A Double-blind Placebo-Controlled Trial of Bupropion Sustained-Release for Smoking Cessation in Schizophrenia

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Abstract: The objective of this study was to examine the efficacy of bupropion for smoking cessation in patients with schizophrenia. Adults with schizophrenia who smoked more than 10 cigarettes per day and wished to try to quit smoking were recruited from community mental health centers, enrolled in a 12-week group cognitive behavioral therapy intervention, and randomly assigned to receive either bupropion sustained-release 300 mg/d or identical placebo. Fifty-three adults, 25 on bupropion and 28 on placebo, were randomized, completed at least 1 postbaseline assessment and were included in the analysis. The primary outcome measures were 7-day point prevalence abstinence in the week after the quit date (week 4) and at the end of the intervention (week 12). Subjects in the bupropion group were significantly more likely to be abstinent for the week after the quit date (36% [9/25] vs. 7% [2/28], $P = 0.016$) and at end of the intervention (16% [4/25] vs. 0%, $P = 0.043$). Subjects in the bupropion group also had a higher rate of 4-week continuous abstinence (weeks 8–12) (16% [4/25] vs. 0%, $P = 0.043$) and a longer duration of abstinence (4.2 [3.2] weeks vs. 1.8 [0.96] weeks, $t = 2.30$, $P = 0.037$). The effect of bupropion did not persist after discontinuation of treatment. Subjects in the bupropion group had no worsening of clinical symptoms and had a trend toward improvement in depressive and negative symptoms. We conclude that bupropion does not worsen clinical symptoms of schizophrenia and is modestly effective for smoking cessation in patients with schizophrenia. The relapse rate is high after treatment discontinuation.

(*J Clin Psychopharmacol* 2005;25:218–225)

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Received August 9, 2004; accepted after revision December 16, 2004.

These data have been presented in part at the 9th Annual Meeting of the Society for Research on Nicotine and Tobacco, New Orleans, LA, February 19 to 22, 2003 and the 156th Annual Meeting of the American Psychiatric Association, San Francisco, CA, May 17 to 22, 2003.

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ISSN: 0271-0749/05/2503-0218

DOI: 10.1097/01.jcp.0000162802.54076.18

Smoking is the leading preventable cause of death in the United States, causing approximately 440,000 premature deaths in the United States annually and approximately US$157 billion in annual health-related costs,[1] and 75% to 85% of people with schizophrenia in the United States smoke, compared with 23% of the general population.[1–3] Schizophrenia is an independent predictor of cigarette smoking after controlling for substance abuse, institutionalization, medication, and socioeconomic status.[2–5] People with schizophrenia die on average 10 years earlier than people in the general population,[6] and age-adjusted rates of death because of cardiac and pulmonary disease are significantly elevated in this population,[6–8] suggesting that tobacco use is an important cause of the excess mortality observed in schizophrenia. An estimated 1.5 to 1.7 million smokers in the United States are diagnosed with schizophrenia.[2,3,9] Safe and effective smoking cessation treatments for patients with schizophrenia are needed.

Despite a 1996 American Psychiatric Association guideline recommending routine treatment of smoking for patients with psychiatric illness and preliminary reports of the safety and efficacy of pharmacological approaches to smoking cessation in schizophrenia,[10–13] physicians rarely advise patients with schizophrenia to quit smoking.[14,15] In 1 study of 1610 visits of smokers to 573 psychiatrists, psychiatrists documented smoking status at 76% of visits by smokers with psychotic disorders but offered smoking cessation counseling at less than 10% of visits and recommended nicotine replacement therapy at no visits.[16] In an older study performed before the American Psychiatric Association guideline, physicians documented smoking status at 78% of visits by patients with schizophrenia, provided advice to quit smoking at 11% of visits and recommended nicotine replacement therapy or other pharmacotherapy for smoking cessation at a mere 0.4% of visits.[17] Without more data on the safety and efficacy of smoking cessation treatment in patients with schizophrenia, treaters may remain reluctant to advise their patients with schizophrenia to quit smoking because of concern that smoking cessation treatments may be ineffective or cause clinical destabilization.

