Bupropion for Smoking Cessation

A Randomized Trial

Joel A. Simon, MD, MPH; Carol Duncan, RD, MPH; Timothy P. Carmody, PhD; Esther S. Hudes, PhD, MPH

Background: Bupropion hydrochloride is recommended for smoking cessation; however, there have been relatively few clinical trials examining its efficacy.

Methods: A total of 244 current smokers were enrolled in an outpatient randomized blinded smoking cessation trial conducted at the San Francisco Veterans Affairs Medical Center, San Francisco, Calif. Of the 244 participants, 121 received a 7-week course of bupropion and 123 received placebo. All participants received 2 months of transdermal nicotine replacement therapy and 3 months of cognitive-behavioral counseling. We determined on-medication treatment, end-of-medication treatment, 3-month, 6-month, and 1-year quit rates.

Results: During treatment with bupropion vs placebo, there was a trend toward increased quit rates among participants randomized to bupropion; the self-reported end-of-medication treatment quit rates were 64% for the bupropion group vs 57% for the placebo group (P = .23). The trend favoring bupropion persisted at 3 months of follow-up (P = .12) but was not apparent at 6 months and 1 year of follow-up (both P > .78). The 12-month quit rates, validated by either saliva cotinine or spousal proxy, were 22% in the bupropion group and 28% in the placebo group (P = .31). Based on biochemical validation, 19% of the bupropion group vs 24% of the placebo group had quit smoking by 1 year (P = .36).

Conclusions: In this randomized blinded trial of mostly veteran participants, the addition of a brief 7-week bupropion trial to treatment with nicotine replacement therapy and counseling did not significantly increase smoking cessation rates.

Arch Intern Med. 2004;164:1797-1803
We assigned participants to the 2 study arms by using a computer algorithm to generate a random list of treatment assignments. Participants randomized to the active treatment arm of the study received a 7-week course of sustained-release bupropion hydrochloride (150 mg daily for the first 3 days, then 150 mg twice daily). Participants randomized to the control arm of the study received an identical course of placebo. All study personnel engaged in providing interventions to participants were blinded to treatment assignment. The cognitive-behavioral intervention was administered by a trained public health educator and was based on social learning theory and the stages of change model of Prochaska and DiClemente. Participants met with the study public health educator in an individual counseling session that lasted between 30 and 60 minutes. In these counseling sessions, the dangers of smoking and the benefits of quitting were reviewed, participants' knowledge, beliefs, and potential barriers to smoking cessation were assessed, and counterarguments to belief barriers were provided according to prespecified guidelines outlined in the study operations manual. Behavioral self-management techniques to counter known relapse triggers, such as stress, the presence of other smokers, alcohol use, and depression, were also discussed. We assessed depressive symptomatology using the Beck Depression Inventory. Participants were provided a 2-month supply for the transdermal nicotine patch along with instructions on its use. The dose of the transdermal nicotine patch was individualized based on the number of cigarettes the participant was smoking at the time of enrollment. A typical NRT course consisted of 4 weeks at 21 mg/d, 2 weeks at 14 mg/d, and 2 weeks at 7 mg/d, with a maximum dose permitted of 21 mg/d. Self-help literature was also distributed. All participants completed the initial counseling session.

After enrollment, all participants received 5 follow-up telephone counseling calls. These calls were made at week 1, week 3, and then monthly for the first 3 months following enrollment. The telephone counseling and follow-up sessions continued the skills training initiated during the face-to-face counseling session and each telephone counseling call lasted 30 minutes or less. Participants who had resumed smoking were encouraged to set new quit dates.

