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Predictors of Early Abstinence in Smokers with Schizophrenia

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Abstract

Background—In patients with schizophrenia, the smoking cessation rate is low and the burden of smoking-related morbidity and mortality is high. Identification of factors associated with abstinence may allow clinicians to optimize treatment prior to a smoking cessation attempt.

Method—To identify factors associated with successful smoking cessation in schizophrenia, baseline data from 114 stable outpatient smokers with schizophrenia who participated in one of two smoking cessation trials were analyzed. The outcome of interest was 4-week, continuous abstinence at the end of a 12-week nicotine dependence treatment intervention. Baseline factors associated with abstinence were identified with univariate methods and entered into a manual, forward selection multivariable regression model to identify independent predictors of abstinence.

Results—Fourteen of 114 participants (12.3%) had biochemically-verified, 4-week, continuous abstinence at week 12. Nine, non-correlated variables with a univariate association with abstinence were included in a multivariable model, controlling for pharmacotherapy, age and gender. Age at initiation of smoking and baseline variability in attentiveness, as measured by Continuous Performance Test (CPT) Hit Reaction Time standard error, were independently associated with abstinence. For every year increase in age at initiation of smoking, the odds ratio for abstinence was 1.36 (95% CI: 1.01–1.83), $p=0.048$. For every millisecond decrease in the variability of the reaction time of CPT, the odds ratio for achieving abstinence was 1.55 (95% CI: 1.07–2.24), $p=0.021$.

Conclusion—Later initiation of smoking was associated with increased and baseline attentional impairment with reduced odds of abstinence. Additional research to further our understanding of the relationship between attentional impairment and cigarette smoking in schizophrenia may lead to improved nicotine dependence treatments for this group.

Keywords

schizophrenia; smoking cessation; nicotine; bupropion; predictors; abstinence; attention; neuropsychological tests

Introduction

Tobacco smoking is the leading preventable cause of death in the United States, causing more than \$167 billion in loss of productivity and annual health-related costs and 440,000 premature deaths in the US annually (1). Seventy-five to eighty-five percent of people with schizophrenia in the United States smoke, compared with 21% of the general population (2,3). Schizophrenia patients are not only more likely to smoke, they are more likely to smoke heavily (4) and extract more nicotine per cigarette than smokers without psychiatric illness (5,6). Schizophrenia is an independent predictor of tobacco smoking after controlling for substance abuse, institutionalization, medication and socioeconomic status (2,3,5,7,8). People with schizophrenia die on average 10 years earlier than people in the general population (9), and age adjusted rates of death due to cardiac and pulmonary disease are significantly elevated in this population (9–11), suggesting that tobacco use is an important cause of the increased mortality observed in schizophrenia. An estimated 1.5–1.7 million smokers in the US are diagnosed with schizophrenia (2,3,12).

Compared with the general population, patients with schizophrenia have low smoking cessation rates, even though they can be both highly motivated and persistent in their attempts to quit smoking (13–16) and, with nicotine dependence treatment such as nicotine replacement therapy (NRT) or bupropion, can tolerate short-term tobacco abstinence without significant exacerbation in clinical or cognitive symptoms (17–20). Identification of patient factors significantly associated with successful smoking cessation in schizophrenia patients may lead to the ability to optimize treatment decisions to increase the probability of a successful cessation in these patients who smoke heavily, have low cessation rates, and have a heavy burden of smoking related illness.