The primary purpose of this study was to extend the finding that bupropion sustained-release (SR) at a dose of 150 mg/d is effective for smoking cessation and reduction in patients with schizophrenia when added to cognitive behavioral therapy (CBT).[10] Our hypothesis was that bupropion at a dose of 300 mg/d would be associated with increased rates of smoking cessation and reduction and with a reduction in expired air carbon monoxide (CO). Based on our previous finding that the changes in psychiatric symptoms in patients with schizophrenia during a quit attempt were mild and not clinically significant in patients treated with low-dose bupropion,[10] our hypothesis was that bupropion treatment in the setting of a smoking cessation attempt would not be associated with significant exacerbation in psychiatric symptoms.

METHODS

The protocol was approved by the appropriate institutional review boards. Subjects were enrolled from August 1999 to March 2003. Subjects were recruited from 5 urban community mental health centers in Massachusetts. Capacity to consent was determined and documented for all participants by a doctoral-level clinician using a formal process established in the Massachusetts General Hospital Schizophrenia Program. Eligible participants were adults who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for schizophrenia or schizoaffective disorder depressed type, had stable symptoms and a stable dose of antipsychotic medication for 30 days, did not meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for current major depression, had baseline HAM-D score <20, smoked 10 or more cigarettes per day, and were willing to set a quit date within 4 weeks of the date of enrollment. Subjects with seizure disorder, history of bulimia, and history of mania or substance abuse disorder other than nicotine or caffeine within 6 months of enrollment were not eligible. Subjects taking clozapine at a dose of >500 mg/d without an adequate dose of an anticonvulsant were also excluded. Although there is some evidence that bupropion may inhibit CYP2D6 activity,[18] subjects treated with medications dependent on CYP2D6 for their metabolism were not excluded.

Interventions

Subjects were randomly assigned to receive bupropion SR 150 mg or identical placebo tablets. Studies of the safety of bupropion as an adjunctive treatment to antipsychotic medications in patients with schizophrenia[11,19] had not been published at the time this study was initiated, so we initiated a conservative titration schedule for study medication. Subjects took 1 tablet daily for 7 days beginning the day of the first group meeting. Subjects were evaluated for change in psychiatric symptoms at the second group meeting, and if they had tolerated study medication for the first week, their dose was increased to 1 tablet twice daily for the remaining 11 weeks of the trial. A 1-week supply of study medications was distributed weekly; medication bottles with leftover medication and self-report of missed doses were collected at the weekly CBT group sessions.

All participants received a 12-week, 12-session group CBT program in addition to study medication. The CBT program was delivered from a written manual adapted for patients with schizophrenia from American Heart Association and American Lung Association materials,[20,21] and delivered by 1 of 2 psychologists who had completed Tobacco Treatment Specialist certification training.[22] A maximum of 6 subjects were included in any group. The CBT program emphasized education, motivational enhancement, problem solving, relapse prevention, individualized planning regarding coping with triggers, and behavioral goal-setting.[10] All participants were encouraged to set a quit date 1 week before the week-4 assessment. In the 3-month follow-up period, subjects were asked to refrain from pharmacotherapy and behavioral treatments for smoking cessation.

Smoking Measures

We assessed smoking behavior at each weekly group meeting by self-report of number of cigarettes smoked in the prior 7 days and expired air CO measurement (Bedfont Micro Smokerlyzer, Bedfont Scientific Ltd, Kent, UK). The CO measurements were taken at the same time each week between 1 and 3 PM. Seven-day point prevalence abstinence was calculated for each subject for each week of the study. Seven-day point prevalence abstinence was defined as a self-report of smoking zero cigarettes in the past 7 days confirmed by expired air CO <9 ppm at the group session. The Heaviness of Smoking Index,[23,24] a simple valid 2-question subset of the Fagerstrom Test for Nicotine Dependence,[25] was administered at baseline, and the Wisconsin Smoking Withdrawal Scale[26] was measured at the weekly group meeting.

