened by a study physician to rule out the following: any unstable medical condition; hypertension; pregnancy, lactation, or refusal to use contraception while on study medication; history of seizure disorder or head injury with loss of consciousness; eating disorder; or panic disorder. Participants agreed to use only study-supplied medication for smoking cessation for the duration of their study participation.

After initial telephone screening, participants who met preliminary criteria were invited to attend informational meetings outlining the study details and were invited to schedule an initial assessment interview. All participants provided written, informed consent prior to study participation. Participants were randomly assigned to one of two treatment sites, where they were to receive one of two manualized group treatments, ST or CBTD. At the initial assessment interview, participants were screened for exclusion criteria and current *DSM*-IV diagnoses, using a structured clinical interview administered by trained research assistants, supervised by Ph.D.-level investigators trained in clinical psychology. Participants then completed a brief medical examination by the study physician, who assessed medical exclusion criteria. Participants were then randomly assigned to receive one of two medication conditions, bupropion or placebo, using the urn randomization technique (Wei, 1978) with assignment based on gender, current depressive symptoms, and level of nicotine dependence. See Figure 1 for detailed information on treatment cell sizes. Participants completed group and medication therapies over 12 weeks.

Measures

Assessments were completed at baseline and at follow-up at 2, 6, and 12 months post-treatment.

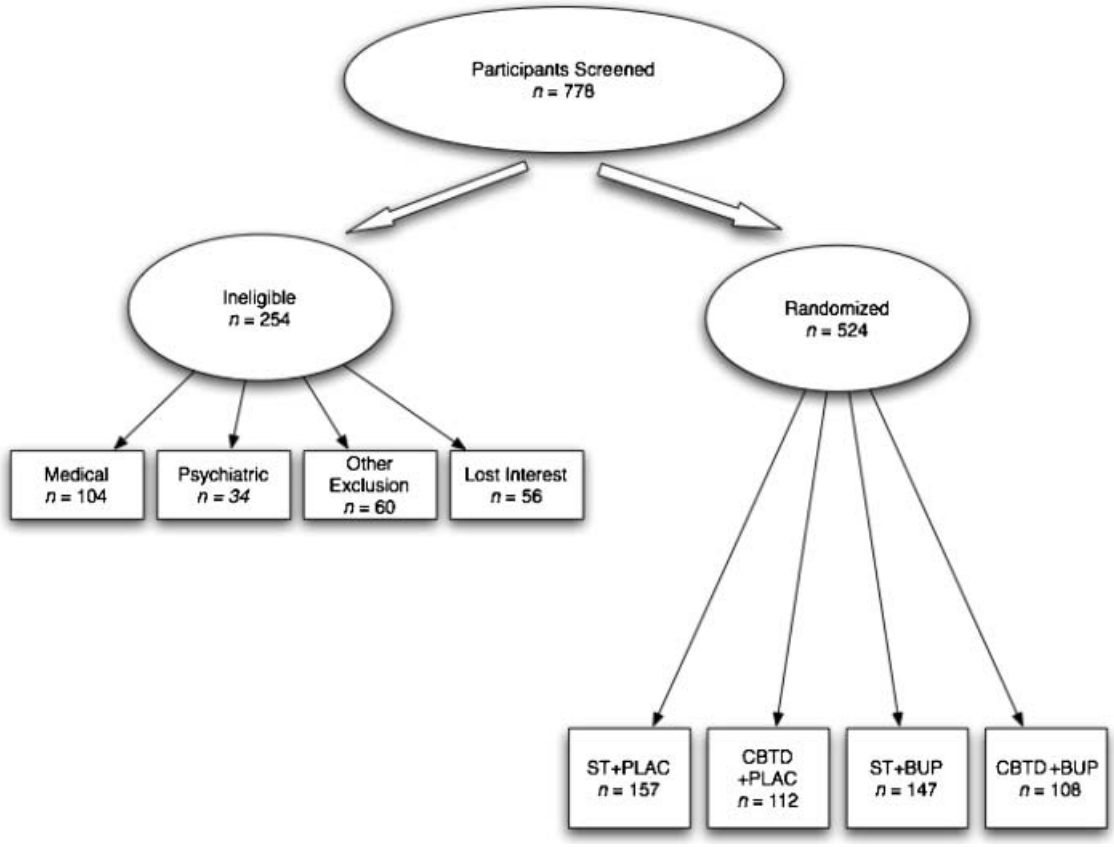

Figure 1. Participant enrollment. BUP, bupropion; CBTD, cognitive–behavioral therapy for depression; PLAC, placebo; ST, standard treatment.

