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A Placebo-Controlled Trial of Bupropion Combined with Nicotine Patch for Smoking Cessation in Schizophrenia*

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Abstract

Background—Schizophrenics smoke at higher rates (58-88%) than the general population (~22%), and have great difficulty with quitting smoking. We determined if the combination of sustained-release (SR) bupropion (BUP) with transdermal nicotine patch (TNP) is well-tolerated, and superior to placebo (PLO) + TNP for smoking cessation in schizophrenia.

Methods—Ten-week, double-blind, placebo-controlled trial of BUP (300 mg/day) in combination with TNP (21 mg/24h) and behavioral smoking cessation therapy for fifty-eight outpatient smokers with schizophrenia. Primary outcome measures were continuous smoking abstinence in the last four weeks of the trial (Days 43-70) and 7-day point prevalence abstinence at six month post-TQD (Week 26).

Results—Smokers assigned to the BUP+TNP group (n=29) were more likely to achieve continuous smoking abstinence (8/29, 27.6%) than the PLO+TNP group (n=29, 1/29, 3.4%) [Fisher's Exact Test Statistic, $p < 0.05$; NNT=5]; at 6-months post-TQD, 4/29 (13.8%) versus 0/29 (0.0%) achieved 7-day point prevalence smoking abstinence ($p = 0.11$; NNT=8). Neither bupropion SR nor smoking abstinence significantly altered the positive or negative symptoms of schizophrenia or depressive symptoms. The combination was well-tolerated in schizophrenic smokers.

Conclusions—Combination therapy with bupropion SR+TNP versus placebo+TNP is well-tolerated and leads to significant improvement in short-term smoking abstinence outcomes in smokers with schizophrenia.

Keywords

Schizophrenia; Nicotine Dependence; Smoking Cessation; Bupropion, sustained-release; Transdermal Nicotine Patch; Clinical Trial

INTRODUCTION

Schizophrenics have a high prevalence of cigarette smoking based on clinical (58-88%) and population-based (~45%) samples compared to the general population (~22%) [1-3]. Furthermore, smoking cessation rates are lower in patients with schizophrenia than in non-psychiatric control smokers [1,3-5]. While schizophrenics constitute only ~1% of the general population, the medical and economic burden of cigarette smoking on mentally ill persons is enormous [1,5,6]. Thus, the development of safe and effective tobacco cessation pharmacotherapies in this population is of considerable public health significance.

Bupropion (BUP) is a weak catecholamine reuptake inhibitor [7], which also is a potent non-competitive ion channel site antagonist at the nicotinic acetylcholine receptor (nAChR) [8]. The sustained-release (SR) formulation of BUP was approved for smoking cessation in the United States in 1997, based on two pivotal studies [9,10]. Transdermal nicotine patch (TNP) has been well-studied as a tobacco pharmacotherapy [11], and delivers a steady dose of nicotine, which may reduce the high basal levels of tobacco withdrawal and craving in cigarette smokers.

Several controlled studies of nicotine replacement therapies (NRTs) or BUP for smoking cessation or reduction have been conducted in schizophrenia [12-18]. Short-term cessation rates in these studies was less than 25% overall. Bupropion appears to have efficacy versus placebo and does not exacerbate psychiatric symptoms.

Interestingly, the combination of TNP+BUP doubles quit rates versus TNP+placebo [19]. Since schizophrenics may smoke to alleviate withdrawal and to remediate dysfunction in nAChRs and their receptor dynamics [20-22], more intensive treatment approaches such as TNP+BUP may have utility in the treatment of tobacco dependence in schizophrenia. Our findings suggest that this combination therapy produces a significant enhancement of short-term smoking abstinence compared to TNP alone and is well-tolerated in these patients.

METHODS

Subjects

Subjects were outpatients with diagnoses of schizophrenia or schizoaffective disorder as determined by SCID-IV [23]. Patients were nicotine-dependent cigarette smokers consuming at least 10 cigarettes per day, with expired breath carbon monoxide (CO) level >10 parts per million. Subjects were clinically stable outpatients with total PANSS scores <70 at study entry. They were required to be on stable doses of their antipsychotic drugs for at least one month prior to randomization, and continued antipsychotic treatment during the trial. Subjects were recruited from the Connecticut Mental Health Center in New Haven, Conn., and had a baseline motivation to quit score of 7 or higher (indicating a willingness to quit in the next 30 days or less) on Contemplation Ladder [24]. Exclusion criteria included the presence of a positive urine drug screen, or evidence of alcohol or illicit drug abuse or dependence in the 3 months prior to screening evaluation, a history of seizure disorders, psychiatric instability including active suicidal or homicidal ideation, unstable medical disorders and inability to give informed consent. Written informed consent was obtained from all participants, and the protocol was approved by the Yale School of Medicine's Human Investigation Committee.

