A Placebo Controlled Trial of Bupropion for Smoking Cessation in Schizophrenia

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Background: *Schizophrenic patients have high rates of cigarette smoking compared with the general population. We compared sustained-release (SR) bupropion with placebo for smoking cessation in patients with schizophrenic disorders. We also examined how antipsychotic class predicts smoking cessation outcomes with bupropion.*

Methods: *Thirty-two subjects meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and nicotine dependence were randomized to bupropion SR (BUP, 300 mg/day) or placebo (PLA). Outcomes included treatment retention, smoking abstinence rates, expired breath carbon monoxide (CO) levels, psychotic symptoms, and medication side effects.*

Results: *Bupropion significantly increased trial endpoint 7-day point prevalence smoking abstinence rates compared with placebo [BUP, 8/16 (50.0%), PLA, 2/16 (12.5%);* $\chi^2 = 5.24$, df $= 1$, $p < .05$*], and reduced CO levels during the trial [Medication* $\times$ *Time interaction;* $Z = 3.09$, $p < .01$*]. Positive schizophrenia symptoms were not altered by BUP, but negative symptoms were significantly reduced. Atypical antipsychotic drug treatment enhanced smoking cessation responses to BUP. Major side effects were dry mouth, gastrointestinal symptoms, headache, and insomnia.*

Conclusions: *Our results suggest that 1) BUP enhances smoking abstinence rates compared with PLA in nicotine-dependent schizophrenic smokers; 2) BUP is well-tolerated and safe for use in these patients; and 3) atypical antipsychotics may enhance smoking cessation outcomes with BUP.* Biol Psychiatry 2002;52:53–61 © *2002 Society of Biological Psychiatry*

Key Words: Bupropion, nicotine dependence, smoking cessation, placebo-controlled trial, schizophrenia, atypical antipsychotic drugs, negative symptoms

Introduction

Schizophrenic patients have high rates of cigarette smoking (58–88%) compared with the general population (~25%) (George et al 2000a) and are often nicotine-dependent smokers who have great difficulty with smoking cessation (Addington 1998; Addington et al 1998; George et al 2000a; Ziedonis and George 1997). Low intrinsic motivation to quit smoking, which may be related to negative and affective symptoms characteristic of schizophrenic illness, has been proposed as a reason for their difficulties with smoking cessation (Addington et al 1997; George et al 2000a; Ziedonis and George 1997). Consequently, schizophrenic patients are often in the earlier stages for motivation to quit smoking as assessed by the "Stages of Change" model (Addington et al 1997; Prochaska and DiClemente 1983). Because patients with schizophrenia are at high risk for developing medical morbidity and mortality related to chronic tobacco use (Allebeck 1989; Lichtermann et al 2001), efforts to assist them in quitting smoking are of considerable importance; however, the few studies of smoking cessation in schizophrenic patients have reported lower trial end point and 6-month follow-up smoking abstinence rates (Addington et al 1998; George et al 2000a; Ziedonis and Trudeau 1997) compared with studies in nonpsychiatric smokers (Hughes et al 1999), indicating a need to develop better treatments for smoking in this population.

There are a number of potential pharmacologic interventions that could improve smoking cessation outcomes in schizophrenic patients. Three preliminary studies with the atypical antipsychotic agent clozapine suggest that this agent may reduce smoking in schizophrenic patients (George et al 1995; McEvoy et al 1995a, 1999), particularly in heavier smokers (George et al 1995). In contrast, the typical antipsychotic agent haloperidol may increase cigarette smoking (McEvoy et al 1995b). Most recently, we have shown that atypical antipsychotic agents may enhance smoking abstinence rates in combination with nicotine patch (George et al 2000a). The antidepressant agent bupropion hydrochloride, as the sustained-release (SR) formulation (Zyban), has been shown to be effective

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for the treatment of nicotine dependence in nonpsychiatric smokers (Hurt et al 1997; Jorenby et al 1999) and received FDA approval for this indication in 1997. There has been a case report that bupropion SR may assist smoking cessation efforts in schizophrenic patients (Evins and Tisdale 1999), and preliminary studies have suggested the efficacy of bupropion SR in reducing cigarette smoking by schizophrenic patients (Evins et al 2001; Weiner et al 2001). It is well appreciated that combining pharmacologic with behavioral treatments enhances outcomes in addictive disorders (Carroll 1997), and preliminary work from our group (George et al 2000a; Ziedonis and George 1997) and others (Addington 1998; Addington et al 1998) has suggested that combining pharmacotherapies with schizophrenia psychosocial interventions (e.g., psychoeducation, social skills training) and smoking cessation behavioral interventions (e.g., motivational enhancement therapy, relapse-prevention therapy) may improve treatment outcomes and acceptability.

In this preliminary study, our primary goal was to evaluate the safety and efficacy of SR bupropion in comparison with placebo for smoking cessation in nicotine-dependent schizophrenic and schizoaffective cigarette smokers who were motivated to quit smoking. The secondary goal of this study was to examine the effects of antipsychotic treatment class (atypical vs. typical antipsychotic agents) on smoking cessation responses to bupropion in schizophrenic patients.

