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A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia

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The purpose of this study was to investigate the effect of adding sustained-release (SR) bupropion to cognitive behavioral therapy (CBT) on smoking behavior and stability of psychiatric symptoms in patients with schizophrenia. We conducted a 3-month, double-blind, placebo-controlled trial of bupropion SR, 150 mg/day, added to a concurrent CBT program with 3-month follow-up in 19 stable outpatients with schizophrenia who wanted to quit smoking. Eighteen subjects completed the trial. Bupropion treatment was associated with significantly greater reduction in smoking, as measured by self-report verified by expired-air carbon monoxide (6/9 subjects, 66%), than placebo (1/9 subjects, 11%) during the 3-month active treatment period and the 3-month follow-up period. One subject in the bupropion group (11%) and no subjects in the placebo group achieved sustained tobacco abstinence for the 6-month trial. Bupropion treatment was associated with improvement in negative symptoms and greater stability of psychotic and depressive symptoms, compared with placebo, during the quit attempt. Subjects in the bupropion group experienced significant weight loss, compared with those on placebo during the smoking cessation attempt. These data suggest that bupropion SR, 150 mg/day, combined with CBT, may facilitate smoking reduction in patients with schizophrenia while stabilizing psychiatric symptoms during a quit attempt.

Introduction

Among samples of patients with schizophrenia, 74–92% smoke cigarettes, compared with 24.7% of the general US adult population (CDC, 1997; de Leon *et al.*, 1995; Goff, Henderson, & Amico, 1992; Hughes, 1986). Patients with schizophrenia also smoke more cigarettes per day (de Leon *et al.*, 1995) and attain higher serum levels of cotinine, the primary metabolite of nicotine (Olincy, Young, & Freedman, 1997). Cigarette smoking has been identified as the single most important source of preventable morbidity and premature mortality in the general US population for over 30 years (McGinnis & Foege, 1993; USDHHS, 1989). Compounding this problem, patients with schizophrenia are less likely to receive adequate routine and preventive medical care (Goldman, 1999; Viewig, Levenson, Pandurangi, & Silverman, 1995), resulting in a significant public health problem for people with schizophrenia (Brown, 1997; Dalmau, Bergman, & Brismar, 1997). However, systematic inquiry into smoking cessation strategies for people with schizophrenia has been limited (Dalack & Meador-Woodruff, 1999; Hartman, Leong, Glynn, Wilkins, & Jarvik, 1991; Ziedonis & George, 1997). There is growing evidence that nicotine receptors are abnormally expressed in some people with schizophrenia (Freedman, Hall, Adler, & Leonard, 1995; Leonard *et al.*, 2000), that nicotinic receptors function abnormally in patients with schizophrenia (Griffith *et al.*, 1998), and that nicotine may provide at least transient cognitive or symptomatic

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benefit to patients with schizophrenia (Adler, Hoffer, Wiser, & Freedman, 1993; Levin, Wilson, Rose, & McEvoy, 1996; McEvoy, Freudenreich, Levin, & Rose, 1995a; Olincy, Ross, Young, Roath, & Freedman, 1998). Despite the possible symptomatic benefits of nicotine in schizophrenia, reports indicate that patients with schizophrenia are aware of the morbidity associated with tobacco smoking and many are motivated to quit (Addington, el-Guebaly, Addington, & Hodgins, 1997; Ziedonis & Trudeau, 1997).

We hypothesized that the cognitive and symptomatic improvement observed following nicotine administration in patients with schizophrenia may be due to associated increase in glutamate and dopamine release. Bupropion is weakly dopaminergic, and sustained-release (SR) bupropion (150 and 300 mg/day) has been shown to be superior to placebo for smoking cessation in non-psychiatric patients (Hurt *et al.*, 1997). Both behavioral counseling and pharmacotherapy are effective for smoking cessation in the general population, and combinations of the two provide the highest success rates (Hughes, 1991; Klesges, Ward, & DeBon, 1996). Our hypothesis was that bupropion SR, 150 mg/day, added to concurrent cognitive behavioral therapy (CBT) for smoking cessation in outpatients with schizophrenia would be associated with (1) increased rates of smoking reduction and cessation, compared with CBT plus placebo; (2) improvement in negative and depressive symptoms, compared with CBT plus placebo; (3) less weight gain, compared with CBT plus placebo. Although a short-term trial did not find acute nicotine abstinence to be associated with an increase in depressive or psychotic symptoms in patients with schizophrenia (Dalack, Becks, Hill, Pomerleau, & Meador-Woodruff, 1999), we hypothesized that the low smoking-cessation rate in patients with schizophrenia may be due in part to symptom exacerbation during a quit attempt that becomes evident over longer follow-up. We studied bupropion SR at a relatively low dose of 150 mg/day because this population is commonly prescribed medications that lower the seizure threshold.

