Original Investigation

Sustained-release bupropion for hospital-based smoking cessation: A randomized trial

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Abstract

Introduction: Bupropion is a first-line pharmacological aid for smoking cessation; however, no clinical trials have been conducted in a general population of hospitalized smokers.

Methods: We enrolled 85 smokers in a hospital-based randomized smoking cessation trial conducted at the San Francisco Veterans Affairs Medical Center. A total of 42 participants received a 7-week course of sustained-release bupropion and 43 participants received placebo. All participants received cognitive–behavioral counseling. We screened 14,997 patients, of whom 25% were current smokers. Of the 536 smokers who met the entry criteria, 451 opted not to enroll. We determined on-medication, end-of-counseling, 3-month, and 6-month smoking cessation rates.

Results: At the end of 7 weeks of drug treatment, self-reported quit rates were equivalent in the bupropion and placebo arms, 37% versus 33%, respectively (p = .82). The validated quit rates for the bupropion and placebo groups were 27% versus 29%, respectively (p = 1.00). At 6 months, the self-reported quit rates were 29% in the bupropion group and 41% in the placebo group (p = .36). In a comparison of 6-month quit rates, validated either by salivary cotinine or by spousal proxy, we found nonsignificantly higher quit rates in the placebo group than in the bupropion group, 31% versus 15% (p = .12).

Discussion: The addition of sustained-release bupropion to counseling did not increase quit rates, but the study was underpowered. Because of the secular trend toward shorter hospital stays, recruitment was very difficult, raising questions regarding the feasibility of future hospital-based smoking cessation trials and interventions.

Introduction

Three pharmacological treatments are approved by the U.S. Food and Drug Administration to help smokers who want to quit: nicotine replacement therapy (NRT), long-acting bupropion, and most recently, varenicline (Ebbert, Sood, Hays, Dale, & Hurt, 2007). Recognizing that hospital admissions present a window of opportunity to reach smokers who often are hospitalized for a smoking-related illness, smoking cessation interventions are now recommended for all hospitalized smokers (Rigotti, Munafò, Murphy, & Stead, 2006). Most hospital-based smoking cessation clinical trials combine behavioral therapy with nicotine replacement (Rigotti, 2002). With the exception of a recently published trial by Rigotti, Thorndike, et al. (2006) that examined the safety and efficacy of sustained-release bupropion among smokers hospitalized for an acute coronary syndrome (ACS), to our knowledge, the efficacy of bupropion as an adjunct to cognitive–behavioral counseling for smoking cessation among hospitalized smokers has not been examined.

We undertook this study to assess the efficacy of sustained-release bupropion for smoking cessation among a general population of hospitalized smokers. We wanted to determine whether bupropion, when initiated in the hospital setting, would be useful in promoting long-term smoking cessation.

Methods

Participants

Between January 2004 and August 2006, we enrolled 82 men and 3 women ranging in age from 33 years to 76 years who were
hospitalized for at least 24 hr (Figure 1). Potential participants were identified through lists of hospitalized patients produced daily at the San Francisco Veterans Affairs Medical Center (SFVAMC). Recruitment was promoted by emphasizing the importance of smoking cessation and the unique opportunity to participate in a study examining the efficacy of sustained-release bupropion for hospital-based smoking cessation. In addition to screening all hospital admissions for eligibility, we mailed informational letters to all patients who were scheduled for an elective hospitalization and included study flyers in the admission packets of all hospitalized patients. All participants reported that they were current smokers during the week prior to hospital admission and smoked at least 5 cigarettes/day during the previous year. We excluded smokers with known contraindications to bupropion, patients admitted for an ACS (i.e., myocardial infarction or unstable angina), those who were terminally ill (defined as an estimated life expectancy of less than 6 months), and any smokers with a serious unstable psychiatric illness (defined by frequent mental health visits or changing psychiatric medication regimens). For safety reasons, we also excluded patients with a family history of seizures, a history of serious head trauma, or a known seizure disorder, as well as women who were pregnant or lactating, potential participants with a history of drug abuse within the prior 3 months, and those who currently consumed at least three 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 (Prochaska & DiClemente, 1983) and recruited participants who were at either the contemplation or the preparation stage of quitting.