Clinical Measures

Clinical outcomes were assessed at baseline, week 4 (1 week after the quit date), and week 12 (trial end point) by the following: Scale for Assessment of Negative Symptoms (SANS,[27] total score and 5 subscale scores), total Hamilton Anxiety Scale[28] and Hamilton Depression Rating Scale[29] scores, and Positive and Negative Syndrome Scale (PANSS,[30] total score and the 5 subscale scores: positive, negative, excitement, cognitive, and depression/anxiety that emerged from a factor analysis in 240 subjects with schizophrenia as described by Lindenmayer et al).[31] Extrapyramidal movements were measured using the Simpson Angus Scale[32] and the Barnes akathisia scale.[33] Adverse events were recorded weekly using the Systematic Assessment for Treatment Emergent Side Effects.[34]

Analysis

The primary outcome measures were 7-day point prevalence of smoking abstinence at the week 4 group meeting (7 days after the quit date), 7-day point prevalence abstinence at the last group meeting (week 12, 9 weeks after the quit date), and 7-day point prevalence abstinence 3 months after discontinuation of study interventions. Secondary smoking outcomes were 4-week continuous abstinence at the end of the trial, 7-day point prevalence abstinence at at least 1 time point in the trial, duration (in weeks) of abstinence, reduction in expired air CO, and reduction in self-report of cigarettes smoked per day. We analyzed the effect of study medication on smoking cessation rates using Fisher exact test. Subjects who received at least 1 week of study medication and were lost to follow-up were included in the analysis as smokers. Four-week continuous abstinence was defined as self-report of smoking zero cigarettes from group meetings 8 to 12 and expired air CO <9 ppm at group meetings 9 to 12. We used a repeated-measures analysis of variance, using Proc Mixed in SAS (SAS Institute, Cary, NC) to determine whether expired air CO was on the average different in the treatment groups from weeks 4 to 12 and whether the difference varied by week of observation.

Clinical measures were analyzed using paired *t* tests. Effects were considered significant if 2-sided $P < 0.05$.

RESULTS

After complete description of the study and provision of informed consent, 62 subjects were enrolled. Fifty-seven subjects were randomized. Fifty-three adults, 25 on bupropion and 28 on placebo, received at least 1 week of study medication and were included in the analysis. At baseline, subjects ranged in age from 24 to 66 years, reported smoking 29.57 (SD = 17.02, range 10–100) cigarettes per day, had an expired air CO of 27.80 (SD = 14.53, range 11–80) ppm, reported a median of 2 (range 0–50) previous smoking cessation attempts, and had made their most recent smoking cessation attempt 5.21 (SD = 2.1, range 1–7) months before enrollment. Mean PANSS score was 60.30 (SD = 13.59). Mean education was 11.6 (3.2) years, but the range was from 1 to 17 years of education. There were no differences between groups in demographic characteristics or clinical symptoms at baseline. (See Tables 1 and 2) More clozapine-treated subjects were randomized to the placebo group. Forty-three subjects (81%) completed the 12-week treatment phase, and 34 (64%) completed the 12-week follow-up. Five of 25 subjects in the bupropion group and 5 of 28 in the placebo group were lost to follow-up at week 12 and were considered smokers for the analysis. Subjects in the bupropion group missed an average of 0.9 (0.58) doses per week, and subjects in the placebo group missed an average of 0.9 (0.60) doses per week by self-report, confirmed by pill count (not significant). CBT groups ranged in size from 3 to 6 participants.

TABLE 1. Baseline Characteristics

	Bupropion	Placebo
	n = 25	n = 28
Age (y)	46.0 (9.4)	45.5 (8.3)
Sex (M/F)	19/6	20/8
Education (y)	12.0 (2.9)	11.2 (2.9)
Baseline CO (ppm)	29.7 (17.3)	26.2 (11.8)
Cigarettes/d	34.2 (20.4)	25.4 (12.2)
HSI	4.5 (1.5)	4.0 (1.4)
WSWS	60.7 (14.6)	59.3 (14.5)
Antipsychotic dose	304.7 (164.7)	430.6 (260.1)
Conventional antipsychotic	2/25	3/28
Second-generation antipsychotic	18/25	23/28
Combination antipsychotic	5/25	2/28
Clozapine	1/25	11/28
Motivation to quit		
Desire to quit	8.3 (2.1)	8.0 (2.2)
Confident that will quit in 1 year	6.6 (3.2)	7.7 (2.3)
Believes smoking is detrimental to health	8.9 (1.9)	9.0 (1.6)
Believes health improves if quit smoking	8.3 (3.2)	9.0 (1.6)
Concern will gain weight if quit smoking	6.0 (3.7)	6.1 (3.5)

Data presented as mean (SD). Baseline characteristics except clozapine treatment are not significantly different ($P > 0.05$). Subjects on clozapine were significantly more likely to have been randomized to placebo, $P = 0.003$, Fisher exact test.

