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A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling

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Efficacy of bupropion SR and individual counseling as smoking cessation treatments was assessed in a randomized, placebo-controlled clinical trial among adult daily smokers. Bupropion SR treatment and counseling were fully crossed in this factorial design so that the efficacy of each treatment and the combination could be estimated, relative to a placebo medication and assessment control condition. Intent-to-treat analyses indicated that bupropion SR increased abstinence rates at the end of treatment, relative to the placebo medication conditions, for both biochemically confirmed 7-day point-prevalence abstinence (*OR*=1.97, 95% *CI* 1.04–3.72) and self-reported prolonged abstinence (*OR*=2.90, 95% *CI* 1.66–5.06). Bupropion SR treatment also improved latency to lapse and relapse and improved the latency between lapse and relapse in survival analyses. Medication effects were more modest for both 12-month point-prevalence abstinence (*OR*=1.47, 95% *CI* 0.74–2.92) and prolonged abstinence (*OR*=1.34, 95% *CI* 0.66–2.72). Counseling was not associated with increases in the likelihood of abstinence at any time point (odds ratios ranged from 0.80 to 1.16 across abstinence outcomes in the full intent-to-treat sample). Counseling and medication did not significantly interact at any time point, and adding counseling did not improve end-of-treatment point-prevalence abstinence (*OR*=1.17, 95% *CI* 0.68–2.03) or prolonged abstinence (*OR*=1.26, 95% *CI* 0.75–2.12) substantially when offered in conjunction with active medication.

Introduction

Research has identified several empirically supported treatments to help people stop smoking successfully. Meta-analyses of randomized clinical trials suggest that these treatments, including pharmacotherapies and psychosocial interventions, roughly double the odds of quitting successfully for at least 6 months (Fiore et al., 2000; Hughes, Stead, & Lancaster, 2004; Lancaster & Stead, 2005; Silagy, Lancaster, Stead, Mant, & Fowler, 2004; Stead, Perera, & Lancaster, 2006). Evidence of the efficacy of many of these treatments has been accruing for years. Recently, however, studies have suggested that empirically supported treatments may be declining in efficacy (Irvin & Brandon, 2000; Irvin, Hendricks, & Brandon, 2003).

The trend in declining efficacy and its possible explanations (e.g., changes in clinical trial methods, ''hardening'' among smokers reflecting increased tobacco dependence among those who continue to smoke; Fagerström et al., 1996; Hughes & Brandon, 2003; Irvin & Brandon, 2000; Irvin et al., 2003; U.S. Department of Health and Human Services, 2003; Warner & Burns, 2003) are controversial, however. Although we do not currently have sufficient information to differentiate among competing explanations regarding declining treatment efficacy, the controversy bespeaks the need for ongoing evaluations of postmarketing pharmacotherapies and widely disseminated psychosocial interventions.

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Data for the current study came from a large-scale, placebo-controlled clinical trial comprising adult smokers interested in quitting. The study tested two independent treatments: sustained-release bupropion (Zyban, GlaxoSmithKline) and multisession individual smoking cessation counseling based on the U.S. Public Health Service (PHS) clinical practice guideline (Fiore et al., 2000). Because the two active treatments in the study were fully crossed, the factorial design allowed us to compare the effects of pharmacotherapy versus psychosocial treatment, alone and in combination. The specific treatments tested are widely used, and evidence supports their efficacy (e.g., Fiore et al., 2000; Richmond & Zwar, 2003).

Study hypotheses

Based on previous research (for reviews, see Fiore et al., 2000; Hughes, Stead et al., 2004; Lancaster & Stead, 2005; Richmond & Zwar, 2003), we expected to see main effects on abstinence for both counseling and medication treatment at the end of treatment and throughout the first year following the target quit date. Meta-analyses of bupropion SR treatment suggest that bupropion SR increases the odds of successfully quitting through at least 6 months by a factor of two (Fiore et al., 2000; Hughes, Stead et al., 2004). In addition, given bupropion's antagonism of nicotinic receptors (Rauhut, Neugebauer, Dwoskin, & Bardo, 2003; Slemmer, Martin, & Damaj, 2000), we also predicted that bupropion would retard progression from a smoking lapse to a full-blown relapse (defined as smoking at least 7 days in a row).

Meta-analyses generally support the efficacy of counseling treatments when offered alone; counseling is associated with a 1.5-fold increase in the odds of quitting smoking successfully, relative to comparison conditions (Fiore et al., 2000; Lancaster & Stead, 2005). Negative findings have been reported, however, particularly for less-intensive, problem-solving-focused counseling interventions (e.g., Bronson, Flynn, Solomon, Vacek, & Secker-Walker, 1989; Burling, Marshall, & Seinder, 1991; Fiore et al., 2004; Jorenby et al., 1995). PHS clinical practice guideline meta-analyses suggested that cessation odds ratios improved with increases in the intensity of counseling (i.e., duration of sessions) and number of sessions (Fiore et al., 2000). For this reason, we used a 10-min minimum for counseling sessions and offered a total of eight sessions in this study.

The majority of trials of bupropion SR efficacy offered some form of psychosocial treatment as an adjunct to the pharmacotherapy (Richmond & Zwar, 2003). However, only two previous trials systematically manipulated the presence of counseling offered in combination with bupropion SR. The first trial to address the question of the additive benefit of counseling was a trial of a group, multisession, cognitive–behavioral treatment (CBT) versus medication management in participants randomized to bupropion SR, nortriptyline, or placebo. The authors of this trial found evidence for the efficacy of CBT as a stand-alone treatment but no evidence that the CBT treatment augmented long-term abstinence rates in the active medication conditions (Hall et al., 2002). The second trial examined the effectiveness of a telephone counseling program versus a tailored mailing program (with one brief phone call) offered in combination with either 150-mg or 300-mg bupropion SR pharmacotherapy in clinical care settings (Swan et al., 2003). This study found no significant effect of increased intensity of behavioral treatment and no interaction between counseling condition and bupropion SR dose at the 3-month follow-up. However, 9 months later, participants who received the moderate-intensity telephone counseling were 1.21 (95% *CI* 1.08–1.32, $p<.001$) times more likely to be abstinent than were those who received only the tailored mailings, regardless of bupropion SR dose. Thus the only two studies to systematically evaluate the effect of psychosocial treatment in the context of bupropion SR pharmacotherapy yielded somewhat discrepant results. Even in the trial reporting positive results (Swan et al., 2003), the effect size for adjuvant counseling versus a tailored mailing was modest, even when compared against a psychosocial treatment that involved very little person-to-person contact.