Materials and methods

The study was approved by appropriate institutional review boards. After complete description of the study to the subjects, written informed consent was obtained. Outpatients at an urban community mental health center with a diagnosis of schizophrenia who had been on a stable dose of antipsychotic medications for at least 4 weeks, and who reported cigarette use greater than half a pack per day and a desire to quit smoking, were eligible for the study. A clinical diagnosis of schizophrenia was confirmed by unstructured interview and chart review (AEE) using DSM-IV criteria. Subjects were excluded if they were experiencing acute exacerbation of psychosis, active co-morbid substance abuse, or bulimia, or if they had history of seizure disorder. Subjects with current but not past major depressive episode were excluded. Concurrent treatment with other antidepressant medications was not exclusionary.

At baseline, all subjects received brief advice to stop smoking from their treating psychiatrist and began study medication and group therapy. Subjects were randomly assigned to 12 weeks of double-blind bupropion SR, 150 mg/day, or an identical appearing placebo tablet added to their usual medication regimen. All subjects participated in a CBT Quit Smoking group program designed for patients with schizophrenia that consisted of nine weekly 1-h group sessions co-led by a nurse experienced in smoking cessation counseling (TT) and a cognitive behavioral psychologist (VKM). The manual for the psychosocial treatment employed in this study was derived from previous protocols (Addington, 1998; Addington, McCleary, & Munroe-Blum, 1998; Klesges *et al.*, 1996; Jerrell & Ridgely, 1999; Washington, Moll, & Pawlick, 1997) and considered the common cognitive deficits associated with schizophrenia, including attention, memory, and complex information processing. Subjects set a quit date between weeks 3 and 4, prior to the week 4 group session. Monetary reinforcement was used for timely group attendance and clinical assessments and was not contingent on change in smoking behavior.

Clinical assessments, completed at baseline and weeks 4, 8, 12, 14, 18, and 24, included the following standard rating scales: Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Negative Symptoms (SANS), Hamilton Rating Scale for Depression (HamD), Abnormal Involuntary Movements Scale (AIMS), Hillside Akathisia Scale, and Simpson-Angus Scale for extrapyramidal side-effects. A research psychiatrist (AEE) interviewed subjects monthly to evaluate for adverse events with the SAFTEE (Guy, Wilson, Brooking, Manov, & Fjetland, 1986). Expiratory CO measurements were collected at each visit to verify self-report of smoking and to reinforce reduction in cigarette use. Weight and serum cotinine were measured every 3 months.

Outcome measures included point prevalence tobacco abstinence or significant reduction in tobacco use at 12 and 24 weeks; sustained abstinence or significant reduction in tobacco use during treatment and follow-up periods; and change in positive, negative, and depressive symptoms of schizophrenia, weight, and side-effects of medications. Smoking cessation was defined as a self-report of tobacco abstinence verified by either an expired-air CO measurement of <9 ppm or serum cotinine of <14 ng/ml. Significant smoking reduction was defined *a priori* as a 50% reduction from baseline in self-report of cigarettes smoked per day combined with a 30% reduction in expired-air CO. Differences in smoking behavior between the bupropion and placebo groups were compared for the active treatment period and the follow-up period by comparing CO measurements during weeks 4 through 12 (active treatment) and during weeks 14 through 24 (follow-up). Differences in smoking behavior were also analyzed for the single time-points at end

Table 1. Baseline demographic data for 18 subjects with schizophrenia completing a 24-week smoking cessation trial

	SR bupropion	Placebo
Age	45.5 ± 7.2	42.7 ± 7.9
Sex	3 female/6 male	4 female/5 male
Ethnicity	8 Caucasian/1 AA	8 Caucasian/1 AA
Education	10.8 ± 2.1	12.5 ± 1.6
Duration illness (years)	24 ± 11	20 ± 7
Cigarettes per day	38 ± 20	30 ± 20
Pack-years	49 ± 30	37 ± 20
Antipsychotic medication[a]	3 conventional, 7 atypical (5 clozapine)	4 conventional, 6 atypical (3 clozapine)
Past psychoactive substance abuse	1 alcohol alone, 4 polysubstance	5 alcohol alone, 1 polysubstance

