Bupropion Sustained Release as a Smoking Cessation Treatment in Remitted Depressed Patients Maintained on Treatment With Selective Serotonin Reuptake Inhibitor Antidepressants

K. N. Roy Chengappa, M.D.; Radha K. Kambhampati, M.D.; Kenneth Perkins, Ph.D.; Rajendra Nigam, M.D.; Tracy Anderson; Jaspreet S. Brar, M.D.; Hari K. Vemulapalli, M.D.; Rebecca Atzert, R.N.; Pamela Key, R.N.; Jasbir S. Kang, M.D.; and Joseph Levine, M.D.

Background: Patients with depressive disorders smoke tobacco more often than the population at large and find quitting more difficult. Furthermore, when they quit smoking, they are more likely to suffer a relapse of depression. We evaluated the addition of bupropion sustained release (SR) for smoking cessation among patients with a history of depressive disorders being maintained in a euthymic state with selective serotonin reuptake inhibitor (SSRI) antidepressants.

Method: Twenty-five adults with DSM-IV major depressive disorder or depressive disorder NOS currently receiving SSRI maintenance treatment and smoking ≥ 15 cigarettes per day participated in the 9-week study. Bupropion SR, 150 mg/day, was added to SSRI treatment and increased to 300 mg/day. Subjects were counseled on smoking cessation measures and chose a target quit date 2 or 4 weeks after the initiation of bupropion SR. Self-reported smoking status, expired carbon monoxide (CO) measurements, Hamilton Rating Scales for Depression and Anxiety scores, and weight were measured at each visit. Subjects were abstinent if they reported not smoking during the prior 7 days, confirmed with an expired-air CO value of ≤ 10 ppm.

Results: Eight (32%) of 25 subjects were abstinent after 9 weeks. At 3-month follow-up, 3 subjects remained abstinent, 3 relapsed, and 2 were lost to follow-up. Eleven subjects (44%) were nonresponders, and 6 (24%) dropped out prior to 3 weeks of treatment due to side effects (N = 3) or were lost to follow-up (N = 3). Mean weight gain was approximately 0.5 lb (0.2 kg) for those completing 9 weeks of bupropion SR treatment. During the 9-week study and the 3-month follow-up, there was no evidence of emergent depression in any subject. Four subjects (16%) spontaneously reported an improvement in SSRI-associated sexual dysfunction.

Conclusion: These open data suggest modest effectiveness for and the safety of bupropion SR as a smoking cessation agent in individuals with depression maintained on treatment with SSRIs. Minimal weight gain, lack of emergent depressive episodes, and improvement of SSRI-associated sexual dysfunction are added advantages.

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Reprint requests to: K. N. Roy Chengappa, M.D., Western Psychiatric Institute and Clinic, University of Pittsburgh, Special Studies Center at Mayview State Hospital, 3811 O'Hara St., Pittsburgh, PA 15213 (e-mail: chengappakn@msx.upmc.edu).

The public health consequences of smoking tobacco have been well known for some time,[1] and compared with the general population, 2 to 3 times as many depressed individuals smoke, rendering these individuals particularly susceptible to the risks of smoking.[2] Studies indicate that over 50% of subjects with major depression are addicted to nicotine.[3,4] However, upon quitting nicotine, a significant percentage of smokers demonstrated depressed mood.[4,5] Furthermore, among smokers with a history of depression, there is a 2-fold higher risk of experiencing recurrent depressive episodes in the 12 months following smoking cessation treatment.[6] These data suggest that there is a need for smoking cessation strategies that are not associated with rebound depressive symptoms or episodes, especially in subjects who already have a history of depressive episodes. One such strategy is the use of bupropion sustained release (SR). This drug has dopamine modulating properties, and dopaminergic systems have been suggested to be associated with reward mechanisms.[7] Bupropion SR is also an effective and safe antidepressant and has been in use for several years for the treatment of depressive disorder.[8–11] Since bupropion SR was

recently approved for use as a smoking cessation treatment in nondepressed smokers,[12,13] this study evaluated the effectiveness and safety of adding bupropion SR to ongoing selective serotonin reuptake inhibitor (SSRI) treatment in individuals who had a history of depression but who were in remission and wanted to quit smoking.