Descriptive and diagnostic measures. Participants provided demographic and background information, such as age, gender, years of education, marital status, number of years of regular smoking, and average number of cigarettes per day. Current and past Axis I diagnoses were determined with the Structured Clinical Interview for *DSM*-IV nonpatient edition (SCID-NP; (First, Spitzer, Gibbon, & Williams, 1995). Severity of nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), a six-item measure with higher scores indicating higher levels of nicotine dependence.

Measures of smoking status and withdrawal. Self-reports of smoking status were obtained at each treatment session from quit date through end of treatment, as well as by telephone at 2, 6, and 12 months. Outcome analyses were based on 7-day point-prevalence abstinence. Participants' reports of abstinence were verified biochemically via two methods: alveolar carbon monoxide (CO) using CMD/CO carbon monoxide monitors (Spirometrics, Inc., Auburn, Maine) and salivary cotinine assay using a 2-ml saliva sample, collected during treatment and at 6- and 12-month follow-up and assayed by American Health Foundation (Valhalla, New York). During follow-up, biochemical measures were obtained in person only from participants reporting 7-day abstinence. Abstinence was confirmed by a combination of $CO \leqslant 10$ ppm and cotinine $\leqslant 15$ ng/ml (Cummings & Richard, 1988; SRNT Subcommittee on Biochemical Verification, 2002). In those few cases where biochemical verification could not be obtained (8.2%), self-reported abstinence was verified through interview with a significant other.

Measures of depressive symptoms. The Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) was used to assess depressive symptoms prior to, during, and after treatment. The scale has demonstrated good reliability and validity (Radloff, 1977) and has been found to be associated significantly with current smoking status and inability to quit in the general population (Anda et al., 1990). History of MDD was assessed via the SCID-NP and used as a covariate in analyses.

Treatments

Medication. Participants were randomized to receive one of two medications: bupropion SR or placebo.

Participants received identically packaged bupropion or placebo pills, prepared by the manufacturer of Zyban (Glaxo-Smith-Kline). Bupropion was delivered according to the standard therapeutic dose (150 mg/day for the first 3 days, followed by 300 mg/day) for a total of 12 weeks. All participants and study staff were blind to medication condition. Study medication side effects were monitored on a weekly basis. Less than 5% (4.8%) of the sample discontinued medication during treatment because of the following: rash, high blood pressure, anxiety, stomach problems, chest pains, swollen tongue, or difficulty concentrating.

Psychosocial intervention. Participants also were randomized to receive one of two intensive group counseling interventions: standard smoking cessation treatment (ST) or standard cessation treatment combined with cognitive–behavioral group therapy for depression (CBTD). Both group treatment conditions provided twelve 90-min sessions and were equated for therapist contact time. Sessions initially occurred twice weekly, followed by weekly and then monthly sessions, for a total of 12 weeks. Quit date began upon awakening on the morning of the seventh session, 3 weeks after session 1. The ST condition was a comprehensive program including self-monitoring, self-management, nicotine fading, relapse prevention, and social support enhancement. The CBTD condition consisted of both standard smoking cessation skills and cognitive–behavioral coping skills for depression that included daily mood ratings, pleasant event scheduling, cognitive restructuring, and assertiveness training. The treatments are described in detail elsewhere (Brown et al., 2001).

Participants were randomized to treatment conditions as follows: 157 ST+PLAC, 112 CBTD+PLAC, 147 ST+BUP, and 108 CBTD+BUP. Whereas we were able to balance the drug and placebo conditions on an individual basis, behavioral treatments were randomized by group and thus were more susceptible to fluctuations in recruitment and to the availability at both sites of pairings of a senior and a junior therapist trained in CBTD. These fluctuations prevented us from fully implementing the study plan to assign four groups within each cohort (two ST and two CBTD groups). On average, participants attended 9.19 (SD=2.53) sessions. Session attendance was not significantly different in any of the four treatment groups (p>.05). Table 1 lists demographic and smoking characteristics of each treatment condition.