AA, African-American.
Education and duration of illness are given in years.
[a] Two (one in each group) subjects were on both an atypical and a conventional antipsychotic medication.

of treatment at week 12 and end of follow-up at week 24. Analyses of smoking outcomes and clinical measures were conducted with repeated-measures analysis of variance (ANOVA) using PROC MIXED in SAS, which allows the use of the data from patients even if some observations are missing. Models were fit with treatment and baseline measurements as explanatory variables. In addition, because graphs of group means over time showed considerable variation, time and an interaction between treatment and time were also included as potential explanatory variables. All values are reported as mean±standard deviation (SD).

Results

Nineteen subjects were enrolled and 18 subjects completed the 6-month smoking cessation trial. One subject dropped out prior to receiving study medication and was not included in the analysis. Baseline measures of age, education, duration of illness, dose of antipsychotic medication, cigarettes per day, and cigarette pack-years were not significantly different between the two groups (Table 1). Mean baseline dose of antipsychotic medication was 12±5 mg/day haloperidol equivalents for subjects on conventional antipsychotics. Two subjects on bupropion and two subjects on placebo had an increase in their antipsychotic medications during the trial. Mean increase was 1.5 haloperidol equivalents in the placebo group and 2.5 haloperidol equivalents in the bupropion group. CBT group attendance was 86%. There were no serious adverse events. Compliance with study medication and antipsychotic medication was monitored by residential staff in all subjects. Baseline CO levels prior to the quit date were 35±9 ppm in the bupropion group and 27±8 ppm in the placebo group, t_{16}=2.0, n.s. Five of 18 subjects refused blood drawing for serum cotinine for at least one of the three time-points. Because this represents nearly one-third of the sample, we relied on expired-air CO verification of self-report to estimate smoking behavior in this sample. There were no baseline differences on clinical measures.

Smoking reduction

Four subjects (three on bupropion SR and one on placebo) achieved abstinence at the quit date as measured by self-report and CO<9 ppm. One subject in the bupropion SR group stopped smoking on the quit date at week 4 and remained abstinent throughout the study. No subject in the placebo group achieved sustained abstinence.

At the end of treatment, six subjects on active drug and one subject on placebo met criteria for significant smoking reduction (self-report of a 50% reduction from baseline in cigarettes smoked per day verified by a 30% reduction in expired-air CO). At 6 months, three subjects on active drug and one on placebo continued to meet criteria for significant reduction. The bupropion group met criteria for significant smoking reduction continuously from the quit date at week 4 through the week 18 follow-up (group mean CO reduced 30% and group mean self-reported smoking reduced 50% from baseline; Figure 1). At no time point did the placebo group meet criteria for significant reduction.

Expired-air CO was significantly more reduced in bupropion-treated patients, compared with placebo, at the 12-week ($F_{1,16}$=6.8, p<0.01) and 24-week ($F_{1,16}$=5, p<0.03) time-points. There was also a significant association of bupropion treatment with reduction in expired-air CO during the 12-week treatment period (weeks 4–12; $F_{1,16}$=18.1, p<0.001) and during the follow-up period (weeks 14–24; $F_{1,16}$=19.5, p<0.001). For a given CO baseline level and visit, the mean CO for patients on bupropion was 14.8 ppm lower than for their placebo-treated counterparts (95% confidence interval, CI, 7–22) during active treatment and 14.3 ppm lower (95% CI, 8–21) during follow-up (Figure 1).

