Sustained-Release Bupropion for Smoking Cessation in African Americans
A Randomized Controlled Trial

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Despite significant reduction in smoking prevalence in the United States, certain groups retain a higher smoking rate than the general population. African Americans living in the inner city, for example, have a smoking rate as high as 45% while the general population’s smoking rate is 25%.1,2 The higher smoking rate among this population is not for lack of motivation to quit. In fact, compared with whites, African Americans are more likely to attempt to quit smoking more times in any given year.3,4 However, the success rate is 34% lower for blacks than it is for whites.3,4 Studies show that the higher number of quit attempts would likely result in sustained abstinence if improved smoking cessation modalities for African Americans are developed and disseminated.3,6

Two randomized clinical trials found a sustained-release form of bupropion hydrochloride (bupropion SR) to be effective for smoking cessation. In one study,7 7-day abstinence rates at 6 months after initiation of the 7-week treatment were 27% for those taking 300 mg of bupropion SR compared with 16% for those taking placebo. In the other study,8 which assessed bupropion SR in combination with the nicotine patch, 7-day abstinence rates at 6 months after initiation of 7-week treatment were 35% for bupropion SR alone, 39% for bupropion SR plus a nicotine patch, and 19% for the placebo group. Although these studies have shown the

See also p 497 and Patient Page.

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efficacy of bupropion SR to help smokers quit, the subjects were predominantly white (>93%) and of a middle or higher socioeconomic status (80% with an educational level of high school or above). The results have limited generalizability for African Americans, since their smoking patterns are quite different from those of whites. African Americans smoke fewer cigarettes per day (15 vs 25 for whites), prefer mentholated and higher tar nicotine cigarettes, and are more likely to smoke within 10 minutes of awakening. Researchers have also found that African Americans metabolize nicotine slower and have higher serum cotinine levels per cigarette smoked than do whites.

If the goals of Healthy People 2010 set by the federal government are to be reached, significant smoking cessation must occur in special populations such as African Americans. Since prior studies of bupropion SR included few African Americans and few smokers from lower socioeconomic groups, we conducted a trial to assess the efficacy of bupropion SR for smoking cessation among inner-city African Americans.

METHODS

Study Design

This study was a double-blind, placebo-controlled, randomized trial of 600 African American smokers. Participants were seen at a community health care center during a 16-month period and were randomly assigned to receive a 7-week supply of bupropion SR or placebo. Both groups received 8 counseling sessions and a previously developed smoking cessation guide. Focus groups, a community advisory board, and a small pilot test assisted in refining the study to maximize cultural sensitivity and enhance recruitment and retention.

Participants provided written informed consent during the first visit. The trial procedures were approved and monitored by the University of Kansas Medical Center’s human subjects committee.

Participants, Screening, and Randomization

Eligible persons described themselves as being either “African American or black,” were at least 18 years of age, smoked at least 10 cigarettes per day, were interested in quitting in the next 30 days, spoke English, and had a permanent home address with a working telephone. Only 1 smoker per household was allowed to enroll. Participants were excluded if they had a contraindication for bupropion SR (predisposition to seizures, excessive alcohol use, bulimia or anorexia nervosa, current use of bupropion, were pregnant, current use of psychoactive medication, use of other forms of tobacco or nicotine replacement in the past 30 days), were in drug treatment during the past 6 months, or were being treated for depression.

Smokers were recruited using clinic, media, and community outreach, including speaking at churches and posting signs in local minority-owned businesses. Participants were randomized between February 11, 1999, and April 26, 2000, with the last 6-month follow-up session completed in December 8, 2000. Of the 1498 people who were screened, 981 met screening criteria and were invited to participate (Figure 1). Sequential enrollment continued until 600 participants were randomized. The randomization codes were generated in blocks of 50 and sent to the pharmaceutical company, which packaged the treatment and then shipped the blinded drug to the investigator. Blinding was successful. At the end of treatment, 38% (150/259) of participants correctly guessed that they received bupropion SR, and 41% (104/253) correctly guessed they received placebo. Sixty-one percent (366/600) of participants attended all medication dispensing visits, a proxy measure for medication adherence.

