Bupropion Sustained Release Added to Group Support for Smoking Cessation in Schizophrenia: A New Randomized Trial and a Meta-Analysis

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ABSTRACT

Objective: To clarify the efficacy and tolerability of bupropion sustained release (SR) for the treatment of cigarette smoking in people with schizophrenia.

Method: The first study is a double-blind, placebo-controlled clinical trial with 32 outpatients from the Maryland Psychiatric Research Center. From May 2003 to July 2007, clinically stable people with a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder who smoked at least 10 cigarettes per day and who were interested in quitting smoking or cutting down were recruited for participation. All participated in a 9-week support group and were randomly assigned to receive 12 weeks of bupropion SR or placebo. The primary outcome measure was 4 weeks' sustained abstinence over the last 4 study weeks. Secondary outcome measures included decrease in smoking behavior and change in symptoms, neuropsychological performance, and side effects. In the second study, we performed an electronic literature search of MEDLINE in September 2008. Articles in English published between 2003 and 2008 were searched for the terms *schizophrenia*, *bupropion SR*, and *smoking*. Bibliographies of studies identified through the MEDLINE search were also examined. Case reports, open-label studies, crossover studies, and studies using nonstandard dosing of bupropion SR were excluded. In this way, 4 studies similar in methodology to the currently presented clinical trial were identified and the individual data combined in a meta-analysis. A random effects meta-analysis using Comprehensive Meta-Analysis software was used to obtain a pooled estimate of the odds ratio for 4-week smoking abstinence between bupropion SR and placebo.

Results: There were no significant results on the primary or secondary smoking measures for the clinical trial, although a numeric advantage favored the bupropion SR group. There were no significant findings for secondary symptom or side effect measures and no significant change in neuropsychological performance. For the meta-analysis totaling 226 subjects, there were significant findings in favor of bupropion SR. The pooled estimate of the odds ratio for 4-week abstinence was 2.7 (95% CI, 1.3 to 5.7; $P = .009$), and clinically significant greater smoking reduction in the bupropion SR group, with pooled difference estimates increasing over time between groups, became statistically significant by week 5 of study medication ($P < .02$).

Conclusions: New clinical trial data and a meta-analysis strongly support the tolerability and efficacy of bupropion SR for the treatment of cigarette smoking in people with schizophrenia.

Trial Registration: clinicaltrials.gov Identifier: NCT00176449

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The rate of tobacco smoking among people with schizophrenia is up to 3 times greater than in the general population.[1] Yet there has been a lack of aggressive treatment for tobacco dependence, even at a time when the general population was being bombarded with media messages and regulatory pressure to quit smoking. Today, physicians[2] and other treatment providers of the chronically mentally ill[3] are still less likely to refer their patients for smoking cessation treatment than are those who provide care for patients in the general population. The reasons for this lack of aggressiveness are very likely multifaceted. Many providers view smoking as a lower priority problem compared to psychosis, and many believe that smokers with schizophrenia cannot tolerate cessation attempts from a psychiatric standpoint, seeing smoking as an attempt at self-medication, with cessation leading to worsening of symptoms or side effects.[4,5] Even when patients have tolerated smoking bans on inpatient units, mental health workers have not been reassured.[6] Unfortunately, without support for abstinence on discharge, most patients resumed smoking on discharge.[7] In the early 1990s, the research literature began to provide evidence that people with schizophrenia can stop smoking[8–10] and, most importantly, that cessation attempts were not associated with worsening in psychiatric status.[11] Subsequently, a number of studies have examined various combinations of bupropion sustained release (SR), nicotine replacement therapy, and support groups to treat nicotine dependence in this population.[12–15] More recent studies have found that bupropion SR helps smokers achieve short-term cessation as compared to those randomized to placebo.[16–19]

The present report includes 2 studies of the efficacy of bupropion SR for smoking cessation in people with schizophrenia. The first is a double-blind, placebo-controlled follow-up study of a previously reported open-label study[13] and the second a meta-analysis merging these new data with 4 previously reported placebo-controlled, parallel-group studies. Particularly as new agents become available for smoking cessation, it is critically important to have a better sense of the efficacy and tolerability of bupropion in people with schizophrenia, so that a more informed decision can be made when choosing from available smoking cessation treatments.