CO is expired air CO in parts per million. HSI is a 2-item subscale of the Fagerstrom Test of Nicotine Dependence. Antipsychotic dose in chlorpromazine equivalents was calculated using the method of Woods.[35] Motivation to quit measures was assessed using a visual analog scale on a scale of 1 to 10, with 1 being not at all and 10 being very much. WSWS, Wisconsin Smoking Withdrawal Scale.

Smoking Cessation

Bupropion-treated subjects were more likely to have achieved 1 week of continuous abstinence immediately after the quit date and at the end of treatment. The 7-day point prevalence of abstinence in the week after the quit date was 36% (9/25) in the bupropion group and 7% (2/28) in the placebo group ($P = 0.016$, Fisher exact test). The 7-day point prevalence of tobacco abstinence at the end of the 12-week intervention was 16% (4/25) in the bupropion group and 0% (0/28) in the placebo group ($P = 0.043$, Fisher exact test) (see Fig. 1). Subjects on bupropion were also more likely to achieve 4-week continuous abstinence at the end of the intervention (16% [4/25]) than those in the placebo group (0% [0/28]) ($P = 0.043$, Fisher exact test).

TABLE 2. Clinical Symptoms at Baseline and End of Treatment in Bupropion and Placebo Groups

		Baseline	Week 12	*P*
SANS				
Total score	Bupropion	40.42 (21.02)	31.79 (12.08)	ns
	Placebo	40.48 (17.44)	35.62 (19.98)	
Affect	Bupropion	10.22 (8.20)	6.69 (6.30)	ns
	Placebo	9.20 (8.21)	9.10 (7.05)	
Alogia	Bupropion	5.58 (4.19)	4.11 (3.22)	ns
	Placebo	7.15 (5.04)	5.72 (5.94)	
Avolition	Bupropion	8.64 (5.26)	7.64 (3.94)	ns
	Placebo	5.77 (4.03)	6.39 (4.41)	
Anhedonia	Bupropion	11.85 (6.25)	10.79 (5.13)	ns
	Placebo	12.29 (5.76)	10.34 (6.27)	
Attention	Bupropion	4.85 (4.41)	2.79 (3.93)	ns
	Placebo	6.39 (3.99)	4.29 (4.63)	
PANSS				
Total score	Bupropion	59.27 (14.45)	53.85 (13.89)	ns
	Placebo	59.00 (12.03)	59.34 (14.83)	
Negative	Bupropion	14.64 (6.50)	13.32 (3.89)	ns
	Placebo	13.72 (4.99)	13.39 (6.23)	
Positive	Bupropion	9.48 (5.04)	8.22 (5.59)	ns
	Placebo	10.58 (4.54)	10.00 (4.48)	
Excited	Bupropion	5.37 (1.71)	5.53 (1.87)	0.017
	Placebo	4.81 (1.33)	6.05 (2.16)	
Depressive	Bupropion	10.43 (3.07)	9.79 (4.29)	ns
	Placebo	9.72 (3.53)	10.53 (4.25)	
Cognitive	Bupropion	10.58 (3.77)	8.79 (2.47)	0.029
	Placebo	11.72 (4.06)	10.77 (3.93)	
HAM-D	Bupropion	9.06 (4.05)	6.90 (5.83)	ns
	Placebo	6.80 (4.57)	7.20 (4.83)	
HAM-A	Bupropion	6.47 (4.48)	5.58 (4.62)	ns
	Placebo	4.80 (4.16)	4.80 (3.97)	

P values are given when paired comparisons of change from baseline in the bupropion and placebo groups were significant at $P < 0.05$. ns indicates not significant.

