Two-Year Follow-Up of a Smoking Cessation Trial in Patients With Schizophrenia: Increased Rates of Smoking Cessation and Reduction

A. Eden Evins, M.D.; Corinne Cather, Ph.D.; Nancy A. Rigotti, M.D.; Oliver Freudenreich, M.D.; David C. Henderson, M.D.; Casey M. Olm-Shipman, B.S.; and Donald C. Goff, M.D.

Background: Long-term success rates of smoking cessation programs for patients with schizophrenia are unknown. This study, conducted between June 2001 and November 2002, evaluated the rate of smoking cessation and reduction in patients with schizophrenia (DSM-IV) 2 years after they had participated in a smoking cessation study in order to determine whether subjects who significantly reduced smoking during the original trial resumed their previous level of smoking at 2 years.

Method: Two years following a double-blind placebo-controlled trial of bupropion sustained release, 150 mg/day, added to cognitive-behavioral therapy for smoking cessation in patients with schizophrenia, subjects were interviewed, medical charts were reviewed, and carbon monoxide in expired air was measured.

Results: Seventeen of 18 subjects completed the follow-up assessment. More subjects were abstinent (22% [N = 4]) at the 2-year follow-up than were abstinent at the end of the trial (6% [N = 1]). Subjects who achieved significant smoking reduction during the trial were more likely to be abstinent at 2 years (4/7) than those who did not significantly reduce smoking during the trial (0/11) ($\chi^2 = 8.1$, $p < .005$). Most subjects who achieved ≥ 50% reduction in smoking at the end of the trial maintained at least that level of reduction at 2 years. Smoking reduction during the treatment intervention was correlated with smoking reduction at follow-up ($r = 0.60$, $p = .01$).

Conclusion: The results from this naturalistic study suggest that behavior changes achieved in smoking cessation programs for patients with schizophrenia may be durable and may predict future smoking behavior. We conclude that further investigation into the relationship between smoking reduction and future smoking cessation in special populations is indicated.

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Corresponding author and reprints: A. Eden Evins, M.D., MGH Schizophrenia Research Program, Freedom Trail Clinic, 25 Staniford Street, Boston, MA 02114 (e-mail: a_eden_evins@hms.harvard.edu).

Schizophrenia is associated with both smoking and heavy smoking. Recent studies have found that 75% to 85% of people with schizophrenia in the United States smoke cigarettes compared with 23% in the general population.[1–3] In samples of severely mentally ill patients, schizophrenia is an independent predictor of cigarette smoking after controlling for substance abuse, institutionalization, medication, and socioeconomic status.[1,2,4,5] People with schizophrenia are also more likely to be heavy smokers: approximately 20% to 40% smoke more than 30 cigarettes per day,[2] and smokers with schizophrenia acquire significantly more nicotine per cigarette than do smokers in the general population, presumably through deeper inhalation.[6]

Smoking is well known to be the leading preventable cause of death in the United States. From 1995 to 1999, smoking caused approximately 440,000 premature deaths in the United States annually and approximately $157 billion in annual health-related costs.[3] It is less well known that people with schizophrenia die on average 10 years earlier than do those in the general population,[7] and natural deaths account for 59% of the excess mortality in schizophrenia.[8] Age-adjusted rates of death due to pulmonary disease, especially pneumonia, are elevated as much

as 130% in this population.[7–9] A preliminary analysis of Massachusetts Department of Mental Health data for the years 1998 to 2000 shows that death rates due to chronic obstructive pulmonary disease, pneumonia, and influenza are increased 2- to 6-fold in patients with major mental illness with significant disability compared with the general population.[3] The development of treatment interventions that can reduce the adverse health effects of smoking in patients with psychiatric illness should therefore be a public health priority.

We previously reported the results of a smoking cessation study[10] in which adults with schizophrenia entered a 12-week, double-blind, placebo-controlled trial of bupropion sustained release (SR), 150 mg/day, plus group cognitive-behavioral therapy (CBT) for smoking cessation. Only 1 of 9 subjects receiving bupropion SR and none of the 9 subjects receiving placebo attained sustained abstinence during the trial. However, those treated with bupropion SR plus CBT had a significantly greater rate of significant reduction (≥ 50%) in smoking than those treated with placebo plus CBT, suggesting that bupropion SR, 150 mg/day, promotes smoking reduction but not cessation in this population.[10] In that study and the present one, significant reduction was defined as a 50% reduction in self-report of cigarettes per day and a 30% reduction in expired air carbon monoxide (CO).