METHOD

The study was conducted at 2 private practice clinics in Pittsburgh, Pa., and 25 consenting eligible subjects participated.

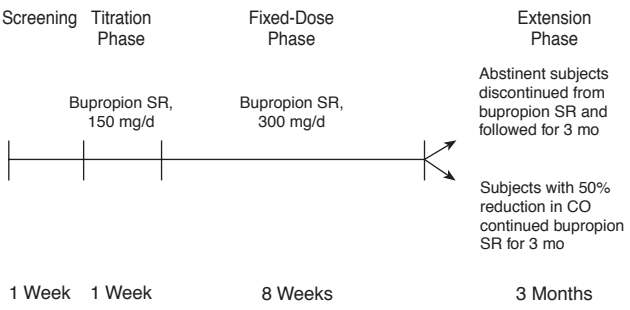
Entry criteria were (1) a history of DSM-IV major depressive disorder with single or multiple episodes or depressive disorder not otherwise specified (NOS), (2) a 21-item Hamilton Rating Scale for Depression (HAM-D)[14] score ≤ 10, (3) age of 18 to 70 years (of either gender and any ethnicity), (4) smoking at least 15 cigarettes per day, and (5) a verbally expressed desire to quit smoking. Patients with previously diagnosed and treated medical conditions such as hypothyroidism, essential hypertension, or type 2 diabetes mellitus were permitted to enter the study if their medical conditions were stable. Also, subjects were required to have been treated with stable doses (for at least 8 weeks) of fluoxetine, sertraline, or paroxetine and considered by the treating psychiatrist to have a nondepressed mood state for at least 8 weeks. Women with childbearing potential were required to be using an acceptable means of contraception and were also required to test negative on a pregnancy test prior to study entry. Finally, a full physical examination and screening laboratory values including a complete blood and differential count, chemistry panel, liver and thyroid functions, urinalysis, and drug screen had to be either negative or within normal limits for qualifying subjects.

Subjects with a present or past history of seizure disorder, current eating disorders, unstable medical conditions, use of any other psychotropic agents, or alcohol or other substance dependence (except nicotine or caffeine) within 3 months of study entry were excluded. Also, subjects with other current Axis I psychiatric conditions were excluded. Finally, participating subjects could not be using other smoking cessation aids such as the nicotine patch or gum.

Study Design

The study consisted of open treatment with bupropion SR added to ongoing SSRI treatment. Consenting subjects were screened for eligibility during a period of up to 1 week and then openly received bupropion SR, 150 mg/day, as a morning dose for 1 week. If tolerated, bupropion SR was increased the following week to 150 mg twice daily, with the second dose being given at 3 p.m. in some subjects to minimize the possible difficulty in falling asleep (Figure 1). The bupropion SR dose of 300 mg/day (in 2 equally divided doses) was continued for an additional 8 weeks. For weekly point-prevalence rates, subjects were considered abstinent if they had a self-report of no smoking during the prior 7 days, confirmed with an expired-air carbon monoxide (CO) value of ≤ 10 parts per million. Abstinent subjects were discontinued from bupropion SR and followed for the next 3 months to evaluate relapse (see Figure 1). Those who reported a reduction in the number of daily cigarettes and had a 50% or greater reduction in their CO readings by 9 weeks of bupropion SR treatment (see Figure 1) could continue bupropion SR at the 300-mg/day dose for an additional 3 months. The purpose was to evaluate if these subjects could choose a second quit date within 2 weeks and become abstinent. Subjects who did not reduce their daily cigarettes and did not achieve a 50% reduction in CO levels by the end of the 9 weeks of bupropion SR treatment were terminated from the study and counseled individually on other smoking cessation options.

Figure 1. Study Design[a]



[a]Abbreviations: CO = carbon monoxide, SR = sustained release.