Methods and Materials

Fifty-six outpatient subjects who met DSM-IV criteria for schizophrenia or schizoaffective disorder and nicotine dependence were screened for this study. After complete description of the study to subjects, written informed consent from 32 eligible subjects was obtained, and these subjects were randomized to the two study groups. The protocol was approved by the Human Investigation Committee of Yale University School of Medicine and conducted at the outpatient smoking research clinic of The Connecticut Mental Health Center (CMHC).

All subjects were evaluated at baseline with the SCID-I for DSM-IV, Positive and Negative Symptoms Scale for Schizophrenia (PANSS), Beck Depression Inventory (BDI), Tiffany Questionnaire for Smoking Urges (T-QSU), Webster Extrapyramidal Symptoms Scale (WEPS), Abnormal Involuntary Movements Scale (AIMS), Fagerstrom Test for Nicotine Dependence (FTND), plasma and urine cotinine (Peter I. Jatlow, MD, Department of Laboratory Medicine, Yale New Haven Hospital), and expired breath carbon monoxide (CO) levels (Bedfont EC50 Microsmokerlyzer II, Kent, UK). Subjects required an FTND score of 5 or higher, an expired CO level $\geq$10 parts per million (ppm) and plasma cotinine level $\geq$150 ng/mL at baseline evaluation for study inclusion. In addition, subjects needed to be clinically stable on psychotic and affective symptomatology before study entry. Schizophrenic subjects screened for this trial needed to express a strong desire to quit smoking at study baseline to participate, as assessed by clinical evaluation over three prerandomization assessment sessions and by a score of 3 or higher on an assessment measure of self-reported motivation (a Likert scale rated 0–4) to stop smoking (George et al 2000a); available on request from TPG. Schizophrenic subjects with a history of epilepsy or seizures were excluded from study participation, as were subjects with a history of alcohol/drug abuse or dependence (except nicotine and caffeine) in the 6 months before study entry. Vital signs (blood pressure, pulse, temperature, and respiration rate) were assessed weekly during the trial.

Eligible subjects (n = 32) were randomly assigned to either bupropion (BUP, 300 mg/day; 150 mg p.o. b.i.d.) or matching placebo (PLA). Both subjects and research staff were blinded to study medication assignment. Study medications were prepared by research pharmacists at CMHC, using encapsulation of SR bupropion tablets with blue 00 opaque capsules; placebo capsules contained only a dextrose matrix. Study medication was begun during the second week of treatment, at 150 mg p.o. daily for the first 3 days, then the dose was increased to 150 mg p.o. twice daily on the fourth day. The smoking "quit date" occurred at the beginning of week 3 (day 15) of the study, during the third group therapy session. Study medications were continued until the end of week 10, at which time they were discontinued. The schizophrenia smoking cessation group therapy was described previously (George et al 2000a; Ziedonis and George 1997) and included motivational enhancement therapy (weeks 1–3) and psychoeducation, social skills training, and relapse-prevention strategies (weeks 4–10) for a total of 10 weeks. Sessions were of 60-min duration. Subjects attended weekly group therapy appointments and weekly research assessments on separate days. At specific points during the trial (weeks 1, 4, 7, and 10), reassessments with the T-QSU, WEPS, AIMS, BDI, and PANSS were performed to determine changes in these measures during the trial.

Seven-day point prevalence smoking abstinence was determined by an absence of self-reported cigarette use during the previous 7 days up to and including the day of assessment, and abstinence was verified during the weekly assessment session with a CO level $<$10 ppm (George et al 2000a; Hurt et al 1997; Jorenby et al 1999). Antipsychotic medications (given as monotherapy with either atypical [ATP] or typical [TYP] agents) were maintained at the prestudy dose for the duration of the study. Subjects requiring a dose change for symptom stabilization or antipsychotic side effects or who were prescribed a second antipsychotic agent for symptom stabilization in the 6 months before study entry were excluded from study participation. Subjects were reassessed at 6 months after study completion to determine 7-day point-prevalence smoking abstinence rates (the 6-month follow-up assessment).

Statistical Analysis

Kaplan-Meier survival analysis (Bland and Altman 1998) was used to determine differences in subject retention between the two medication treatment groups (George et al 2000a). Smoking cessation outcome data (end point and last 4 weeks of trial continuous abstinence) was analyzed using chi square. Further-

more, logistic regression analyses were used to determine the effects of study medication (BUP vs. PLA; a randomized factor) in combination with antipsychotic class (ATP vs. TYP agents; a subject variable) in predicting trial end point smoking abstinence. For determination of smoking abstinence rates, an "intention-to-treat" analysis was used. Subjects who were lost during the trial or at 6-month follow-up were counted as smokers. Hierarchical linear modeling (HLM; Gibbons et al 1993) was used to determine whether the linear rate of change across the course of the study in continuous outcome measures (e.g., CO levels) varied as a function of study medication (George et al 2000a). The majority of statistical analyses were done using Statistical Package for the Social Sciences (SPSS) version 10.0; MIXREG software was used for HLM analyses. Differences were considered significant when $p < .05$.