Treatment Period

At the baseline visit, participants were randomly assigned to receive either 150 mg of bupropion SR (Zyban, GlaxoSmithKline, Research Triangle Park, NC) once a day or placebo once a day for 3 days, after which the dosages were increased to twice a day for a total of 7 weeks. Study staff instructed all participants to continue taking pills for the full 7 weeks regardless of their smoking status. Tablets were packaged in bubble-sheets containing a 1-week supply. The 45-minute counseling session at the baseline visit included exploring ambivalence about quitting, preparing to quit, problem solving difficult situations, and medication adherence. All counselors were African American, had master’s degrees, received training in motivational interviewing, and followed semistructured counseling scripts. In general, participants received counseling from the same person for all 8 sessions. At the baseline visit, participants also received the smoking cessation guide Pathways to Freedom and completed a battery of assessments.

Participants set a target quit date a week after the start of medication, and...
returned on that day (quit day) for a second in-person visit (week 0). They returned the following week (week 1) and at weeks 3 and 6. These visits consisted of brief counseling sessions, completion of short batteries of assessments, and distribution of medications (weeks 1 and 3). Counselors provided brief supportive telephone calls 3 days after the target quit day and at week 5.

Posttreatment Period
A brief relapse prevention telephone call occurred 7 weeks after the target quit day, and follow-up assessments occurred at months 3 and 5 (telephone), and at month 6 (in-person).

Retention
Postcard appointment reminders were sent before every visit and participants who missed appointments were called up to 3 times to reschedule their visit. For the 6- and 26-week visits staff attempted to call participants as many as 6 times after having mailed appointment postcards. Participants received token gifts at every visit (eg, magnet, T-shirt, tote bag, water bottle) and were reimbursed a total of $100 at baseline for the previous 7 days. Secondhand smoking prevalence in the household was determined as having smoked no cigarettes—not even a puff—for the previous 7 days. Secondary outcomes include 7-day point prevalence smoking cessation at week 26, defined as having smoked no cigarettes—"not even a puff"—since quit day. We allowed participants to miss no more than 1 in-person visit prior to each assessment. Self-reported abstinence was confirmed with expired carbon monoxide assessment (≤10 ppm) and discrepancies were resolved by obtaining saliva for cotinine analysis (≤20 ng/mL). Withdrawal symptoms, nicotine dependence, and depressive symptoms were also reassessed at weeks 6 and 26.

Data Management
Surveys were double-data entered and exported into SAS version 8.21 Once the 2 versions of the database were identical, range and logic checks were performed using SAS statistical software.

Statistical Analysis
The sample size was determined a priori assuming a 2-tailed χ² test with a type I error of .05, a power of 80%, and a 6-month biochemically verified (carbon monoxide) quit rate of 14% in the placebo and 24% in the treatment groups,22 assuming those lost to follow-up would be imputed as smokers. Under these assumptions 300 smokers were to be randomly assigned to each group. The 6-month period was chosen because evidence suggests that cessation rates at 6 and 12 months do not differ substantially in lower socioeconomic status populations, and in a lower socioeconomic status population, it may have been difficult to follow up all participants for a year.

Categorical baseline variables were summarized by frequencies and percentages, and quantitative variables were summarized by mean (SD) for each treatment regimen. Baseline categorical variables were compared using the χ² test, and quantitative baseline variables were compared using the 2-sample t test.

All statistical analyses were performed on an intention-to-treat basis. Seven-day point prevalence and continuous abstinence at weeks 1, 3, 6, and 26, and change in the number of cigarettes smoked at weeks 6 and 26. Continuous abstinence was defined as no cigarettes—not even a puff—since quit day. We allowed participants to miss no more than 1 in-person visit prior to each assessment. Self-reported abstinence was confirmed with expired carbon monoxide assessment (≤10 ppm) and discrepancies were resolved by obtaining saliva for cotinine analysis (≤20 ng/mL). Withdrawal symptoms, nicotine dependence, and depressive symptoms were also reassessed at weeks 6 and 26.