In the present study, we expected counseling and bupropion SR to interact such that the effect of counseling would be larger in the context of placebo medication than in the context of active bupropion SR treatment because several studies have failed to find an effect for the addition of psychosocial treatment to other forms of pharmacotherapy (e.g., Jorenby et al., 1995; Lancaster & Stead, 2005; Lando et al., 1997), despite research demonstrating the efficacy of psychosocial treatments used by themselves (Fiore et al., 2000; Lancaster & Stead, 2005; Orleans et al., 1991). In addition, neither of the studies that examined the additive effect of counseling interventions offered with bupropion SR (Hall et al., 2002; Swan et al., 2003) yielded compelling evidence of a counseling-attributable benefit. Although earlier research indicated that behavioral counseling had a modest additive effect when offered with nicotine patch therapy (Fiore, Smith, Jorenby, & Baker, 1994), such additive effects have been elusive in more recent research, (e.g., Fiore et al., 2004).

The hypotheses stated above were tested using data from a sample of 463 adult, daily smokers who enrolled in this randomized, placebo-controlled, double-blind clinical trial of bupropion SR and

individual counseling. Participants engaged in extensive prequit assessment prior to a 9-week treatment phase and were followed through 1 year after the target quit date. In accordance with recent recommendations regarding the reporting of smoking cessation outcomes (Hughes et al., 2003), we present multiple abstinence endpoints, including prolonged abstinence and biochemically verified 7-day point-prevalence abstinence at the end of treatment, at 6-months postquit, and at the end of the 12-month follow-up period. We also present results from survival analyses based on time to the first lapse to smoking following the quit day, time to the end of prolonged abstinence, and time between a first lapse and full relapse.

Method

Design

Enrolled smokers were randomly assigned to receive either active or placebo bupropion SR with either eight sessions of brief (10-min) individual cessation counseling or a control condition involving medication management and assessment only with no counseling. The study used a two (active drug vs. placebo) × two (counseling vs. no counseling) factorial design (Figure 1).

Participants

Participants were adults (aged 18 years or older) recruited in the Madison, Wisconsin, area via mass media calls for volunteers who reported smoking at least 10 cigarettes/day and whose expired carbon monoxide (CO) levels exceeded 9 ppm. Participants reported being motivated to quit smoking (as reflected by a score of at least 3 on a 4-point self-report scale) and being willing to fulfill study requirements. Potential participants were screened for serious psychopathology (bipolar disorder or psychosis), current depression, and contraindications to use of bupropion SR (e.g., uncontrolled hypertension, history of seizure disorder, history of eating disorders, current heavy drinking, risk of pregnancy, or current breast feeding). Participants were excluded if their score on the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977) was above 16, except when an interview with a licensed clinician suggested that symptoms were related to a cause other than clinical depression. This exclusion criterion was included to prevent negative effects of a smoking cessation attempt on already depressed participants' mood and safety.

Target enrollment was 480 participants based on a priori power analyses to ensure power greater than .75 to detect at least 7% differences in 12-month abstinence rates. A total of 463 participants passed all screening, enrolled in the study, and attended the first study visit. Demographic characteristics of the enrolled sample are summarized in Table 1.

Measures

At early office visits, participants provided demographic information (Table 1) and a battery of self-report measures assessing nicotine dependence, smoking history, affect, and psychiatric symptoms. Except for the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), these measures are not discussed further in this report.

Self-report data regarding smoking behavior were collected via palmtop computer and interview. Electronic diaries (Palm Vx Palmtop Computer, Palm, Inc., Santa Clara, California) were programmed by invivodata Inc. (Pittsburgh, Pennsylvania) to administer multiple ecological momentary assessment reports (Stone & Shiffman, 1994) during the waking day. Morning reports assessed any smoking since bedtime and prompted medication use. Random prompts occurred at four to seven pseudo-random times during the day and assessed any smoking since the last report. Evening reports completed at bedtime assessed the number of cigarettes smoked over the preceding 24 hr and reminded participants to take medication. Participants also were asked to initiate reports following "slips" in which they smoked after the quit date. In addition, daily smoking totals were assessed throughout the treatment and follow-up phases using a time-line follow-back smoking calendar interview method through 1-year postquit.

Procedures

All study procedures were approved by an Institutional Review Board. Individuals responding to mass media calls for volunteers were screened for eligibility by telephone. Eligible individuals were invited to a group orientation session at which the study was described in detail and written informed consent was obtained. Additional screening (e.g., CO testing) was performed at the orientation session and at the first office visit (e.g., physical exam). Participants were considered enrolled if they passed all three rounds of screening. Data regarding attrition at each point of the screening process was available only for later cohorts (these data were not retained for initial cohorts). Rates of prospective participant loss and exclusion based on two cohorts are depicted in Figure 1.

Randomization occurred at enrollment. Staff who screened and enrolled participants were unaware of