Results

Demographic and Clinical Characteristics in Bupropion and Placebo Groups

A comparison of baseline demographic and clinical characteristics of BUP and PLA groups is presented in Table 1. On each of the baseline measures, there were no significant differences between study groups. Forty-eight percent of participants were men; 53% were Caucasian; 57% had a schizophrenia (vs. schizoaffective) diagnosis, smoked more than 1 pack per day of cigarettes, had multiple (~3 or more) previous quit attempts, had a moderate to high degree of nicotine dependence and high motivation to quit smoking, had minimal psychotic and depressive symptoms and extrapyramidal side effects, and had similar antipsychotic drug exposure (as assessed by chlorpromazine equivalents in mg/day). Biochemical measures of smoking consumption, including expired breath CO levels and plasma and urine cotinine levels, were consistent with the heavy smoking (>1 pack per day) reported by these subjects.

Treatment Retention in BUP versus PLA Groups

We compared treatment retention in BUP ($n = 16$) and PLA ($n = 16$) groups during the 10-week trial using: 1) the proportion of subjects in each group remaining at trial end point and 2) the Kaplan-Meier survival curve method (Bland and Altman 1998). There were no significant differences in subject retention at trial end point (week 10: BUP, 14/16; PLA, 11/16; $\chi^2 = 1.65$, $df = 1$, $p = .20$). Furthermore, survival curve analysis (data not shown) revealed that there were no significant differences in the proportion of schizophrenic subjects retained in treatment during the course of the 10-week trial (log rank test; $\chi^2 = 1.61$, $df = 1$, $p = .20$).

Table 1. Demographic and Clinical Characteristics of Schizophrenic Smokers in Bupropion and Placebo Groups[a]

Variable	Bupropion ($n = 16$)	Placebo ($n = 16$)
Age (years)	45.4 ± 11.9	40.9 ± 9.4
Sex	10 M/6 F	8 M/8 F
Race	10 W/6 B	10 W/5 B/1 O
Diagnosis	9 SCZ/7 SCA	11 SCZ/5 SCA
Education (years)	11.4 ± 2.0	11.8 ± 1.8
Cigarettes/day	25.0 ± 11.5	23.3 ± 9.5
Previous quit attempts	2.9 ± 2.9	4.3 ± 5.3
Time since last quit attempt (months)	27.7 ± 60.4	22.8 ± 39.2
Baseline CO level (ppm)	17.1 ± 6.9	22.3 ± 12.6
FTND score	7.1 ± 0.9	7.3 ± 1.6
Baseline plasma cotinine (ng/mL)	315 ± 73	259 ± 144
Baseline urine cotinine (ng/mL)	1913 ± 1266	1652 ± 1003
Motivation to quit smoking (0–4)	3.4 ± 1.2	3.8 ± .4
PANSS positive score	12.1 ± 3.5	13.6 ± 4.3
PANSS negative score	11.8 ± 3.6	11.8 ± 4.2
PANSS general score	24.4 ± 3.7	25.9 ± 5.8
PANSS total score	48.5 ± 6.0	51.4 ± 12.4
AIMS score	1.0 ± 1.4	1.4 ± 2.2
Webster EPSE score	1.8 ± 1.8	2.4 ± 2.6
Antipsychotic class	12 ATP/4 TYP	10 ATP/6 TYP
CPZ equivalents (mg/day)	719 ± 500	795 ± 576
Baseline BDI score	11.1 ± 12.0	12.6 ± 6.4

W, white; B, black; O, other race; CO, carbon monoxide; SCZ, schizophrenia; SCA, schizoaffective disorder; FTND, Fagerstrom Test for Nicotine Dependence; BDI, Beck Depression Inventory; PANSS, Positive and Negative Symptoms Scale for Schizophrenia; AIMS, Abnormal Involuntary Movements Scale; EPSE, extrapyramidal side effects; CPZ, chlorpromazine; ATP, atypical antipsychotic; TYP, typical antipsychotic.

[a] $p > .05$, all comparisons.

Rates of Smoking Cessation in BUP versus PLA Groups

We determined rates of smoking cessation during the trial using two methods (Figure 1): 1) trial end point (week 10) 7-day point prevalence smoking abstinence and 2) smoking abstinence during the last 4 weeks (weeks 7–10) of the trial. In the BUP group, 8 of 16 subjects (50.0%) and achieved trial end point smoking abstinence ($\chi^2 = 5.24$, $df = 1$, $p < .05$) compared with 2 of 16 subjects in the PLA group (12.5%). For last 4 weeks of trial continuous smoking abstinence, 6 of 16 (37.5%) subjects in the BUP group and 1 of 16 (6.3%) subjects in the PLA group achieved this level of smoking abstinence ($\chi^2 = 4.57$, $df = 1$, $p < .05$); however, 6-month follow-up 7-day point prevalence smoking abstinence rates (Figure 1) were not significantly different between the treatment groups: BUP, 3 of 16 (18.8%); PLA, 1 of 16 (6.3%; $\chi^2 = 1.14$, $df = 1$, $p = .29$).