Baseline characteristics such as older age at initiation of smoking, low level of nicotine dependence, high degree of motivation to quit, low alcohol consumption, and longer duration of previous abstinence have been associated with successful smoking cessation in the general population (21–24). Male gender is associated with successful smoking cessation in clinical populations (23). It is not known if these baseline characteristics are predictive of abstinence in schizophrenia patients. Smokers with schizophrenia differ from smokers in the general population in several fundamental ways. Those with schizophrenia have abnormalities in nicotinic acetylcholine receptor expression and function (25–27) and abnormalities in attention, memory, and motor speed (28–31) that may be improved with nicotine (32–36) and worsened by tobacco abstinence (37). There is also evidence that not only do schizophrenia patients smoke with greater prevalence than those in the general population, but also are more likely to be heavy smokers and to smoke each cigarette more intensively, with more puffs per cigarette and shorter inter-puff intervals (2,3,5,38–41). As a result baseline characteristics associated with successful smoking cessation for smokers with schizophrenia may differ from those in the general population. We examined the association between baseline characteristics and ability to attain 4 weeks continuous tobacco abstinence in 114 smokers with schizophrenia in order to (1) test the strength of association of factors previously identified with abstinence in the general population in a sample of smokers with schizophrenia who participated in a smoking cessation program; (2) explore the association of baseline clinical and cognitive symptoms with tobacco abstinence in schizophrenia; and (3) create a multivariable model to identify patient characteristics independently associated with tobacco abstinence. It is hoped that identification of predictors of abstinence in this sample of smokers with schizophrenia and replication in an independent sample will eventually inform the development of appropriate smoking cessation interventions in this population.

Methods

Participants

Data were included from participants in one of the following two trials: (1) a double-blind, placebo-controlled trial of bupropion or placebo added to cognitive behavioral therapy (CBT) in 53 schizophrenia patients (18); or (2) a double-blind, placebo-controlled trial of bupropion or placebo added to nicotine replacement therapy (NRT) and CBT in 51 schizophrenia patients (42). An additional 10 subjects from the later trial who were not medically eligible for bupropion randomization, but who received open NRT and CBT (unpublished), were included in the analysis. Patients were enrolled from 5 urban community mental health centers in Massachusetts from March 1999 to February 2004. The protocols were approved by appropriate institutional review boards. Capacity to consent was determined and documented for all participants by a doctoral level clinician using a formal process.

Eligible subjects were adult outpatients with schizophrenia or schizoaffective disorder depressed type by DSM-IV criteria with stable psychiatric symptoms and a stable dose of antipsychotic medication for at least 30 days, who smoked ≥ 10 cigarettes/day and were willing to set a quit date within 4 weeks of enrollment. Potential subjects who met DSM-IV criteria for current major depressive disorder were not eligible. Patients with a substance use disorder other than nicotine or caffeine within 6 months of screening were not eligible, nor were patients taking bupropion or using NRT at the time of screening. Patients with seizure disorder, history of bulimia, history of mania, or taking clozapine >500 mg/day without a therapeutic dose of an anticonvulsant were not eligible for randomization to bupropion or placebo.

Interventions

All participants attended a 12-session weekly smoking cessation group program described previously (43). CBT groups ranged in size from 3–7 participants. All subjects set a quit date before the 5th group meeting. In the second trial, nicotine patches (Habitrol) and nicotine polacrilex gum were initiated on the quit date. Nicotine patch was dosed at 21 mg/day for 4 weeks, 14 mg/day for 2 weeks and 7 mg/day for 2 weeks and then discontinued. Nicotine polacrilex gum (2mg) was distributed to subjects for prn use up to 9 pieces (18 mg) per day. Bupropion SR was dosed at 150 mgs bid.

Outcome measure

Four-week continuous abstinence was the outcome of interest. This was defined as meeting criteria for 7-day point prevalence abstinence at group meetings 9–12 of a 12-week study intervention. Seven-day point prevalence abstinence was defined as self-report of smoking no cigarettes (not even a puff) for the past 7 days and expired air carbon monoxide (CO) <9 ppm. Continuous abstinence for 4 weeks rather than 7 days was chosen as the endpoint because 4-week continuous abstinence is likely to be a better predictor of long-term abstinence than 7-day point prevalence abstinence. It was not possible to examine predictors of sustained tobacco abstinence at 6 or 12 months because relapse rates following discontinuation of nicotine dependence treatment was very high.