STUDY I (CLINICAL TRIAL): METHOD

Subjects

Clinically stable outpatients from the Maryland Psychiatric Research Center, Baltimore, Maryland, volunteered for participation and were screened for study eligibility. Subjects had a *Diagnostic and Statistical Manual of Mental Disorders,*

Fourth Edition (*DSM–IV*) diagnosis of schizophrenia or schizoaffective disorder made through a best-estimate diagnostic approach utilizing information from the Structured Clinical Interview for *DSM-IV*,[20] direct assessment, family informants, and past records. Subjects were interested in decreasing their smoking, smoked at least 10 cigarettes per day, and had a total score of at least 4 (moderate) out of a possible 10 (severe) on the Fagerstrom Test for Nicotine Dependency (FTND).[21] Participants were excluded if they had a neurologic diagnosis, current major depressive episode, substance dependence (other than nicotine) in the last 6 months or substance abuse (excluding nicotine) in the last 3 months, if they were not medically stable, or if they were currently taking bupropion.

The University of Maryland School of Medicine Institutional Review Board approved the study protocol. Written informed consent was obtained after study procedures were explained, and the informed consent process was documented. Participants were told at consent that the goal was to stop smoking, but they were encouraged to continue participation even if they could not achieve complete cessation. The trial was registered at clinicaltrials.gov (NCT00176449).

Study Design

Random assignments made by the statistician were stratified by sex and use of first- versus second-generation antipsychotic medication, as these factors have been shown to influence the likelihood of successfully quitting.[22–26] A power analysis based on our previous open-label study, which had detected a 44% reduction in end-expired carbon monoxide (CO) levels with bupropion treatment, suggested that 10 subjects in each group would be needed to detect the same effect. Because open-label studies tend to inflate observed effects, the recruitment goal was for 20 subjects in each group. The study design included an evaluation phase to ensure clinical stability, including standard laboratory measures, clinical behavioral and symptom assessments, and smoking measures. Subsequently, all participants entered the 14-week treatment phase beginning with the 9-week Group Support Program led by staff trained in the educational model of the American Cancer Society Fresh Start Program modified for people with schizophrenia.[8] Each session was structured and incorporated relaxation exercises with practice "homework." The first group sessions were designed to increase awareness of specific smoking habits and to develop a "Quit Plan." A Quit Day Ceremony was held at the fifth group session, 2 weeks after the initiation of study medication. Subsequent sessions focused on reworking the Quit Plan. Later groups focused on strategies for subjects' minimizing weight gain, managing "high risk" situations, and imagining themselves as nonsmokers. Subjects started study medication (bupropion SR 150 mg or placebo) the evening after the third group session (treatment phase week 2), with dosing once daily for 3 days and then twice daily for the remainder of the study. There was flexibility in dosing so that, if needed, study drug could be decreased to once per day. Nicotine gum was offered to all participants on Quit Day, but none of the participants chose to use the gum. Following the conclusion of the Group Support Program, participants remained on study medication therapy for 6 weeks, until the end of study. Medication compliance was assessed by weekly pill count review, with 75% compliance judged acceptable.

Study Assessments

Smoking measures. The primary efficacy outcome measure was *sustained abstinence*, defined as end-expired CO levels less than 10 ppm at the last 4 study visits of the treatment phrase.[27] Secondary efficacy measures included *point prevalence abstinence*, defined by CO levels less than 10 ppm at a specific time point; change in CO levels between baseline and each time point; reduction in urine levels of the nicotine metabolite cotinine[28]; and change in FTND total score from baseline to end of study. End-expired CO levels were collected weekly, and cotinine and FTND measures were collected at evaluation phase and treatment phase weeks 2, 4, 8, and 14. End-expired CO levels were measured by having participants exhale forcefully and completely into a Smokerlyzer breath CO monitor (Bedfont Scientific Ltd, Maidstone, United Kingdom) at the same time each week to ensure a steady-state lung CO level. End-expired CO levels measured this way have been shown to be a valid measure of smoking status in individuals who have achieved steady state.[27,28]

Safety measures. Clinical measures. To study whether bupropion or withdrawal from nicotine might affect psychiatric symptoms, assessments were obtained at evaluation phase and treatment phase weeks 2, 4, 8, and 14. The Brief Psychiatric Rating Scale (BPRS)[29] was performed to assess positive symptoms, depression, and anxiety, and the Scale for the Assessment of Negative Symptoms (SANS)[30] was used to assess negative symptoms.