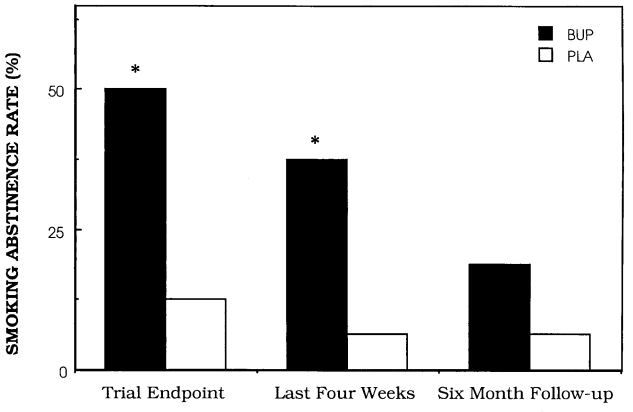

Figure 1. Smoking cessation rates in schizophrenic patients treated with bupropion or placebo. Results are presented for 1) trial end point (week 10) smoking abstinence rates, 2) last four weeks of trial (weeks 7–10) continuous smoking abstinence rates, and 3) 6-month follow-up smoking abstinence rates. *$p <$ .05 versus placebo using χ^2 analyses. BUP, bupropion; PLA, placebo.

Effects of BUP versus PLA on Expired Breath CO Levels

The effects of study medication on the change in expired breath CO levels over time was determined during the 10-week trial (Figure 2). BUP significantly reduced CO levels compared with PLA over the course of the 10-week trial (two-factor repeated measures ANOVA Medication × Time interaction; $F = 4.29$, $df = 1,30$, $p < .05$). Because treatment retention between study groups was not significantly different, we used HLM procedures to account for missing CO level data in the sample. Analysis of the CO data using HLM procedures produced a similar result, with a significant Medication × Time interaction ($Z = 3.09$, SE = .29, $p < .01$).

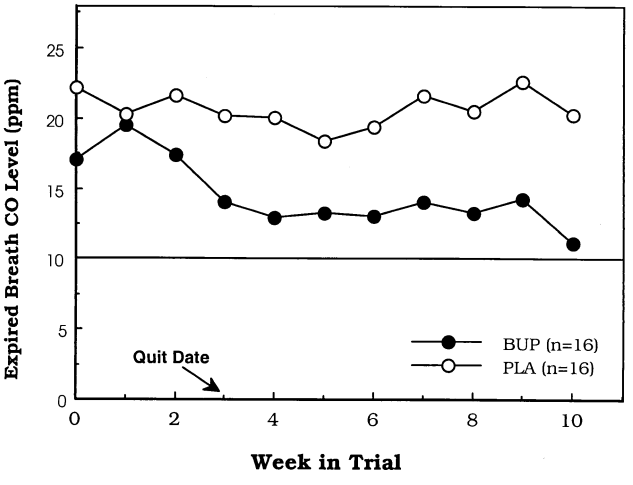

Figure 2. Effects of bupropion versus placebo during the 10-week trial on expired breath carbon monoxide (CO) levels in schizophrenic smokers. Data are expressed as CO levels in parts per million (ppm) for each experimental group. BUP, bupropion; PLA, placebo.

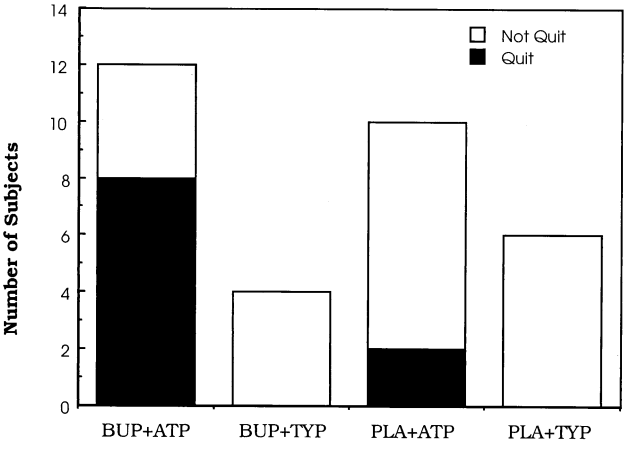

Figure 3. Smoking cessation responses to bupropion and placebo as a function of antipsychotic class treatment. The graph presents smoking cessation responses for all study subjects (Not Quit or Quit) as a function of study medication (BUP or PLA) and antipsychotic treatment class (ATP or TYP). All subjects were maintained on their prestudy antipsychotic medications and dosages during the duration of the 10-week trial. BUP, bupropion; PLA, placebo; ATP, atypical antipsychotic drug; TYP, typical antipsychotic drug.

There was a significant reduction in self-reported cigarettes smoked per day in the BUP versus PLA group (data not shown), as evidenced by a significant Medication × Time interaction [$F = 5.00$, $df = 1,30$, $p < .05$]. Furthermore, in a subset of schizophrenic subjects ($n = 16$) from whom repeated plasma cotinine levels were obtained during the trial at weeks 1, 4, and 10, BUP nonsignificantly reduced plasma cotinine levels compared with PLA (Medication × Time interaction: $F = 1.39$, $df = 1,14$, $p = .26$). We did, however, confirm trial end point smoking abstinence (week 10) in three quitters, all treated with BUP, with undetectable plasma cotinine levels at this time point.