Variable selection

Data were gathered on the following variables that have been identified in the general population as associated with tobacco abstinence: gender; age; age at initiation of smoking; stage of change; duration of previous abstinence; level of nicotine dependence; proportion of smokers in the household; and marital status (22–24,33). Patients with schizophrenia have deficits in attention and memory, functions that are improved with nicotine. Moreover, neuropsychologic deficits have been associated with smoking cessation treatment failure in

patients with schizophrenia (44). Therefore, in our study, data were gathered on neuropsychologic performance on tests of attention (Continuous Performance Test-AX [CPT-AX]), verbal learning and memory (California Verbal Learning Test (CVLT), working memory (Digit Span) and executive function/inhibition (3-Card Stroop). Standard clinical data were also gathered using the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), Hamilton Depression Rating Scale, Barnes Akathisia Scale, Simpson Angus Scale, and Abnormal Involuntary Movement Scale (AIMS). Variables were selected for inclusion in the multivariable analysis that had a univariate association with the dependent variable with $p < 0.25$. Collinearity among these variables was investigated according to the guidelines of Hosmer and Lemeshow (45). Diagnostics were run for variables with correlation coefficients greater than 0.50. Highly correlated variables with $r > 0.50$ that were also associated with the outcome with $p < 0.20$ were included in an automated stepwise logistic regression model. In addition, factors independently associated with the outcome of $p < 0.05$ were included in the multivariable model.

Multivariable Model

A manual, stepwise, forward-selection multivariable logistic regression analysis was performed to identify factors independently associated with 4-week continuous abstinence. Association with the outcome of $p < 0.20$ was required for entry, and association of $p < 0.05$ was required to remain in the model. Smoking and demographic predictors of cessation differ by gender in some samples (46). Possible effect modification by gender was examined by adding an interaction term between gender and each of the predictor variables. The same was done for bupropion treatment. If the interaction term was not significant, the analysis was carried out on the pooled sample. All models were adjusted for medication treatment, age and gender. The results are presented as effect estimates for continuous variables and odds ratios with 95% confidence intervals for dichotomous variables. All statistical analyses were performed in SAS version 8 (SAS Institute, Cary NC).

Results

Fourteen subjects (12%) met criteria for a greater than or equal to 4-week continuous abstinence period at week 12. Seventy-seven percent (11) of the 14 subjects who achieved 4-week abstinence were male and 67% (67) of the 100 subjects who were unable to achieve 4-week abstinence were male. Of these 14 subjects 9 (64%) received either bupropion or NRT, 5 (36%) received both bupropion and NRT, and none (0%) received placebo. Of the 100 subjects who were unable to achieve a 4-week continuous abstinence at week 12, 54 (54%) received either bupropion or NRT, 18 (18%) received both bupropion and NRT, and 28 (28%) received placebo. These differences were not statistically significant. Nor were there significant differences in race. Those who achieved 4-week abstinence had slightly higher mean ratings of motivation (9.29, $SD = 1.64$) compared to those who were unable to achieve 4-week abstinence (8.48, $SD = 1.89$); however, this difference was not statistically significant.

A univariate screen identified 16 variables significantly associated with continuous abstinence. Seven variables were highly correlated: Positive and Negative Symptom Scale (PANSS) total score; PANSS cognitive symptom subscore; PANSS negative symptom subscore; Scale for the Assessment of Negative Symptoms (SANS) total score; SANS affective flattening subscore, SANS alogia subscore; and SANS attention subscore. A stepwise logistic regression was performed with $p < 0.20$ for entry and $p < 0.05$ to select clinical variables independently associated with the outcome for inclusion in the multivariable model. From the seven correlated variables associated with abstinence, only the SANS alogia subscore was independently associated with 4 weeks continuous abstinence and was included in the variable list for the multivariable model.