Neuropsychological measures. A neuropsychological battery was designed to assess whether decreased smoking might impair cognitive function, since nicotine may improve cognition in people with schizophrenia.[31,32] The battery, administered in the evaluation phase and treatment phase week 14, consisted of the following: the Rey Auditory Verbal Learning Test,[33] the Brief Visual-Spatial Memory Test[34] to measure verbal and visual memory; the Wechsler Adult Intelligence Scale, Third Edition,[35] Letter Number Sequencing test to measure verbal working memory and Digit Symbol-Coding task to measure processing speed; the Gordon Diagnostic System Continuous Performance Task[36] to measure attention; and the Grooved Peg Board[37] to measure manual dexterity.

Adverse effect measures. The Simpson-Angus Scale (SAS)[38] was used to assess for the emergence of motor side effects possibly occurring as a result of an increase in antipsychotic blood levels caused by decreased cigarette consumption. These levels were obtained at evaluation phase and end of study. Other common side effects were assessed using the Side Effect Checklist (SEC), an unpublished 22-item list (developed by R.W.B.) in which subjects rate their complaints on a 1 (none) to 4 (severe) scale. Assessments were obtained during evaluation phase and treatment

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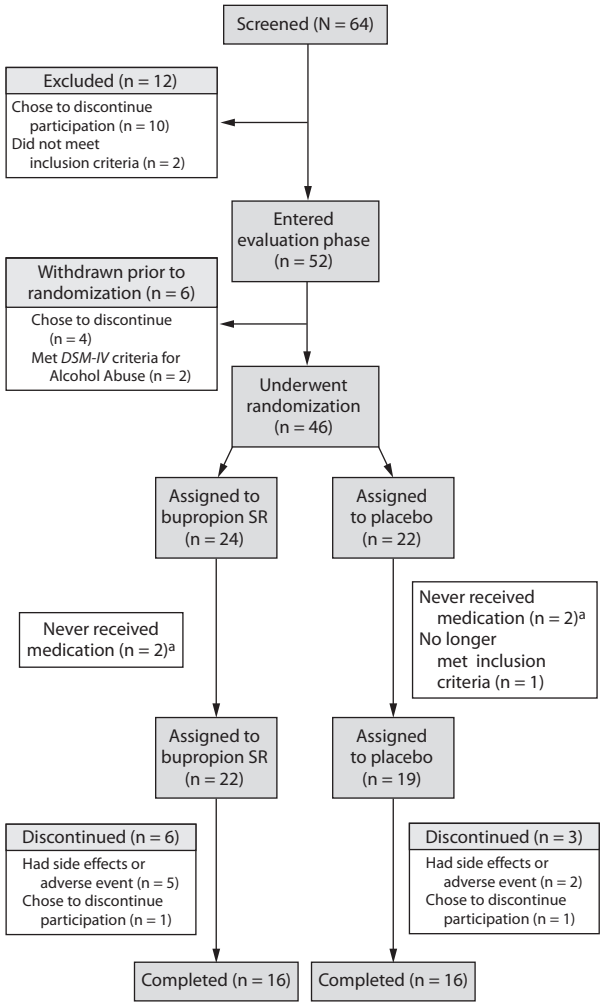
Figure 1. Consolidated Standards of Reporting Clinical Trials Flow Sheet: a 12-Week Trial of Bupropion Sustained Release or Placebo for Smoking Cessation in Outpatients With Schizophrenia (N = 46)



[a]Protocol closed due to end of study drug supply.
Abbreviations: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, SR = sustained release.

phase weeks 2, 4, 8, and 14. (Copies of the SEC are available from the corresponding author upon request.)

Statistical Analyses

Smoking measures. Abstinence at each weekly visit was defined by an end-expired CO level measurement < 10 ppm. For analysis of sustained abstinence, participants who dropped out early or had missing data were imputed as *not abstaining*. Fisher exact test measured differences in the percentage of participants who achieved sustained abstinence at the end of the double-blind treatment phase. For the secondary analyses, all observations collected during double-blind treatment were used in an intention-to-treat analyses; imputation was not used for missed visits following dropouts. In these analyses, the baseline visit was week 2 (the last visit prior to the start of study medication), and a mixed model for analysis of covariance (ANCOVA) for unbalanced repeated measures was used. Post hoc *t* tests based on estimates and standard errors from the general mixed-model ANCOVAs were performed to determine whether there were significant differences between groups at each study milestone. Point prevalence of smoking cessation was analyzed using the generalized estimating equation method for repeated-measures logistic regression.[39]

Table 1. Baseline Demographic and Clinical Characteristics of Outpatients With Schizophrenia (N = 46) Assigned to Bupropion Sustained Release or Placebo for 12 Weeks for Smoking Cessation