Table 1. Baseline Characteristics of the Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sustained-Release Bupropion (n = 300)</th>
<th>Placebo (n = 300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>44.0 (10.9)</td>
<td>44.4 (11.3)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>212 (70.7)</td>
<td>208 (69.3)</td>
</tr>
<tr>
<td>Married or living with a partner, No. (%)</td>
<td>117 (39.0)</td>
<td>113 (37.7)</td>
</tr>
<tr>
<td>Monthly family income &lt;$1800, No. (%)</td>
<td>158 (52.6)</td>
<td>164 (54.6)</td>
</tr>
<tr>
<td>≤High school graduate, No. (%)</td>
<td>151 (60.3)</td>
<td>149 (49.7)</td>
</tr>
<tr>
<td>No. of cigarettes smoked per day, mean (SD)</td>
<td>16.1 (7.5)</td>
<td>17.1 (8.5)</td>
</tr>
<tr>
<td>Smoke mentholated cigarettes, No. (%)</td>
<td>235 (78.3)</td>
<td>236 (78.7)</td>
</tr>
<tr>
<td>Fagerström score, mean (SD)*</td>
<td>4.6 (2.1)</td>
<td>4.7 (1.9)</td>
</tr>
<tr>
<td>No. of previous serious attempts to quit, mean (SD)</td>
<td>2.1 (4.7)</td>
<td>2.2 (4.4)</td>
</tr>
<tr>
<td>Salivary cotinine, mean (SD), ng/mL</td>
<td>287.2 (138.8)</td>
<td>296.5 (147.0)</td>
</tr>
<tr>
<td>Exhaled carbon monoxide, mean (SD), ppm</td>
<td>22.1 (13.2)</td>
<td>23.3 (15.2)</td>
</tr>
<tr>
<td>Previous use of sustained-release bupropion, No. (%)</td>
<td>23 (7.7)</td>
<td>24 (8.0)</td>
</tr>
<tr>
<td>Other smokers in the household, No. (%)</td>
<td>104 (34.7)</td>
<td>96 (32.0)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>82.8 (22.6)</td>
<td>81.6 (20.1)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>29.0 (7.0)</td>
<td>28.7 (6.3)</td>
</tr>
<tr>
<td>CES-D, mean (SD)+†</td>
<td>11.7 (8.8)</td>
<td>11.9 (8.7)</td>
</tr>
<tr>
<td>Possible clinical depression, No. (%)†</td>
<td>79 (26.4)</td>
<td>84 (28.0)</td>
</tr>
</tbody>
</table>

*The Fagerström test score for nicotine dependence ranges from 0 to 10. Scores of 6 or higher indicate greater levels of nicotine dependence.
†Center for Epidemiologic Studies Depression Scale (CES-D) scores can range from 0 to 60. Scores of 16 or higher indicate the likelihood of clinical depression because it represented the 80th percentile in a representative population.18

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26 were summarized using frequencies and percentages. The χ² test was used to compare treatments on our primary dichotomous outcome; 7-day point prevalence at 6 months; and our secondary dichotomous outcomes; 7-day point prevalence at week 1, week 3, week 6; and continuous abstinence at all 4 times, between treatments. For comparisons on 7-day point prevalence cessation at weeks 26, 6, 3, and 1, we considered those subjects who failed to return within their scheduled visit window as smokers. Scheduled visit windows were 3 days before to 7 days after for week 1, 7 days before and after for week 3, 14 days before to 30 days after for week 6, and 30 days before and after for week 26. Secondarily, for 7-day point prevalence cessation, we also compared only those who returned regardless of their returning outside of their follow-up visit interval, and we treated those lost to follow-up as missing. Treating those lost to follow-up or those being outside the visit window as smokers provides a conservative estimate but may underestimate the variance, whereas, analysis on only those who return may overestimate the cessation rate.

We also used generalized estimating equations to conduct longitudinal analyses comparing verified 7-day point prevalence at weeks 1, 3, 6, and 26 between the 2 groups. This procedure allows inclusion of subjects who returned outside the appointment window and is appropriate assuming data are missing completely at random.

Changes in the number of cigarettes smoked were summarized and compared across groups for all 600 participants imputing no change for those who missed follow-up or who did not return within scheduled visit windows. Mean (SD) summarized the change in the number of cigarettes smoked at weeks 6 and 26. Given the large sample size and the lack of skewness, the 2-sample t test was used to compare the change in the number of cigarettes smoked at weeks 6 and 26 between the 2 treatment groups.

Frequencies and percentages were used to summarize adverse events by type over the entire treatment period. Due to the small number of adverse events, the Fisher exact test was used, for each type of adverse event, to compare the percentage of subjects who experienced an adverse event between the 2 groups.

The mean (SD) change in depression scores was summarized at weeks 6 and 26. The 2-sample t test was used to compare the changes between the 2 groups at weeks 6 and 26. Weight and withdrawal symptom scores were compared between the 2 treatment groups over time (day 0, week 1, week 3, and week 6) using mixed linear models, assuming an autoregressive correlation structure, adjusting for baseline (before week 1) levels and whether a subject had been continuously abstinent from quit day to week 6. Mixed linear models allow for modeling longitudinal data using fixed and random effects while taking into account the correlation structure between repeated observations on individuals over time. This method was chosen over the traditional repeated measures design to include all subjects in the analysis whether or not they had returned for all of the visits after quit day.