The long-term course of smoking following smoking reduction is unknown in schizophrenia. In the general population, smoking reduction may be maintained over time,[11] may be associated with reduction in biomarkers of harm,[12] and may lead to future smoking cessation.[13] We conducted the follow-up trial, from June 2001 to November 2002, to investigate whether those who reduced their smoking by ≥ 50% in the trial would maintain that reduction, resume their previous level of smoking, or attain abstinence. The degree to which smoking reduction facilitates abstinence in patients with schizophrenia trying to quit smoking is not known. People in the general population who are unwilling to try to quit smoking can achieve significant smoking reduction, and a substantial minority can maintain that reduction at 2 years.[11,14] Because nicotine corrects certain information processing and cognitive psychomotor abnormalities and reduces sedative effects of antipsychotic medication,[15,16] patients with schizophrenia would be expected to have greater difficulty maintaining smoking reduction or achieving abstinence than those in the general population. Our hypothesis was that the majority of schizophrenia subjects who significantly reduced smoking during the trial would have resumed their previous level of smoking at the 2-year follow-up.

METHOD

The study was approved by the appropriate review boards. Subjects signed informed consent forms after the study procedures were fully explained. Subjects met DSM-IV criteria for schizophrenia as per chart review and patient interview by a research psychiatrist (A.E.E.) and completed a 12-week trial of bupropion SR, 150 mg/day, or placebo added to an 8-week group cognitive-behavioral therapy program for smoking cessation. The initial trial protocol has been described previously.[10] Two-year follow-up assessments included a self-report of smoking in the past 7 days, measurement of expired air CO, a standard battery of clinical rating scales,[10] and chart review. Expired air CO was measured with an EC50 Micro III Smokerlyzer (Bedfont Scientific Ltd., Rochester, Kent, U.K.). Medical records were reviewed to determine type and dose of antipsychotic medication at the time of the 2-year follow-up as well as to document interval use of bupropion SR and nicotine replacement therapy.

Analysis of outcomes for the follow-up included (1) rate of significant smoking reduction at 2 years as a function of significant reduction during the trial, (2) rate of tobacco abstinence at 2 years as a function of significant reduction during the trial (tobacco abstinence was defined as self-report of smoking zero cigarettes in the past 7 days and expired air CO < 9 ppm at the time of the evaluation), (3) expired air CO at 2 years compared with baseline and CO at end of trial, and (4) predictors of abstinence at 2 years.

Chi-square analysis was used to compare significant reduction and abstinence rates at 2 years among those who significantly reduced smoking during the trial with those who did not, and to compare the smoking cessation rate at 2 years with the cessation rate at the end of treatment. Paired t tests were used to compare expired air CO at 2 years with expired air CO at baseline and at the end of the trial. Pearson correlation was used to analyze the relationship between reduction in expired air CO at the end of the trial and reduction at follow-up. All tests were 2-tailed, with the level of significance set at .05.

RESULTS

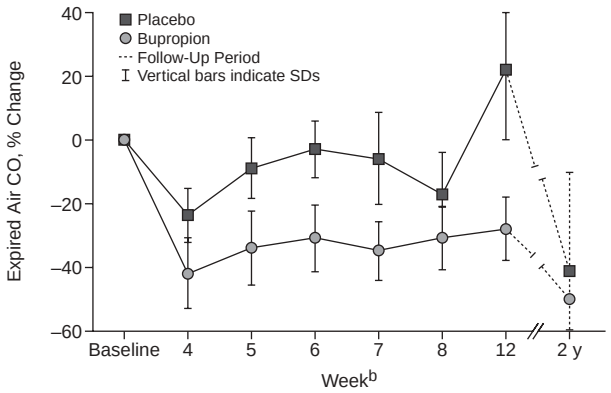
Follow-up interviews were conducted at 23 ± 1.1 months after the start of the smoking cessation trial with 17 of the 18 subjects who completed the trial. One subject was lost to follow-up and was considered a smoker for the analysis. Eighty-eight percent of subjects (N = 15) were white and 12% (N = 2) were African-American; 65% (N = 11) were male. Participants ranged in age from 29 to 58 years, had a mean of 12 ± 2.3 years of education (range, 7–15 years), had smoked for 24 ± 6.3 years, smoked 32 ± 19 cigarettes per day (range, 20–80 cigarettes per day), and had had a diagnosis of schizophrenia for 24 ± 9.5 years.