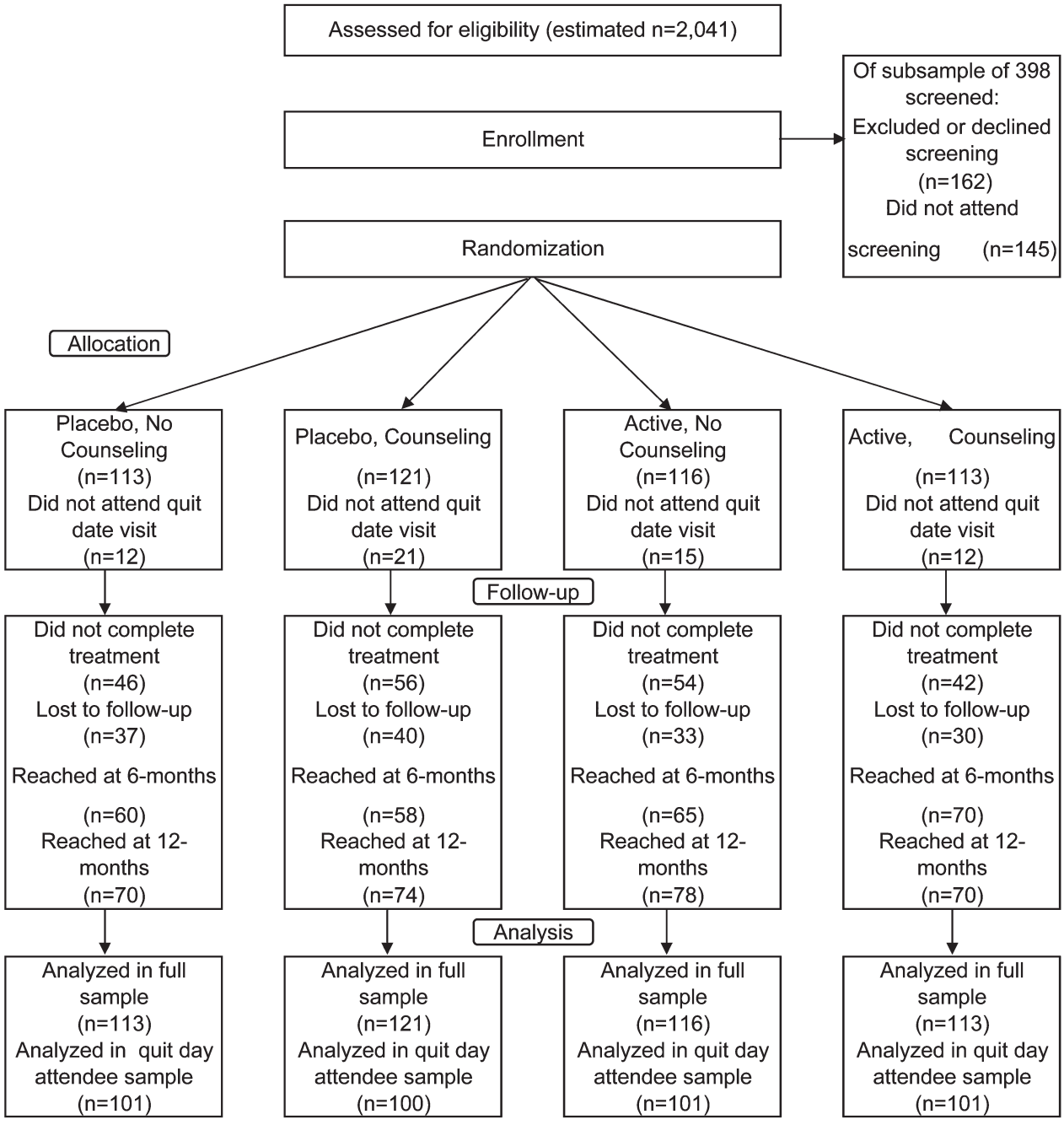

Figure 1. Participation flow diagram. Numbers of participants enrolled, treated, followed, and analyzed are depicted for the entire enrolled sample. Number of people screened for enrollment is estimated, as data were not available for all cohorts, assuming a 22.86% enrollment rate based on two cohorts for which data were available.

the experimental condition to be assigned. Randomization via random number list was not blocked. Study pills, which looked identical in the placebo and active medication conditions, were packaged in containers labeled with participant identification numbers prior to participant enrollment. Research staff who interacted with participants were blind to participants' medication condition assignment. Neither research staff nor participants were blind to counseling condition.

Participants attended five office visits (including the baseline assessment session) in the 3 weeks prior to the quit date. Participants attended another eight office visits over the 8 weeks following the quit date (at days 0, 3, 7, 14, 21, 28, 42, and 56 post-quit) and then completed monthly follow-up phone calls. Participants provided breath samples for CO testing at all visits and provided a blood sample to assess cotinine (the first metabolite of nicotine) levels at baseline and again at the end of treatment, if they claimed abstinence.

Table 1. Demographic characteristics of enrolled sample by treatment condition.

Variable and value	Placebo, no counseling	Placebo, counseling	Active medication, no counseling	Active medication, counseling
Sex (*N*=463)				
Female	61 (54.0%)	63 (52.1%)	57 (49.1%)	52 (46.0%)
Race/ethnicity (*n*=460)				
Hispanic	1 (0.9%)	0	3 (2.6%)	1 (0.9%)
White	104 (92.0%)	104 (86.7%)	103 (89.6%)	101 (90.2%)
Black	5 (4.4%)	6 (5.0%)	7 (6.1%)	8 (7.1%)
Other	4 (3.5%)	10 (8.3%)	5 (4.3%)	3 (2.7%)
Marital status (*n*=461)				
Married	45 (40.2%)	42 (34.7%)	55 (47.4%)	56 (50.0%)
Divorced	29 (25.9%)	16 (13.2%)	22 (19.0%)	18 (16.1%)
Never married	23 (20.5%)	46 (38.0%)	26 (22.4%)	22 (19.6%)
Cohabitating	9 (8.0%)	12 (9.9%)	9 (7.8%)	14 (12.5%)
Separated	4 (3.6%)	3 (2.5%)	1 (0.9%)	2 (1.8%)
Widowed	2 (1.8%)	2 (1.7%)	3 (2.6%)	0
Education (*n*=461)				
<High school	6 (5.3%)	6 (5.0%)	3 (2.6%)	5 (4.5%)
High school	30 (26.5%)	18 (15.0%)	30 (25.9%)	26 (23.2%)
Some college	50 (44.2%)	65 (54.2%)	53 (45.7%)	56 (50.0%)
College degree	27 (23.9%)	31 (25.8%)	30 (25.9%)	25 (22.3%)
Employment status (*n*=455)				
Employed	93 (82.3%)	95 (78.5%)	91 (78.4%)	97 (85.8%)
Unemployed	6 (5.3%)	9 (7.5%)	5 (4.3%)	5 (4.4%)
Homemaker	3 (2.7%)	2 (1.7%)	5 (4.5%)	8 (7.2%)
Student	5 (4.5%)	3 (2.5%)	3 (2.7%)	1 (0.9%)
Retired	2 (1.8%)	6 (5.0%)	6 (5.4%)	0
Disabled	3 (2.7%)	5 (4.2%)	2 (1.8%)	0
Household income (*n*=453)				
<US$25,000	30 (27.5%)	53 (44.2%)	35 (31.02%)	23 (20.7%)
$25,000–$34,999	20 (18.3%)	16 (13.3%)	13 (11.5%)	21 (18.9%)
$35,000–$49,999	25 (22.9%)	13 (10.8%)	24 (21.2%)	26 (23.4%)
>$50,000	34 (31.2%)	38 (31.7%)	41 (36.3%)	41 (36.9%)
Mean age, years (*N*=463)	39.42 (11.34)	37.82 (12.82)	41.03 (12.64)	36.76 (11.39)
Mean age at first cigarette, years (*N*=463)	13.42 (3.51)	13.53 (3.53)	13.97 (4.45)	12.97 (3.78)
Mean number of cigarettes smoked per day (*N*=463)	21.37 (8.11)	21.98 (11.90)	22.47 (10.10)	21.87 (11.24)
Mean number of previous quit attempts (*n*=425)	6.86 (13.88)	6.95 (11.41)	5.86 (9.84)	4.09 (4.40)
Mean baseline CO level (*n*=462)	25.04 (11.73)	21.91 (10.91)	24.79 (11.03)	25.90 (12.28)
Mean baseline FTND score (*n*=457)	5.27 (2.07)	4.95 (2.56)	5.12 (2.30)	5.10 (2.51)

Note. Mean values include standard deviations in parentheses. All other values are numbers of subjects with percentages. FTND, Fagerström Test of Nicotine Dependence.

Adverse events were assessed at each visit during the treatment phase. In addition to attending visits, participants completed electronic diary entries as described above for 2 weeks preceding, and 4 weeks following, the target quit date. People who claimed abstinence at 6- or 12-months postquit were asked to attend an office visit for CO testing within 5 days of the telephone interview. Total remuneration for attendance of study visits, including the follow-up CO-confirmation visits, did not exceed US$200. Participants were informed that payment was contingent on return of the electronic diary at the end of the recording period.