Therapists. Each group was led by two Ph.D.-level psychologists who were experienced in the use of CBT. A total of 13 therapists (8 male, 5 female) conducted treatment sessions, and all therapists provided treatment across both conditions. Richard A. Brown provided therapist training and oversight. A junior therapist was always paired with a more senior therapist trained extensively in the treatment protocols. All group sessions were audiotaped for purposes of supervision and assessment of therapist adherence to protocol.

Data analyses

To examine the effects of treatments on point-prevalence abstinence at post-treatment and the three follow-ups, we conducted repeated-measures analyses for categorical outcomes using generalized estimating equations (GEEs; Liang & Zeger, 1986; Zeger & Liang, 1986). GEE analysis allows for inclusion of both categorical and continuous independent variables and for appropriate modeling of covariance structures when observations are correlated across time. Analyses were conducted in SAS using PROC GENMOD, with the Logit link function and an unstructured correlation matrix specified.

The following four covariates were used in the GEE analyses: gender, average daily smoking rate, baseline CES-D score, and history of MDD, which was dichotomized simply as history positive or history negative given the extremely low number of individuals with a history of recurrent MDD. In addition, a variable carrying the linear effect of time was included in all models. In our initial models, we also included a term for treatment site and interactions with treatment site and treatment. However, no

Table 1. Baseline characteristics of participants in each treatment condition.[a]

Characteristic	ST+PLAC (n=157)	CBTD+PLAC (n=112)	ST+BUP (n=147)	CBTD+BUP (n=108)
Age	45.16 (10.98)	44.40 (9.89)	43.89 (9.95)	43.36 (10.57)
Female (%)	47.10%	44.60%	51.0%	46.30%
Cigarettes/day	25.54 (9.62)	25.40 (11.34)	24.46 (9.88)	24.06 (9.30)
CES-D score	6.31 (5.99)	5.44 (6.70)	6.53 (6.73)	5.77 (6.09)
CES-D score>16 (%)	7.7%	7.2%	8.8%	11.1%
MDD history (%)	22.9%	23.4%	19.0%	16.8%

Note. BUP, bupropion; CBT, cognitive–behavioral therapy for depression; CES-D, Center for Epidemiological Studies Depression Scale; MDD, major depressive disorder; PLAC, placebo; ST, standard treatment. [a]Values are means with standard deviations or percentages.

significant effects were found (all p values>.25, and these terms were dropped from the analyses. After testing the main effects of treatment, we tested interactions between treatment condition and time to determine whether treatment effects weakened at later follow-ups. We then tested simultaneously the interactions between CBTD and the four covariates, followed by tests of interactions between bupropion and the covariates. Finally, we tested the interaction between CBTD and bupropion and three-way interactions between CBTD, bupropion, and the two measures of depression vulnerability (MDD history and CES-D).

For our primary analyses, only individuals who had smoking abstinence confirmed at a given follow-up were considered abstinent; those with missing data were considered nonabstinent. In this way, our reported abstinence rates correspond to the reporting of abstinence in most smoking cessation trials and allow for cross-study comparisons. However, in the GEE analyses, we also ran analyses in which no assumptions were made about missing data, using only available data for each participant. Those analyses excluded the 12 participants who provided no follow-up data. Results using no assumptions regarding missing data were highly concordant with those using a worst-case assumption and therefore are not detailed here.

Results

Of the 524 participants randomized to treatment, 249 (47.5%) were women, and 322 (61.4%) were married. The mean age of the sample was 44.27 years (SD=10.38), and the mean number of years of education was 13.61 (SD=2.25). The majority of participants (92%) identified themselves as White (n=482), with 3.8% African American (n=20), 2.3% Hispanic (n=12), and 1.9% (n=10) identifying themselves as coming from other racial/ethnic origins. Prior to treatment, participants reported smoking on average 24.6 cigarettes/day (SD=10.0) and had smoked for an average of 26.0 years (SD=10.64). The sample mean on the FTND was 6.41 (SD=1.90). The majority of participants (94.5%) had made at least one quit attempt that lasted more than 12 hr. The sample baseline mean on the CES-D (Radloff, 1977) was 6.08 (SD=6.37). Most participants (79.0%; n=414) had no history of MDD, 17.6% of participants (n=92) had single-past-episode MDD, 3.1% of participants (n=16) had recurrent MDD, and information on past history of MDD was missing for two participants (0.4%). Overall rates of any history of substance use disorder were high (43.7%). Specifically, 39.5% met criteria for lifetime alcohol abuse (n=120) or dependence (n=87), and 19.1% met criteria for lifetime drug abuse (n=41) or dependence (n=59).