Characteristic	Bupropion SR (N = 24)	Placebo (N = 22)
Age, mean ± SD, y	49.5 ± 7.8	47.8 ± 8.2
Sex, male, %	79.2	81.8
Race, white, %	62.5	77.3
Baseline end-expired CO, mean ± SD, ppm	26.9 ± 11.9	26.0 ± 14.6
FTND score, mean ± SD	6.3 ± 1.7	5.3 ± 1.8
First-generation antipsychotic, n (%)	3 (12.5)	2 (9.1)
Clozapine, n (%)	7 (29.2)	6 (27.3)
Other second-generation antipsychotic, n (%)	14 (58.3)	14 (63.6)
BPRS positive symptom factor score, mean ± SD	6.9 ± 3.9	7.1 ± 3.5
BPRS anxiety and depression factor score, mean ± SD	6.0 ± 3.5	6.8 ± 3.4
SANS total score, mean ± SD	24.5 ± 2.4	24.9 ± 2.5

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CO = carbon monoxide, FTND = Fagerstrom Test for Nicotine Dependency, SANS = Scale for the Assessment of Negative Symptoms.

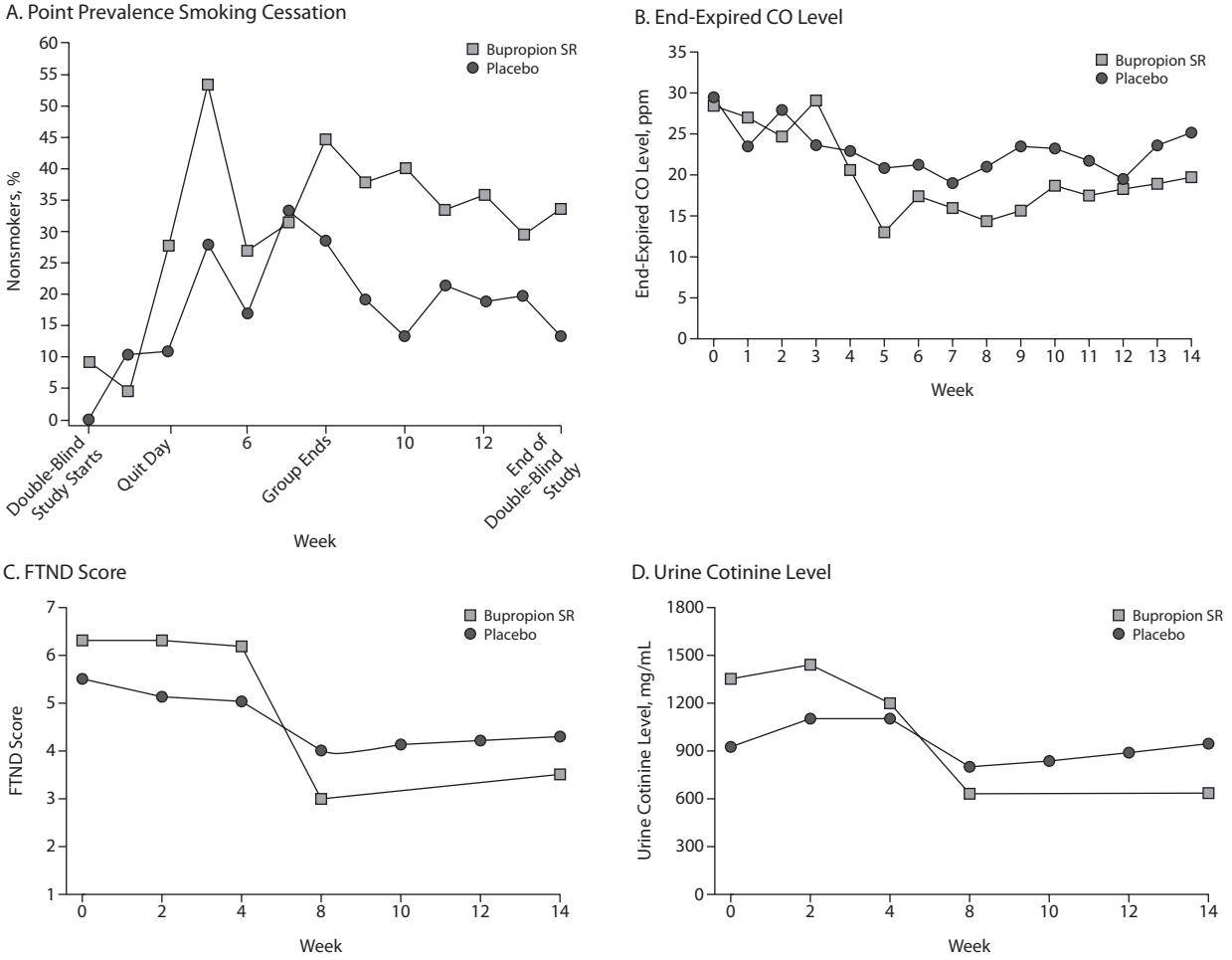
Safety measures. Mixed-model ANCOVAs were used to assess group differences on symptom measures.[40] For each neuropsychological test, participant scores were converted to *z* scores (*z* = [score—baseline mean]/baseline SD). An overall composite *z* score was computed from the mean of the individual test *z* scores.[41]