We screened 14,997 patients admitted to the hospital, of whom 3,697 (25%) were current smokers. Of the eligible 536 smokers, we were able to enroll 85 in the study. Local institutional review committee approval was obtained, and all participants signed an informed consent to enroll in the study. Of the 85 participants enrolled, 2 died during the study (1 bupropion and 1 placebo subject); thus, 83 subjects were available for the intention-to-treat analysis (see Figure 1). The two participants lost to follow-up and the seven participants who dropped out of the study were considered smokers in analyses that required biochemical or spousal confirmation of quitting.

**Interventions**

We assigned participants to the two 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 upon enrollment a 7-week course of sustained-release bupropion (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-appearing placebo. All study personnel engaged in providing interventions to participants were blinded to intervention assignment. The same cognitive–behavioral intervention was administered to both groups by a research associate trained as a public health educator. The intervention was based on social learning theory (Bandura, 1986) and the stages-of-change model (Prochaska & DiClemente, 1983). Participants met with the research associate in the hospital in an individual counseling session that lasted 30–60 min. During this session, 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 pre-specified guidelines. Behavioral self-management techniques to counter known relapse triggers, such as stress, the presence of other smokers, alcohol use, and depression, also were discussed (Shiffman, Paty, Gnych, Kassel, & Hickcox, 1996). All participants who were enrolled and randomized completed the initial counseling session.

After hospital discharge, all participants received five follow-up telephone counseling calls. These calls were made at week 1, week 3, and then monthly (beginning at week 4) 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 min or less. Participants who had resumed smoking were encouraged to set new quit dates.

Data collection
The research associate collected baseline questionnaire data on age, race/ethnicity, sex, marital status, presence of other smokers in the household, level of education completed, history of drug or alcohol abuse (defined as two or more positive responses to the CAGE questionnaire (Ewing, 1984) or a self-reported history of current alcohol use of more than three drinks daily), medical illness, history of depression, and reason for hospital admission. The assessment of medical problems was based on medical record review and participants’ self-report. We assessed depressive symptomatology using the Beck Depression Inventory (BDI) (Beck & Steer, 1987). Body mass index 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 (COPD), vascular disease, diabetes mellitus, hypertension, and tobacco-related malignancy (i.e., cancer of the lung, bladder, kidney, oropharynx, or larynx), were recorded based on participant interviews and, when available, chart review.

We obtained self-reported data on preenrollment level of cigarette smoking (in cigarettes/day), pack-years of tobacco smoked (average packs per day × number of years of smoking), and number of prior attempts at smoking cessation. The estimated level of nicotine dependence was based on the Fagerström Tolerance Questionnaire (Fagerström, Heatherton, & Kozlowski, 1990). 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 (Velicer, DiClemente, Rossi, & Prochaska, 1990). Symptoms of nicotine withdrawal were assessed at weeks 1, 3, 5, and 7 during treatment using a previously described withdrawal scale (Hughes & Hatsukami, 1986).

The nine items in the withdrawal scale included 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 the nine 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 hr), current level of smoking, and date of the last cigarette smoked. The 6-month questionnaire asked participants to guess whether they were assigned to active medication or placebo. We used an intention-to-treat analysis as the principal method to compare smoking cessation rates in the two treatment arms. We monitored side effects of the study medications during the telephone calls that took place at weeks 1, 3, 5, and 7 of follow-up.

Smoking cessation and biochemical validation
We recorded point prevalence self-reported tobacco abstinence (defined as no smoking for 7 days) at each follow-up phone counseling call and at the 6-month telephone interviews. For participants who reported that they had quit smoking at the end of treatment and at the 6-month telephone interview, we obtained saliva samples for cotinine testing. Because many of the participants live great distances from the SFVAMC, we used salivary cotinine levels (≥15 ng/ml) as an indicator of current tobacco use, rather than measuring carbon monoxide in person (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987). We permitted the mailing of saliva samples in special envelopes when necessary. For self-reported quitters who had salivary 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. We considered three participants (two in the buproprion arm and one in the placebo arm) to be nicotine dependent and, thus, smokers. Similarly, participants who had stopped smoking cigarettes but continued to use other tobacco products were considered to be 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 6-month follow-up.

Participants were reimbursed US$100 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 to the participants self-addressed stamped envelopes and plastic vials for saliva samples, along with a letter offering $100 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 three participants from the placebo group. Spousal proxy has been reported to be reliable (Chen, Rennie, & Dosman, 1995).