### DATA COLLECTION

We collected baseline questionnaire data on age, race, sex, marital status, presence of other smokers in the household, level of education, history of drug or alcohol abuse, medical illness, and history of depression. Body mass index (calculated as weight in kilograms divided by the square of height in meters) and change in weight over time were determined using self-reported or medical record data. Medical problems, such as coronary disease, chronic obstructive pulmonary disease, vascular disease, diabetes mellitus, hypertension, and tobacco-related malignancy (ie, cancer of the lung, bladder, kidney, oropharynx, and larynx) were recorded based on participant interviews and, when available, medical chart review. We obtained self-reported data on preenrollment level of cigarette smoking (in cigarettes per day), pack-years of tobacco smoked (average packs per day multiplied by the number of years of smoking), and number of prior attempts at smoking cessation. Estimated level of nicotine dependence was based on the Fagerström Tolerance Questionnaire. Two 20-item self-efficacy questionnaires were administered at baseline to assess whether confidence in quitting and resistance to the temptations of smoking were associated with long-term cessation. Symptoms of nicotine withdrawal were assessed at 1 week, 8 weeks, and 12 weeks after self-reported quitting using a previously described withdrawal scale. The 9 items included in the withdrawal scale in-
cluded craving for a cigarette, depressed mood, difficulty falling asleep, awakening at night, irritability/frustration/anger, anxiety, difficulty with concentration, restlessness, and increased appetite. Each symptom was scored from 0 (absent) to 4 (severe), and the scores for each of the 9 items were summed for each participant who reported quitting.

At the 6-month telephone follow-up, additional data were obtained regarding the number of quit attempts since enrollment (defined as cessation for at least 24 hours), current level of smoking, and date of the last cigarette smoked. At the 12-month telephone follow-up, we collected data on self-reported smoking status, the number of quit attempts over the previous 6 months, date of last cigarette smoked, longest period of tobacco abstinence, participation in nonstudy smoking cessation programs, use of other tobacco products, use of NRT during the previous 6 months, alcohol use, employment status, weight, and medical visits over the previous 12 months. We asked participants to guess whether they were assigned to active medication or placebo on the 12-month questionnaire.

We assessed compliance with study medication by self-report and considered participants compliant if they reported taking 80% or more of their study drug during the initial 7 weeks of the study. Compliance was recorded during the telephone counseling that took place at weeks 1, 3, and 8 of follow-up. We used an intention-to-treat analysis as the principal method to compare smoking cessation rates in the 2 treatment arms, but also performed per protocol analyses based on self-reported compliance of 80% or more with study medication. We monitored adverse effects of the study medications during the telephone calls that took place at weeks 1, 3, and 8 of follow-up.

SMOKING CESSATION AND BIOCHEMICAL VALIDATION

We recorded self-reported tobacco abstinence (defined as no smoking for 7 days) at each follow-up phone counseling call and at the 6- and 12-month telephone interviews. For participants who reported that they had quit smoking at the 12-month telephone interview, we obtained saliva samples for cotinine testing. We used cotinine levels of 15 ng/mL or higher as an indicator of current tobacco use.13 For self-reported quitters who had saliva cotinine levels of 15 ng/mL or higher, we ascertained by telephone interview whether they were using NRT at the time the sample was provided. There were 6 such participants whom we considered as nicotine dependent and thus, smokers. Similarly, patients who had stopped smoking cigarettes, but continued to use other tobacco products were considered as smokers in the analyses. Continuous quitters were defined as participants who were self-reported quitters at each follow-up assessment and who had biochemical or proxy validation of smoking cessation at the 12-month follow-up.

Participants were reimbursed for providing the saliva specimen for cotinine assay but were otherwise uncompensated. All saliva samples were stored at –21°C at the SFVAMC until assayed. Saliva samples were stored at –21°C at the SFVAMC until assayed. To maximize outcome ascertainment among difficult-to-reach participants, we mailed subjects self-addressed stamped envelopes and plastic vials for saliva, along with a letter offering $20 for the provision of a saliva sample. For all self-reported quitters who provided no saliva specimen for cotinine assay, we attempted to obtain a statement by a spouse or significant other regarding their current smoking status. Proxy reports were used for 7 participants, 3 from the bupropion group and 4 from the placebo group. Spousal proxy reports have been reported to be reliable.18

HOSPITAL ADMISSIONS AND MORTALITY

To determine whether the bupropion intervention was associated with subsequent hospitalizations and 1-year mortality, we monitored hospital admissions among the participants during the year after enrollment. Hospital records were reviewed and adjudicated by a physician investigator in a blinded fashion. Admissions or deaths were judged principally smoking-related if they were secondary to cardiovascular disease (including congestive heart failure, coronary disease, peripheral arterial disease, and stroke), chronic obstructive pulmonary disease, pneumonia, and cancers of the throat, larynx, esophagus, stomach, lung, and urinary bladder.