To test for group differences in extrapyramidal symptoms (EPS), a rank correlation score was calculated between SAS score and visit. Then the distribution of these scores was compared using a rank test selective for sensitivity to the presence of differences between groups. Rank correlations were also used to examine the relationship between end-expired CO levels and antipsychotic blood levels. For the SEC, Fisher exact test was used to compare groups on the percentage of patients who had any new incidence or worsening of a side effect during double-blind treatment.

RESULTS

Forty-six participants were randomized, and 32 completed the 14-week treatment phase (see Consolidated Standards of Reporting Trials flowchart, Figure 1). While the target completion number was 40, there was insufficient study drug available to meet this goal. Of the 32 who completed the study, 5 left before beginning double-blind treatment and are not included in the analyses. The 30% dropout rate is within the range seen in similar studies. There were no group differences on any demographic characteristics. There were no significant differences on severity of positive or negative

Figure 2. Secondary Smoking Measures for Treatment Phase of a 12-Week Trial of Bupropion Sustained Release or Placebo for Smoking Cessation in Outpatients With Schizophrenia (N = 46)



Abbreviations: CO = carbon monoxide, FTND = Fagerstrom Test for Nicotine Dependency.

symptoms, degree of dependency (as measured by the FTND or end-expired CO level), or the percentage of participants taking first- or second-generation antipsychotic medications or clozapine (Table 1). Participants all achieved the goal of 75% compliance.

Smoking Measures

The rates of sustained abstinence were 4 of 22 (18%) for bupropion participants and 2 of 19 (11%) for placebo participants (Fisher exact test, $P = .67$). Because of the low rates of achievement on this measure, no further analysis was done.

With regard to the secondary smoking measures, weekly point prevalence cessation rates tended to favor numerically the bupropion group at most visits during the double-blind treatment phase (Figure 2). However, the repeated-measures logistic regression analyses suggested no overall treatment effect ($\chi^2_1 = 1.10$, $P = .29$), no overall time effect ($\chi^2_{11} = 14.55$, $P = .20$), and no evidence that time trends varied between the groups ($\chi^2_{11} = 7.41$, $P = .77$). Similarly, scores of the other secondary measures showed a numerical advantage for the bupropion group over placebo, especially after Quit Day, but no statistically significant group differences were observed (Table 2 and Figure 2). Specifically, when the change in end-expired CO levels between the start of the double-blind treatment phase and each treatment phase week was compared between groups, mixed-model ANCOVA revealed no significant overall treatment effect of bupropion ($F_{1,37} = 0.38$, $P = .54$),) and no evidence that time trends varied between the groups ($F_{11,310} = 1.52$, $P = .12$). There was a significant time effect for both groups ($F_{11,310} = 4.16$, $P = .001$), showing a decrease in end-expired CO levels for both groups over time. For the FTND total score, the mixed-model ANCOVA revealed no significant group differences in mean nicotine dependency ($F_{1,30} = 2.08$, $P = .16$), but there was a significant time effect ($F_{2,52} = 7.39$, $P < .001$). The treatment-by-time effect was not significant ($F_{2,52} = 2.33$, $P = .11$). For urine cotinine, there were no significant group differences in mean urine cotinine levels ($F_{1,24.2} = 2.51$, $P = .13$), but there was a significant main effect of time ($F_{2,23.4} = 3.61$, $P = .043$). The treatment-by-time effect was not significant ($F_{2,23.4} = 0.35$, $P = .71$).