Hospital readmissions and mortality
To determine whether the sustained-release bupropion intervention was associated with subsequent hospitalizations and
mortality, we monitored SFVAMC hospital admissions among the participants during the 6 months after enrollment. Hospital records were reviewed and adjudicated by a physician investigator in a blinded fashion. Admissions or deaths were judged to be principally smoking related if they were secondary to cardiovascular disease (including congestive heart failure, coronary disease, peripheral arterial disease, and stroke), COPD, pneumonia, or cancer of the throat, larynx, esophagus, stomach, lung, or urinary bladder.

Data analyses

To compare the baseline variables of the two study arms, we used two-sample t tests for continuous variables and chi-square tests for categorical variables. We calculated the relative risk of quitting and the corresponding 95% CI associated with randomization to the bupropion group. Standard formulae were used for the calculation of relative risk of smoking cessation. We considered two-tailed p values of less than .05 to be statistically significant. We estimated at the start of the study that approximately 120 participants per group would be required to have 80% power to detect an absolute difference of 15% in the quit rates between the two study arms. Analyses were performed using SPSS software.

Results

We recruited participants on a continuous basis for approximately 2.5 years, screening almost 15,000 patients for eligibility (see Figure 1). Of those screened, 25% (n = 3,697) were smokers, and of the 451 smokers who were eligible to enroll but declined, 66% of those reported not wanting to quit, 18% did not want to take bupropion, 11% did not wish to participate in a clinical study, and 5% did not want to take the risk of being randomly assigned to receive the placebo. Only 16% of eligible smokers (n = 85) opted to enroll in the study. More than 3,000 smokers were ineligible to enroll. The main reasons for ineligibility included a current history of alcohol abuse (18%), smoking fewer than five cigarettes daily (12%), current drug abuse (11%), an active psychiatric disorder (9%), a hospital stay of less than 24 hr (9%), past or current stroke (8%), current use of bupropion (6%), history of a seizure disorder (5%), and an ACS (4%). Approximately 16% of admissions were elective.

We found no statistically significant differences in any of the baseline demographic or medical characteristics of participants randomized to the two study arms (all p values ≥.12; see Table 1). Study participants were predominantly unmarried, White, overweight, middle-aged men, all of whom were U.S. veterans. A history of alcohol abuse and depression was common. The smoking history, history of depression, and past drug abuse were similar in the two study arms. Study participants were moderate to heavy smokers at the time of enrollment, with a mean of 43.4 pack-years of smoking, and were smoking, on average, 16 cigarettes/day.

We assumed participants to be abstinent at the time of enrollment during their hospitalization, and 40% of all study participants reported not smoking at the 1-week follow-up. At the 3-week follow-up, self-reported smoking cessation was 39% in the bupropion group versus 45% in the placebo group (p = .67; Table 2). However, at 7 weeks, which was the end of the treatment period with bupropion or placebo, the self-reported quit rates were similar in the bupropion group and the placebo group, 37% versus 33%, respectively (p = .82). When comparing the validated quit rates between the two groups at 7 weeks, we found that 27% of the bupropion group and 29% of the placebo group had quit (p = 1.00). Only three participants reported using NRT during the study, two in the bupropion group and one in the placebo group.

At 6 months of follow-up, self-reported quit rates were non-significantly lower in the bupropion group compared with the placebo group, 29% versus 41% (p = .36). We confirmed quitting by measurement of salivary cotinine or, when not available, by spousal proxy. We found no significant difference in the smoking cessation rates between the two study arms assessed either way; 15% of the bupropion group and 31% of the placebo group had quit smoking (p = .12). Overall rates of self-reported quitting (35%) were higher than those confirmed biochemically (19%). The rates for continuous abstinence assessed at 6 months of follow-up were 15% for the bupropion arm and 21% among the placebo study arm (p = .57). The mean number of quit attempts during the 6-month study period was 3 for bupropion subjects and 4 for placebo subjects (p = .39). At the end of follow-up, quitters, as expected, gained more weight than nonquitters; +1.05 kg versus –0.45 kg (p = .44). Although we found no significant difference in weight change between validated quitters