Sixteen subjects achieved 7-day point prevalence abstinence at least once in the trial. Subjects in the bupropion group were more likely to have achieved 7-day point prevalence abstinence at at least 1 time point 12/25 versus 4/28 ($P = 0.015$, Fisher exact test). The mean duration of abstinence was longer in the bupropion group (2.0 [3.05] weeks) than the placebo group (0.25 [0.7] weeks), $t = 2.95$, $P = 0.005$. Among those who quit smoking for at least 1 week, the duration of abstinence was also greater in the bupropion group (4.17 [3.24] weeks) than the placebo group (1.75 [0.96] weeks), $t = 2.30$, $P = 0.037$.

Two weeks after discontinuation of study interventions, the abstinence rate was 8% (2/25) in the bupropion group and 3.6% (1/28) in the placebo group (not significant). At follow-up 3 months after the end of the study intervention, the 7-day point prevalence abstinence rate was 4.0% (1/25) in the bupropion group and 3.6% 1/28 in the placebo group (not significant). Subjects were asked to refrain from smoking cessation interventions in the community during the 3-month follow-up, and all subjects reported refraining from smoking cessation treatment during the 3-month follow-up period.

Smoking Reduction

In the weeks after the quit date while the study intervention was being given, weeks 4 to 12, the CO levels were significantly lower in the bupropion group than the placebo group, $F = 4.94$, $P = 0.029$ (see Fig. 2). Those in the bupropion group had a mean reduction in expired air CO from baseline of 44%, and those in the placebo group had a mean 20% reduction. The effect of study drug on expired air CO was not sustained after discontinuation of study medication and group treatment (weeks 14–24).

From baseline to week 12, subjects on bupropion had an average reduction of 26.5 (16.5) cigarettes per day, and those in the placebo group had a mean reduction of 10.2 (13.0) cigarettes per day, $t = 3.39$, $df = 36$, $P = 0.002$. Among the 34 subjects who were not abstinent at week 12, those in the bupropion group had a reduction of 24.72 (18.1) cigarettes per day, and those on placebo reported a reduction of 10.2 (13.0), $t = 2.74$, $df = 32$, $P = 0.010$.

Two weeks after discontinuation of study interventions, the advantage of bupropion in reduction in cigarettes per day persisted. Those on bupropion reported smoking 25.3 (16.4) fewer cigarettes than at baseline, and those on placebo smoked 12.9 (10.6) fewer, $t = 2.51$, $df = 28$, $P = 0.018$. By 6 weeks after discontinuation of study medication and CBT, the effect of bupropion on the number of cigarettes smoked per day was no longer significant; the reduction from baseline in cigarettes per day was 14.5 (16.9) cigarettes per day in the bupropion group and 9.2 (8.2) in the placebo group (not significant), and at 3-month follow-up, the reduction

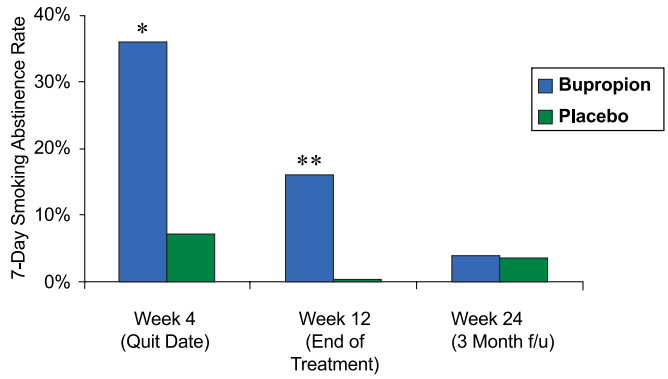

FIGURE 1. Seven-day point prevalence smoking abstinence rates. *$P = 0.016$, **$P = 0.043$ versus placebo, Fisher exact test.