RESULTS

There were no significant differences in the baseline characteristics of participants between treatment groups (Table 1). The average age of the participants was 44 years, and 70% were women. On average, they smoked 17 cigarettes a day, with about half having previously tried nicotine replacement therapy. Three difference tests established that the study had high internal and external validity. First, randomized participants did not differ in sex and number of years they smoked, but they were older than those who were eligible but did not return for randomization (44.2 vs 38.8 years). Second, neither treatment allocation nor baseline number of cigarettes smoked differed between those lost to follow-up and those who returned at weeks 1, 3, 6, or 26. The only sociodemographic smoking-related variable listed in Table 1 that differed was baseline age. Therefore, age at baseline was included as a covariate in the generalized estimating equation models for 7-day point prevalence abstinence. Third, for those lost to follow-up at weeks 1, 3, 6, and 26, there were no differences on these same variables between groups. Of the 600 participants, 470 (78.3%) were followed up at week 6 and 411 (68.5%) at week 26 (Figure 1). For the 189 participants lost to follow-up at week 26, 107 were seen outside the study window, 81 were not locatable, and 1 withdrew consent.

The biochemically confirmed point-prevalence abstinence for the treatment and control groups is shown in TABLE 2. The cessation rate for the treatment group was significantly better than the placebo group at the end of the treatment phase (36.0% vs 19.0%, P < .001) and the improvement was maintained over 26 weeks (21.0% vs 13.7%, P = .02). These results remained statistically significant when we analyzed only those subjects who returned, treating those lost to follow-up as missing. Since our data were determined to be missing completely at random, we compared the treatment effect longitudinally on 7-day point prevalence using generalized estimating equations, with and without controlling for baseline age. When controlling for baseline age, we found significantly higher rates of smoking cessation in the bupropion SR group than in the placebo group (OR, 1.19; 95% CI, 1.12–1.26; P < .001). In addition, after assessing the effect of sex on smoking cessation, we found no sex by treatment interactions nor main effect due to sex when controlling for treatment.

Rates of continuous abstinence (Figure 2) were significantly higher for the bupropion SR group at weeks 1, 3, and 6 (P < .001 for all comparisons) and at week 26 (P = .01). Among all participants, the week-6 mean (SD) reduction in number of cigarettes smoked among those taking bupropion SR was 11.5 (8.4) vs 10.1 (9.1) among those taking placebo (P = .06). At week 26, the reduction among those taking bupropion SR was 8.3 (10.3) vs 7.9 (8.8) among those taking placebo (P = .61).
Withdrawal, Weight, and Depression Symptoms

We assessed the effects of bupropion SR on withdrawal scores and weight over 6 weeks using mixed linear models adjusting for baseline values. For withdrawal scores over time (Figure 3), there was a significant effect for continuous abstinence ($b_{\text{abs}} = -2.12; P < .001$) but no effect for treatment ($b_{\text{trt}} = -0.27; P = .40$) and no significant interaction effect ($b$ represents the estimated slope parameter). Those who were continuously abstinent had lower average withdrawal scores compared with those who relapsed.

For weight over time, there were significant differences for continuous abstinence ($b_{\text{abs}} = 1.25; P < .001$) and treatment ($b_{\text{trt}} = 0.62; P = .03$) but no significant interaction effect. Those who were continuously abstinent at week 6 had a significantly higher average weight over time, and those taking bupropion SR had significantly lower average weight over time. The differences in weight gained between the 2 groups were not maintained at the week-26 follow-up session.

However, there were differences among the 2 groups in the effect of bupropion SR on depressive symptoms. Participants who received bupropion SR experienced a significantly greater mean (SD) reduction in their depressive symptoms (2.96 [9.45] vs 1.13 [8.84]; $P = .03$) at 6 weeks compared with baseline depressive symptoms. At the week-26 follow-up session, which is 4½ months after discontinuation of study medications, this reduction in depressive symptoms was no longer significant (1.56 [9.04] vs 1.12 [8.74]; $P = .59$).

Adverse Events

Table 3 shows the percentages of participants who reported adverse events at any of the study contact points through week 6 of drug treatment. Problems sleeping and dry mouth were the most commonly reported adverse events. There were no reports of rhinitis, abnormal or bizarre dreams, or seizures. The bupropion SR group was significantly more likely to report problems sleeping ($P = .02$). Twelve participants reported being hospitalized during the treatment phase, 11 of which were known to be unrelated to the medication, and 1 was suspected to be unrelated to the medication.