STATISTICAL ANALYSIS

To compare the baseline variables of the 2 study arms, we used 2-sample t tests and Wilcoxon rank sum tests for continuous variables and chi-squared tests for categorical variables. We calculated the relative risk and 95% confidence interval associated with randomization to the bupropion group.

We also examined whether factors other than treatment assignment were associated with quitting. In these analyses, all simple and multivariate logistic regression models were adjusted for treatment assignment. We used a backward stepwise procedure to examine the relation between demographic and historical variables and self-reported smoking cessation at 6 months and biochemically validated smoking cessation at 12 months. Race/ethnicity was entered as white, African American, or other using dummy variables. Variables were retained in the model if they remained associated with quitting at P≤.20. We used the Hosmer-Lemeshow goodness-of-fit test to assess the adequacy of the multiple logistic regression models (all P≥.40). We considered 2-tailed P values <.05 to be statistically significant. Analyses were performed using Stata statistical software (release 7.0; Stata Corp, College Station, Tex).

RESULTS

There were no statistically significant differences in any of the baseline demographic or medical characteristics of participants randomized to the 2 study arms (all P>.08) (Table 1). Study participants were predominantly unmarried, white, overweight, middle-aged men who were US veterans. A history of alcoholism was common. Smoking history and history of depression and drug abuse were similar in the 2 groups. Study participants were moderate smokers at the time of enrollment, with a mean of 39 pack-years of smoking, and were smoking, on average, slightly more than 1 pack of cigarettes per day.

INTENTION-TO-TREAT ANALYSES

Approximately 75% of participants reported quitting at the time of their assigned quit date, and 81% of all study participants reported quitting at 1 week of follow-up. There were no differences in the rate of self-reported smoking cessation at 3 weeks of follow-up (P>.82) (Figure 2 and Table 2). However at 7 weeks, which was the end of the treatment period with bupropion or placebo, the quit rates were nonsignificantly higher in the bupropion group than in the placebo group: 64% vs 57%, respectively (P=.23). Over the next 4 to 5 weeks, participants assigned to active drug continued to report a higher quit rate compared with participants assigned to placebo (57% vs 47%, respectively), but these differences in the point prevalence of quitting were not statistically significant (P=.12).

At 6 months and 12 months of follow-up, self-reported quit rates were virtually identical in both study
Table 1. Baseline Characteristics of 244 Study Participants*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bupropion Group (n = 121)</th>
<th>Placebo Group (n = 123)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50 ± 12</td>
<td>49 ± 11</td>
<td>.46</td>
</tr>
<tr>
<td>Men</td>
<td>106 (88)</td>
<td>103 (84)</td>
<td>.39</td>
</tr>
<tr>
<td>White</td>
<td>79 (65)</td>
<td>90 (73)</td>
<td>.18</td>
</tr>
<tr>
<td>Black</td>
<td>28 (23)</td>
<td>24 (20)</td>
<td>.49</td>
</tr>
<tr>
<td>Married (n = 239)</td>
<td>28 (24)</td>
<td>33 (28)</td>
<td>.48</td>
</tr>
<tr>
<td>Veteran</td>
<td>99 (82)</td>
<td>95 (77)</td>
<td>.38</td>
</tr>
<tr>
<td>Level of education, y</td>
<td>14 ± 2</td>
<td>14 ± 2</td>
<td>.96</td>
</tr>
<tr>
<td>BMI</td>
<td>26 ± 5</td>
<td>27 ± 5</td>
<td>.53</td>
</tr>
<tr>
<td>Age began smoking, y</td>
<td>17 ± 5</td>
<td>16 ± 5</td>
<td>.41</td>
</tr>
<tr>
<td>Current tobacco use, cigarettes per day</td>
<td>22 ± 15</td>
<td>23 ± 11</td>
<td>.44</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>39 ± 26</td>
<td>39 ± 24</td>
<td>.90</td>
</tr>
<tr>
<td>Beck Depression</td>
<td>9 ± 6</td>
<td>9 ± 7</td>
<td>.61</td>
</tr>
<tr>
<td>Fagerström score</td>
<td>3.8 ± 1.7</td>
<td>4.0 ± 1.7</td>
<td>.45</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); COPD, chronic obstructive pulmonary disease.
*Data are given as mean ± SD value or number (percentage) of patients.
†Current tobacco use was defined as the usual number of cigarettes smoked per day during the 2 weeks prior to enrollment.