At 12 weeks, serum cotinine was reduced from baseline by 127±179 ng/ml in the bupropion group, corresponding to a 30±38% decrease, and was increased in the placebo group by 13±105 ng/ml, a 9±45% increase. The mean between-group difference during active treatment was 108 ng/ml (95% CI, 81–298). At week 24, cotinine was reduced 99±125 ng/ml in the

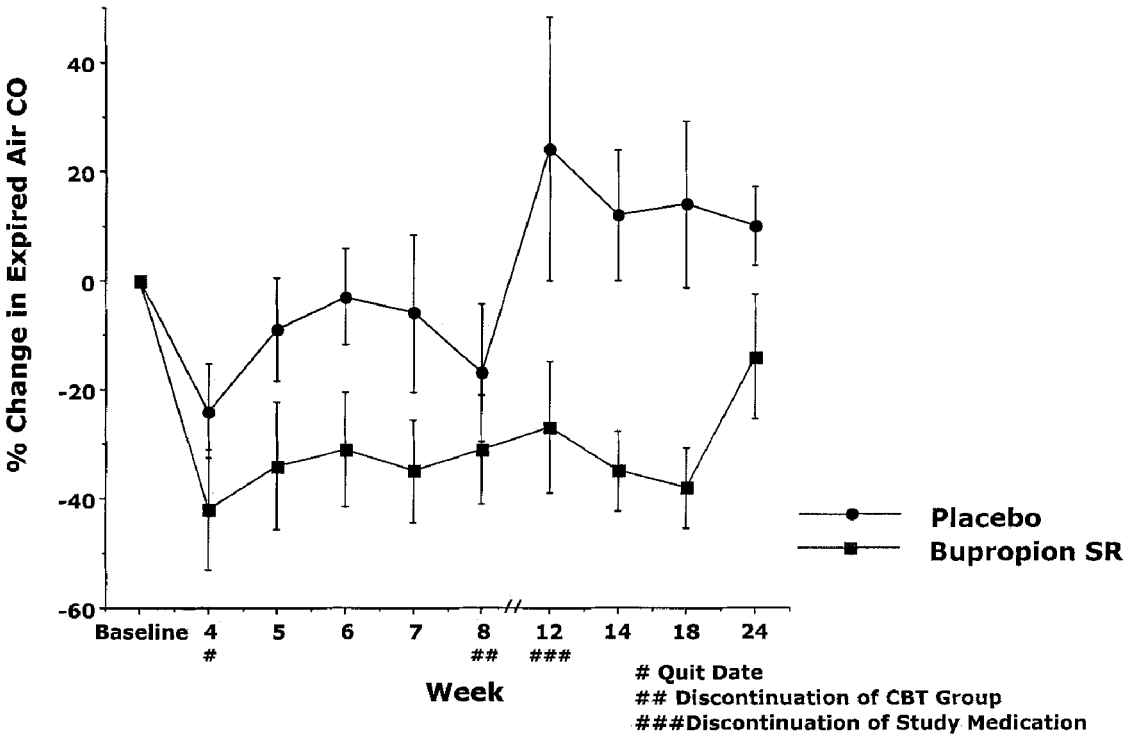

Figure 1. Change in expired air carbon monoxide during a 24-week smoking cessation trial in patients with schizophrenia. Bupropion treatment was associated with greater reduction in expired air CO during the treatment period (weeks 4–12; $F_{1,16}$=18.1, p<0.001) and during the follow-up period (weeks 14–24; $F_{1,16}$=19.5, p<0.001) than placebo by mixed-model ANCOVA. CO, carbon monoxide; n=9 per group. Error bars represent standard deviation. –●– Placebo; –■– bupropion SR. # Quit date; ## discontinuation of CBT group; ### discontinuation of study medication.