Ten variables had univariate association with the outcome with a p-value of ≤ 0.25 ; these variables were not correlated and were included in a forward selection logistic regression model. These variables were study medication (NRT, bupropion or both), baseline expired air CO, self report of a history of worsening of psychiatric symptoms with a past smoking cessation attempt, SANS alogia subscore, CPT hit reaction time, CPT hit reaction time variability, Stroop interference reaction time, age at initiation of regular smoking, and 2 variables scored with a 10 point visual analog scale: 'How much do you want to quit?' and 'How confident are you that you will be abstinent one year from now?'.

Interactions were tested and removed if not significant. All models included the potential confounding variables: gender, age and study medication (Table 1). In the multivariable model, controlling for medication, age and gender, CPT-AX Hit Reaction Time standard error was significantly associated with abstinence such that for every millisecond increase in the variability of the reaction time of CPT, the odds ratio for achieving abstinence was 1.55 (95% CI: 1.07–2.24), $p=0.021$; because the effect size is negative, the OR reported is an inverse OR. Additionally, age at initiation of smoking was significantly associated with abstinence such that for every year increase in age at initiation of regular smoking the odds ratio for abstinence was 1.36 (95% CI: 1.00–1.83), $p=0.048$. All analyses were also run with 7-day point prevalence abstinence at end of treatment as the dependent variable, and the results of both univariate and multivariable predictor models were identical.

Missing data

There were 114 subjects with the outcome measure, and 14 with the outcome of interest. CPT data were missing for 31 subjects, 6 of whom had the outcome of interest. Age of smoking initiation was missing for 3 subjects and none with the outcome of interest. To examine whether this could have confounded the results, 4-week continuous abstinence rates for those with CPT data were compared with those for subjects with missing CPT data. Abstinence rates were 9/83 (10.8%) and 5/31 (16.1%) respectively, $p=0.52$ Fisher's Exact, indicating that confounding by missing data is unlikely.

Discussion

This is the first forward-selection analysis to our knowledge of predictors of abstinence in nicotine dependence treatment in patients with schizophrenia. This was an exploratory analysis that included factors associated with ability to quit smoking in the general population as well as measures of psychiatric symptom severity and neuropsychological function. Factors that were associated on univariate analysis with the ability to attain abstinence during nicotine dependence treatment included factors associated with ability to quit smoking in the general population: pharmacotherapy for nicotine dependence, confidence in ability to quit, and age of initiation of smoking, as well as measures of psychiatric symptom severity and cognitive dysfunction: PANSS total score and cognitive subscale score, SANS total score and alogia and attention subscale scores, Stroop interference reaction time, CPT hit reaction time and CPT hit reaction time standard error. Factors that were identified as independently associated with tobacco abstinence in this sample of 114 schizophrenia patients were CPT hit reaction time (a measure of attention) standard error and age at initiation of smoking.

These results indicate that factors associated with the ability to quit smoking in the general population are important for smoking cessation in patients with schizophrenia and that factors associated with schizophrenia such as psychiatric and cognitive symptom severity are also important factors in determining success or failure of a given smoking cessation attempt. Nicotine and nicotinic agonists improve both learning/memory and attention in animals and in humans (47–54), while nicotinic antagonists impair cognitive performance (49,53,55) (see Levin et al. 2005 for review). Some studies have shown that nicotine improves cognitive

performance in non-smokers with attentional impairment (56–59). Other studies have shown that nicotine withdrawal produces cognitive deficits in smokers with and without psychiatric illness (60–64). Nicotine and nicotinic agonists improve and/or normalize memory and attentional deficits specifically in people with schizophrenia (32,33,35,36,65,66). Furthermore, neuropsychologic deficits have been implicated in smoking cessation treatment failure in people with schizophrenia, but not in normal controls (44). Our results support the hypothesis that nicotine may be therapeutic for patients with schizophrenia. Attentional deficits are strongly associated with schizophrenia, and those with greater attentional impairment were less likely to quit smoking.

Bupropion has been shown to be moderately effective for smoking cessation in this population (18,43,67,68). In this sample, baseline attentional impairment and age of smoking initiation are more strongly associated with abstinence than is medication treatment. Studies have shown that bupropion may improve attentional impairment in patients with ADHD (69–72) and schizophrenia (60). We did not find a significant interaction between bupropion treatment and baseline CPT hit reaction time standard error.