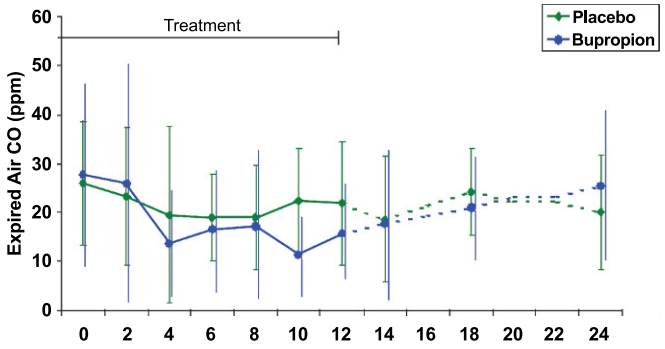

FIGURE 2. Expired air CO during the 12-week smoking cessation. Expired air CO in parts per million. Significant medication effect during treatment period using linear mixed-model analysis of variance, F = 4.939, *P* = 0.029. No significant effects during follow-up period.

was 5.0 (13.7) and 6.0 (9.3) cigarettes per day (not significant).

Effect of Antipsychotic Type on Abstinence

Of those who were abstinent at the end of the trial, 2 were on olanzapine and 2 were on risperidone. There was no significant effect of type of antipsychotic (atypical vs. conventional) or any individual antipsychotic medication on abstinence outcomes. Among those randomized to bupropion, those who were on an atypical antipsychotic had a greater reduction in CO (45.1% [33%] reduction in CO) compared with those who were on a conventional antipsychotic alone or in combination with an atypical (3.7% [56%] reduction), $t = 2.46$, $P = 0.026$ (see Fig. 3). Because there was unequal randomization of clozapine-treated subjects across medication groups with more clozapine-treated patients being randomized to placebo, we were unable to assess an interaction between clozapine and bupropion on smoking cessation and reduction. Baseline expired air CO was not different in clozapine-treated subjects, 28.17 (11.28), from non–clozapine-treated patients, 25.95 (16.211), but those on clozapine reported smoking fewer cigarettes per day at baseline (21.42 [7.52]) than those not on clozapine (31.95 [18.30]), $t = 2.93$, $df = 45$, $P = 0.005$.

Effect of Bupropion on Clinical Symptoms of Schizophrenia

Among bupropion-treated subjects, there was a trend for mean SANS, Hamilton Depression Rating Scale, and PANSS total scores to decrease from baseline to week 12 (see Table 2). SANS scores in the bupropion group decreased from 40.42 (21.02) at baseline to 31.79 (12.08) at week 12, $t = 1.78$, $P = 0.091$, 95% confidence interval 12.4 to −1.5. There was a trend for SANS affective flattening, alogia, and attention subscales to improve among bupropion-treated subjects from baseline to week 12. There was also a trend for mean Hamilton Depression Rating Scale scores to decrease from 9.05 (4.05) at baseline to 6.90 (5.83) at week 12, $t = 2.03$, $P = 0.057$, 95% confidence interval 0.08 to −4.39. There was a trend for PANSS total score to decrease in the bupropion group from 59.27 (14.45) at baseline to 53.85 (13.89) at week 12, $t = 1.65$, $P = 0.11$, 95% confidence interval 12.4 to −1.5.

The bupropion group had greater reductions in clinical ratings than the placebo group on the PANSS depressive and cognitive subscales only (see Table 2). There was also no significant effect of bupropion compared with placebo on clinical measures after controlling for smoking status. Using the SD observed in the sample at baseline, we had 80% power to detect a difference between treatment groups of 10.3 points on the PANSS total and 14.9 points on the SANS total score.

Nicotine Withdrawal Symptoms and Adverse Events

Wisconsin Smoking Withdrawal Scale scores were high at baseline. There was no change in smoking withdrawal