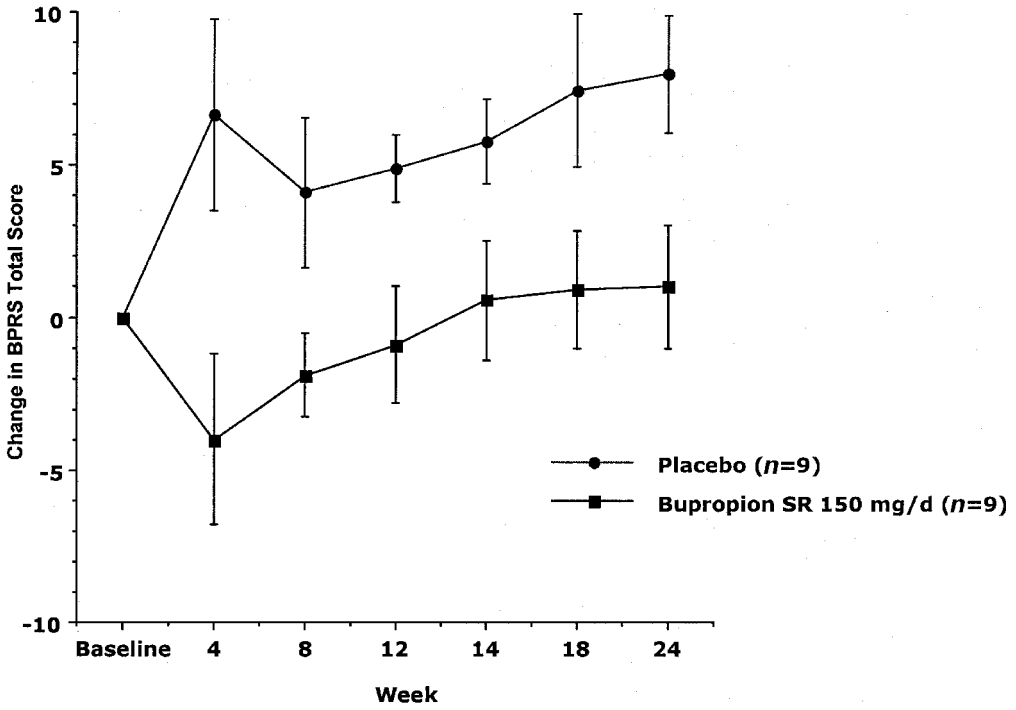

Figure 2. Change in BPRS during a 6-month smoking cessation trial in patients with schizophrenia. –■– Placebo (n=9); –■– bupropion SR 150 mg/day (n=9). Scores on the Brief Psychiatric Rating Scale (BPRS) total score increased in the placebo group relative to the bupropion group during study treatment ($F_{1,16}$=5.6, p=0.03) and follow-up ($F_{1,16}$=6.1, p=0.02).

Scores on the Brief Psychiatric Rating Scale (BPRS) total score increased in the placebo group relative to the bupropion group during study treatment ($F_{1,16}$=5.6, p=0.03) and follow-up ($F_{1,16}$=6.1, p=0.02).

bupropion group, a 25±37% decrease, and increased 33±89 ng/ml in the placebo group, an 11±32% increase.

Clinical symptoms

During the 3-month treatment period and active attempt to quit smoking, scores on the BPRS decreased in the bupropion group and increased in the placebo group; the mean difference was 4.2 (95% CI, 0.4–8), reflecting decreased overall psychiatric symptoms in the bupropion group, compared with the placebo group ($F_{1,16}$=5.6, p=0.03; Figure 2). During the 3-month follow-up, increased psychiatric symptoms in the placebo group, relative to the bupropion group, persisted ($F_{1,16}$=6.1, p=0.02). For a given BPRS baseline level and visit, the mean BPRS score for patients on bupropion was 5.3 units lower than for those on placebo (95% CI, 0.8–10). Analysis of the BPRS scores revealed that positive symptoms of psychosis (hallucinations, delusions, and formal thought disorder) and depressive symptoms were responsible for the significant difference in BPRS scores between the groups.

Positive symptoms of schizophrenia, as measured by the positive symptom subscale of the BPRS, remained stable in the bupropion group, compared with the placebo group during the active treatment period ($F_{1,16}$= 5.6, p=0.03; Table 2). The mean difference on the BPRS positive symptom subscale score was 2.3 units (95% CI, 0.2–4). During the follow-up period, positive symptoms were not significantly different across treatment groups; the mean difference was 1.6 units (Table 2).

During active treatment, depressive symptoms decreased in the bupropion group, relative to the placebo group ($F_{1,16}$=8.3, p<0.01). For a given HAM-D baseline level and visit, the mean HAM-D score for patients in the bupropion group was 2.4 units lower than their placebo counterparts (95% CI, 0.6–4). During follow-up, the difference between bupropion and placebo in depressive symptoms was not significant ($F_{1,16}$=4.2, p=0.06), with a mean difference of 1.6 between groups (Figure 3). Patients on placebo had significant worsening of depressive symptoms from baseline to weeks 8 (t=–2.3, p=0.05), 12 (t=–2.2, p=0.05), 14 (t=–4.5, p=0.002), and 18 (t=–2.3, p=0.05) (Table 2).