Eighty-six percent of subjects (6 of 7) who had significantly reduced smoking at the end of the trial, defined as ≥ 30% reduction in expired air CO and ≥ 50% reduction

Table 1. Abstinence From and Significant Reduction in Tobacco Use in a Group of Patients With Schizophrenia at the End of and 2 Years Following a Smoking Cessation Treatment Study

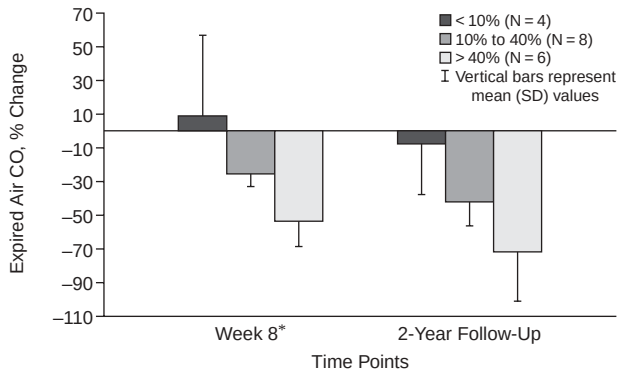
Tobacco Use	All Subjects, N (%) (N = 18)	Randomly Assigned to Bupropion SR, N		Received Bupropion SR in Trial or Follow-Up, N (%)	
		Yes (N = 9)	No (N = 9)	Yes (N = 14)	No (N = 4)
Tobacco abstinence					
End of 12-wk trial	1 (6)	1	0		
At 2-y follow-up	4 (22)	2	2	3	1
Both	1	1	0		
Significant reduction					
End of 12-wk trial	7 (39)	6	1		
At 2-y follow-up	11 (61)	5	6	9 (64)	2 (50)
Both	3	3	0		

Figure 1. Percent Change in Expired Air CO at 2-Year Follow-Up of a Smoking Cessation Study in Patients With Schizophrenia[a]



[a]Subjects had significantly lower CO at 2 years than at baseline (t = 3.91, df = 17, p = .001) or at week 12 (t = 3.07, df = 17, p < .01) (paired t tests).
[b]From baseline to week 8, subjects received cognitive-behavioral therapy. They received bupropion SR or placebo from baseline to week 12. From week 12 to the 2-year follow-up, 61% of subjects obtained pharmacotherapy for smoking cessation.
Abbreviation: CO = carbon monoxide.

Figure 2. Correlation Between Change in Expired Air CO During a Smoking Cessation Trial and at 2-Year Follow-Up[a]



[a]Smoking reduction during treatment intervention was correlated with smoking reduction at 2 years, r = 0.60, p = .01.
*Week 8 was the end of full treatment intervention (CBT + study medication).
Abbreviations: CBT = cognitive-behavioral therapy, CO = carbon monoxide.

in cigarettes per day, had maintained at least a 50% reduction in smoking at 2 years (Table 1). Subjects who had significantly reduced smoking at the end of the trial were more likely to have quit smoking at 2 years (4 of 7 subjects) than those who did not significantly reduce smoking during the trial (0 of 11 subjects) ($\chi^2 = 8.1$, $p < .005$). The mean expired air CO for the entire group was significantly lower at 2 years than at baseline (t = 3.91, df = 17, p = .001) or at week 12 (t = 3.07, df = 17, p < .01) (Figure 1). Overall, reduction in expired air CO at the end of the combined smoking cessation treatment intervention (study medication plus CBT) was significantly correlated with reduction at the 2-year follow-up (r = 0.60, p = .01) (Figure 2).

At the end of the smoking cessation intervention, 1 subject (6% of the total sample) was abstinent; at the 2-year follow-up, 4 (22%) of 18 subjects were abstinent, including the subject who was abstinent at the end of the trial ($\chi^2 = 3.5$, p = .06) (Table 1). Three of the 4 subjects abstinent at follow-up received bupropion SR during the trial or during the follow-up period; the fourth subject quit during an extended medical hospitalization. Two of the 4 subjects who were abstinent at 2 years were in the bupropion SR treatment group during the initial trial.