The visits were weekly until visit 5 and every 2 weeks until visit 8 for a total of 9 weeks of bupropion SR treatment. Visits were every 4 weeks for those subjects participating in the extension phase for 3 additional visits until visit 11, when the study was terminated (see Figure 1).

Prior to beginning the study medication, subjects were counseled based on a National Cancer Institute counseling program called "How to Help Your Patients Stop Smoking" and given detailed instructions on choosing a target quit date that was usually within 2 to 4 weeks after initiating bupropion SR treatment. Detailed instructions regarding bupropion SR use, side effect profiles, titration, and dosage were reviewed with each subject. Following the screening baseline visit and at each visit, exhaled CO was measured using a calibrated carbon monoxide monitor (Vitalograph, Inc., Lenexa, Kan.). Patients were made comfortable and counseled on the use of the CO monitor such that an accurate reading in expired air was obtained. The CO measurements were supervised by the study staff. Also, treatment-emergent side effects were elicited using an open-ended question, and, if affirmed, the particular side effect(s) was probed further. Patients spontaneously reporting side effects were probed for further details. Brief re-

view of smoking status, mental status, body weight, and ratings of depression and anxiety using the HAM-D and Hamilton Rating Scale for Anxiety (HAM-A)[15] were also conducted at each visit.

Concomitant Medications

Limited use (3 to 4 days per week) of chloral hydrate (500 mg or 1000 mg) or zolpidem (up to 10 mg) at night for insomnia was permitted up to visit 6, with none thereafter. Similarly, limited use of lorazepam, p.r.n., was permitted for severe emergent anxiety up to visit 6, with none thereafter. Medications provided for stably treated medical conditions such as essential hypertension or hypothyroidism were continued unchanged through the study period.

Responder Criteria

Subjects were considered abstinent if they had a self-report of no smoking during the prior 7 days, confirmed with an expired-air CO value of ≤ 10 parts per million.

RESULTS

Twenty-five adult men and women with a history of DSM-IV major depressive disorder or depressive disorder NOS (Table 1) participated in the study. Among those completing the initial 9 weeks of treatment (N = 19), there was no emergent depression as judged clinically or by the HAM-D scores. For those completing 9 weeks, the mean ± SD HAM-D score was 4.2 ± 2.5 at baseline and was reduced to a mean of 3.4 ± 2.0, a statistically significant difference (t = 2.13, df = 18, p = .048). There was a similar trend for the HAM-A scores, decreasing from a baseline mean of 4.0 ± 2.5 to 3.2 ± 2.0 at 9 weeks (t = 2.0, df = 18, p = .06). Those who participated in the extension phase of the study (N = 11) also showed no evidence of emergent depression or anxiety. All subjects had previously tried a variety of smoking cessation measures with partial to no success. All subjects tolerated the titration of bupropion SR to 300 mg daily without significant problems.

Screening Physical Examination and Laboratory Measures

All subjects were physically healthy, and the screening laboratory measures, including a urine screen for drugs and alcohol and a pregnancy test, were either negative or within acceptable limits. Vital signs including pulse and blood pressure remained within acceptable limits throughout the study period.

Primary Outcomes

Of 25 subjects entering the study, 19 subjects (76%) completed the study, and 6 subjects (24%) dropped out early, i.e., prior to 3 weeks of treatment. Among the intent-to-treat population (N = 25), 8 subjects (32%; 6 women, 2 men) met the abstinence criteria.

Table 1. Demography and Diagnosis of Study Subjects[a]

Variable	Subjects (N = 25)
Gender, N	
Men	7
Women	18
Ethnicity, N	
White	23
African American	2
Age, y, mean ± SD (range)	45.8 ± 9.5 (27–65)
Employment, N	
Full time	14
Part time	3
Unemployed	5
Retired	3
DSM-IV Axis I diagnosis, N	
Major depression, recurrent	21
Major depression, single episode	1
Depression NOS	3
DSM-IV Axis V GAF score, mean ± SD	68 ± 8
SSRI antidepressant used for maintenance, N	
Fluoxetine	10
Sertraline	9
Paroxetine	6

[a]Abbreviations: GAF = Global Assessment of Functioning, NOS = not otherwise specified, SSRI = selective serotonin reuptake inhibitor.