COMMENT

To our knowledge, this study is the first to establish the efficacy of bupropion SR for smoking cessation among African Americans. The 21% quit rate at 26 weeks for the bupropion SR group was slightly lower than the rates found in 2 previous studies, which reported 27% and 35% quit rates among mostly white, middle-class participants. Our difficulty locating participants within an acceptable time frame, combined with counting those lost to follow-up as smokers, may underestimate the actual quit rate. Alternatively, participants in our study may have had higher relapse rates due to high amounts of stress associated with lower-income populations. However, the 13.7% quit rate in our placebo group was comparable with the 16%7 and 19%8 quit rates found in these 2 studies. Higher levels of nicotine addiction among African Americans, as suggested by some epidemiological and laboratory data, may partially account for these results. Although lower FTND scores suggest lower nicotine dependence, the FTND score heavily weights quantity of smoking and therefore is a less sensitive measure of dependence among lighter smokers, such as those in our study. It has also been suggested that African Americans develop depen-
Problems sleeping. Smoking these types of cigarettes. Smoking these cigarettes. Smoking these cigarettes. Smoking these cigarettes. Smoking these cigarettes. Smoking these cigarettes.

- There is some evidence that smokers using menthol cigarettes may be less likely to quit than those not smokers using menthol cigarettes.
- The vast majority of participants finally, the vast majority of participants in this trial smoked menthol cigarettes. There is some evidence that smokers using menthol cigarettes may be less likely to quit than those not smoking these types of cigarettes.
- Our study also found that bupropion SR attenuated weight gained by participants. Concern about weight gain after smoking cessation is a barrier keeping many smokers from quitting.
- Data from the third National Health and Nutrition Examination Survey (NHANES III) found that more than half of African American women are overweight compared with a third of the general population. Obesity-related diseases such as diabetes, hypertension, and coronary artery disease are more prevalent among African Americans. A medication that can help African Americans quit smoking is also associated with less weight gain compared with those who received placebo. Although this might be explained by a higher level of depressive symptoms among participants in our study vs what participants in other studies may have experienced, the use of different depressive symptom measures precluded a direct comparison. However, participants in our study had, on average, lower income and educational levels, and they were less likely to be living with a partner than participants in other studies. This suggests that there may be related differences in stress and distress levels that could account for the discrepant results.

There are a number of strengths of this study. To our knowledge, it is the largest treatment-based trial of smoking cessation in any ethnic minority conducted to date. We successfully randomized 600 African American smokers at a community health care center in a 14-month period. This study also shows that smokers no matter their economic status want to quit smoking and are successful. We also achieved good internal and external validity.

There are some limitations to our findings. First, our findings cannot be generalized to all African Americans. Although this is a community-based study, it remains a single-site study with certain eligibility criteria such as the requirement to have access to a telephone for study participation. Second, similar to our other published work with African American smokers, the majority of participants were women. This may result in a lower overall quit rate in our study populations because African American women appear to have lower quit rates in the short- and long-term. Third, smokers in cessation clinical trials are a self-selected group who are motivated to quit, which limits the generalizability but does represent the group of smokers for whom pharmacotherapy may be most appropriate. Fourth, although our behavioral intervention was more than it might be in the “real world,” it was less intensive than the behavioral interventions discussed in the other trials using bupropion SR.

Bupropion SR was effective in assisting African American smokers to quit. Translating this scientific finding to the population of African American smokers is critical to further decrease the prevalence of smoking and to reach the goals of Healthy People 2010. In addition, reductions in smoking will also aid in reducing the excess smoking-attributable morbidity and mortality that exists between African Americans and other segments of the population. Expanding access to medication through health insurance programs, especially government programs, such as Medicare and Medicaid, may be a wise investment to reduce some of the health disparities that exist in the United States.

TABLE 3. Participants Reporting Adverse Events at Any Time Point

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sustained-Release Bupropion (n = 300)</th>
<th>Placebo (n = 300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems sleeping*</td>
<td>88 (29.3)</td>
<td>62 (20.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>84 (28.0)</td>
<td>72 (24.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (2.3)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (3.3)</td>
<td>12 (4.0)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Skin problems</td>
<td>17 (5.7)</td>
<td>15 (5.0)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (11.7)</td>
<td>26 (8.7)</td>
</tr>
<tr>
<td>Admitted to hospital, known to be unrelated to medication</td>
<td>6 (2.0)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Admitted to hospital, unknown if related to medication</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*P = .02 by Fisher exact test (2-tailed).
†Participant could not be reached to confirm reason for hospitalization.

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