### Table 1. Baseline characteristics of study participants (N = 85)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bupropion (n = 42)</th>
<th>Placebo (n = 43)</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>55 ± 8</td>
<td>57 ± 7</td>
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</tr>
<tr>
<td>Men (%)</td>
<td>39 (93)</td>
<td>43 (100)</td>
<td>.12</td>
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<tr>
<td>White (%)</td>
<td>33 (79)</td>
<td>30 (70)</td>
<td>.46</td>
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<tr>
<td>African American (%)</td>
<td>5 (12)</td>
<td>7 (16)</td>
<td>.76</td>
</tr>
<tr>
<td>Married (%)</td>
<td>12 (29)</td>
<td>20 (47)</td>
<td>.12</td>
</tr>
<tr>
<td>Level of education (years)</td>
<td>13 ± 2</td>
<td>14 ± 2</td>
<td>.26</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 5</td>
<td>28 ± 7</td>
<td>.31</td>
</tr>
<tr>
<td>Age at smoking initiation (years)</td>
<td>17 ± 7</td>
<td>16 ± 4</td>
<td>.18</td>
</tr>
<tr>
<td>Current tobacco use (cigarettes/day)</td>
<td>16 ± 11</td>
<td>16 ± 9</td>
<td>.99</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>43 ± 31</td>
<td>44 ± 24</td>
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</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>11 ± 8</td>
<td>13 ± 11</td>
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</tr>
<tr>
<td>Fagerström score</td>
<td>4.4 ± 2.1</td>
<td>4.4 ± 2.2</td>
<td>.97</td>
</tr>
</tbody>
</table>

**Note.** COPD = chronic obstructive pulmonary disease.

*Plus–minus values are means with SDs. Other values are numbers of subjects with percentages. Unpaired two-tailed t tests were used to compare continuous variables, and chi-square tests were used to compare categorical variables.

Current tobacco use was defined as the usual number of cigarettes smoked per day during the 2 weeks prior to enrollment.
in the bupropion group and validated quitters in the placebo group, on average, bupropion quitters gained 0.02 kg, whereas placebo quitters gained 1.5 kg ($p = .75$). We observed no significant differences over the course of the study on BDI scores either within or between groups.

We asked participants at the end of the study to guess the group to which they had been randomized. A greater number of participants randomized to the bupropion arm were able to correctly guess their treatment assignment: 45% for bupropion versus 22% for placebo ($p = .10$). Participants randomized to the bupropion arm reported greater withdrawal symptoms at 1 week ($p = .03$), but these differences were no longer detected at weeks 3, 5, and 7.

We examined whether treatment with bupropion was associated with several other health-related outcomes. Rates of hospitalization in the two study groups were similar over the course of follow-up. Among the 85 participants, 29% of the bupropion group and 37% of the placebo group reported at least one hospital admission ($p = .49$). We found no significant difference between the groups in the number of quit attempts during the 6 months of follow-up ($p = .39$). By the end of the study, two participants had died: one in the bupropion group and one in the comparison group.

A total of 15 participants (18%) reported one or more side effects during the drug treatment phase of the study, 11 in the bupropion group (26%) and 4 in the placebo group (9%). Side effects reported solely by the bupropion group were hyperactivity and insomnia. We observed no evidence that bupropion affected participants’ blood pressure.

### Discussion

When added to standard cognitive–behavioral therapy for smoking cessation, a 7-week course of sustained-release bupropion started during hospitalization did not significantly increase quit rates at any point during 6 months of follow-up. We enrolled hospitalized patients admitted for any illness other than an ACS and found, similar to Rigotti, Thorndike, et al. (2006), who enrolled only hospitalized smokers with ACS, that the addition of sustained-release bupropion to standard cognitive–behavioral therapy did not increase long-term quit rates. We observed a nonsignificant trend toward increased smoking cessation and reduced withdrawal symptoms during the 7-week period when participants were taking active medication. However, these effects were not sustained once the course of bupropion was completed.

The present study was limited by the great difficulty we encountered in recruiting eligible participants. Although we discerned no long-term efficacy of sustained-release bupropion when started in the hospital setting, we believe the main lessons of our study relate to the general feasibility of conducting modern hospital-based smoking cessation studies. The standard cognitive–behavioral counseling intervention appeared to work well, with 31% of the placebo group having a verified quit rate at 6 months. This quit rate is higher than is typically observed for such interventions. However, our finding that bupropion appears to be worse than placebo, albeit nonsignificantly, is most likely a chance finding related to the limited study enrollment and consequent underpowering of the study.