Treatment

Participants began taking one pill (150-mg of bupropion SR or placebo) in the morning 1 week before the quit day and then increased to two 150-mg pills/day, 4 days prior to quitting. Participants were instructed to continue taking 300-mg/day for 8 weeks postquit. Counseling consisted of two prequit sessions, one session on the quit day, and five postquit sessions over the first 4 weeks following the quit day. In accordance with recommendations in the PHS clinical practice guideline (Fiore et al., 2000), these 10-min counseling sessions focused on (a) preparation for the quit day (e.g., disposing of all cigarettes, putting away paraphernalia; striving for complete abstinence), (b) coping and problem solving (e.g., identifying triggers for relapse, applying lessons learned from past lapses and relapses to the current quit attempt, providing psychoeducation regarding distraction and coping), (c) relapse prevention (e.g., through long-term planning and psychoeducation regarding relapse risks), and (d) intratreatment social support (e.g., empathy, encouragement). Counseling also aimed to promote maintenance of quit-smoking motivation by encouraging participants to identify and record multiple reasons for quitting and to

develop ways to remind themselves of these reasons after the quit day. Participants who did not receive counseling received psychoeducation regarding medication use and adherence, information about their target quit day, and general support and encouragement from study staff, but did not receive the specific counseling interventions listed above. Participants in the no-counseling conditions completed the same study visits and assessments as did those in the counseling conditions, but they had slightly shorter sessions than did those assigned to counseling. Thus the no-counseling comparison condition had roughly 80 fewer minutes of contact with staff and did not receive the targeted interventions offered in the counseling condition.

Attrition

Prior to the quit date, 13.0% of the enrolled sample dropped out of the study (Figure 1), leaving 403 participants who were exposed to treatment and made a quit attempt. A total of 265 participants (57.2% of enrollees) attended all 12 study visits, without misses or early termination. Monthly follow-up contact rates ranged from 47% of enrollees at 9-months postquit to 63% at 12-months postquit. The mean number of study visits attended was 9.67 (SD=3.41) out of a possible 12, and the mean number of follow-up interviews completed was 5.21 (SD=4.09) out of a possible 10 monthly phone calls between 3 and 12 months post-quit. Attrition rates did not differ by treatment condition at the quit date, at the conclusion of the treatment phase, or at any follow-up point (chi-square; all p values $>$.05).

Minority status and gender were unrelated to attendance at any point (chi-square; all p values $>$.05). College graduates were significantly more likely to attend the quit date visit, complete all study visits, and complete every follow-up interview than were those with lower levels of education (chi-square; all p values $<$.05). Total FTND score was inversely related to the probability of staying in the study through the quit date (OR=0.87, 95% CI 0.77–0.98). Follow-up interview completion was negatively related to FTND score and baseline CES-D score and positively related to age in univariate logistic regressions at some time points (not shown). These variables, along with gender and ethnic minority status, were included as covariates in models predicting abstinence, given reports of relations among these baseline characteristics and relapse risk (Ahluwalia, Harris, Catley, Okuyemi, & Mayo, 2002; Burns et al., 2000; Hall et al., 2002; Niaura et al., 2001; Shiffman et al., 1996; Smith et al., 2003; Swan et al., 2003; Wetter et al., 2005). All models were tested both with and without these baseline covariates included in the model to assess the robustness of treatment effects on abstinence.

Smoking outcome coding

The timing of the first lapse and first relapse (first 7 consecutive days of smoking, at any level; Hughes et al., 2003) was determined based on a dichotomous variable indicating any smoking versus abstinence on a given day, based on electronic diary reports and retrospective smoking calendar data.

The 7-day point-prevalence abstinence at the end of treatment was confirmed biochemically via CO testing and serum cotinine testing. A total of 10 individuals (9%) with CO-confirmed 7-day point-prevalence abstinence had end-of-treatment cotinine levels that exceeded the conventional cutoff for abstinence of 15 ng/ml (SRNT Subcommittee on Biochemical Verification, 2002). In addition, 40 individuals (8.6% of the total sample and 36.0% of the 111 participants with CO-confirmed claims of abstinence) declined to provide a blood sample for cotinine testing, which required a separate visit to the laboratory. Analyses were conducted two ways. In the first approach, individuals who did not provide serum cotinine were considered relapsed. In the second approach, all people who had CO-confirmed abstinence but did not provide a blood sample were considered abstinent. Results were consistent across both approaches.

Abstinence rates at 6- and 12-months postquit were based on self-reported complete abstinence from smoking in the 7 days preceding the follow-up interview and an average CO reading of 10 ppm or less. At the 6-month follow-up, 65 of 87 (74.7%) people claiming abstinence provided breath samples. At the 12-month follow-up, 83 of 99 (83.8%) self-reported abstainers provided breath samples. Two claims of abstinence (3.1% of those tested) were disconfirmed using CO at 6-months postquit; four claims (4.8% of those tested) were disconfirmed at 12-months postquit. When five extreme cases in which CO testing was 4–8 weeks early or late were excluded, the average delay between self-report and CO assessment was 4.30 (SD=3.32) days at the 6-month follow-up and 5.81 (SD=8.13) days 12-month postquit.

We also computed prolonged abstinence outcomes, as recommended by Hughes et al. (2003). Participants were given a 2-week grace period and were considered to have failed at prolonged abstinence if they reported smoking 7 days in a row at any point between 2 weeks postquit and the end of treatment, 6-months postquit, or 1-year postquit. Participants who stopped providing study data before the end of the follow-up period were treated as relapsed. Prolonged abstinence claims were based on self-report measures collected over the course of the follow-up period and were not subject to biochemical verification, which cannot differentiate between a lapse (smoking fewer than 7 days in a row)

and a relapse (smoking for at least 7 days). In three instances, people who claimed never to have relapsed provided breath samples marked by high CO levels (≥10 ppm) after the end of the 2-week grace period. Treating these individuals as relapsed rather than as achieving prolonged abstinence did not change the direction or significance level of any relations between treatment conditions and prolonged abstinence outcome reported below.

Results

Treatment adherence

In the full intent-to-treat sample (N=463), participants attended, on average, more than six of the eight counseling sessions. Those who also received medication attended nonsignificantly more sessions (M=6.65, SD=2.54) than did those who received placebo pills (M=6.19, SD=2.69); $F(1, 461)=3.63$, $p<.06$. In addition, 81% of people in the counseling conditions attended at least four of the eight sessions, and 67% attended all eight. People who received active medication were no more likely to attend at least four sessions than were those in the placebo groups (85.0% vs. 76.9%; $\chi^2[1, 234]=2.47$, $p<.17$) but were more likely to attend all eight counseling sessions than were those in the placebo condition (75.2% vs. 58.7%; $\chi^2[1, 234]=7.20$, $p<.01$). Thus, it appears as though those who received active medication received a greater dose of counseling than did those in the placebo medication condition. Because treatment outcome is likely related to dropout (i.e., people who do not quit successfully are more likely to drop out of treatment), this differential counseling attendance may reflect differences in the efficacy of active versus placebo medication.

