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Predictors of Abstinence and Changes in Psychiatric Symptoms in a Pooled Sample of Smokers with Schizophrenia receiving Combination Pharmacotherapy and Behavioral Therapy for Smoking Cessation

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To the Editors:

Adults with schizophrenia have higher rates of smoking and nicotine dependence and lower rates of smoking cessation than other adults (1-3). Further, the medical and economic burden of smoking on mentally ill persons is enormous (3, 4) so the development of safe and effective pharmacotherapies for these smokers is of considerable public health significance. FDA-approved smoking cessation pharmacotherapies like nicotine replacement therapy (NRT) and sustained-release bupropion (Zyban®, GlaxoSmithKline) appear to be safe and efficacious for smokers with schizophrenia (see (5) for review); however quit rates are modest and it is therefore important to determine characteristics of those who are responsive to interventions. Further, it is important to address the continued clinical concern that smoking cessation will exacerbate psychiatric symptoms for patients with serious mental illnesses (6).

The current analyses examined predictors of smoking abstinence and changes in psychiatric symptoms in a pooled sample (N=135) from three sequential controlled clinical trials for nicotine dependent adult cigarette smokers with schizophrenia or schizoaffective disorder conducted through the Program for Research in Smokers with Mental Illness (PRISM) at the Yale University School of Medicine between 1998 and 2007 (see (7-9) for study details).

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The first study ((7); N=45) was an open-label trial of transdermal nicotine patch (TNP; 21mg/24h) plus one of two behavioral treatments. Participants in the second study ((8); N=32) received sustained-release bupropion (300 mg/day) or placebo and participants in the third study ((9); N=58) received TNP (21 mg/24h) with sustained-release bupropion (300 mg/day) or placebo. All studies had similar treatment protocols (e.g., 10 week duration), similar research staff, included manualized group behavioral counseling, and stratified treatment by antipsychotic medication class. Written informed consent was obtained from all participants and research protocols were approved by the Yale University School of Medicine's Human Investigation Committee.

Participants in all studies completed measures of demographics, daily smoking (cigarettes per day, CPD), nicotine dependence (Fagerström Test for Nicotine Dependence, FTND, (10)), and psychiatric symptoms (Positive and Negative Symptoms Scale for Schizophrenia, PANSS, (11); Beck Depression Inventory-II, BDI-II, (12)). The primary outcome measures were smoking abstinence during the last week of the trials (End of Trial, EOT) and continuous abstinence (CA) over the last four weeks of the trials. Self-reported abstinence was biochemically verified by expired breath carbon monoxide (CO) levels < 10 ppm.

Study differences in demographics and smoking were analyzed using chi-square analyses for categorical data and one-way Analyses of Variance (ANOVA) for continuous data. Logistic regression analysis was used to identify baseline patient factors that predicted abstinence at EOT and CA in the two studies that included bupropion treatment (studies 2 and 3). The dependent variable was smoking status (smoking=0, abstinent=1). Predictor variables included: diagnosis, baseline depressive symptoms, baseline positive and negative symptoms of schizophrenia, nicotine dependence (measured by the Time to First Cigarette (TTFC) item of the FTND), and antipsychotic medication class. Three normal linear regression analyses were conducted to examine the relationship between EOT and CA smoking abstinence and each type of psychiatric symptom (PANSS Positive Symptoms, PANSS Negative Symptoms, BDI), adjusted for baseline levels. Predictor variables were the same as the previous analyses with the addition of smoking status. Patch effects were included as a covariate in all analyses to examine the association between the baseline predictors and abstinence beyond the effects of TNP treatment. CPD was included as a covariate in all analyses due to significant baseline differences among studies. All continuous predictors were standardized to zero mean and unit variance across the entire sample, using the sample summaries from Table 1.

There were no significant study differences in participant age, race, gender, or nicotine dependence (Table 1). Between-study differences included a higher CPD in Study 1 and higher CO, quit attempts, and psychotic symptoms in Study 3. While there were no significant differences in chlorpromazine equivalents, the percent of participants taking atypical antipsychotic medications increased over time ($p<0.01$). Studies did not significantly differ in EOT ($\chi^2=2.97$, $df=2$, $p=0.23$) or CA ($\chi^2=2.54$, $df=2$, $p=0.28$) quit rates (Table 1).

The overall model for prediction of abstinence was significant ($\chi^2=21.35$, $df=9$, $p<0.05$). Treatment with active bupropion medication was the only significant predictor and increased the odds of EOT abstinence more than twofold (Odds Ratio=2.14; 95% Confidence Interval =0.66-3.26; $p=0.002$). The results did not substantively change with CA as the measure of abstinence.

EOT smoking abstinence was not associated with EOT psychiatric symptoms ($ps>0.05$). EOT symptoms of schizophrenia and depression were related significantly to baseline measures of the respective symptoms (positive symptoms $p<0.001$; negative symptoms

$p < 0.001$; depression $p < 0.01$). EOT negative symptoms were related to between-study variability ($p < 0.05$), confounded with TNP use. There was a trend for abstinence to be related to an increase in depression symptoms ($p = 0.06$). Abstinence was associated with a 2.97 unit increase in BDI scores as compared to no change in BDI scores for non-abstinent participants with all other variables in the model being held constant. The results did not substantively change with CA as the measure of abstinence.