Negative symptoms were significantly reduced in the bupropion group from baseline to week 4 (t=3.8, p<0.005) and week 8 (t=2.9, p<0.02) and were not significantly reduced at week 12 (t=1.9, p=0.09). The change in negative symptoms in the bupropion treatment group, relative to the placebo group, was not significant during the overall treatment ($F_{1,16}$= 2.1, p=0.17) or follow-up period ($F_{1,16}$=3.6, p=0.08). During the treatment period, the mean SANS score was 6.5 units lower in the bupropion group than in the placebo group. During the follow-up period, the mean SANS score was 8 units lower in the bupropion group than in the placebo group (Table 2).

Subjects in the bupropion group had a mean 4.7±3.5 lb weight reduction from baseline to week 12, whereas subjects in the placebo group had a mean 2.9±6.2 lb weight gain (t_{16}=3.02, p<0.01). The difference in weight at the end of treatment by medication group reflected a large effect size, ES=1.19. From baseline to week 24, subjects in the bupropion group lost 2.3±5.8 lb and those in the placebo group gained 4.6±11.7 lb (n.s.; Table 2). Measures of extrapyramidal symptoms and akathisia did not differ by medication status at baseline, end of treatment, or follow-up.

Discussion

In this pilot trial, we found 12 weeks of therapy with bupropion SR, 150 mg/day, to be safe and effective for smoking reduction but not abstinence in patients with

Table 2. Change from baseline in ratings of positive and negative symptoms and body weight during a 24-week smoking cessation trial in patients with schizophrenia

	Bup SR (n = 9)			Placebo (n = 9)		
	Baseline	Week	Change	Baseline	Week	Change
BPRS	6.6 ± 3.0	4	–0.3 ± 1	6.7 ± 4.8	4	3 ± 4
Positive		8	1 ± 2		8	2 ± 4
		12	0.2 ± 1		12	2 ± 3
		14	1 ± 0.7		14	2 ± 1
		18	1 ± 0.6		18	3 ± 1
		24	1 ± 0.5		24	3 ± 1
SANS	37.9 ± 22	4	–12 ± 9	27.3 ± 19	4	3 ± 14
		8	–8 ± 9		8	1 ± 12
		12	–7 ± 11		12	3 ± 14
		14	–4 ± 11		14	10 ± 17
		18	0.2 ± 15		18	15 ± 10
		24	3.6 ± 16		24	11 ± 9
Weight[a] (lb)	192 ± 46	12	–4.7 ± 3.5	202 ± 26	12	2.9 ± 6.2
		24	–2.3 ± 5.8		24	4.6 ± 11.7

Baseline values and change units are expressed as mean ± standard deviation (SD).
[a] One subject in the placebo group did not have a baseline weight measurement and thus could not be included in the analysis.