Self-report data regarding medication usage suggested a high level of adherence. Analysis of completed electronic diary records indicated that participants reported taking 97.0% of the morning medication doses and 94.8% of evening doses. When missing cases (because of missed reports or equipment problems) were counted as noncompliant, the rates declined slightly to 95.0% for the morning dose and 93.0% for the evening dose. Adherence differed by treatment condition, such that those in the two active medication conditions reported significantly lower medication self-administration in both the morning (95.9% vs. 98.2%, $\chi^2[1, 11{,}927]=51.31$, $p<.001$) and the evening (93.1% vs. 96.6%, $\chi^2[1, 10{,}218]=64.87$, $p<.001$) than did participants in the two placebo medication conditions. Self-reported medication adherence rates exceeded 90% in all groups, however. Medication adherence did not differ across counseling conditions; $\chi^2(1, 11{,}084)=.04$, $p<.84$, for morning medication; $\chi^2(1, 10{,}317)=.07$, $p<.40$, for evening medication.

Adverse events

The total counts of adverse events reported during treatment are displayed in Table 2, along with the number and percentage of participants in each medication condition reporting each adverse event. Odds ratios for the active medication condition, relative to the placebo condition, and confidence intervals also are presented. Most adverse events were mild or moderate, but a few serious adverse events occurred (e.g., stroke and aneurysm; both occurred in the placebo condition). Participants in the active medication condition reported any adverse event more frequently than did participants in the placebo medication conditions and reported

Table 2. Total count of events reported and number (and percentage) of participants in placebo vs. active medication conditions reporting adverse events, collapsed over counseling conditions.

Symptom	Count	Placebo medication	Active medication	Odds ratio	95% Confidence interval
Any adverse event	318	75 (32.1%)	102 (44.5%)	1.70	1.17–2.49
Insomnia	45	10 (4.3%)	35 (15.3%)	4.04	1.95–8.37
Upper respiratory infection	44	21 (9.0%)	19 (8.3%)	0.92	0.48–1.76
Depression	41	25 (10.7%)	15 (6.6%)	0.59	0.30–1.14
Headache	19	5 (2.1%)	14 (6.1%)	2.98	1.06–8.42
Lower respiratory problem	16	7 (3.0%)	8 (3.5%)	1.17	0.42–3.29
Feeling jittery	16	5 (2.1%)	11 (4.8%)	2.31	0.79–6.76
Nausea	15	5 (2.1%)	9 (3.9%)	1.87	0.62–5.68
Feeling dizzy or lightheaded	12	3 (1.3%)	9 (3.9%)	3.15	0.84–11.79
Dry mouth	10	1 (0.4%)	9 (3.9%)	9.53	1.20–75.86
Digestive problems	7	1 (0.4%)	6 (2.6%)	6.27	0.75–52.49
Trouble concentrating	6	2 (0.9%)	4 (1.7%)	2.06	0.37–11.37
Increased blood pressure	6	2 (0.9%)	4 (1.7%)	2.06	0.37–11.37
Fatigue	5	3 (1.3%)	2 (0.9%)	0.68	0.11–4.10
Vertigo	3	0	3 (1.3%)	—[a]	—
Vivid dreams	3	1 (0.4%)	2 (0.9%)	2.05	0.19–22.80
Other	70	24 (10.3%)	35 (15.3%)	1.58	0.91–2.75

Note. [a]The odds ratio and confidence interval could not be computed for vertigo.

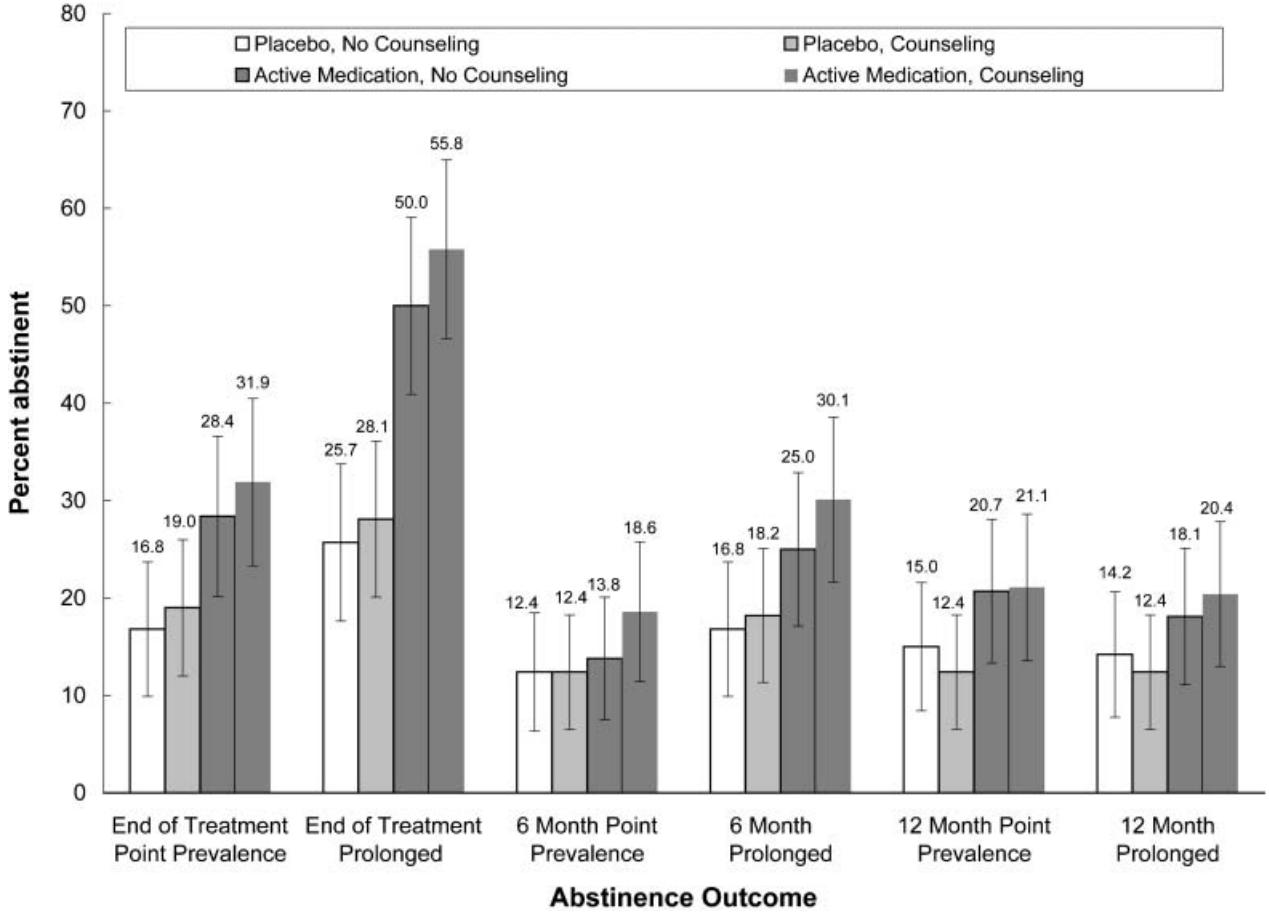

Figure 2. Abstinence rates by treatment conditions. The proportions of people attaining biochemically confirmed abstinence at the end of treatment, 6-month follow-up, and 12-month follow-up are presented, along with the proportion of participants maintaining prolonged abstinence between 2-weeks postquit and each follow-up time point. The percentage abstinent is presented above each column. Error bars represent 95% confidence intervals.