While gender may be important in determining success of smoking cessation programs in patients with schizophrenia, illness-specific factors appear to be more important factors.

Limitations of this trial are the small sample size and the small number of patients who achieved continuous abstinence. Additionally, the predictors of abstinence reported here are data-driven and may not be generalizable to the larger population of outpatients with schizophrenia who try to quit smoking. It will be important to conduct a confirmatory analysis in a separate sample. Several predictors strongly associated with abstinence in the general population were not significant predictors in this sample with schizophrenia. However, because patients with major depressive disorder and also those with concurrent substance abuse were excluded, we are not able to comment on the association between these symptoms and abstinence. There was very little variability in Fagerström Test for Nicotine Dependence (FTND) scores in the sample; most subjects had a FTND ≥ 5 , indicating heavy dependence that is common in patients with schizophrenia. It is therefore possible that low level of dependence in patients with schizophrenia, while uncommon, may be a positive predictor of success in a smoking cessation program. Similarly, baseline smoking rate and expired air CO were on average quite high and may not have had the variability necessary to assess an association with abstinence in the model. These factors may be significant for other groups of patients with schizophrenia. Finally, it should be emphasized that the high relapse rates in this population following termination of therapy has limited this study to examining predictors of early 4-week abstinence, not long-term smoking cessation.

Conclusion

The main finding of our analysis is that attentional impairment in patients with schizophrenia is associated with failure in nicotine dependence treatment. This finding points to the need to identify treatments for cognitive impairment in patients with schizophrenia as a part of smoking cessation programs. Nicotine, nicotinic receptor agonists and bupropion improve attention in those with schizophrenia and in other populations (73). Certain cholinergic medications, such as donepezil and galantamine, have been shown to improve cognitive deficiencies in patients with Alzheimer's disease. Some trials of donepezil and galantamine in patients with schizophrenia have reported moderate improvements in memory (74–77). Other trials have not found that donepezil or galantamine improves cognition in patients with schizophrenia compared to placebo (27,78–81); it should be noted, however, that most of these trials included patients with nicotine dependence. It is possible that failure to respond to cholinesterase inhibitors is due to nicotinic receptor desensitization from prolonged heavy tobacco use or due

to maximization of cognitive improvement from the nicotine itself and that a cholinergic medication would not provide an additional benefit over nicotine alone. However, one trial of galantamine was conducted in non-smokers and found galantamine inferior to placebo (81). Neither donepezil nor galantamine has been tested for treatment of cognitive dysfunction during nicotine withdrawal. Other cholinergic medications for potential treatment of cognitive dysfunction and nicotine dependence in patients with schizophrenia, such as anabesine, varenicline or long-term nicotine replacement therapy, have not yet been adequately explored.

Long-term treatment with nicotinic receptor agonists may improve success rates in nicotine dependence treatment programs for patients with schizophrenia. Further studies of cholinergic medications and long-term nicotine replacement therapy are warranted, as are further studies of the role of learning, memory and attention in smoking cessation and relapse prevention in schizophrenia.

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Table 1

Demographics by Continuous Abstinence Status

Demographic	Abstinent (n=14)		Not Abstinent (n=100)	
	Number	%	Number	%
Male	11	79%	67	67%
Married	0	0%	7	7%
Race				
Caucasian	9	64%	72	72%
African-America	2	14%	16	16%
American Indian	1	7%	1	1%
Hispanic	2	14%	5	5%
Study Medication				
Placebo	0	0%	28	28%
NRT or bupropion	9	64%	54	54%
NRT & bupropion	5	36%	18	18%
	Mean	SD	Mean	SD
Education (highest year completed)	11.50	2.93	11.52	2.79
IQ	92.31	17.67	88.09	16.98
Level of nicotine dependence (FTND)	6.14	1.88	5.59	2.15
1=no dependence; 10=severe				
Average baseline CO	30.07	12.13	25.16	13.94
Pack years	35.68	25.73	37.82	28.20
How much do you want to quit?	9.29	1.64	8.48	1.89
(1=very little; 10=very much)				