Effects of Atypical (ATP) versus Typical (TYP) Antipsychotic Drugs on Smoking Cessation Responses to Bupropion

We examined trial end point smoking abstinence rates among the four possible groups derived from study medication treatment status (BUP or PLA) and antipsychotic drug treatment class (ATP or TYP; Figure 3). Results of this analysis revealed the following smoking abstinence rates: BUP + ATP, 8/12 (66.7%); BUP + TYP, 0/4 (0.0%); PLA + ATP, 2/10 (20.0%), PLA + TYP, 0/6 (0.0%). For smokers with schizophrenia maintained on ATP agents, treatment with BUP significantly enhanced

Table 2. Effects of Bupropion versus Placebo on Psychotic Symptoms, Depressive Symptoms, Cigarette Craving, and Antipsychotic Drug Side Effects during the 10 Week Trial

	Week 1	Week 3	Week 7	Week 10
Positive symptoms				
Bupropion	11.4 ± 3.7	12.2 ± 3.5	11.8 ± 3.8	11.6 ± 3.9
Placebo	11.8 ± 2.8	11.2 ± 3.2	11.3 ± 2.4	11.8 ± 3.3
Negative symptoms[a]				
Bupropion	12.1 ± 4.3	11.1 ± 4.1	10.7 ± 3.7	10.7 ± 3.0
Placebo	10.8 ± 4.1	11.1 ± 4.1	10.7 ± 3.7	10.8 ± 2.6
General Symptoms				
Bupropion	26.2 ± 4.4	27.0 ± 4.3	23.8 ± 3.6	24.9 ± 3.1
Placebo	25.0 ± 3.4	23.5 ± 4.1	24.9 ± 5.0	23.9 ± 3.4
Beck Depressive Inventory				
Bupropion	8.5 ± 5.1	4.9 ± 3.0	6.6 ± 5.5	5.4 ± 5.1
Placebo	10.7 ± 7.0	11.0 ± 5.5	10.6 ± 7.7	7.5 ± 6.4
Cigarette craving (T-QSU Factor 1, Positive Effects)				
Bupropion	4.83 ± 1.13	4.28 ± 1.16	3.79 ± 1.14	3.63 ± 1.54
Placebo	4.76 ± 1.12	4.22 ± 1.04	3.59 ± 1.77	3.62 ± 1.54
Cigarette craving (T-QSU Factor 2, Negative Effects)				
Bupropion	3.87 ± 1.43	3.82 ± 1.59	2.93 ± 1.42	2.92 ± 1.14
Placebo	4.39 ± 1.35	3.54 ± 1.50	3.09 ± 1.99	3.96 ± 1.15
Webster Extrapyramidal Scale				
Bupropion	1.79 ± 1.53	1.73 ± 1.56	1.40 ± 1.35	1.10 ± 1.45
Placebo	2.00 ± 2.52	1.55 ± 1.75	2.67 ± 4.00	2.33 ± 2.50
Abnormal Involuntary Movements Scale				
Bupropion	1.00 ± 1.44	.91 ± 1.04	.70 ± 1.06	.60 ± 1.08
Placebo	1.42 ± 2.23	.91 ± 1.22	2.00 ± 2.45	1.78 ± 2.28

T-QSU, Tiffany Questionnaire for Smoking Urges.
[a]Significant Medication × Time interaction; $F = 4.32$, $df = 1,30$, $p < .05$.

smoking cessation outcomes compared with PLA ($\chi^2 = 4.79$, $df = 1$, $p < .05$). Furthermore, logistic regression analysis indicated that treatment with BUP in patients maintained on ATP agents predicted a significantly enhanced rate of smoking abstinence compared with the other three treatment groups (Wald statistic = 445.1, $df = 1$, $p < .01$). The individual atypical agents prescribed in the BUP + ATP subgroup and the respective end point smoking cessation rates were clozapine (1/1, 100.0%), risperidone (2/6, 33.3%), and olanzapine (5/5, 100.0%). In the PLA + ATP subgroup, the respective end point smoking cessation rates were clozapine (0/2, .0%), risperidone (0/3, 0%), and olanzapine (2/5, 40.0%).

Effects of BUP versus PLA on Positive and Negative Symptoms, Depressive Symptoms, Cigarette Craving, and Antipsychotic Drug Side Effects

We also examined the effects of BUP versus PLA on a variety of clinical symptoms, tobacco craving and withdrawal and antipsychotic medication side effects (Table 2). There were no effects of BUP versus PLA on positive symptoms of schizophrenia, but there was a reduction (~15%) in negative symptoms by BUP during the trial, and a significant Medication × Time interaction ($F = 4.32$, $df = 1,30$, $p < .05$). There were no significant effects of BUP versus PLA on depressive symptoms ($F = 1.33$, $df = 3,87$, $p = .27$) as measured by the Beck Depression Inventory (Killgore 1999). Tobacco craving as assessed by the Tiffany Questionnaire for Smoking Urges (T-QSU) (Tiffany and Drobes 1991) revealed no effects on BUP versus PLA on positive (Factor 1; Intention to Smoke and Anticipation of Positive Effects) or negative (Factor 2; Anticipation of Relief from Withdrawal and Negative Affect) effects of cigarette smoking. Finally, there were no significant effects of BUP on dyskinetic (AIMS) or extrapyramidal symptoms (Webster Extrapyramidal Scale).