insomnia, dry mouth, and headache significantly more often than did placebo recipients.

Efficacy

Point-prevalence and prolonged abstinence rates are displayed by treatment in Figure 2. Table 3 presents odds ratios and confidence intervals for each active treatment versus the control condition for 7-day point-prevalence and prolonged abstinence (fewer than 7 days of smoking in a row) at 2- (end of treatment), 6-, and 12-months postquit.

Active bupropion SR treatment recipients were 2.0–4.2 times more likely to achieve point-prevalence or prolonged abstinence at the end of treatment than were those receiving placebo pills, regardless of counseling status. Bupropion SR and counseling did not interact to influence abstinence at the end of treatment (point-prevalence: *OR*=1.01, 95% *CI* 0.42–2.43; prolonged: *OR*=1.11, 95% *CI* 0.51–2.42). Among the 229 participants receiving active medication, the addition of counseling was associated with a modest increase in the odds of quitting, but the confidence intervals for these effects were large (point-prevalence: *OR*=1.17, 95% *CI* 0.68–2.03; prolonged: *OR*=1.26; 95% *CI* 0.75–2.12).

At 6-months postquit, odds ratios for point-prevalence abstinence rates were more modest (1.6 or less) for all treatment conditions relative to the control condition. At the same time, however, prolonged abstinence (which did not require CO verification) was 1.6–2.2 times as likely in the active medication conditions as it was in the control condition. The odds ratios for the interaction term suggested an additive counseling effect, but confidence intervals were wide (point-prevalence: *OR*=1.43, 95% *CI* 0.50–4.09; prolonged: *OR*=1.17, 95% *CI* 0.48–2.86). Among those receiving active medication, the addition of counseling was not significantly predictive of point-prevalence abstinence (*OR*=1.43, 95% *CI* 0.70–2.90) or prolonged abstinence (*OR*=1.29, 95% *CI* 0.72–2.31) at 6-months postquit.

The 12-month follow-up odds ratios ranged from 1.3 to 1.6 for the active medication conditions versus the control condition and confidence intervals were

Table 3. Results of logistic regression analyses predicting abstinence[a] at key time points by treatment condition for the full intent-to-treat sample and for the sample that attended the quit-day visit.

	End of treatment point prevalence		End of treatment prolonged		6-Month point prevalence		6-Month prolonged		12-Month point prevalence		12-Month prolonged	
	OR	95% *CI*	*OR*	95% *CI*	*OR*	95% *CI*	*OR*	95% *CI*	*OR*	95% *CI*	*OR*	95% *CI*
Intent-to-treat sample (*N*=463)												
Placebo, no counseling	1.00											
Placebo, counseling	1.16	0.59–2.27	1.13	0.63–2.02	1.00	0.46–2.18	1.10	0.56–2.16	.80	0.38–1.69	.86	0.40–1.83
Active, no counseling	1.97	1.04–3.72	2.90	1.66–5.06	1.13	0.52–2.44	1.65	0.86–3.15	1.47	0.74–2.92	1.34	0.66–2.72
Active, counseling	2.31	1.23–4.35	3.65	2.08–6.40	1.61	0.78–3.36	2.13	1.13–4.02	1.52	0.77–3.02	1.55	0.77–3.12
Quit-day attendees (*n*=403)												
Placebo, no counseling	1.00											
Placebo, counseling	1.29	0.65–2.55	1.28	0.70–2.33	1.10	0.50–2.41	1.22	0.61–2.42	.87	0.41–1.86	.94	0.44–2.02
Active, no counseling	2.09	1.09–4.01	3.35	1.87–6.26	1.17	0.54–2.54	1.74	0.90–3.36	1.54	0.77–3.08	1.40	0.68–2.86
Active, counseling	2.39	1.26–4.55	4.12	2.28–7.42	1.63	0.78–3.42	2.19	1.15–4.19	1.54	0.77–3.08	1.57	0.77–3.18

Note. CI, confidence interval; *OR*, odds ratio. [a]Point-prevalence abstinence at each time point is defined as 7-day point-prevalence abstinence with biochemical verification. Prolonged abstinence at each time point is defined as not smoking for at least 7 consecutive days between 2 weeks and the time point specified.

large. Bupropion SR and counseling did not significantly interact to influence point-prevalence abstinence (*OR*=1.29, 95% *CI* 0.49–3.45) or prolonged abstinence (*OR*=1.35, 95% *CI* 0.49–3.67). Although these odds ratios suggest an additive benefit for counseling, the confidence intervals are large and the addition of counseling among those receiving active medication (*n*=229) did not increase the odds of achieving either point-prevalence abstinence (*OR*=1.03, 95% *CI* 0.55–1.95) or prolonged abstinence (*OR*=1.16, 95% *CI* 0.60–2.23) at 1-year postquit.

The overall pattern of results was the same regardless of inclusion of baseline control variables (i.e., gender, minority status, college education, age, baseline FTND and CES-D scores) in the regression models (not shown). Similarly, results were consistent in the intent-to-treat sample (*N*=463) and in the subsample that attended through the quit date (*n*=403), although effects tended to be stronger in the self-selected sample of quit-day attendees (Table 3).

Survival analysis

Kaplan–Meier survival analyses, in which lost cases from the full intent-to-treat sample were treated as censored, are presented in Table 4 and Figure 3. Results revealed significant differences in survival prior to a first lapse, relapse (defined as the end of

Table 4. Results of survival analyses for latency (in days) to first lapse, to end of prolonged abstinence, and to relapse following initial lapse, by treatment, with missing cases treated as censored.