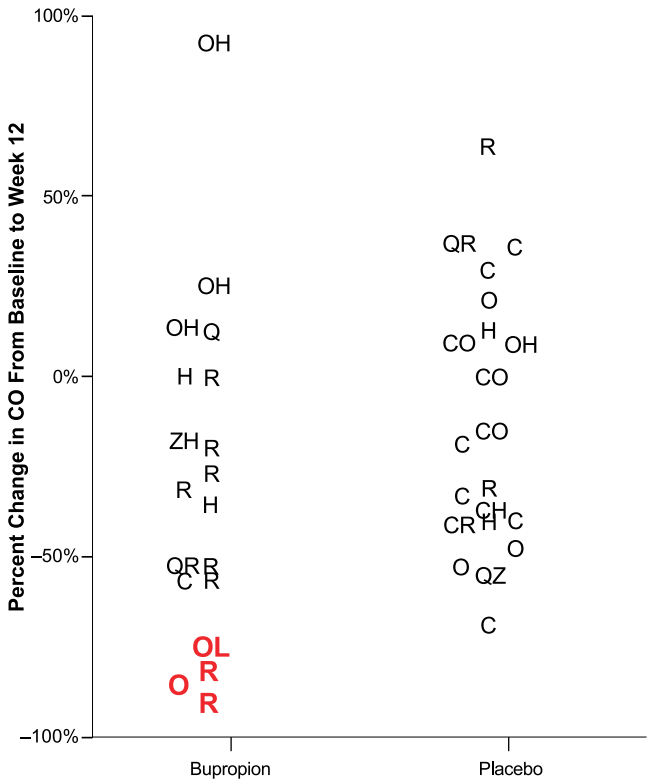

FIGURE 3. Type of antipsychotic medication and percent change from baseline in expired air CO at week 12 in subjects treated with bupropion or placebo for smoking cessation. Subjects who were abstinent at the end of the trial are represented in red. C indicates clozapine; H, high-potency conventional; L, low-potency conventional; O, olanzapine; Q, quetiapine; R, risperidone; Z, ziprasidone.

symptoms from baseline for the group as a whole and no significant medication effect on withdrawal symptoms at any time point.

Bupropion was generally well tolerated. There was no significant effect of bupropion or smoking cessation on extrapyramidal symptoms. There was no difference between the bupropion and placebo groups in doses of study medication missed at any single week or in the average of doses missed per week over the course of the study. Three subjects experienced a serious adverse event that required discontinuation of study medication. One subject who was randomized to bupropion experienced hives, urticaria, and wheezing in the first week on study medication, consistent with an allergic reaction to bupropion. Two subjects experienced suicidal ideation during the trial. Both were randomized to placebo. One of the subjects had not changed his smoking behavior at the time of the suicidal ideation, was hospitalized, and discontinued from the study. The other subject had reduced from 50 to 5 cigarettes per day at the time of the suicidal ideation, was not hospitalized, and was discontinued from the study. The rate of staying on study drug for 12 weeks was 80% for the bupropion group and 82% for the placebo group (not significant).

CONCLUSIONS

In this randomized controlled trial, we confirmed findings from a smaller study that bupropion SR at a dose of 300 mg/d is effective for smoking cessation in people with schizophrenia and that bupropion is not associated with symptom exacerbation in this population.[11]

In this study, we found that 16% of subjects randomized to bupropion SR 300 mg/d were abstinent at trial end point. This 7-day point prevalence abstinence rate on bupropion treatment at trial end point was higher than the 11% abstinence rate of schizophrenia subjects randomized to bupropion SR at a dose of 150 mg/d[10] but lower than the 50% abstinence rate reported in a similar trial of bupropion SR 300 mg/d added to CBT in patients with schizophrenia.[11] All 3 published studies of bupropion for smoking cessation in schizophrenia have shown a significant effect of bupropion. Larger studies will be needed to ascertain a more precise estimate of the expected abstinence rate in this population.

Relapse after withdrawal of smoking cessation treatment is a major clinical problem in smokers without major mental illness and is poorly understood. Up to 90% of all cigarette smokers who quit resume smoking within 1 year.[36] Consistent with this and a previous report in patients with schizophrenia,[11] we found that the rate of relapse is quite high after discontinuation of smoking cessation treatment. This may reflect a strong inherent appeal of nicotine to patients with schizophrenia, possibly caused by a beneficial effect on auditory sensory gating or visuospatial working memory[37–39] and/or behavioral effects of smoking.[40] Patients with schizophrenia may also have heightened sensitivity to environmental smoking-related cues that lead to relapse in the general population.[41] These cues are notoriously prevalent in the environment of patients with schizophrenia. As the effect of bupropion plus CBT was significant until these treatments were discontinued at week 12 and CBT alone was not effective at producing abstinence at week 12, a longer trial of bupropion plus CBT in this population may be warranted to reduce relapse rates. Longer duration of bupropion pharmacotherapy delays relapse in normal populations[42] and may delay relapse in patients with schizophrenia as well. It is important to note that the trials that established efficacy of bupropion for smoking cessation in the normal population used bupropion combined with substantial behavioral treatment. Efficacy of bupropion for smoking cessation in the absence of behavioral treatment is still poorly understood.