Of the 524 participants who began treatment, 426 participants or their significant others (81.3%) provided complete outcome data at all follow-ups: post-treatment, 2 months, 6 months, and 12 months. A total of 64 participants (12.2%) lacked complete outcome data at one of the four follow-ups, 13 (2.5%) lacked data at two follow-ups, 9 (1.7%) lacked data at three follow-ups, and 12 (2.3%) lacked data at all follow-ups. The odds of completing follow-ups were not significantly related to treatment condition.

Seven-day point-prevalence abstinence rates at the end-of-treatment, 2-month, 6-month, and 12-month follow-ups, respectively, for the four cells in our 2×2 design were as follows: ST+PLAC, 24.8%, 21.0%, 17.8%, and 15.3%; CBTD+PLAC, 25.9%, 25.9%, 15.2%, and 17.9%; ST+BUP, 49.7%, 42.9%, 27.9%, and 22.5%; CBTD+BUP, 38.9%, 25.0%, 23.2%, and 17.6%. These outcomes are shown in Figure 2. Rates of continuous abstinence (confirmed abstinence at post-treatment, 2 months, 6 months, and 12 months) were 8.9%, 11.6%, 17.7%, and 11.1%, respectively.

The initial GEE model with time, the four covariates (gender, smoking rate, baseline CES-D score, and MDD history), and the main effects of treatment showed a significant effect of time (B=−0.31 SE=0.04, OR=0.73, p<.0001), reflecting the strong tendency for abstinence rates to decrease after treatment. The main effect of cigarettes smoked per week also was significant, with greater smoking being related to lower odds of abstinence (B=−0.02, SE=0.09, OR=0.98, p=.03). The effects of the other three covariates were nonsignificant. The main effect of BUP was significant (B=0.68, SE=0.17, OR=1.97, p<.0001), with those receiving BUP having a greater odds of abstinence than those receiving PLAC. The main effect of CBTD was nonsignificant (B=−0.21, SE=0.17, OR=0.81, p=.22).

In the second step of the analysis, interactions between BUP and CBTD were added along with interactions between BUP and time and CBTD and time. Only the BUP × time interaction was significant (B=−0.20, SE=0.07, OR=0.82, p=.009). This result indicated that the decrease in the rate of abstinence from post-treatment to 12 months was significantly steeper for those receiving BUP than for those receiving PLAC. At post-treatment, the main effect for BUP compared with PLAC was highly robust (B=0.88, SE=0.19, OR=2.41, p<.0001). The effect was weaker by 2 months post-treatment (B=0.61, SE=0.20, OR=1.84, p=.002) and 6 months post-treatment (B=0.54, SE=0.22, OR=1.72, p=.01), and was substantially weaker and nonsignificant by 12 months (B=0.26, SE=0.23, OR=1.30, p=.26). For the remaining models, the BUP × time interaction was retained and the other two interactions were dropped from the model.