Figure 2. Proportion of self-reported quitters among participants randomized to bupropion vs placebo over 12 months of follow-up.

Bupropion arm correctly guessed their treatment assignment; 59% for bupropion vs 47% for placebo (P=.07). Participants randomized to the bupropion arm experienced significantly fewer withdrawal symptoms at 1 week (P=.04) and 8 weeks of follow-up (P=.08), but these differences were not detected at 3 months (P=.46). The specific withdrawal symptoms improved by bupropion treatment were craving for a cigarette and depressed mood.

Other variables were associated with smoking cessation at P≤.20, independent of treatment assignment. In simple logistic regression models, African American participants had an approximately 3-fold increased odds of quitting at 6 months compared with other nonwhite participants (P=.04). In multivariate models, 2 variables, African American race/ethnicity and being currently married, were associated respectively with an approximately 3.6-fold and a 2-fold increased odds of quitting at 6 months (both P<.05). There were no significant interactions detected between any of the variables and treatment assignment at 6 months.

Using a saliva cotinine level of less than 15 ng/mL as the criterion for validated smoking cessation, we examined predictors of quitting at 12 months of follow-up. In simple logistic models that controlled for treatment assignment, increasing level of nicotine dependence, as assessed by the Fagerström score, was associated with a 17% decreased odds of smoking cessation (P=.04). In multivariate models, a history of alcohol abuse was significantly associated with an approximately 2-fold increased odds of smoking cessation (P=.03), whereas increasing level of nicotine dependence was associated with a 20% decreased odds of quitting (P=.03). We found no interactions between treatment assignment and the other variables.

We examined whether treatment with bupropion was associated with several other health-related outcomes. Rates of hospitalization in the 2 study groups were similar over the course of follow-up. Among the 229 participants for whom we had such data, 19% of the placebo...
Table 2. Smoking Cessation Rates and the Relative Risk of Quitting

<table>
<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report at 3 wk</td>
<td>1.02 (0.88-1.17)</td>
</tr>
<tr>
<td>Self-report at 7 wk (end of treatment)</td>
<td>1.13 (0.92-1.39)</td>
</tr>
<tr>
<td>Self-report at 12 wk</td>
<td>1.21 (0.95-1.54)</td>
</tr>
<tr>
<td>Self-report at 6 mo</td>
<td>0.96 (0.71-1.30)</td>
</tr>
<tr>
<td>Self-report at 12 mo</td>
<td>1.01 (0.69-1.46)</td>
</tr>
<tr>
<td>Validated at 12 mo*</td>
<td>0.79 (0.51-1.24)</td>
</tr>
<tr>
<td>Validated at 12 mo†</td>
<td>0.80 (0.49-1.30)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Validated by saliva cotinine level or spouse proxy. Participants lost to follow-up were considered smokers.
†Validated by saliva cotinine level or spouse proxy. Participants lost to follow-up and participants with nonsmoking status ascertained by spouse proxy were considered smokers (ie, nonsmoking status based solely on biochemical validation by saliva cotinine).

We found that the addition of a brief 7-week course of bupropion to standard smoking cessation therapy that included cognitive-behavioral counseling and NRT did not significantly increase quit rates at any point during a 12-month period of follow-up. We did, however, observe a nonsignificant trend toward higher self-reported quit rates in the bupropion group by the end of the 7-week drug treatment period. This trend favoring bupropion lasted as long as 3 months. This ostensible beneficial effect was no longer apparent as follow-up continued. Variables associated with successful quitting included a history of alcohol abuse and a lower score on the Fagerstrom questionnaire for nicotine dependence. The observation that a history of alcohol abuse was associated with an increased likelihood of quitting was unexpected and may be a chance finding. However, it is possible that such participants had previously acquired skills helpful in quitting as a result of therapy for alcohol dependence.