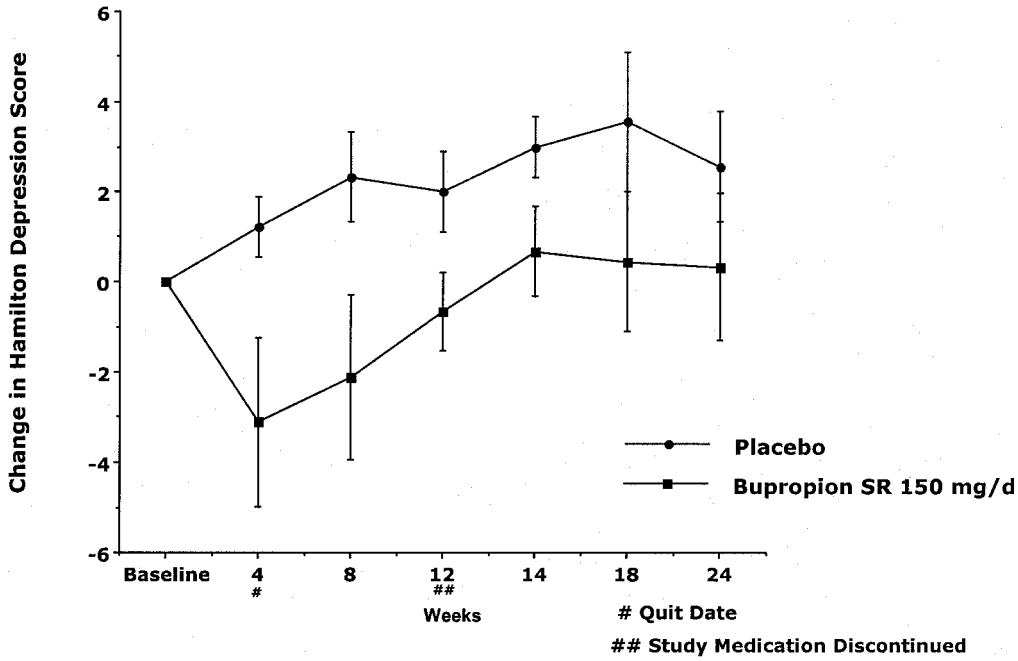

Figure 3. Change in depressive symptoms in subjects with schizophrenia during a 24-week smoking cessation study. –●– Placebo; –■– bupropion SR 150 mg/day. # Quit date; ## study medication discontinued. Depressive symptoms were decreased in the bupropion group, relative to the placebo group, during study treatment ($F_{1,16}$=8.3, p<0.01) and follow-up, ($F_{1,6}$=4.2, p=0.06). Placebo was associated with significant worsening of depressive symptoms from baseline to weeks 8 (t=–2.3, p=0.05), 12 (t=–2.2, p=0.05), 14 (t=–4.5, p=0.002), and 18 (t=–2.3, p=0.05).

Depressive symptoms were decreased in the bupropion group, relative to the placebo group, during study treatment ($F_{1,16}$=8.3, p<0.01) and follow-up, ($F_{1,6}$=4.2, p=0.06). Placebo was associated with significant worsening of depressive symptoms from baseline to weeks 8 (t=–2.3, p=0.05), 12 (t=–2.2, p=0.05), 14 (t=–4.5, p=0.002), and 18 (t=–2.3, p=0.05).

chronic, stable schizophrenia. Subjects in the bupropion group demonstrated a significantly greater reduction in smoking than did subjects in the CBT plus placebo group during active treatment, an effect that persisted for 3 months after discontinuation of study medication. These subjects with schizophrenia demonstrated a high level of motivation to try to quit smoking and exceptional compliance with the smoking cessation program. There was consistent evidence of a beneficial effect of bupropion on measures of clinical symptoms, with large between-group effect sizes during the active treatment phase. Negative symptoms improved from baseline in the bupropion group. Additionally, contrary to previous findings during short-term nicotine abstinence in patients with schizophrenia, subjects in the placebo group demonstrated significant worsening in psychotic symptoms, depressive symptoms, and overall psychopathology, relative to the bupropion group, during their smoking cessation attempt, indicating that patients with schizophrenia may be vulnerable to exacerbation in psychotic and depressive symptoms during a smoking cessation attempt. This finding must be interpreted cautiously in light of the unexpected finding that psychiatric symptoms remained elevated above baseline in the placebo group after study intervention was discontinued.

Limitations of this study include very small sample size with low power to detect differences between treatment groups. However, despite limited power, we found a significant effect of bupropion on smoking reduction and clinical symptoms. Clozapine treatment has been reported to be associated with reduction in cigarette smoking (George, Sernyak, Ziedonis, & Woods, 1995; McEvoy *et al.*, 1995b), and ongoing clozapine treatment in several subjects in each group may confound interpretation of the effect of bupropion on smoking behavior in this small sample. The one subject who achieved sustained abstinence was on clozapine treatment. High variability of cotinine measurements and high rate of refusal of blood drawing made interpretation of cotinine measurements difficult, requiring use of expired-air CO instead of serum cotinine as validation of self report of smoking reduction and cessation. A placebo-only group would be needed to assess the effectiveness of CBT for smoking cessation for people with schizophrenia. Tests of cognitive functioning were not included in this pilot trial. Worsening in measures of psychotic symptoms during a smoking cessation attempt may be associated with or caused by worsening in neuropsychiatric function; this possibility will need to be clarified with further study.

On the basis of this small, pilot trial, further study of bupropion SR and CBT for harm reduction in patients with schizophrenia is warranted. If shown to be safe and effective in larger trials, bupropion SR, already widely used for depression in this population, may play an important role in harm reduction by facilitating smoking reduction while possibly improving stability of psychiat-

ric symptoms during an attempt to quit smoking. It will be important to determine whether smoking reduction is maintained and whether smoking reduction increases the probability of future smoking cessation in this population. Importantly, the mechanism by which bupropion may stabilize symptoms of schizophrenia during a quit attempt is not known. It remains to be determined whether bupropion SR at a dose of 300 mg/day or a combination of bupropion SR with nicotine replacement therapy would further enhance effectiveness for smoking cessation and sustained abstinence in patients with schizophrenia.

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