These 8 abstinent subjects were discontinued from bupropion SR at the end of 9 weeks and followed for an additional 3 months. Three of the 8 subjects remained abstinent, 3 relapsed, and 2 were lost to follow-up (Table 2).

The 6 subjects who reported a reduction in daily cigarette consumption and also met the 50% decrease in CO measurement continued on bupropion SR treatment for an additional 3 months. These 6 subjects chose a second target quit date to occur within a 2- to 3-week period. However, none of these 6 subjects ceased smoking.

Five subjects treated with bupropion SR did not decrease their daily cigarette smoking and were terminated from the study at 9 weeks. They were counseled on an individualized basis regarding other smoking cessation measures.

Six of the 25 subjects dropped out of the study early. In fact, they dropped out prior to 3 weeks of bupropion SR treatment. Three subjects were lost to follow-up, and 3 experienced adverse events noted below. Compliance with medication was assessed by patient self-report. The majority of the subjects were adherent, with an occasional missed dose being reported.

Adverse Events

One subject developed a macular skin rash and pruritus on her back, shoulder, and face during the second week of treatment, which resolved without further problems on discontinuation of bupropion SR. Another subject reported nervousness and shakiness during the third week of treatment, and these symptoms resolved on discontinuation of bupropion SR. One male subject reported abdominal pain for 2 days during the third week of treat-

Table 2. Study Outcome Measures and Treatment-Emergent Side Effects (N = 25)[a]

Variable	N
Subjects completing 9 weeks of treatment	19 (76%)
Abstinence	8[b]
Decreased cigarettes + 50% ↓ CO	6
Nonresponders	5
Early withdrawals	6/25 (24%)
Adverse effects	3
Rash	1
Nervousness	1
Abdominal pain	1
Lost to follow-up	3
Extension phase (3-month) follow-up of abstinent subjects; no bupropion SR	8
Abstinent	3
Relapsed	3
Lost to follow-up	2

[a]Abbreviations: CO = carbon monoxide, SR = sustained release.
[b]Six women and 2 men.

ment, which resolved on discontinuation of bupropion SR. Three subjects experienced insomnia in the first 2 to 3 weeks of treatment that resolved by shifting the night dose of bupropion SR to an earlier time and/or the temporary use of zolpidem. These 3 subjects with initial insomnia did go on to complete the 9 weeks of bupropion SR treatment. Importantly, the majority of subjects tolerated the combination of bupropion SR and concomitant SSRI treatment, since only 3 subjects (12%) withdrew from the study due to adverse events.

Body Weight and Body Mass Index Changes

Body weight and body mass index (BMI) were measured in participating subjects and tracked during the study visits. These data are reported for the 19 subjects who completed 9 weeks of bupropion SR treatment. The BMI was calculated using the nonmetric conversion formula: weight in pounds times 704.5 divided by height in inches squared.[16]

Body weight changes were considered first on the basis of smoking status. Abstinent subjects (N = 8) lost a mean of 1.2 ± 6.0 lb (0.5 ± 2.7 kg) at 9 weeks of treatment, whereas nonabstinent subjects gained a mean of 2.0 ± 5.5 lb (0.9 ± 2.5 kg), a difference that was not statistically significant. At the 3-month follow-up, 2 abstinent subjects had gained 4 lb (1.8 kg) and 7 lb (3.2 kg), respectively, whereas 1 abstinent subject had no weight change. Three abstinent subjects relapsed. These 3 relapsed subjects lost 11, 9, and 6 lb (5.0, 4.1, and 2.7 kg), respectively, at the 3-month follow-up.