Two early studies examining bupropion for smoking cessation were reported in abstract form. After obtaining promising results from a pilot study among 42 male smokers, Ferry and Burchette conducted a randomized blinded trial of immediate-release bupropion hydrochloride (300 mg/d for 12 weeks) in 190 nondepressed smokers. Smokers assigned to the intervention group that received behavior modification and active drug treatment achieved a continuous abstinence rate of 28% vs 24% in the placebo group. Results at 6 and 12 months, however, were not reported. Gonzales and colleagues reported that a 12-week course of treatment with bupropion increased continuous abstinence rates among 450 smokers followed for 6 months who had failed previous treatment with bupropion. However, these investigators also reported that the effect of bupropion waned over

PER PROTOCOL ANALYSES

Because we wished to examine whether actual drug use rather than randomization status affected the likelihood of quitting, we performed additional analyses among those participants who reported that they were at least 80% compliant with taking their study medication. Approximately 62% of the participants randomized to both study groups were compliant in taking their study medication. Among the compliant participants, the average quit rates were similar at 1 week and 3 weeks of follow-up (ie, approximately 93% at 1 week and 91% at 3 weeks in both groups [both P > .27]). However, as drug treatment continued, there was a nonsignificant trend favoring participants in the bupropion group; 82% of the bupropion group vs 73% placebo group were self-reported quitters by the end of drug treatment at 7 weeks of follow-up (P = .24). After 3 months of follow-up, 69% of compliant participants in the bupropion group reported quitting compared with 57% of compliant participants in the placebo group (P = .13). However with continued follow-up, the quit rates were very similar in both groups. At 6 months, the self-reported quit rates were 49% for the bupropion arm vs 53% for the placebo arm (P = .63). Among compliant study participants, 1-year quit rates validated biochemically or by spousal proxy were 33% for the bupropion arm vs 27% for the placebo arm (P = .48). Using the saliva cotinine assays alone to validate smoking cessation yielded similar findings; 28% of compliant users of bupropion quit compared with 22% of compliant placebo users (P = .45).
time, an effect consistent with findings in our study. After 6 months of follow-up, continuous abstinence rates had declined from over 30% to approximately 12% with a 6-month point prevalence of quitting among the bupropion group of 21%. Hurt and colleagues conducted a randomized blinded trial of 7 weeks of sustained-release bupropion among 615 nondepressed men and women who received either placebo or 1 of 3 bupropion treatments (a total daily dose of 100 mg, 150 mg, or 300 mg). All participants also received brief individual counseling, and 36% of the participants failed to complete the 12-months of follow-up. Biochemically confirmed quit rates at 1-year were 12% in the placebo group compared with 20% to 23% in the bupropion groups. Unlike our study, participants did not use NRT and received only brief counseling, which may in part account for the different findings. Jorenby and colleagues conducted a randomized blinded trial in 893 nondepressed smokers, all of whom received individual counseling and 1 of 4 treatments (placebo, NRT alone, sustained-release bupropion alone, or bupropion plus NRT) lasting 9 weeks. Participants who received placebo had a 1-year quit rate of 16% compared with 16% in the NRT group, 30% in the bupropion-only group, and 36% in the combined NRT plus bupropion group. Like Jorenby and colleagues, we found that smoking cessation rates declined as the duration of follow-up continued to 12 months. Unlike that study, however, we failed to see a sustained benefit from the addition of bupropion therapy to individual counseling and NRT and observed a greater effect from NRT throughout the 12 months of follow-up. Most recently, Ahluwalia et al examined the effect of bupropion vs placebo among 600 African Americans. Participants in that study, 32% of whom were lost to follow-up, received 7 weeks of sustained-release bupropion, and were followed for 6 months. The large initial benefit observed with bupropion decreased over time, such that by 6 months the quit rates were 21% for the bupropion group and 14% for the placebo group.