Safety Measures

Clinical measures. There were no significant between-group differences in the BPRS positive symptom item (conceptual disorganization, suspiciousness, unusual thought content, and hallucinatory behavior) ($F_{1,25.9} = 1.19$; $P = .29$),

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Table 2. Secondary Smoking Measures at Evaluation Phase and End of Study for Outpatients With Schizophrenia (N = 46) Assigned to Bupropion SR or Placebo for 12 Weeks for Smoking Cessation

	Baseline				Start of Double-Blind Treatment				Quit Day				End of Group				End of Double-Blind Treatment			
	Bupropion		Placebo		Bupropion		Placebo		Bupropion		Placebo		Bupropion		Placebo		Bupropion		Placebo	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
End-expired CO level, ppm	18	28.4 ± 11.9	17	29.4 ± 17.4	22	24.6 ± 11.8	18	27.9 ± 14.0	18	20.7 ± 13.7	18	23.0 ± 13.8	18	14.4 ± 11.2	14	21.0 ± 17.9	15	19.5 ± 13.7	15	25.1 ± 20.0
FTND score	24	6.3 ± 1.9	22	5.5 ± 1.9	19	6.3 ± 1.8	18	5.1 ± 2.1	19	6.2 ± 2.2	16	5.0 ± 2.1	19	3.0 ± 2.6	15	4.0 ± 2.9	16	3.5 ± 2.9	16	4.3 ± 2.7
Urine cotinine level, ng/mL	17	1,351.3 ± 972.7	13	920.5 ± 819.2	16	1,448.1 ± 1,116.0	11	1,100.0 ± 972.9	16	1,199.5 ± 931.1	11	1,099.9 ± 801.0	16	630.2 ± 675.0	11	781.0 ± 783.7	15	634.2 ± 705.2	10	942.7 ± 974.3

Abbreviations: CO = carbon monoxide, FTND = Fagerstrom Test for Nicotine Dependency, SR = sustained release.

BPRS anxiety/depression factor ($F_{1,30.6} = 0.22$; $P = .64$), or SANS total scores ($F_{1,29.9} = 1.11$; $P = .30$).

Neuropsychological measures. The change in the overall composite *z* score was not significantly different between groups (Wilcoxon test $P = .34$), and the heterogeneity of effect analysis was also not significant ($\chi^2_4 = 4.66$, $P = .32$), which suggests that there were no differential effects of bupropion on any of the individual measures. Therefore, no follow-up analyses were done for the individual test scores.

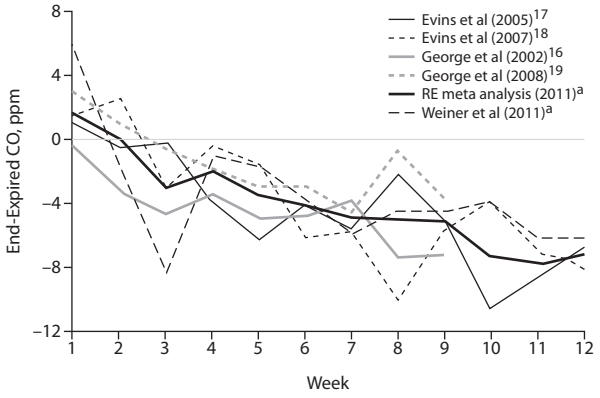
Adverse events/side effects. Five of the 6 participants who dropped out from the bupropion group complained of adverse events or side effects. Of those 5, 2 dropped-out at week 1 with a complaint of restlessness/anxiety, and another who was quite ill at baseline and often had mild exacerbations complained of worsening of psychosis. One participant was terminated from the study after 2 weeks of study medication due to the development of a rash that resolved after study medication was discontinued. Another participant, with a history of polydipsia, had a seizure at week 13 and was found to be hyponatremic. The remaining participant discontinued his participation at week 11 due to reported loss of motivation to stop smoking. Of the 3 participants randomized to placebo who discontinued, 2 participants dropped out at week 4: 1 secondary to loss of motivation and 1 due to worsening anxiety and restlessness. The third participant dropped out at week 5, with nonspecific complaints of sedation and malaise.

When the side effect data were analyzed, there were no group differences on any of the SEC measures, including the common bupropion side effects of restlessness, insomnia, dry mouth, and sedation. There was a numeric increase in dry mouth in the bupropion group. With respect to motor side effects, SAS total score means were low at baseline in both groups and remained low throughout the study, most likely due to the high percentage of subjects taking novel antipsychotics. Among 8 subjects (4 taking bupropion, 4 taking placebo) treated with olanzapine who had drug levels at both evaluation phase and end of study, the Spearman rank correlation between change in end-expired CO levels and change in olanzapine level from evaluation phase to end of study was $R = -0.78$, $P = .023$. Of these subjects, 6 had no change in reported level of sedation. One subject with a small reduction in olanzapine level reported a 1-point increase in sedation; a second, whose olanzapine level dropped by 24, had a 1-point reduction in sedation. Notably, none of the subjects whose olanzapine levels were increased at EOS reported a change in level of sedation.