	Lapse latency				End of prolonged abstinence latency				Lapse–relapse latency			
Treatment	Median survival	95% *CI*	Log rank	*p* value	Median survival	95% *CI*	Log rank	*p* value	Median survival	95% *CI*	Log rank	*p* value
Placebo, no counseling	1	—	16.23[a]	.001	40	21.54–58.46	11.82[a]	.008	29	23.01–34.99	9.30[a]	.03
Placebo, counseling	1	0.49–1.51			55	29.44–80.56			42	22.86–61.15		
Active, no counseling	4	1.62–6.38	.65[b]	.42	103	79.53–126.47	1.52[b]	.22	79	49.71–108.29	1.02[b]	.31
Active, counseling	8	0–19.02			155	106.70–203.31			121	43.65–198.35		
Placebo vs. Active medication	1	—	15.27[c]	.001	48	35.53–60.47	10.44[c]	.001	33	29.86–36.14	7.86[c]	.005
	5	2.31–7.69			114	74.15–153.85			88	58.50–117.50		
No counseling vs. Counseling	2	0.86–3.14	.02[d]	.89	73	45.85–100.15	1.17[d]	.28	42	27.10–56.90	1.22[d]	.27
	2	0.29–3.71			100	63.26–136.74			63	38.54–87.46		

Note. CI=confidence interval. [a]Log-rank chi-square and *p* value for overall comparison across all four treatment conditions (*df*=3, *N*=463).[b]Log-rank chi-square and *p* value for comparison of "active, no counseling" and "active, counseling" conditions (*df*=1, *n*=229). [c]Log-rank chi-square and *p* value for comparison of placebo vs. active medication conditions, collapsed over counseling conditions (*df*=1, *N*=463). [d]Log-rank chi-square and *p* value for comparison of no counseling vs. counseling conditions, collapsed over medication conditions (*df*=1, *N*=463).

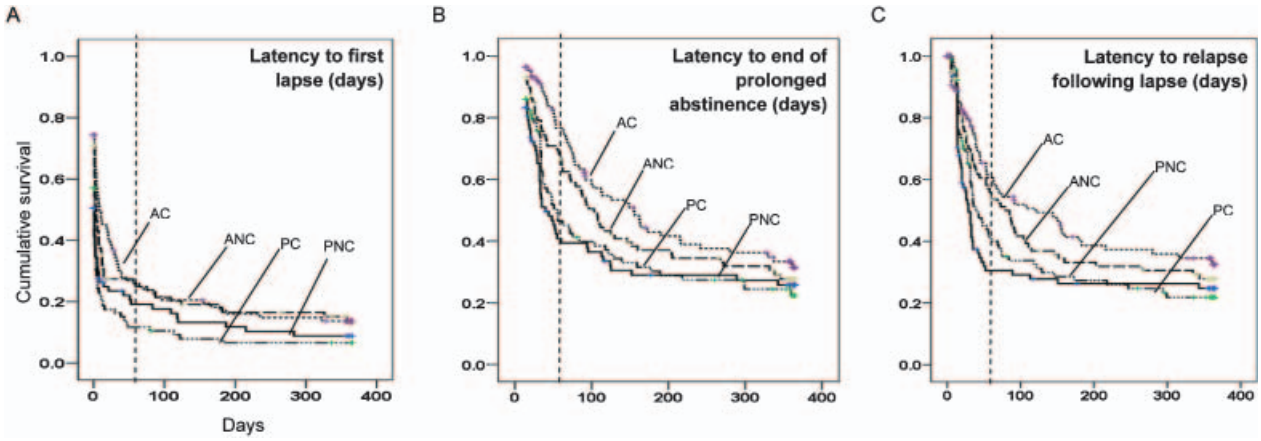

Figure 3. Kaplan–Meier survival curves by treatment. The *x*-axis represents latency in days to a smoking event after the quit date for the full sample of enrollees. The vertical broken line marks the end of treatment (day 56). The *y*-axis represents the cumulative proportion of participants who had not lapsed or relapsed at that time. Plus signs depict censored cases who did not lapse or relapse within 365 days of the quit date or who were lost to follow-up. Panel A depicts survival prior to a first lapse. Panel B depicts prolonged survival after a 2-week grace period starting on the quit date. Events in this panel represent a return to smoking for at least 7 days in a row. Panel C depicts latency between the first lapse and relapse (smoking at least 7 days in a row).

prolonged abstinence between 2- and 52-weeks postquit), and between a lapse and relapse across the four treatment conditions. Those receiving active medication had significantly longer survival times prior to lapse and relapse than did those receiving placebo medication, when collapsed over counseling conditions. No main effect of counseling was observed and no additive effect of counseling in the context of active medication was detected (see Table 4 for log-rank chi-square and associated *p* values for these comparisons).

More conservative, intent-to-treat survival analyses that assumed that all smokers who were lost to follow-up resumed smoking the day they last provided data yielded similar results. Lapse and relapse days were estimated for a total of 72 participants (15.6% of the enrolled sample), only 7 of whom provided data after the target quit date; all others were assumed not to have quit for even one day. Median survival times followed the same pattern (differing as a function of medication but not counseling) as in the previous analysis but were lower overall (ranging from 0 to 5 days to lapse and from 14 to 48 days for relapse across conditions, and equal to 6 days between lapse and relapse in all conditions).

Restricting survival analyses to the participants who attended the quit date visit did not change the pattern of results. Conducting survival analyses using Cox regression analyses including baseline covariates (not shown) did not change the overall pattern of results. Although the significance level of specific comparisons varied as a function of the sample and covariates included in survival models, the general pattern of significant medication effects and no counseling effects persisted across models.

Discussion

The present study provided evidence that bupropion SR produced higher short-term abstinence rates among adult daily smokers, increased the latency to lapsing, and prolonged the duration of the lapse-to-relapse interval. Evidence regarding sustained bupropion SR benefits likely to translate into health benefits was weaker. Results showed little evidence of any meaningful benefit of individual counseling in the context of either placebo or active medication.

The pattern of results characterized by moderate initial medication effects and a lack of benefit attributable to counseling persisted across many variations in outcome coding and modeling, and across different samples of participants. Although the abstinence rates and odds ratios for prolonged abstinence appeared more impressive, reports of prolonged abstinence (not smoking 7 days in a row after a 2-week grace period) were based on self-report data and were not biochemically confirmed and should thus be interpreted with caution. This lack of confirmation also may account for the discrepancy between 6-month point-prevalence and prolonged abstinence combination treatment effects.

Results from the present study partially replicate prior findings regarding the efficacy of bupropion SR. For example, observed 1-year prolonged abstinence rates are similar to prolonged or continuous abstinence rates for people treated with bupropion SR reported elsewhere (e.g., Ferry & Burchette, 1994; Hall et al., 2002; Jorenby et al., 1999; Tonnesen et al., 2003). Biochemically confirmed 12-month point-prevalence abstinence rates also were similar to those reported in earlier bupropion SR trials (e.g., 23.1%, Hurt et al., 1997; Swan et al., 2003) and in a recent

study of bupropion treatment in clinical practice (21.0%, Paluck et al., 2006).