Three-hundred eighteen subjects were assessed for study eligibility, and 259 subjects were excluded, which included not meeting study eligibility criteria (n=146) and lack of interest or refusing to participate in the trial (n=109) (see supplemental flowchart for more details). Four subjects who were deemed to be eligible ultimately refused enrollment. A total of 59 subjects were randomized. Fifty-eight subjects received at least one dose of study medication; therefore, data from the N=58 randomized smokers with schizophrenia who received study medication are reported as the intention-to-treat sample. Twenty-three of 29 subjects in the BUP+TNP group and 19/29 subjects in the PLO+TNP group completed the trial. Data from all 58 randomized subjects was included in the analysis, with subjects who were lost to follow-up counted as smoking.

Study Procedures

This 10-week double-blind, randomized placebo-controlled trial, included 10 weekly sessions of manualized group behavioral therapy lasting approximately 50 minutes conducted by a trained Master's (J.C.V.) or doctoral (A.H.W., K.A.S.) level clinician as described previously [17,18].

Study Medications

Bupropion SR 150 mg tablets (Zyban™; GlaxoSmithKline) and Nicoderm® CQ transdermal nicotine patch (21 mg/24h) were obtained from commercial suppliers. BUP study medications were prepared using blue 00 opaque capsules, while matching placebo capsules contained only a dextrose matrix. BUP study medications were inducted on Day 8 of the trial at 150 mg po qd × 3 days, and then increased to 150 mg po bid and continued until the end of the trial (Day 70) when they were discontinued. TNP was applied at Day 15 concurrent with the target quit date, and continued until Day 70.

Determination of Smoking Abstinence

Smoking abstinence was determined by self-reported cigarette smoking abstinence using the timeline follow-back assessments [25] in combination with expired breath CO level < 10 ppm [26].

Assessment of Psychiatric Symptoms

Psychotic symptoms were assessed using the Positive and Negative Symptoms Scale for Schizophrenia (PANSS; [27]), while depressive symptoms were rated using the Beck Depression Inventory (BDI-II) [28].

Statistical Analyses

Comparison of demographic and clinical characteristics, and adverse events between the two study groups were performed by Chi square and Independent samples t-tests. Kaplan-Meier survival analysis [29] was used to compare treatment retention in the two study medication groups. Smoking abstinence outcomes [7-day point prevalence at end of trial (EOT; Days 63-70), last four weeks of trial (Day 43-70) and six month follow-up assessment post-TQD] were assessed using Fisher's Exact Test. In addition, Number Needed to Treat (NNT) with 95% Confidence Intervals was calculated for smoking abstinence outcomes. Two-way (Group x Time) repeated measures analysis of variance (ANOVA) was used to determine the effects of study medications and smoking abstinence during the course of the trial on positive and negative symptoms of schizophrenia. An "intention-to-treat" approach was used for all analyses; subjects who were lost during the trial or at 6-month follow-up assessment were counted as smoking [30]. Statistical analyses were performed using SPSS v.14.0 software for PC. Statistical tests were two-tailed and differences were considered significant when $p < 0.05$.

RESULTS

1) Demographics

The two groups were comparable on age, racial composition, gender, smoking consumption, duration of smoking, level of nicotine dependence, antipsychotic exposure, and psychiatric symptomatology (all p 's > 0.05).

2) Treatment Retention

Participants in the BUP+TNP group attended 8.5 ± 2.7 visits while participants in the PLO+TNP group attended 7.7 ± 2.8 visits ($t = 1.01$, $df = 56$, $p = 0.32$). A Kaplan-Meier survival analysis was conducted to determine whether attrition was associated with treatment condition. The 1-df chi-square for differences in survival across groups was not significant [Log Rank (Mantel-Cox), $\chi^2 = 1.05$, $df = 1$, $p = 0.16$].

3) Medication Compliance

Compliance was assessed using: 1) weekly pill counts; 2) detection of urinary riboflavin by Wood's lamp fluorescence [31]. While no significant differences were found between groups on pill counts, for urinary riboflavin data, 77% of urines in the BUP+TNP and 86% of urines in the PLO+TNP were positive ($\chi^2 = 4.07$, $df = 1$, $p = 0.04$).

4) Smoking Abstinence (Figure 1)

For continuous abstinence (Days 43-70), 8/29 (27.6%) subjects on BUP+TNP and 1/29 (3.4%) on PLO+TNP were abstinent (OR 10.67, 95% CI 1.24, 91.98; Fisher's Exact Test, $p < 0.03$; NNT 5, 95% CI 2.4, 15.2). For trial endpoint (Week 10) abstinence, 10/29 (34.5%) on BUP+TNP, and 3/29 (10.3%) on PLO+TNP met trial endpoint abstinence (OR 4.56, 95% CI 0.96,

18.86; Fisher's Exact Test, $p=0.056$; NNT 5, 95% CI 2.2, 27.8). For the six month post-TQD assessment, 4/29 (13.8%) subjects on BUP+TNP and 0/29 (0.0%) on PLO+TNP were abstinent (Fisher's Exact Test, $p=0.11$; NNT 8, 95% CI 3.8, 80.5).

5) Psychiatric Symptoms

There were no medication group differences on positive and negative symptoms of schizophrenia or symptoms of depression (all p 's >0.28). Moreover, there were no effects of smoking abstinence on positive and negative symptoms or depression (all p 's >0.29).