Discussion

There were baseline differences among participants in the three sequentially-conducted studies including differential rates of second-generation antipsychotic (SGA) prescription, psychiatric symptoms, and daily smoking. Smokers in the most recent study reported greater number of quit attempts and a non-significantly lower quit rate than smokers in the previous studies. As the data was collected in a similar manner, the differences may be a reflection of sample characteristics changing over time. Reviews of smoking cessation trials for non-psychiatric smokers have reported similar decreases in abstinence rates over time (13, 14) highlighting the need to continue improving interventions for treatment resistant-smokers (see (15) for a review on enhancing tobacco treatment in smokers with psychiatric disorders)

Bupropion was useful for smokers with schizophrenia regardless of specific patient variables consistent with reports that bupropion is safe and effective for smokers with schizophrenia (5) although a recent report (16) found that bupropion treatment did not significantly predict CA for smokers with schizophrenia. Despite the usefulness of bupropion, many smokers with schizophrenia are still unable to quit therefore it is important to determine ways to enhance the efficacy of bupropion. For example, bupropion treatment may need to be extended and/or paired with intensive behavioral treatments (e.g., (17)).

There were no clinically meaningful increases in psychotic symptoms during the study with end-of-trial or continuous smoking abstinence, consistent with other studies of bupropion and NRT for smokers with schizophrenia (5). While our analyses suggested a borderline statistically significant increase in depressive symptoms with abstinence; we do not consider this small increase to be clinically meaningful (~3 points with possible scores ranging from 0 to 63). In general, our results suggest that both bupropion and smoking cessation are safe for smokers with psychiatric disorders. Medical and mental health care providers should encourage patients with psychotic disorder to quit smoking and work with patients to provide safe and effective treatment for smoking cessation including bupropion.

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Table 1
Pre-Treatment Demographic and Clinical Characteristics (Mean \pm SD) of Participants across the Three Trials

	Overall Sample (n=135)	Study 1 (n=45)	Study 2 (n=32)	Study 3 (n=58)	p-value
Gender	78M/57F	25M/20F	18M/14F	35M/23F	0.87
Race	74C/51AA/10O	26C/14AA/5O	20C/11AA/1O	28C/26AA/4O	0.42
Age	41.1 \pm 12.4	40.9 \pm 8.9	43.2 \pm 10.8	40.2 \pm 8.1	0.34
Diagnosis (% Scz)	51.9%	42.2%	62.5%	53.4%	0.20
Antipsychotic Medication Type (% Atypical)	65.2%	46.7%	68.8%	77.6%	<0.01
Chlorpromazine Equivalents (mg/day)	528 \pm 405	544 \pm 409	530 \pm 470	515 \pm 369	0.94
Baseline CPD	25.9 \pm 12.4	30.3 \pm 14.1 ^a	24.1 \pm 10.4 ^{ab}	23.4 \pm 11.1 ^b	<0.05
Baseline CO level (ppm)	24.0 \pm 12.1	24.2 \pm 11.0 ^{ab}	19.7 \pm 10.4 ^a	26.2 \pm 13.4 ^b	<0.05
FTND	6.9 \pm 1.6	6.7 \pm 1.7	7.2 \pm 1.3	6.8 \pm 1.6	0.41
# of Past Quit Attempts	6.5 \pm 13.0	----	3.6 \pm 4.2	8.2 \pm 16.0	=0.05
PANSS Positive	13.9 \pm 4.2	13.6 \pm 5.6	12.9 \pm 4.0	14.8 \pm 2.7	0.11
PANSS Negative	13.9 \pm 5.0	14.2 \pm 7.1 ^{ab}	11.8 \pm 3.9 ^a	14.7 \pm 3.0 ^b	<0.05
PANSS General	28.6 \pm 7.5	28.4 \pm 10.5 ^{ab}	25.2 \pm 4.8 ^a	30.5 \pm 4.9 ^b	<0.01
PANSS Total	53.3 \pm 13.7	56.2 \pm 18.9 ^{ab}	49.9 \pm 9.7 ^a	60.0 \pm 8.9 ^b	<0.01
BDI	11.5 \pm 8.7	12.2 \pm 8.7	11.9 \pm 9.5	10.8 \pm 8.3	0.23
EOT Abstinence (% abstinent)	28.1%	35.6%	31.3%	20.7%	0.23
Continuous Abstinence (% abstinent)	14.8%	9.1%	21.9%	15.5%	0.29

Key: M, male; F, female; C, Caucasian; AA, African-American; O, Other; Scz, Schizophrenia; CPD, cigarettes per day; CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence; PANSS, Positive and Negative Symptoms of Schizophrenia Scale; BDI, Beck Depression Inventory; EOT, End of Trial

Note: Means with different superscripts are significantly different within rows