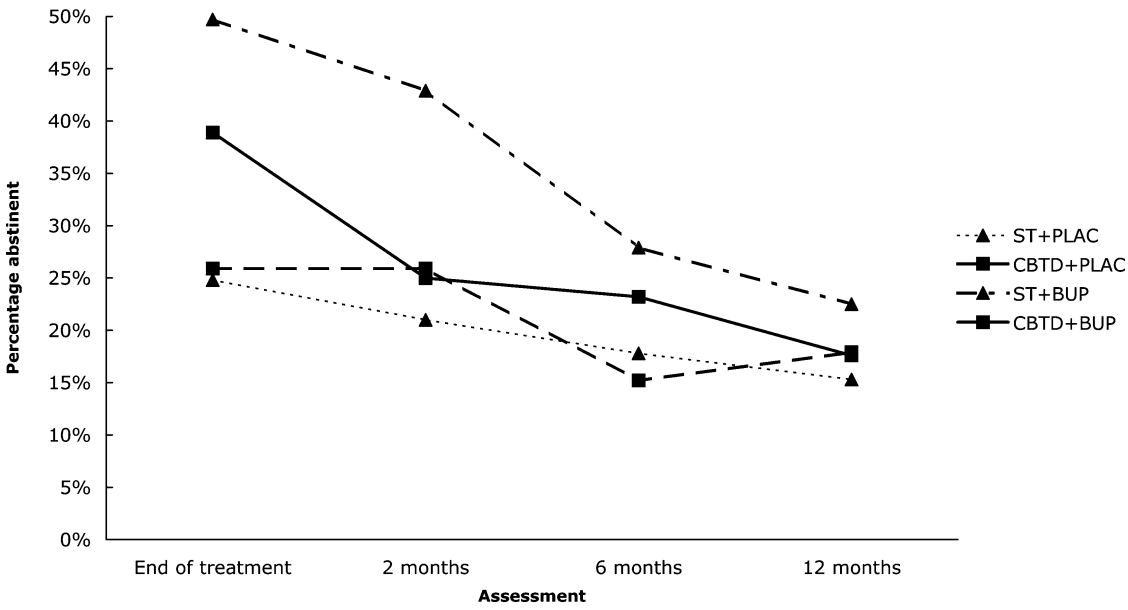

Figure 2. Rates of confirmed 7-day point-prevalence abstinence at the end of the treatment period, as well as at 2, 6, and 12 months after treatment ended. BUP, bupropion; CBTD, cognitive–behavioral therapy for depression; PLAC, placebo; ST, standard treatment.

In the third step, variables carrying the interactions between CBTD and the four covariates (gender, smoking rate, baseline CES-D score, and MDD history) were added simultaneously to the model described above. None of the interactions was significant (p values$>$.19). We then removed these interactions and added the interactions between BUP and the four covariates. Again, none of the interactions was significant (p values$>$.07). Correlations among the covariates were generally weak; all r values were less than .10, except for the correlation between female gender and smoking rate, $r(522)=-.20$, $p<.0001$, and the correlation between MDD history and baseline CES-D score, $r(519)=.18$, $p<.0001$. Given the multicollinearity among these covariates, we also tested each covariate's interaction with treatment individually. Again, all interaction effects tested were nonsignificant.

Finally, to test the potential synergistic effects of BUP and CBTD for those with depressive risk factors, we ran a model in which we added the two-way and three-way interactions of MDD history and CES-D with BUP, CBTD, and BUP × CBTD. Neither the MDD history × BUP × CBTD interaction nor the CES-D × BUP × CBTD interaction was significant (p values$>$.30). Thus we found no evidence of synergistic effects for smokers with depressive vulnerabilities.

Discussion

This is the first study to examine the efficacy of bupropion when combined with intensive group smoking cessation treatment in the context of a randomized, double-blind, placebo-controlled clinical trial. Strengths of the study include a large sample size, 12-month follow-up with high retention rates, and biochemically verified smoking outcomes. Primary aims of the study were to examine the efficacy of bupropion when combined with intensive cognitive–behavioral smoking cessation treatment, with and without the addition of CBTD. Consistent with previous studies, bupropion, compared with placebo, resulted in better smoking outcomes in both intensive group treatments; bupropion was associated with higher rates of abstinence at the end of treatment and at follow-up time points. Adding CBTD to standard intensive group treatment did not result in improved smoking cessation outcomes. In addition, neither CBTD nor bupropion was differentially effective for smokers with depression vulnerability factors such as MDD history or elevated depressive symptoms.

Although the treatment effect of bupropion was significant in the present study, we also expected that the addition of CBTD would offer extra benefit to smokers with depression vulnerability factors. Our previous work (Brown et al., 2001) and that of Hall and colleagues (Haas et al., 2004) demonstrated that adding CBTD to smoking cessation treatment was efficacious only for smokers with recurrent MDD. Thus, in an effort to extend the efficacy of this treatment to smokers with the depression vulnerability factors of single-past-episode MDD and elevated depressive symptoms, we increased the "dosage" of CBTD in this study from 8 sessions to 12 sessions. Contrary to our hypothesis, adding CBTD to standard cognitive–behavioral smoking