We can only speculate as to possible reasons for the differences in the findings. Jorenby and colleagues enrolled a larger number of participants compared with our study and hence had greater power to observe an association. Other differences between our study and that of Jorenby and colleagues that may partially account for some of the differences in findings include a shorter duration of bupropion therapy (7 weeks vs 9 weeks), a greater percentage of male participants (86% vs 48%), and a lower level of nicotine dependence (Fagerstrom score of 4 vs 7) in our study. Our study participants also differed from those enrolled in other studies; we enrolled a diverse group of mostly male veteran smokers, whereas most participants in the Hurt et al and Jorenby et al studies were white and female and only African Americans were enrolled by Ahluwalia and colleagues. Blinding appeared to be effective in our study; an approximately equal number of participants were able to guess what their treatment had been at the end of the study. While unblinding might have been expected to increase the ostensible effect of the active treatment regimen, we observed in the intention-to-treat analyses the converse, that is, treatment with counseling plus NRT plus bupropion was (non-significantly) inferior to that of counseling plus NRT plus placebo at 12 months of follow-up. Of note, Hays and colleagues reported recently that persons who stopped smoking with 7 weeks of bupropion treatment and who were then randomized to receive an additional 45 weeks of bupropion (vs placebo), had a delay in smoking relapse over the second year of follow-up, but ultimately had similar quit rates at the end of the study (week 104 of follow-up): 40% for the placebo group vs 42% for the bupropion group (P < .05).

Although our study was a randomized, double-blind, placebo-controlled study, there were potential limitations. First, our study population of mostly middle-aged white male veterans may not be generalizable to other populations of smokers. Our study participants were, on average, long-term heavy smokers. We collected only self-reported data on smoking cessation at all time points except for the final 12 month follow-up; hence, we were unable to verify biochemically the smoking cessation point prevalences at the other times. A significant percentage of participants were able to guess whether they were taking either active bupropion or placebo. We believe that any bias resulting from such unblinding would be expected to produce findings favoring the active treatment group, which we did not observe. We estimated medication compliance by self-report and therefore cannot be certain that participants assigned to the bupropion group actually took their medication as directed. We observed, however, a nonsignificant trend toward higher quit rates in the bupropion group at the end of treatment and at the 3-month follow-up, suggesting that the bupropion was being taken, but that its effect was not sustained. Furthermore, participants assigned to the bupropion arm reported significant decreases in some withdrawal symptoms. Per-protocol analyses among self-reported medication compliers also failed to reveal a sustained statistically significant benefit from bupropion use. We cannot exclude the possibility that our study results reflect a type II (false-negative) error, especially since we observed a nonsignificant beneficial effect of bupropion on quitting at 12 weeks of follow-up (relative risk, 1.21; 95% confidence interval, 0.95-1.54) and the results of the per-protocol analyses suggested a modest, albeit nonsignificant, 6% beneficial effect of bupropion on validated quitting at 12 months of follow-up. Furthermore, the cessation counseling that was used was intensive and involved a 30 to 60 minute face-to-face session in addition to follow-up telephone counseling sessions. This level of counseling intensity may have contributed to the high quit rates in the comparison group and in turn, the failure to observe a significant difference in quit rates between the study groups. Alternatively, we cannot exclude the possibility that the 7-week course of bupropion was too brief to produce a detectable and sustained difference in quit rates.

There have been comparatively few studies of bupropion for smoking cessation, a drug now recommended for first-line use in smoking cessation. We were unable to demonstrate a sustained benefit from a 7-week course of bupropion when combined with cognitive-behavioral counseling and NRT. Additional studies would be helpful in selecting those smokers
most likely to benefit from treatment with bupropion for smoking cessation.

Accepted for publication December 17, 2003.

This study was entirely funded by grant 7RT-0033 from the California Tobacco-Related Disease Research Program, Oakland, Calif.

Correspondence: Joel A. Simon, MD, MPH, General Internal Medicine Section (111A1), Veterans Affairs Medical Center, 4150 Clement St, San Francisco, CA 94121 (jasimon@itsa.ucsf.edu).

REFERENCES