We screened almost 15,000 hospital admissions over a period of two-and-a-half years for potential participants. Of these patients, approximately 25% were current smokers. However, of the current smokers, 84% did not meet eligibility criteria, and of those who were eligible, only 16% chose to enroll. We encountered daunting obstacles because of the increasingly very brief duration of hospital stays, which effectively precluded the timely identification of, consenting, and cognitive–behavioral intervention for potential participants. We initially stipulated that participants would need to be hospitalized for a minimum of 48 hr but modified the study protocol to permit enrollment with a hospital stay of at least 24 hr. We also changed our entry criteria to permit the enrollment of light smokers, with a minimum smoking level of 5 cigarettes daily, in contrast to the original study protocol, which stipulated a minimum level of 15 cigarettes daily. Finally, we decided to follow participants for smoking outcomes for 6 months rather than 12 as planned initially, to permit greater time for recruitment. None of these modifications resulted in our achieving the targeted sample size. The trend toward shorter hospitalizations that we encountered has been confirmed by the Centers for Disease Control and Prevention’s National Hospital Discharge Survey (Popovic & Hall, 2001). Additionally, because of intensive smoking cessation efforts in the recent past, many of our hospitalized smokers...
had participated previously in smoking cessation studies or in local smoking cessation programs and declined enrollment.

While underscoring and acknowledging that the present study was underpowered, we nevertheless observed no beneficial effect from sustained-release bupropion when compared with standard but intensive cognitive–behavioral counseling alone. We found a lack of sustained efficacy of sustained-release bupropion in an earlier study comparing the effect of bupropion plus nicotine patches and counseling with placebo plus nicotine patches and counseling (Simon, Duncan, Carmody, & Hudes, 2004). In a study of sustained-release bupropion for smokers hospitalized with ACS, bupropion improved short-term, but not long-term, smoking cessation rates when added to intensive counseling (Rigotti et al., 2006). Other studies have reported that the effect of bupropion wanes over time (Ahluwalia, Harris, Cately, Okuyemi, & Mayo, 2002; Gonzales et al., 2001; Jorenby et al., 1999). Sustained-release bupropion is an effective first-line therapy to aid in smoking cessation; compared with placebo, it doubles, on average, the odds of quitting, as assessed in a Cochrane Review (Hughes, Stead, & Lancaster, 2004). However, 10 of the 21 studies cited by the review failed to observe a statistically significant increase in abstinence at 6 months or greater follow-up (Hughes et al., 2004) and the results of individual studies have been variable.

The present study had significant limitations. First, the study population consisted of mostly middle-aged, White male veterans, limiting the generalizability of the results. Study participants were, on average, long-term heavy smokers. We collected data on self-reported smoking cessation at all timepoints but were able to verify biochemically smoking cessation point prevalence only at 7 weeks and 6 months of follow-up. A significant percentage of participants were able to guess correctly whether they were taking active bupropion or placebo. We believe that any bias as a result of such unblinding would have favored the active treatment group, which we did not observe. We found a large discrepancy between the self-reported 6-month smoking cessation rate among the bupropion study arm (29%) and the 6-month quit rate as verified by salivary cotinine or spousal proxy (15%), which suggests unblinding, with participants reporting the outcome they assumed the investigators desired. Because we did not measure withdrawal symptoms at baseline, we were unable to assess change in withdrawal scores from baseline. Finally, and most important, the study was limited by its inability to recruit a large enough sample size to test properly the study hypothesis. That is, we were underpowered to test the main research question regarding the efficacy of hospital-based bupropion for smoking cessation.

In conclusion, we did not observe any evidence of higher quit rates among hospitalized smokers who received sustained-release bupropion and cognitive–behavioral counseling, compared with smokers who received placebo plus cognitive–behavioral counseling. The study was limited markedly by a small sample size, and we cannot exclude the possibility that a larger sample size might have produced different results. More important, if our difficulty in identifying and recruiting hospitalized smokers applies to other populations and settings, it will likely have implications for future hospital-based smoking cessation programs and research. Although hospitalization presents a window of opportunity and a teachable moment for patients to quit smoking, overcoming secular trends toward very brief hospital stays may necessitate new approaches for reaching this at-risk population.

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### Declaration of Interests
None declared.

### References


