Bupropion for Smoking Cessation

A Randomized Trial

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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.

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Current guidelines for smoking cessation recommend that smokers who want to quit receive cognitive-behavioral counseling, nicotine replacement therapy (NRT), and self-help materials. In general, such approaches have been modestly successful in helping smokers achieve long-term abstinence. One-year quit rates between 20% and 40% are typically reported in clinical trials using these treatment modalities. Because smoking remains the single most important cause of premature death in the United States, other approaches to increase smoking cessation rates have been studied, including use of antidepressant medications. Several recent studies have reported that bupropion hydrochloride, an antidepressant chemically unrelated to other antidepressants, may be useful in increasing smoking cessation rates among smokers trying to quit. One of these clinical studies reported an absolute 20% increase in 1-year quit rates among participants receiving combined bupropion plus NRT compared with participants receiving NRT alone.

We undertook this study to confirm and expand the results of the previous studies that have examined the efficacy of bupropion for smoking cessation. We wanted to determine in our study population of mostly veteran men whether the addition of bupropion to transdermal NRT and cognitive-behavioral counseling would increase quit rates compared with standard therapy using NRT and cognitive-behavioral counseling only.

METHODS

PARTICIPANTS

Between September 1, 1998, and March 31, 2001, we enrolled in our study 210 men and 34 women 20 years and older (Figure 1). Potential participants were identified through enriched lists of known smokers from our previous smoking cessation clinical studies at the San Francisco Veterans Affairs Medical Cen-
ter (SFVAMC), San Francisco, Calif, from hospital-based advertising at major teaching hospitals affiliated with the University of California, San Francisco, and from local Bay Area advertising and radio public service announcements. Recruitment was promoted by emphasizing the importance of smoking cessation and the unique opportunity to participate in a study examining the efficacy of bupropion for smoking cessation. All participants reported that they were current smokers, which was defined as smoking 20 or more cigarettes during the week prior to enrollment. We excluded smokers with contraindications to bupropion or NRT, as well as persons with serious psychiatric illnesses, including major depression. Potential participants were also excluded if they reported a recent history of alcohol abuse within the prior 3 months or were consuming more than 3 alcoholic beverages daily. Participants had to have a telephone and no plans to leave the SFVAMC catchment area during the study period. We assessed readiness to quit smoking using the stages of change model of Prochaska and DiClemente. Participants met the criteria 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-month 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.17 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, participants 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. 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.58

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 χ² 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 to heavy 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.

IN 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
arms: approximately 40% at 6 months and 32% at 12 months of follow-up (Figure 2). We confirmed quitting by measurement of saliva cotinine or when not available, by spousal proxy. There was no difference in the smoking cessation rates between the 2 study arms assessed by saliva cotinine or spousal proxy validation; 22% of the bupropion group and 28% of the placebo group had quit smoking (P = .31). Overall rates of self-reported quitting (32%) were higher than those confirmed biochemically (22%). When the most conservative criterion for validating smoking cessation (ie, a saliva cotinine assay <15 ng/mL) was used, the quit rate was 19% among the bupropion arm and 24% among the placebo study arm (P = .36). The rates for continuous quitting assessed at 12 months of follow-up were 15% for the bupropion arm and 19% among the placebo study arm (P = .43). There was no difference in the 12-month number of median quit attempts by treatment assignment: 3.6 for bupropion vs 3.1 for placebo (P = .74). At the end of follow-up, quitters, on average, gained more weight than nonquitters: 2.65 kg vs 0.41 kg (P = .01). Furthermore, there was no difference in weight gain between participants randomized to the 2 study groups (P = .90) nor between quitters in the bupropion group compared with quitters in the placebo group: 2.92 kg vs 2.43 (P = .78).

We asked participants at the end of the study to guess which group they had been randomized. A slightly greater number of participants randomized to the 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 an approximately 2-fold increased 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 treatment...
group and 13% of the bupropion group reported at least 1 hospital admission (P = .22). There was no significant difference between the groups in the number of quit attempts during the 12 months of follow-up (P > .07) nor in the number of hospitalizations for a smoking-related illness (P = .56). By the end of the study, 5 participants had died: 2 in the bupropion group and 3 in the comparison group.

A total of 55% of participants reported 1 or more adverse effects during the drug treatment phase of the study: 60% in the bupropion group vs 49% in the placebo group (P = .07). The most common adverse effects reported were insomnia (18%), dry mouth (15%), and abnormal dreams (8%), but the frequency of insomnia and abnormal dreams were similar in both groups (both P > .54). Compared with the placebo group, however, the bupropion group reported a dry mouth (22% vs 8%; P < .01) gastrointestinal upset (9% vs 1%; P < .01) more frequently. In contrast, placebo-treated participants tended to have more headaches than the bupropion participants (7% vs 2%; P = .06).

**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).

**COMMENT**

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...
time, an effect consistent with findings in our study. Af-
ter 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 bu-
propion group of 21%.19 Hurt and colleagues7 con-
ducted 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 coun-
seling, 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 dif-
ferent findings. Jorenby and colleagues8 conducted a ran-
domized blind trial in 893 nondepressed smokers, all of
whom received individual counseling and 1 of 4 treat-
ments (placebo, NRT alone, sustained-release bupro-
piom alone, or bupropion plus NRT) lasting 9 weeks. Par-
ticipants 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,8 we
found that smoking cessation rates declined as the du-
ration 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 coun-
seling and NRT and observed a greater effect from NRT
throughout the 12 months of follow-up. Most recently,
Ahluwalia et al20 examined the effect of bupropion vs pla-
ouce 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 fol-
lowed 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 colleagues8 en-
rolled a larger number of participants compared with our
study and hence had greater power to observe an asso-
ciation. 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 per-
centage 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 partici-
pants in the Hurt et al7 and Jorenby et al8 studies were
white and female and only African Americans were en-
rolled by Ahluwalia and colleagues.20 Blinding appeared
to be effective in our study; an approximately equal num-
ber of participants were able to guess what their treat-
ment had been at the end of the study. While unblind-
ing 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, treat-
ment 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
colleagues9 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 re-
lapse 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 limi-
tations. 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 ex-
cept 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 tak-
ing either active bupropion or placebo. We believe that
any bias resulting from such unblinding would be ex-
pected to produce findings favoring the active treat-
ment group, which we did not observe. We estimated
medication compliance by self-report and therefore can-
not be certain that participants assigned to the bupro-
piom 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 treat-
ment 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 bu-
propion arm reported significant decreases in some with-
drawal symptoms. Per-protocol analyses among self-
reported medication compliers also failed to reveal a
sustained statistically significant benefit from bupro-
piom 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 bu-
propion 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,
although nonsignificant, 6% beneficial effect of bupropion
on validated quitting at 12 months of follow-up. Fur-
thermore, the cessation counseling that was used was in-
tensive and involved a 30 to 60 minute face-to-face ses-
sion in addition to follow-up telephone counseling ses-
sions. This level of counseling intensity may have con-
tributed to the high quit rates in the comparison group
and in turn, the failure to observe a significant differ-
ence in quit rates between the study groups. Alterna-
tively, we cannot exclude the possibility that the 7-week
course of bupropion was too brief to produce a detect-
able and sustained difference in quit rates.

There have been comparatively few studies of
bupropion for smoking cessation, a drug now recom-
mended for first-line use in smoking cessation.2 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.

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