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Relationship Between Tobacco Smoking and Positive and Negative Symptoms in Schizophrenia

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In an attempt to understand the reasons behind the high prevalence of tobacco smoking in patients with schizophrenia, the study examined whether specific symptoms of schizophrenia were associated with smoking. Standardized assessments of nicotine dependence (Fagerstrom Test for Nicotine Dependence) and psychopathology (Positive and Negative Syndrome Scale) were performed on 87 inpatients with schizophrenia. Nearly 76% of patients were nicotine dependent. Significant positive correlations were found between Fagerstrom scores and the total negative symptom score and scores on the negative symptom subscales of blunted affect, social withdrawal, difficulty in abstract thinking, and stereotyped thinking. Fagerstrom scores were also significantly associated with impairment in attention, orientation, thinking, and impulse control. Positive symptoms were not significantly associated with smoking. A combination of negative symptoms, duration of illness, and alcohol use optimally predicted smoking in the sample. Neurobiological mechanisms could possibly underlie some of our findings and require further investigation.
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Although adult tobacco use in the general population has declined in recent years, individuals with schizophrenia have shown no appreciable reduction in smoking (Lasser et al., 2000). The prevalence of smoking among schizophrenic patients is reported to range from 50 to 88%, nearly three times higher than that in the general population, and to exceed smoking rates observed in patients with other psychiatric illnesses (Diwan et al., 1998; Hughes et al., 1986; Lasser et al., 2000). Notably, compared to the general population, schizophrenic patients smoke more heavily, use higher tar- and higher nicotine-containing cigarettes, extract more nicotine from cigarettes, and have substantially lower quit rates (Olincy et al., 1997; O'Farell et al., 1983; Ziedonis et al., 1994). The high rates of smoking in schizophrenia are important from a health perspective as well as in terms of economic impact. Along with the well-recognized cardiovascular and pulmonary risks, smoking has also been linked to uncommon medical consequences such as the syndrome of self-induced water intoxication and psychosis in schizophrenic patients (Masterson & O'Shea, 1984; Shutty, 1996). Epidemiological studies have estimated that patients with schizophrenia in the United States smoke about $20 billion worth of cigarettes annually, a disproportionately high economic burden to patients and society, considering the low prevalence rate of schizophrenia (Lohr & Flynn, 1992).

As tobacco use has become recognized as a significant problem among schizophrenic patients, there has been an increased interest in understanding the relationship between smoking and clinical aspects of schizophrenia. Several models have been proposed to explain the high rates of smoking in this population. These include: "self-medication" of depressive, anxiety, and psychotic symptoms (Glynn & Sussman, 1990), an effort to alleviate the attentional and cognitive processing deficits stemming from the illness (Adler et al., 1998), smoking as a "filler" to combat boredom (Smith, 1996), nonspecific effects of social factors such as lower income and education (Lohr & Flynn, 1992), and attempts to reduce neuroleptic-induced extrapyramidal symptoms (Goff et al., 1992). The determinants of tobacco use in schizophrenic patients remain unclear and probably include both psychosocial and biological factors. The research data have yet to be utilized to develop consistently effective smoking cessation strategies for this population. However, some studies have indicated that a multicomponent program that combines nicotine replacement with motivational enhancement

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and relapse prevention (Ziedonis & George, 1997), as well as use of atypical antipsychotics such as clozapine (McEvoy et al., 1999), may hold promise for treatment of tobacco smoking in schizophrenic patients.

In recent years, an increased understanding of the neurobiological effects of nicotine has led researchers to investigate whether there could be a biological rationale for specific schizophrenic symptoms to be associated with tobacco use. Considerable preclinical evidence indicates that acute administration of nicotine stimulates dopamine release in the mesolimbic system, possibly through activation of nicotinic receptors located on the dopaminergic neurons (Dalack et al., 1998). Moreover, tobacco smoke has been shown to decrease the activity of monoamine oxidase B enzyme in the brain by as much as 40%, thereby reducing the degradation of dopamine and providing an additional mechanism for enhancing the effects of nicotine-mediated dopamine release (Fowler et al., 1996). Negative symptoms have been considered to be related to a hypodopaminergic state and found to respond to dopamine agonists (Sandyk & Kay, 1990); it has been speculated that nicotine may help to reduce negative symptoms by increasing dopamine in the brain (Glassman, 1993). Additional support for this hypothesis comes from findings that schizophrenics preferentially abuse stimulants with dopaminergic properties such as cocaine, compared with other categories of illicit drugs (Patkar et al., 1999). Furthermore, clozapine, an atypical antipsychotic that is effective against negative symptoms, has been reported to decrease smoking in patients with schizophrenia (George et al., 1995). Other authors have suggested that the dopaminergic effect of nicotine may be associated with worsening of positive symptoms or may increase the dosage requirements for antipsychotic medications (Lohr and Flynn, 1992). A separate line of research has also found that altered expression and function of the alpha 7 nicotinic cholinergic receptor, and its interaction with dopamine and glutamate systems in specific regions of the brain, may be responsible for the sensory gating deficit seen in schizophrenic patients (Adler et al., 1998). There is some evidence that the receptor dysfunction may have a genetic basis and that it may be linked to learning and attention difficulties (Griffith et al., 1998). Because a high concentration of nicotine is necessary to activate the altered receptor, it is postulated that heavy smoking may be an attempt to correct the receptor deficit.