None of the weight or BMI changes were statistically significant for the group as a whole (mean weight gain = 0.5 ± 5.9 lb [0.2 ± 2.7 kg]) or for each gender considered separately. Eight (7 women, 1 man) of the 19 subjects treated for 9 weeks with bupropion SR lost weight, ranging from 0.6% to 8.0% of their baseline body weight, of whom 2 lost greater than 5% of their baseline body weight. Two subjects (1 man, 1 woman) had no change in body weight during this period, and 9 subjects gained from 0.4% to 7.2% of their baseline body weight, of whom 2 women gained more than 5% of their baseline body weight.

Changes in BMI were noted, too. However, with 1 exception, all the changes (increases or decreases) occurred within the same BMI category for each individual.

SSRI-Associated Sexual Dysfunction

Four male subjects (16%) spontaneously reported an improvement in SSRI-associated erectile dysfunction, of which they had previously complained to the treating psychiatrist. Since this issue was not systematically assessed in this study, it was not possible to state how many subjects had erectile dysfunction at baseline prior to the study but did not improve.

DISCUSSION

Controlled trials of short-duration bupropion SR treatment (7 weeks) for smoking cessation in nondepressed individuals have shown that 44.2% of subjects receiving bupropion SR at 300 mg/day are abstinent, and by the end of 1 year 23.1% remain abstinent.[12] A history of depression appears to predict lower short-term abstinence (e.g., 4 weeks), with rates of 33% in those with a history of depression versus 57% in those without a history of depression.[17] The rate of 32% reported in the present study is close to that reported by Glassman et al.[17] In fact, reports suggest that smoking cessation can lead to an increase in depressive symptoms[4] and an increase in depressive episodes.[6,18] It was also suggested that nicotine may have antidepressant properties in nonsmokers with depression.[19]

Hayford et al.[20] analyzed the data from a previously reported double-blind, placebo-controlled clinical trial comparing 3 fixed doses of bupropion SR (100 mg/day, 150 mg/day, 300 mg/day) for smoking cessation[12] based on whether smokers had a former history of major depression or alcoholism. The results of that analysis suggested that bupropion SR was efficacious whether or not smokers had a history of major depression or alcoholism. Those authors also reported that an increase in Beck Depression Inventory scores for 2 weeks following smoking cessation among those who were continuously abstinent was associated with relapse to smoking.[20] In spite of the large overall numbers (N = 615 smokers) and the randomized, placebo-controlled study design, the study limitations included a relatively small number of subjects with a history of major depression (15%), which limited the statistical power to detect differences in smoking outcome.[20] Nonetheless, these study results are encouraging given that a former history of depression has been associated with higher rates of failure to quit smoking and relapse.

The rationale for an add-on strategy was based on the evidence that a substantial portion of patients with a his-

tory of multiple depressive episodes are maintained on antidepressant treatment and a "switch" to bupropion SR may possibly have led to either relapses or recurrence of depressive symptoms or episodes in some subjects, and these events could confound the interpretation of the primary outcome. Our data suggest that this strategy may be justified, since no treatment-emergent depressive symptoms or episodes were reported by the subjects, at least in the 25 weeks of the total study period. Another rationale for adding bupropion SR to ongoing SSRI treatment was that this combination is often used in clinical practice and is generally not expected to result in significant drug-drug interactions. For instance, this combination strategy may sometimes alleviate sexual dysfunction associated with the use of SSRI antidepressants,[21–24] and 4 male subjects in this study spontaneously reported an improvement in SSRI-associated sexual dysfunction following the addition of bupropion SR.