Comparison of Medication Side Effects of BUP Compared with PLA

The major side effects noted in the BUP versus PLA group were dry mouth (62.5% vs. 25.0%), headache (56.3% vs. 37.5%), difficulty falling asleep (43.8% vs. 27.8%), memory problems (50.0% vs. 31.3%), blurred vision (50.0% vs. 25.0%), irregular heartbeat (37.5% vs. 12.5%), nausea/vomiting (43.8% vs. 18.8%), diarrhea (50.0% vs. 25.0%),

anxiety/agitation (50.0% vs. 25.0%), and tremor (31.3% vs. 12.5%); all differences were nonsignificant, with the exception of dry mouth ($\chi^2 = 4.57$, $df = 1$, $p < .05$). There were high rates of certain reported side effects in both BUP and PLA groups (e.g., dry mouth, memory problems, blurred vision), likely due to the prescription of other concurrent medications (e.g., antipsychotic drugs, anticholinergic drugs) in this sample of stabilized schizophrenic patients. Accordingly, in our analysis of adverse events data from this trial, we coded a subject's report of an adverse event as absent if the subject reported the event at week 1 before initiation of study medication, and it did not increase in severity during the course of treatment with the study medication.

Other Outcome Measures

Among subjects in the BUP group, there was an increase of 2.81 ± 5.37 pounds from baseline to trial end point (week 10), and in the PLA group, the respective increase was 3.93 ± 8.37 pounds ($t = -.45$, $df = 29$, $p = .66$). There were no significant changes in weight between trial baseline and end point in BUP- and PLA-treated quitters, and a one-factor ANOVA suggested that there were no significant Medication × Smoking Status interactions ($F = .20$, $df = 3,30$, $p = .90$); however, there were very few placebo quitters ($n = 2$), making these Medication × Smoking Status effects on weight difficult to interpret.

Research staff who ran the weekly group therapy program and did the majority of research assessments on the study subjects rated, for each subject, what study medication (BUP or PLA) they believed subjects had been assigned (JCV, AT). The percentage correct ratings were 19/32 (59.4%) and 14/32 (43.8%) respectively for JCV and AT, which was not significantly different ($\chi^2 = 1.88$, $df = 1$, $p = .17$), and nonsignificant for both raters versus chance (50%; JCV, $\chi^2 = 3.63$, $df = 1$, $p = .08$; AT, $\chi^2 = .31$, $df = 1$, $p = .65$).

Discussion

Our data suggest that bupropion (BUP) is safe for use and efficacious for the treatment of nicotine dependence in patients with schizophrenia who are motivated to quit smoking. Furthermore, BUP significantly reduced expired breath CO levels during the trial compared with placebo; however, the durability of the antismoking effects of BUP in these patients was short lived, as there was substantial relapse to cigarette smoking at the 6-month follow-up assessment. This lack of durability of treatment effects may be related to the beneficial effects of nicotine and cigarette smoking on clinical and cognitive deficits observed in schizophrenic smokers (George et al 2002), high sensitivity to smoking cues, and other common determinants associated with smoking (Tidey et al 1999, 2001) that frequently leads to smoking relapse in nonpsychiatric smokers and to a loss of motivation to remain smoking abstinent after completing the smoking cessation intervention (Addington et al 1998; George et al 2000a; Ziedonis and George 1997). There were no significant baseline demographic or clinical differences between the study groups that could explain differences on group outcomes. Treatment retention was similar between BUP and PLA groups, suggesting that BUP was well tolerated in this population. The tolerability and favorable side-effect profile of BUP in this population was further supported by data from ratings of medication assignments by the research staff, because the observed attribution of medication assignment for each subject by the two raters was not any better than that expected by chance, suggesting that they could not reliably ascertain to which study medication (drug or placebo) subjects were assigned. Our data are similar to recent findings by other groups (Evins et al 2001; Weiner et al 2001) who found that BUP at 150 to 300 mg/day reduces cigarette smoking in nicotine-dependent schizophrenic patients in combination with weekly cognitive behavioral smoking cessation group therapy. Our use of the highest approved dose of BUP for the treatment of nicotine dependence (300 mg/day), in combination with intensive weekly group therapy emphasizing motivational enhancement and relapse-prevention therapies, in individuals with schizophrenia who were highly motivated to quit smoking may have contributed to our high trial end point abstinence rates compared with those in a study (Evins et al 2001) that used a lower daily dose of BUP (150 mg/day; BUP 1/9 [11.1%] quitters; PLA, 0/9 [0%] quitters); however, the reduction in CO levels in our study was not as marked as our previous study, which was conducted under similar conditions with the nicotine patch (George et al 2000a).

Furthermore, similar to our previous study (George et al 2000a) suggesting that atypical compared with typical antipsychotic drugs could augment smoking abstinence rates in combination with the nicotine patch, we found that prescription of BUP and maintenance on prestudy atypical (ATP) antipsychotic drugs predicted the highest quit rates in schizophrenic patients (Figure 3). Subjects prescribed PLA and ATP agents had lower quit rates; no subjects prescribed BUP or PLA and maintained on typical agents quit smoking. Samples sizes for smoking cessation outcomes with individual atypical agents were small but suggested the superiority of olanzapine to risperidone, consistent with our previous findings with nicotine patch (George et al 2000a); definitive conclusions await the results of larger controlled trials. Nonetheless, our data

suggest that prescription of atypical compared with typical agents predicts better smoking cessation outcomes with BUP. The exact mechanism(s) for this effect is unclear but may relate to additive effects of BUP and atypical agents in ameliorating prefrontal cortical dopamine (DA) deficits associated with schizophrenia (George et al 2000a; George et al 2002; Knable and Weinberger 1997).