DISCUSSION

The present study shows a numeric but not a statistically significant benefit of bupropion for smoking cessation in schizophrenia. A small but consistent benefit of bupropion is seen across the secondary smoking measures, but none of the group differences reached statistical significance, possibly due to lack of power. Viewed graphically (Figure 2), it appears that the bupropion group response was generally better than the placebo group. Importantly, we replicated previous studies

Figure 3. Random Effects Meta-Analysis of Odds Ratios for Successful 4-Week Abstinence From Smoking in 5 Studies of Participants With Schizophrenia Assigned to Bupropion Sustained Release Versus Placebo



[a]The present study.
Abbreviations: CO = carbon monoxide, RE = Random Effects.

that showed bupropion can be used safely in this population. Despite individual cases of bupropion-related side effects, there were no significant group differences, including those that might have emerged from an elevation in antipsychotic blood levels, as subjects decreased their smoking. There was no statistically significant worsening on any of the clinical measures, although 1 subject of the 6 randomized to bupropion withdrew due to worsening of psychiatric symptoms. There was no worsening of cognitive function, despite a decrease in cigarette consumption. Finally, neither a beneficial nor a detrimental effect was observed for negative symptoms. The relatively low level of negative symptoms in this study cohort may have precluded our being able to replicate previous reports of a beneficial effect of bupropion for these symptoms.[13]

There are several possible explanations for our inability to detect a statistical advantage for the bupropion group. Most obvious is the problem of attempting to measure a low-probability outcome (smoking cessation) in a relatively small number of study participants. This confound was further complicated by the large variability in the outcomes measured. Group differences were further obscured by the fact that both groups responded to the psychosocial treatment.

STUDY II (META-ANALYSIS): METHOD

Using our data, we performed a meta-analysis to obtain a more definitive estimate of bupropion's therapeutic effect. In September 2008, we performed a MEDLINE search for articles in English published between 2003 and 2008 that included the terms *schizophrenia*, *bupropion SR*, and *smoking*, excluding case reports, open-label studies, crossover studies, and studies using nonstandard bupropion dosing. Bibliographies of studies identified through the MEDLINE search were also examined. We identified 4 studies similar to our own presented here.[16–19] All were double-blind, placebo-controlled; used standard dosing; offered group support; and used end-expired CO levels as the smoking outcome measure. The duration of administration of study medications varied, with 12 weeks in the Evins et al[17,18] and Weiner et al (present) studies, and 9 weeks in the George et al[16,19] studies. The Evins et al (2007)[18] and George et al (2008)[19] studies also made use of nicotine replacement therapy, whereas the Evins et al (2005),[17] George et al (2002),[16] and the present study did not. Together, these studies included a total of 119 participants randomized to bupropion and 121 randomized to placebo. Participant retention rates varied among studies from 73% to 81%.

Statistical Analyses

Individual participant data, provided by George and A.E.E., were reanalyzed together with the data from the present study in a meta-analysis to examine the percentage of participants achieving sustained abstinence and to examine week-by-week mean differences in end-expired CO levels between treatment groups. Performing this secondary analysis allowed us to utilize all of the participant data, not just data from those who completed a study.

Comprehensive Meta-Analysis software,[42] version 1 (Biostat, Englewood, New Jersey), was used to obtain a pooled estimate of the odds ratio for sustained abstinence between bupropion SR and placebo and to estimate week-by-week mean differences in end-expired CO levels between groups. Dropouts and subjects with missed visits were classified as smokers.

A Rosenthal's estimate was calculated to estimate the number of negative studies it would take to cancel a statistically significant result.[43]

RESULTS

Study-specific odds of successful 4-week abstinence at the end of treatment with bupropion versus placebo ranged from 1.7 to 11.9. The pooled estimate of the odds ratio for 4-week abstinence was 2.7 (95% CI, 1.3–5.7; $P = .009$), indicating that bupropion SR treatment is associated with a higher probability than placebo of successful abstinence from smoking. The Rosenthal's formula[43] estimated that it would require 8.9 studies whose mean odds ratio was 1.0 to raise the *P* value for the combined odds ratio to a nonsignificant level.