An aminoketone, bupropion is structurally unrelated to other antidepressants such as monoamine oxidase inhibitors (MAOIs), heterocyclic antidepressants, or SSRI antidepressants. Although concurrent administration of bupropion and MAOIs is contraindicated, there is no such exclusion for the concurrent use of bupropion and SSRI antidepressants. Bupropion has minimal effects on serotonin reuptake, unlike the SSRI antidepressants, and its antidepressant activity is mediated through dopaminergic and/or nonadrenergic (not norepinephrine reuptake) pathways.[8,9,25] So, it is possible that the combination of bupropion SR and SSRIs may have added benefits in those who have not responded to either agent alone or in subjects in whom side effects associated with SSRI antidepressants (e.g., sexual dysfunction) need remediation. Also, data from the package insert for bupropion[26] indicate that bupropion is primarily metabolized to its major active metabolite, hydroxybupropion, by the cytochrome P450 2B6 (CYP2B6) isoenzyme and to a much lesser extent by CYP1A2, 2A6, 2C9, 2E1, and 3A4 isoenzymes. So, there is diminished potential for drug-drug interactions when bupropion is added to SSRI antidepressant treatment, since fluoxetine, sertraline, and paroxetine are primarily metabolized by other Cytochrome P450 isoenzymes.

The adverse effects in 6 subjects were expected and resolved spontaneously or upon discontinuation of bupropion SR. Overall, the combination of the SSRI antidepressants and bupropion SR was generally well tolerated in this study.

To our knowledge, this clinical study is the first to report the add-on strategy of adding bupropion SR to ongoing SSRI antidepressant treatment as a smoking cessation strategy. At first glance, the results of the present study suggest a modest response rate for smoking cessation (32%) over 9 weeks of treatment, although 3 of the 8 abstinent subjects eventually relapsed during the 3-month follow-up. Bupropion SR treatment was discontinued abruptly in the abstinent subjects at 9 weeks as was previously reported in nondepressed subjects.[12] At the time we designed the study, it was agreed to permit nonabstinent subjects who had reduced their daily cigarette intake and achieved a 50% or greater reduction in CO measure by 9 weeks of treatment to continue bupropion SR for an additional 3 months. The reason for this extension was to evaluate if these subjects would choose a second target quit date and become abstinent. However, none of these subjects became abstinent, suggesting no advantage for a longer trial in those formerly depressed subjects who do not quit smoking within a 9-week period. However, these data are only preliminary, and in selected individuals with depression the clinical practice of using bupropion SR for longer may be justified unless future data indicate otherwise.

Weight gain is one among several reasons for women smokers not to try to quit smoking.[27] The present data suggest that during a 9-week period, there was a minimal weight gain of 0.5 lb (0.2 kg) for the group as a whole. Although some subjects lost weight and others gained weight, the results with bupropion SR as an agent for smoking cessation are favorable from the perspective of weight gain. Also, with 1 exception, all subjects moved up or down within their own BMI category rather than switching upward to a less healthy BMI category. These benefits of bupropion SR from the weight gain perspective are consistent with the reported literature.[28,29] Recent double-blind, placebo-controlled data suggest bupropion SR is efficacious in obesity.[30] However, the present study has small numbers of subjects and no placebo or active comparator, so the data are only suggestive from the weight-neutral perspective.

Even though there was a statistically significant reduction of the HAM-D depression scores and a similar trend emerged for anxiety scores, these scores were low to begin with (i.e., the "floor effect") and may not be clinically relevant. However, these data suggest there is no worsening of either depression or anxiety with bupropion SR, at least during 25 weeks of treatment.

In summary, these data suggest modest effectiveness of bupropion SR as a smoking cessation agent when added to ongoing SSRI treatment in individuals with a history of depression, and, importantly, this combination is fairly well tolerated. Also, the lack of emergent depressive episodes upon smoking cessation as well as improvements in sexual functioning and the near lack of weight gain are added advantages for bupropion SR as an add-on treatment. The minimal-to-no weight gain potential may provide an especially useful strategy in treating women with bupropion SR, since they often do not try to quit smoking secondary to issues relating to weight gain.[27] Finally, a longer duration of treatment and follow-up as well as the inclusion of behavioral techniques for smoking cessation are warranted in this population of smokers, especially if controlled longer-term relapse prevention studies are planned.

Drug names: bupropion (Wellbutrin, Zyban), fluoxetine (Prozac), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft), zolpidem (Ambien).

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