Eleven (61%) of the 18 subjects (Table 1) obtained pharmacotherapy for smoking cessation in the interval between the trial and follow-up: 50% (N = 9) used bupropion SR and 11% (N = 2) used nicotine replacement therapy. All subjects were treated with antipsychotic medication; 10 subjects at baseline and 11 at follow-up were treated with atypical antipsychotic medication, including clozapine. There was no difference in change in smoking behavior at the 2-year follow-up between participants taking a conventional antipsychotic and those taking an atypical antipsychotic. Of the 4 patients who were abstinent at the 2-year follow-up, 3 were taking clozapine and 1 was taking haloperidol at follow-up. Of the 3 subjects who

reduced their smoking at both follow-up and end of the 12-week trial, 1 was taking olanzapine and 2 were taking haloperidol. Of the 11 subjects who significantly reduced their smoking at follow-up, 4 were taking clozapine, 1 was taking olanzapine, 1 was taking quetiapine, and 5 were taking either haloperidol or fluphenazine.

The data from the clinical rating scales were explored to determine whether baseline clinical characteristics might distinguish the participants who were able to significantly reduce smoking.[10] No measure of clinical symptoms was significantly correlated with reduction in expired air CO at the 2-year follow-up, and there were no differences in clinical symptoms on the Brief Psychiatric Rating Scale, Hamilton Rating Scale for Depression, Scale for Assessment of Negative Symptoms, Abnormal Involuntary Movement Scale, or Simpson-Angus Scale between the 2 treatment groups or between those who had significantly reduced smoking at 2 years and those who had not.

CONCLUSIONS

To our knowledge, this is the first report of long-term follow-up of a smoking cessation treatment trial in patients with schizophrenia. Our data suggest that patients with schizophrenia who achieve significant smoking reduction during a treatment intervention can maintain at least that level of smoking reduction at 2 years. These data also suggest that smoking reduction during an intervention predicts later smoking cessation in patients with schizophrenia. These findings are contrary to our hypothesis that patients who did not quit smoking during the trial would resume their previous level of smoking shortly after the end of the intervention because of a high level of sensitivity to smoking cues in their environment, biological vulnerability to nicotine addiction, and possible improvement in memory, attention, and negative symptoms from nicotine.[15–18]

Inherent in our hypothesis was the assumption that subjects would not be likely to seek further smoking cessation treatment following the trial. To the contrary, most participants actively sought further pharmacotherapy and supportive treatment for smoking cessation during the follow-up period. Reduced-cost smoking cessation treatments were widely available in the Boston area during the follow-up period due to funding from the tobacco settlement, although none were targeted for patients with major mental illness.[19] When we learned that most subjects sought smoking cessation treatment following the trial, we speculated that patients would have made use of this increased availability of smoking cessation treatment even without participation in the study. To investigate this hypothesis, we conducted a brief 2-year follow-up evaluation of the 10 subjects from our clinic who were excluded from the study because of a medical contraindication to bupropion but who met other eligibility requirements for the trial. These subjects were highly motivated to quit, were eligible for nicotine replacement therapy, and were referred for smoking cessation treatment in the community. This follow-up evaluation revealed that none of those 10 subjects had followed up on the referral for low-cost smoking cessation treatment in the community. None had quit or significantly reduced smoking. An alternative explanation for our finding that most patients sought additional treatment following the study intervention is that participation in the cognitive-behavioral therapy program in the trial may have improved patients' sense of self-efficacy or motivation to seek further treatment for smoking cessation.

Limitations to this study include small sample size and absence of a no-treatment control group. The self-selected nature of the group would select for patients who are highly motivated to quit smoking. Also, because of the naturalistic nature of the follow-up, we cannot draw firm conclusions about the role of bupropion SR in the outcome at 2 years.

The results of this trial extend previous pharmacotherapy studies of smoking cessation in schizophrenia[20–25] and suggest that in patients with schizophrenia, significant smoking reduction may not only be maintained over time[1] but may lead to future smoking cessation. Despite its limitations, this naturalistic follow-up study provides evidence that patients with schizophrenia, following a cognitive-behavioral intervention, will persist in their attempt to quit smoking. We find these results encouraging in that these patients continued to seek smoking cessation treatment following the conclusion of a research trial. We conclude that further investigation into the relationship between smoking reduction and future smoking cessation in special populations is warranted. Further investigation into the relationship between sustained smoking reduction and harm reduction is also needed.

Drug names: bupropion (Wellbutrin and Zyban), clozapine (Clozaril and others), fluphenazine (Permitil, Prolixin), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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