6) Study Medication-Related Adverse Events

There were significant ($p<0.05$) group differences on concentration, jitteriness, lightheadedness, muscle stiffness, and frequent nocturnal awakening. Three serious adverse events (SAEs) were reported, which involved psychotic decompensation, two in the placebo group, and the other in the bupropion group. All three SAEs were deemed to be unrelated to study medications.

DISCUSSION

The combination of transdermal nicotine patch (TNP) with sustained-release bupropion (BUP) was well-tolerated, and superior to TNP and placebo for short-term smoking cessation in schizophrenia. Our results are similar to another study of the combination of BUP with high dose NRT (patch + gum) to NRT alone in schizophrenia [32]. In this trial, significant effects of the combination were noted on short-term abstinence during the trial ($p<0.03$; NNT=5), but the difference between groups on long-term abstinence (13.8% vs 0.0%) was not significant ($p=0.11$; NNT=8). Our long-term abstinence rate with the combination treatment was consistent with previous trials in schizophrenia (0-13%) [14-16,18]. Accordingly, our findings suggest that the combination may be a clinically useful treatment for tobacco dependence in smokers with schizophrenia, and appears to be safe and well-tolerated. However, it should be noted that given the low abstinence rates for TNP alone on short-term and long-term outcomes, the efficacy of the behavioral treatment and the nicotine patch employed in this study appears to be minimal, suggesting that BUP was the active intervention. Given the substantial relapse to smoking from the end of trial (Week 10) to Week 26 of the study, a longer duration of treatments for smokers with schizophrenia should be examined in a subsequent randomized controlled trial.

Side effects of the combination were generally modest, and included poor concentration, lightheadedness, muscle stiffness, activation and insomnia. The increase in muscle stiffness may well relate to elevation of antipsychotic drug levels through de-induction of CYP 1A2 by smoking cessation [33] or inhibition of CYP 2D6 by bupropion [34].

Limitations of this study include: 1) small sample size, 2) lack of applicability to the typical outpatient smoker with schizophrenia, since subjects were highly motivated to quit smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Smoking Abstinence Rates in Bupropion SR and Placebo Groups during the 10-week Trial and at the Six Month Assessment. Abbreviations: BUP, Bupropion; PLO, placebo; TNP, transdermal nicotine patch; EOT, End of Trial; CA, Continuous Abstinence; 6MFU, Six Month Follow-up (Week 26)

* Fisher's Exact 2-Sided Test for EOT, $p=0.056$; CA, $p<0.03$; 6MFU, $p=0.11$

Table 1

Demographic and Clinical Characteristics of Schizophrenic Smokers Randomized to Study Medication Groups and Preliminary Abstinence Results in the Trial (n=58)

Baseline Measure	Study Medication		p-value
	Bupropion (n=29)	Placebo (n=29)	
Age (years)	41.2 ± 9.2	39.3 ± 6.9	0.37
Race(W/B/O)	14C/13AA/2H	14C/13AA/2H	1.00
Gender (M/F)	17M/12F	18M/11F	0.79
Education (years)	11.8 ± 2.0	11.3 ± 2.4	0.43
Psychotic Diagnosis	18 schizophrenic/11 schizoaffective	14 schizophrenic/15 schizoaffective	0.29
Cigarettes Per Day	24.3 ± 10.3	22.4 ± 11.9	0.52
Duration of Smoking (years)	22.9 ± 10.1	22.2 ± 8.9	0.80
Carbon Monoxide (CO) Level (ppm)	26.0 ± 13.3	26.8 ± 13.7	0.83
FTND Score	6.8 ± 1.8	6.8 ± 1.7	0.88
Plasma Cotinine Level (ng/ml)	451 ± 268	428 ± 178	0.71
Motivation to Quit	7.1 ± 0.6	6.9 ± 0.8	0.28
PANSS-Positive	14.8 ± 2.8	14.8 ± 2.7	0.79
PANSS-Negative	14.2 ± 2.4	15.3 ± 3.5	0.21
PANSS-General	29.8 ± 3.8	31.2 ± 5.7	0.32
PANSS-Total	58.8 ± 7.5	61.1 ± 10.0	0.39
HDRS-17	5.4 ± 4.1	5.6 ± 3.7	0.85
Antipsychotic Class	23 Atypical/6 Typical	22 Atypical/7 Typical	0.75
Chlorpromazine Equivalents (mg/day)	472 ± 316	583 ± 440	0.28
Antipsychotic Medications	Clozapine (3) Risperidone (9) Olanzapine (9) Quetiapine (1) Haloperidol (1) Fluphenazine (3) Perphenazine (1) Aripiprazole (1) Thiothexene (1)	Clozapine (6) Risperidone (10) Olanzapine (5) Quetiapine (1) Haloperidol (2) Fluphenazine (4) Perphenazine (1)	0.77

Abbreviations: C=Caucasian; AA=African American; H=Hispanic; M=Male; F=Female; FTND=Fagerstrom Test for Nicotine Dependence; PANSS=Positive and Negative Symptom Scale for Schizophrenia; HDRS-17=Hamilton Depression Rating Scale (17-item)