cessation treatment did not significantly improve outcomes for smokers with a history of MDD or for those with elevated levels of depressive symptoms. The prevalence of past-episode MDD was on the low end of the range found in previous smoking cessation studies, and only 16 participants had recurrent MDD, which prohibited us from conducting analyses specifically within that subgroup. Thus our results speak primarily to the effects of CBTD on those with single-episode MDD. Consistent with previous findings (Brown et al., 2001; Hall et al., 1996) and despite the increased dosage, we found no evidence for a beneficial effect of CBTD on smoking cessation among predominantly single-past-episode MDD smokers. However, only 108 smokers had a history of MDD, limiting our statistical power to find effects of CBTD in this group. For example, with 108 participants, we had a power of approximately .80 to find a significant effect of CBTD at any given follow-up if we assumed a true effect size of $h=.50$ (e.g., 20% abstinence vs. 43% abstinence; $OR=3.0$), which is an effect of medium size (Cohen, 1988). The effect of CBTD in those with past MDD was much smaller than this value, with an odds ratio of only 1.30 in the GEE analysis.

Findings with regard to the vulnerability factors of recurrent MDD and elevated depressive symptoms are less certain. As noted above, small sample size prohibited us from testing the effects of CBTD in those with recurrent MDD. Similarly, smokers in our sample had an overall low level of depressive symptoms. Therefore, we do not know whether CBTD would have been differentially effective for smokers with clinically elevated levels of depressive symptoms.

A strong body of literature supports the use of bupropion for smoking cessation. However, our results also point to the waning effect of bupropion in smoking cessation treatment. During the 12 months after the discontinuation of bupropion, abstinence rates declined such that treatment with bupropion no longer showed an advantage over placebo. Continuing to prescribe bupropion following the discontinuation of intensive group smoking cessation treatment may be necessary to maintain smoking abstinence and to prevent smoking relapse. Support for this suggestion is found in a multicenter, randomized, double-blind, placebo-controlled study in which smokers who were abstinent after 7 weeks of open-label bupropion were randomly assigned to 45 more weeks of either placebo or bupropion (Hays et al., 2001). In that study, the 52-week point prevalence of smoking abstinence was significantly higher in the bupropion group than in the placebo group. Median time to relapse and continuous abstinence also were higher in the treatment group. Therefore, continuation of bupropion use for smoking cessation may be a promising maintenance strategy following intensive group treatment.

The low prevalence of smokers with significant depression vulnerability limited our ability to test hypotheses about the impact of bupropion and CBTD on this at-risk subpopulation of smokers. There may be several explanations for these low rates of depression vulnerability. First, we excluded participants who were currently taking prescribed psychotropic medications or were currently engaged in psychotherapy. Individuals with significant depression vulnerability are among the most likely to be receiving one or both of these forms of treatment already. Additionally, the exclusion of individuals with various types of medical comorbidities may have resulted in lower participation among depression-vulnerable smokers, given the high rates of medical morbidity among individuals with depression (Wells et al., 1989).

The present study sample was relatively homogeneous with regard to racial composition; almost all participants were White. Although our sample reflected the racial characteristics of the prevailing local population, non-White individuals may respond differently to these treatments. As always, caution is indicated before making direct generalizations of these results to other populations. Although this study featured two intensive group smoking cessation treatments that were equated for contact time, a limitation of this design is the lack of inclusion of a control condition to estimate the efficacy of these intensive treatments. Finally, an imbalance existed between participants assigned to the two group treatments. However, given the lack of between-group differences, we are confident that the study conclusions would not have differed had the groups been balanced.

In summary, our study and those of others have shown that bupropion is effective across a range of depression vulnerability factors. The present study supports the previously observed lack of effect of CBTD for smoking cessation among smokers without a history of MDD or with single-past-episode MDD. Although CBTD appears promising for smoking cessation among smokers with recurrent MDD (Brown et al., 2001; Haas et al., 2004), the present study was unable to evaluate the effects of CBTD for this at-risk population. With regard to elevated depressive symptoms, neither CBTD nor bupropion appeared to have differential efficacy across the low to moderate ranges of depressive symptoms. Future studies should evaluate the effects of these treatments among smokers with clinically elevated levels of depressive symptoms. Further, an a priori test of CBTD for smokers with recurrent MDD is warranted given that the effects of CBTD in this population have been found in post-hoc tests of

interactions rather than in studies designed specifically to test CBTD in smokers with this vulnerability factor.

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