In a meta-analysis of ANCOVA-adjusted week-by-week treatment differences in end-expired CO levels (Figure 3), the pooled difference estimates increased over time between participants taking bupropion SR versus placebo, with differences that were statistically significant ($P < .02$, unadjusted for multiple comparisons) by week 5 of double-blind treatment.

DISCUSSION

The meta-analysis results provide strong evidence for the efficacy of bupropion for the treatment of cigarette smoking in people with schizophrenia, and they provide a much more precise estimate of the effect of bupropion SR when combined with group support for smoking cessation in schizophrenia.

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All of these clinical trials, including our study, have been hampered by the difficulty of studying a low-probability outcome in relatively low-powered studies. Although the other studies were able to show a significant advantage for the bupropion group, performing the meta-analysis and thereby incorporating our current study data helps to provide greater clarity as to the magnitude of the benefit. In addition, incorporating our data with the other studies helps to address the "file drawer" problem of ignoring nonsignificant (usually not published) studies, a notorious obstacle to meta-analysis and accurate estimation of the true efficacy and effectiveness of interventions. Thus, this meta-analysis provides a more reliable estimate of the odds ratio for effectiveness than any of the individual studies, revealing that bupropion may help those with schizophrenia to be over 2½ times more likely to achieve sustained smoking cessation than those taking placebo.

Although the actual number of people with schizophrenia who are able to successfully quit smoking with bupropion is numerically smaller than that seen in the general population, the relative magnitude of the bupropion effect is possibly greater than the benefit observed in the general population.[44,45] In addition, the meta-analysis demonstrated clearly that participants taking bupropion had a decrease in their end-expired CO levels over time, implying that, even if participants were unable to quit, they were able to reduce their smoking to a greater extent than those subjects randomized to placebo. These findings provide clear support for using bupropion for treating smoking addiction in people with schizophrenia. Although we were not able to examine the possibility of psychiatric worsening due to either nicotine withdrawal or as a side effect of bupropion in the meta-analysis, the studies used in the meta-analysis are in agreement that, although there may be individual cases of psychiatric worsening, there is no evidence of a statistical difference in the likelihood of psychiatric worsening in subjects randomized to bupropion compared to those randomized to placebo. If anything, there is suggestive evidence from our open-label study,[13] Evins et al,[16] and George et al[17] that bupropion may improve negative symptoms. Similarly, with respect to side effects, although there may be individual cases of the common bupropion side effects, significant differences do not appear between the bupropion and placebo groups in double-blind studies.

The overall impression from both the current study and our pilot study[13] is that group support has an important effect on the ability of participants to reduce and quit smoking, although we did not examine this question directly. In both the pilot study and the clinical trial presented above, the study design included 2 weeks of group intervention before initiating study medications and 3 weeks of study medication following the termination of the group intervention. In both studies, participants decreased their cigarette consumption even before study medications began, and the gains made were lessened after the group intervention ended. These observations suggest that support is a meaningful component for people with schizophrenia in their fight against smoking addiction. A meta-analysis reviewing group support in the general population literature demonstrates that group support, compared to self-help or no group, approximately doubles the odds of smoking cessation.[46] Unfortunately, group-oriented smoking cessation treatment is not easily available to people with schizophrenia living in the community. In a study with psychotic patients, there was evidence of a dose-dependent relationship between the amount of psychosocial intervention and the likelihood of successful cessation.[47] Further research is necessary to clarify which components of the support are essential and whether group support provides any additional benefit compared to individual support, which is more easily incorporated into various treatment settings. In this area, the general population meta-analysis provides little direction, as there are neither data to support the use of any particular components of group intervention nor sufficient data with which to compare group intervention to individual counseling of similar intensity.[46]

In conclusion, there are compelling scientific data to support the use of bupropion SR for the treatment of nicotine addiction in schizophrenia, and evidence-based practice guidelines are supporting its use.[48] Recently, there have been a number of studies supporting the use of pharmacologic combination therapies to increase the odds of quitting in medically ill smokers in primary care settings,[49,50] with one study providing evidence for the use of triple combination therapy.[51] There have been no similar studies in psychiatric patients, despite calls for more work to address the needs of this under treated, high risk population.[52,53] Therefore, if one assumes that data from the general population literature are applicable to patients with schizophrenia, although a less robust response might be seen in the latter group, the evidence to date would suggest a multipronged approach to aggressively treat dependence on tobacco-derived nicotine or tobacco dependence in people with schizophrenia. Further studies should focus on a more aggressive nicotine-dependence treatment approach for smokers with schizophrenia.

Drug names: bupropion (Zyban), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa).

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