In addition, BUP did not significantly alter positive symptoms of schizophrenia (based on PANSS) but significantly reduced negative symptoms (Table 2). One previous report found that BUP at 300 mg/day could exacerbate positive symptoms of psychosis in psychotically depressed and schizoaffective patients who were not treated with haloperidol (Goode and Manning 1983); schizophrenic subjects enrolled in this study were on stable doses of antipsychotic drugs for at least 6 months before study entry and had minimal positive symptoms at study baseline (see Table 1). Similar findings for positive and negative symptoms have been presented by other groups (Evins et al 2001; Weiner et al 2001). Our data suggesting that BUP reduces negative symptoms are consistent with the notion that schizophrenic disorders are associated with reduced prefrontal cortical DA (Knable and Weinberger 1997), and thus a putative catecholamine reuptake inhibitor such as BUP (Ascher et al 1995) may have utility as a treatment for the negative symptoms of schizophrenia through augmentation of hypofunctional prefrontal cortical DA systems. Recent preclinical studies indicate, however, that BUP more potently antagonizes the high-affinity nicotinic acetylcholine receptor (nAChR) by binding noncompetitively to the nAChR ion channel site (Slemmer et al 2000). This is the site of action of mecamylamine, a high-affinity nAChR antagonist, which is approved for use in human subjects (Young et al 2001). This property may contribute to the antidepressant properties of BUP (Slemmer et al 2000) and to the lack of an effect of BUP insofar as positive symptom exacerbation.

Certain antipsychotic drugs (e.g., haloperidol, chlorpromazine, clozapine, olanzapine) are metabolized by the hepatic enzyme system (CYP 1A2) that is induced by cigarette smoking (Perry et al 1993; Ziedonis and George 1997), and smoking cessation may lead to increased antipsychotic plasma levels of these drugs, which could increase extrapyramidal symptoms. Consistent with previous smoking cessation studies (Addington et al 1998; George et al 2000a), however, we did not find evidence for a change in extrapyramidal symptoms or signs of tardive dyskinesia during the trial in the BUP versus PLA groups (Table 2) or in schizophrenic quitters versus nonquitters (data not shown). This failure to detect group differences may have been due to 1) the low levels of extrapyramidal and dyskinetic symptoms in our sample, 2) differential effects of smoking abstinence on individual antipsychotic plasma levels, and 3) lack of prolonged abstinence in several subjects who quit smoking at trial end point. Prospective measurement of antipsychotic plasma levels during smoking cessation trials in schizophrenic patients is warranted.

Smoking cessation has been reported to produce increases in body weight, and bupropion may reduce the weight gain during smoking cessation (Hurt et al 1997); however, in our study, there were no significant differences between treatment groups on weight changes during the trial, which may relate to 1) lack of power to detect significant changes in weight due to the small study sample size, and the small number of quitters in the placebo group, or 2) failure of some patients who quit smoking to achieve sustained smoking abstinence during the trial, which would minimize such weight gain. It is also important to note that differential changes in body weight in patients treated with atypical versus typical antipsychotic agents were not expected because these subjects were on stable regimens of these agents before initiating this trial with bupropion. Thus, any such weight changes (e.g., weight gain) produced by treatment with antipsychotic drugs would likely have occurred before the trial and should not have been a confounding variable in our analysis.

The results of our study extend previous pharmacotherapy studies that have investigated smoking cessation or reduction in schizophrenic patients (Addington et al 1998; Evins et al 2001; George et al 1995; George et al 2000a; McEvoy et al 1995, 1999; Weiner et al 2001) and suggest that BUP may be a safe and efficacious pharmacologic treatment for nicotine dependence in schizophrenia. In addition, antismoking responses to BUP appear to be enhanced in schizophrenic patients treated with atypical antipsychotic agents. We speculate that BUP may be particularly effective for treatment of nicotine dependence in schizophrenic patients through antagonism of high-affinity nAChRs (Slemmer et al 2000) on mesolimbic DA ("reward pathway") neurons (George et al 2000b) thereby decreasing the reinforcing effects of nicotine and smoking in these patients, and through augmentation of hypofunctional cortical DA systems associated with this disorder (Knable and Weinberger 1997), as suggested by the significant reduction in negative symptoms in the BUP group.

Limitations of this study include the small sample size and lack of an objective assessment of compliance with study medications. Thus, the results of this study should be considered preliminary, and further studies of BUP for smoking cessation in schizophrenic patients, including BUP in combination with nicotine replacement therapies, are warranted.

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References

Addington J (1998): Group treatment for smoking cessation among persons with schizophrenia. *Psychiatr Serv* 49:925–928.

Addington J, el-Guebaly N, Addington D, Hodgins D (1997): Readiness to stop smoking in schizophrenia. *Can J Psychiatry* 42:49–52.