Table 2

Univariate Predictors of Continuous Abstinence From Smoking

Predictor	Abstinent (n=14)		Not Abstinent (n=100)		Univariate p-value
	Mean	SD	Mean	SD	
Male	11		67		0.380
Married	0		7		0.307
Education (highest year completed)	11.50	2.93	11.52	2.79	0.979
IQ	92.31	17.67	88.09	16.98	0.410
Current alcohol use: (1=no etoh; 5=>5 drinks/day)	1.14	0.36	1.24	0.64	0.598
Level of nicotine dependence (FTND 1=no dependence; 10=severe)	6.14	1.88	5.59	2.15	0.362
Average baseline CO	30.07	12.13	25.16	13.94	0.213
Pack years	35.68	25.73	37.82	28.20	0.789
Age of smoking initiation	19.86	7.08	16.80	5.95	0.084
Proportion of smokers in house	0.70	0.24	0.77	0.24	0.449
Number of previous quit attempts	5.31	8.38	3.89	8.04	0.558
Previous quit lasted 91 days or longer	4		16		0.250
Psychiatric problems with past quit	13		76		0.150
How much do you want to quit? (1=very little; 10=very much)	9.29	1.64	8.48	1.89	0.137
How confident are you that you will be one year from now? (1=very little; 10=very much)	8.43	1.70	6.99	2.63	0.051
How much do friends and family want you to quit? (1=very little; 10=very much)	6.00	3.40	6.97	3.40	0.324
How helpful would people be if you quit? (1=very helpful; 10=not very helpful)	3.36	2.62	4.18	2.80	0.304
Categorical medication variable: 1=bup OR NRT only; 2=bup AND NRT only)	1.36	0.50	0.90	0.67	0.016
PANSS Total	55.93	7.68	63.04	15.47	0.095
PANSS Positive Subscale	9.93	4.89	10.36	4.64	0.747

Predictor	Abstinent (n=14)		Not Abstinent (n=100)		Univariate p-value
	Mean	SD	Mean	SD	
PANSS Negative Subscale	11.86	4.37	14.24	5.85	0.147
PANSS Cognitive Subscale	9.86	2.71	11.76	3.92	0.082
PANSS Excited Subscale	5.50	1.79	6.15	2.44	0.336
PANSS Depressive Subscale	10.36	3.18	11.37	4.03	0.372
SANS Total	31.14	11.51	41.46	20.04	0.063
SANS Affective Subscale	6.36	4.77	10.22	7.93	0.079
SANS Alogia Subscale	3.00	2.63	6.24	4.76	0.014
SANS Avolition Subscale	7.86	4.66	7.28	4.93	0.678
SANS Anhedonia Subscale	10.57	5.53	11.88	5.86	0.434
SANS Attention Subscale	3.79	3.81	6.11	4.02	0.044
HAM-D Total	9.43	5.46	9.08	5.88	0.836
Barnes Total	1.29	2.05	1.30	2.18	0.983
Simpson-Angus Total	2.64	3.39	2.06	2.82	0.484
AIMS Total	2.29	3.93	1.86	2.73	0.606
Stroop Interference Reaction Time	1065.76	167.47	1203.23	165.87	0.032
CPT Hit Reaction Time	378.56	59.39	457.12	99.78	0.003
CPT Hit Reaction Time Standard Error	12.02	5.22	19.16	12.36	0.110
Fingertapping Non-Dominant Total	36.96	10.45	36.45	8.78	0.862
Fingertapping Dominant Total	42.15	9.77	41.07	8.76	0.713
Digit Span Total Forward and	12.69	2.75	13.74	3.81	0.344
CVLT Total Trials 1-5	35.00	8.16	34.06	12.01	0.786