Several studies have suggested that antipsychotic medication type may have an important impact on smoking behavior in patients with schizophrenia. Haloperidol increases smoking and causes dose-dependent impairment in motor function and attention that is reduced by nicotine.[43–45] Clozapine is associated with decreased smoking in patients with schizophrenia,[46–48] and atypical antipsychotic medications have been shown to have a synergistic effect with treatment with nicotine patch.[12] In this study, subjects on atypical antipsychotic medications only who were randomized to bupropion had greater reduction in smoking than those who were taking a conventional antipsychotic alone or in combination with an atypical antipsychotic medication. It will be important to determine in future prospective studies if clozapine or other atypical antipsychotic medications are associated with an increased cessation rate in patients on bupropion. As the majority of clozapine-treated subjects were randomly assigned to placebo, we are unable to test for an interaction between clozapine and bupropion in this study.

Previous studies have described an effect of bupropion on reduction in negative symptoms in schizophrenia.[10,11] There was a trend toward reduction in ratings of negative and depressive symptoms in the bupropion group and no evidence of clinical worsening on any clinical parameter measured. With the variability in this sample at baseline, we had 80% power to detect a 15-point reduction in SANS scores in the bupropion group relative to the placebo group. The reduction in negative symptoms in the bupropion group was not of that magnitude, and there was some improvement in negative symptoms in the placebo + CBT group as well. We cannot rule out an effect of the CBT group intervention on clinical symptoms in the placebo and bupropion groups, thus reducing our ability to detect a difference between the groups. Withdrawal symptom scores appeared to be nonspecifically high at baseline, perhaps reflecting the overlap

between nicotine withdrawal symptoms and psychiatric symptoms in patients with schizophrenia and limiting the ability to detect an effect of bupropion on withdrawal symptoms.

Although we did not detect an effect of abstinence on extrapyramidal symptoms, cigarette smoking can affect the pharmacokinetic and pharmacodynamic properties of many psychotropic drugs. Polycyclic aromatic hydrocarbons present in cigarette smoke induce hepatic aryl hydrocarbon hydroxylases, thereby increasing metabolic clearance of drugs that are substrates for these enzymes.[49] Polycyclic aromatic hydrocarbons have been shown to induce 3 hepatic cytochrome P450 (CYP) isozymes, primarily CYP1A1, 1A2, and 2E1. Increased metabolism and/or decreased plasma concentrations of olanzapine, clozapine, fluphenazine, haloperidol, chlorpromazine, imipramine, clomipramine, fluvoxamine, trazodone, alprazolam, lorazepam, oxazepam, and diazepam have been described in smokers.[49] Increased plasma levels of clozapine and clinical signs of toxicity with clozapine and olanzapine have been reported in association with cessation of heavy smoking.[50,51] Smoking cessation was associated with a 30% to 42% reduction in activity of CYP1A2 in 1 study.[52] The half-life of this reduction was 27 to 54 hours. Therapeutic drug monitoring and dose reduction of 10% over the first 4 days of tobacco abstinence have thus been recommended.[52]

In conclusion, bupropion SR 300 mg/d appears to be modestly effective for smoking cessation in patients with schizophrenia and may be associated with a trend toward improvement in negative and depressive symptoms. The rate of relapse to smoking is high. We speculate that longer duration of bupropion therapy may reduce relapse rates. As both bupropion and nicotine replacement therapy have been shown to be modestly effective for short-term smoking cessation in schizophrenia, study of combination treatment of bupropion with nicotine replacement therapy may be warranted in this population.

ACKNOWLEDGMENTS

This work was supported by a NARSAD Young Investigator Award and by NIDA grants RO3 DA12542 and K23 DA00510 (Dr Evins), K24 MH02025 (Dr Goff), and K24 HL04440, (Dr Rigotti). GlaxoSmithKline provided bupropion SR and placebo tablets.

The authors thank Beth Ewy for her assistance with the Tobacco Treatment Specialist training and Alan Birnbaum, PhD, who conducted smoking cessation groups.

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