Addington J, el-Guebaly N, Campbell W, Hodgins DC, Addington D (1998): Smoking cessation treatment for patients with schizophrenia. *Am J Psychiatry* 155:974–976.

Allebeck P (1989): Schizophrenia: A life-shortening disease. *Schizophr Bull* 15:81–89.

Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, et al (1995): Bupropion: A review of its mechanism of antidepressant activity. *J Clin Psychiatry* 56:395–401.

Bland JM, Altman DG (1998): Survival probabilities (the Kaplan-Meier Method). *Br Med J* 317:1572.

Carroll KM (1997): Manual-guided psychosocial treatment: A new virtual requirement for pharmacotherapy trials? *Arch Gen Psychiatry* 54:923–928.

Evins AE, Mays VK, Rigotti NA, Tisdale T, Cather C, Goff DC (2001): A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. *Nicotine Tob Res* 3:397–403.

Evins AE, Tisdale T (1999): Bupropion and smoking cessation in schizophrenia. *Am J Psychiatry* 156:798–799.

George TP, Sernyak MJ, Ziedonis DM, Woods SW (1995): Effects of clozapine on smoking in chronic schizophrenic outpatients. *J Clin Psychiatry* 56:344–346.

George TP, Verrico CD, Picciotto MR, Roth RH (2000b): Nicotinic modulation of mesoprefrontal dopamine systems: Pharmacologic and neuroanatomic characterization. *J Pharmacol Exp Ther* 295:58–66.

George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, et al (2002): Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology* 26:75–85.

George TP, Zeidonis DM, Feingold A., Pepper WT, Satterburg CA, Winkel J, et al (2000a): Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* 157:1835–1842.

Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, et al (1993): Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Arch Gen Psychiatry* 50:739–750.

Goode DJ, Manning AA (1983): Comparison of bupropion alone and with haloperidol on schizo-affective disorder, depressed type. *J Clin Psychiatry* 44:253–255.

Hughes JR, Goldstein MG, Hurt RD, Shiffman S (1999): Recent advances in the pharmacotherapy of smoking. *JAMA* 281:72–76.

Hurt RD, Sachs DPL, Glover ED, Offord KP, Johnston JA, Dale LC, et al (1997): A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 337:1195–1201.

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al (1999): A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 340:685–691.

Killgore WD (1999): Empirically derived factor indices for the Beck Depression Inventory. *Psychol Rep* 84:1005–1013.

Knable MB, Weinberger DR (1997): Dopamine, the prefrontal cortex and schizophrenia. *J Psychopharmacol* 11:123–131.

Lichtermann D, Ekelund E, Pukkala E, Tanskanen A, Lonnqvist J (2001): Incidence of cancer among persons with schizophrenia and their relatives. *Arch Gen Psychiatry* 58:573–578.

McEvoy J, Freudenreich O, Levin E, Rose J (1995b): Haloperidol increases smoking in patients with schizophrenia. *Psychopharmacology* 119:124–126.

McEvoy J, Freudenreich O, McGee M, VanderZwaag C, Levin E, Rose J (1995a): Clozapine decreases smoking in patients with chronic schizophrenia. *Biol Psychiatry* 37:550–552.

McEvoy JP, Freudenreich O, Wilson WH (1999): Smoking and therapeutic response to clozapine in patients with schizophrenia. *Biol Psychiatry* 46:125–129.

Perry PJ, Miller DD, Arndt SV, Smith DA, Holman TL (1993): Haloperidol dosing requirements: The contributions of smoking and nonlinear pharmacokinetics. *J Clin Psychopharmacol* 13:46–51.

Prochaska JO, DiClemente CC (1983): Stages and processes of self-change of smoking: Toward an integrative model of change. *J Consult Clin Psychol* 51:390–395.

Slemmer JE, Martin BR, Damaj MI (2000): Bupropion is a nicotinic antagonist. *J Pharmacol Exp Ther* 295:321–327.

Tidey JW, Higgins ST, Bickel WK, Steingard S (1999): Effects of response requirement and the availability of an alternate reinforcer on cigarette smoking by schizophrenics. *Psychopharmacology* 145:52–60.

Tidey JW, Rohsenow D, Swift R, Monti P, Kaplan G (2001): *Smoking Cue Reactivity among People with Schizophrenia.* Vol 7. Seattle, WA: Society for Research on Nicotine and Tobacco.

Tiffany ST, Drobes DJ (1991): The development and initial validation of a questionnaire on smoking urges. *Addiction* 86:1467–1476.

Weiner E, Ball MP, Summerfelt A, Gold J, Buchanan RW (2001): Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. *Am J Psychiatry* 158:635–637.

Young JM, Shytle RD, Sanberg PR, George TP (2001): Mecamylamine: new therapeutic uses and safety profile. *Clin Ther* 23:533–565.

Ziedonis DM, George TP (1997b): Schizophrenia and nicotine use: Report of a pilot smoking cessation program and review of neurobiological and clinical issues. *Schizophr Bull* 23:247–254.

Ziedonis DM, Trudeau K (1997a): Motivation to quit using substances among individuals with schizophrenia: Implications for a motivation-based treatment model. *Schizophr Bull* 23:229–238.