The magnitude of the treatment effects in this study was only partially consistent with previous research, however. Observed odds ratios for bupropion SR treatment were generally within or close to confidence intervals for bupropion SR effects reported in recent meta-analyses (Fiore et al., 2000; Hughes, Stead et al., 2004; Wu, Wilson, Dimoulas, & Mills, 2006), but our confidence intervals were wide. Similarly low odds ratios at long-term follow-ups have been reported previously in the literature (e.g., Hays et al., 2001; Zellweger, Boelcskei, Carrozzi, Sepper, & Hider, 2005), even for treatments that yielded much higher initial abstinence rates than we observed.

Unlike Swan and colleagues (2003), we did not observe a reliable increase in the likelihood of quitting when counseling was added to bupropion SR treatment, and the magnitude of the effect was modest and lower than expected based on previous research (e.g., odds ratios ranging from 1.4 to 1.7 for individual counseling; Fiore et al., 2000). Hall and colleagues (2002) similarly reported a lack of additive benefit when an efficacious stand-alone psychosocial treatment was combined with pharmacotherapy.

We failed to demonstrate that eight sessions of individual counseling affected point-prevalence or prolonged abstinence or latency to a return to smoking in the presence of placebo medication as well. This failure to replicate the efficacy of counseling that emphasizes motivation, social support, and problem solving demands examination, although such failures are not unprecedented (e.g., Bronson et al., 1989; Fiore et al., 2004). Counseling attendance would not seem to account for the lack of counseling efficacy, as participants attended an average of six of the eight counseling sessions offered. An alternative explanation is that intensive assessment and contact with study staff may have provided nonspecific but potent ingredients of counseling interventions to all participants in the study, not just to those slated to receive counseling. Our abstinence rates were higher than those reported among unassisted quitters (roughly 5%; Centers for Disease Control and Prevention, 2002) and this finding may reflect the nonspecific effects of study participation beyond which counseling did not have an effect. If this were the case, it would suggest that the content of counseling beyond medication management and assessment is unimportant. Another possible explanation is that we delivered the counseling ineffectively. Our counselors were college-aged or bachelor's-level staff who were trained and supervised, using periodic audiotape review, by a licensed psychologist with several years of experience as a smoking cessation counselor. Problems in the execution of counseling may account for the lack of efficacy, even if such problems were not detected using our quality control measures.

Finally, our disappointing results might reflect a broader trend of diminishing efficacy in smoking cessation treatment. If the remaining population of smokers is indeed hardening (i.e., becoming more nicotine dependent or characterized by relatively higher levels of risk factors), this may account for declining effect sizes in individual counseling interventions over time (Irvin & Brandon, 2000). Hardening also may account for the fact that, recently, only very intensive psychosocial treatments tend to produce effects of large magnitude (e.g., Hall, Humfleet, Reus, Munoz, & Cullen, 2004).

Power was adequate (above .75) to detect a 10% increase in abstinence rates between active and control conditions in this sample. Results indicated, however, that even the strongest effect (active medication and counseling versus the control condition) was small by conventional standards. The number needed to treat with the combination of medication and counseling to get one more person than in the control condition to achieve 12-month prolonged or 12-month point-prevalence abstinence is 16. Effects of this size correspond to a Cohen's d between 0 and .2 (Kraemer & Kupfer, 2006). As such, the small magnitude of treatment effects observed, rather than lack of power, likely explains our failure to demonstrate significant main effects for either bupropion SR or counseling at the 1-year follow-up. We would require a very large sample (1,113 in each group) to achieve good power (.80) to detect a significant difference in our observed abstinence rates as a function of adding counseling to bupropion SR. Expressed in terms of number needed to treat, which is preferred over odds ratios (Kraemer & Kupfer, 2006), we would need to treat 43 additional smokers with individual counseling to get one more person to achieve 1-year prolonged abstinence in the context of active bupropion SR treatment.

Limitations

The interpretation of both significant and null results in this study should be tempered by the following concerns. First, the lack of a no-treatment control condition makes it impossible to rule out the possibility that placebo medication effects reduced our ability to detect treatment differences, particularly between the no-counseling and counseling placebo medication conditions. We can only conclude from the current data that the counseling we offered conferred no substantial or reliable benefit on participants receiving placebo or active medication.

Second, our ability to generalize the results to the broader population of smokers may be limited. The majority of smokers who attempt to quit smoking do so without formal assistance, and these individuals may differ from the participants in this research in diverse ways (Hughes, Keely, & Naud, 2004). Although our sample did not report unusually heavy smoking and did not have particularly high scores on the FTND, these may not be the most sensitive measures of dependence or the best predictors of cessation success (Piper, McCarthy, & Baker, 2006), particularly as environmental restrictions force smokers to change their smoking patterns. Research volunteers may differ from other smokers in many other ways, as well.

In addition, assessment reactivity and attrition may render our results less replicable or generalizable. We do not know how our frequent and prolonged assessment of smokers may have influenced their reporting or behavior. Our initial abstinence rates were similar to those reported in a study of high-dose patch therapy and group cognitive–behavioral therapy that involved similarly intensive electronic diary assessment, however (Shiffman et al., 2006). For example, 7-day point-prevalence abstinence rates 1 month into treatment were 29% and 55% in the placebo and active patch conditions, respectively, in the Shiffman et al. (2006) study, which are similar to the 1-month point-prevalence rates (30% in placebo conditions, 49% in active bupropion conditions) observed in the present study. However, other researchers have reported null results regarding counseling regimens, without the burden of ecological momentary assessment (Bronson et al., 1989; Burling et al., 1991; Dornelas, Sampson, Gray, Waters, & Thompson, 2000).

Although attrition was a problem in the present study, we consider it unlikely that attrition substantially skewed the results for several reasons. Attrition was roughly equivalent across treatment conditions and is therefore an unlikely explanation for weak treatment effects. Second, the results were similar in analyses conducted with the full intent-to-treat sample and the subsample of smokers who remained in the study through the target quit day. This consistency weakens the argument that treatment effects were diluted by prequit attrition. Third, the majority of people who dropped out reported that they returned to smoking prior to their loss to follow-up. Indeed, only seven people reported complete postquit abstinence prior to dropping out of the study. Thus our intent-to-treat analyses are likely to be accurate.

Conclusion

Results from this randomized, controlled clinical trial of bupropion SR and multisession individual smoking cessation support the efficacy of bupropion SR while treatment is ongoing but do not provide compelling evidence of the long-term efficacy of bupropion SR or individual counseling. These data join a growing body of research that suggests that the efficacy of previously validated treatments may be waning, at least among smokers who volunteer for clinical trials of intensive treatments (e.g., Irvin & Brandon, 2000). These shifting sands suggest that we need to continue evaluating even well-established treatments to promote understanding and eventual reversal of these negative trends. Our results also suggest the need for improved and prolonged, rather than acute, treatments for tobacco dependence.

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