Despite promising neurobiologic rationales, the relatively few studies that systematically examined the relationship between particular symptom clusters and tobacco use in schizophrenia have yielded inconclusive findings. For example, in a sample of chronic schizophrenics from Japan, Fukui et al. (1995) found a significant positive correlation between severity of nicotine dependence and negative symptoms. Similarly, Hall et al. (1995) reported that current smokers were likely to report more negative symptoms than former smokers in chronic schizophrenia. However, contradictory results were observed in a study from Spain that found an inverse association between nicotine dependence and negative symptoms (Arias et al., 1997). Other studies have found a positive association of smoking with primarily positive symptoms (Ziedonis et al., 1994), both positive and negative symptoms (Goff et al., 1992), prodromal symptoms (Hamera et al., 1995), and neurotic symptoms (Herran et al., 2000) or found no consistent effect of smoking cessation on any particular symptom patterns (Addington et al., 1998; Dalack et al., 1999). Possible reasons for the conflicting data could be differences in sample characteristics, different definitions and assessments of nicotine dependence and psychopathology, and the heterogeneous nature of schizophrenia.

The goal of the present study was to investigate the relationship between positive and negative symptoms and tobacco smoking in schizophrenia. For this purpose we assessed the rate and severity of nicotine dependence in our sample and then examined the association between positive and negative symptom clusters and severity of smoking.

Methods

Recruitment

Subjects were recruited from a pool of individuals who were admitted to a locked inpatient psychiatric unit of Thomas Jefferson University Hospital, a university-affiliated general hospital in Philadelphia that serves a predominantly inner-city population. Thus, the sample comprised recently hospitalized patients. The unit receives about 300 admissions a year, and about 50% of patients are diagnosed with schizophrenia. Most of the admissions occur after assessments in the Crisis Center, a part of the emergency services of the hospital. On admission, the risks of smoking are reviewed with each patient, and nicotine replacement is offered for those who are willing to stop smoking. Patients who refuse to quit smoking are permitted to smoke in a designated room at specific times.

The research project was approved by the Institutional Review Board of the University. All patients who had an admitting diagnosis of schizophrenia, were not in seclusion, and were considered compe-

tent to consent were invited to participate in the study. Following a description of the study, written informed consent of subjects was obtained. The diagnosis of schizophrenia was made clinically by two independent psychiatrists. Individuals with schizoaffective disorder, bipolar disorder, mental retardation, and organic mental disorders were excluded from the study. If patients abused illicit drugs or alcohol, they were included only if their primary diagnosis was schizophrenia. All study subjects underwent a physical examination, routine blood work, and urine drug screens as a part of the admission procedure. Relevant clinical data such as demographics, drug and alcohol abuse, duration of illness, and medication doses were recorded. For typical neuroleptics the dose was recorded in chlorpromazine equivalents (Wyatt, 1976), whereas doses of atypical neuroleptics were recorded separately for individual medications.

Assessments of Smoking and Psychopathology

These assessments were performed within 72 hours of admission. Individuals were initially assessed to determine whether they fulfilled DSM-IV criteria for nicotine dependence. For those who were nicotine dependent, smoking status was rated on the Fagerstrom Test for Nicotine Dependence (FTND), a widely used and validated six-item questionnaire to assess severity of smoking (Heatherton et al., 1991). This is a modified version of the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom, 1978) and can be completed in 2 to 3 minutes. The scores on FTND range from 0 to 10. Patients who had not smoked in the previous 12 months were considered former smokers, and those who had smoked less than 100 cigarettes in their lifetime were considered nonsmokers. Subjects were also assessed on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) by interviewers who were trained in the use of this instrument and who were blind to the smoking status of the subjects. The PANSS provides a standardized assessment of different symptom clusters in schizophrenia and has been widely used in clinical and research settings. It consists of 30 items that include 7 items that primarily reflect positive symptoms, 7 items that represent negative symptoms, and 16 items that reflect general psychopathology. Each item and each level of severity are operationally defined, which contributes to high interrater reliability (Kay et al., 1988).

Statistical Analyses

Comparisons between smokers and nonsmokers were performed using t tests (two-tailed) for continuous variables and χ^2 tests for categorical variables. Correlations between scores on FTND and PANSS were performed using Pearson product moment correlation. The approach to dealing with potential type I error associated with multiple tests (30 subscales of PANSS) was to perform a test of overall significance using total scores on each of the three main scales of PANSS, as recommended by Cohen and Cohen (1983). Only in the case of a significant result ($p < .05$) or trend ($p < .10$) for the main scale were tests of significance performed for the subscales. Multiple regression analyses (backward elimination method) were used to predict smoking from combinations of independent variables.

Results

Subjects

Of the 110 patients invited to participate, 102 consented to the study. Fourteen subjects had their diagnosis revised to schizoaffective, bipolar, or drug-induced psychotic disorder after the clinical interview and were excluded. One patient reported that he chewed tobacco exclusively and was dropped from the study. Thus a total of 87 schizophrenic subjects were studied. Sixty-six (75.9%) patients were currently nicotine dependent, 4 (4.6%) were former smokers, and 17 (19.5%) were nonsmokers. For the purpose of data analysis, nonsmokers and former smokers were considered as a single group. On average, patients smoked 32 cigarettes daily, had been smoking for 21 years, and had a mean FTND score of 6.2. No patient was receiving nicotine replacement treatments. As expected, a strong positive association was found between a DSM-IV diagnosis of nicotine dependence and FTND scores ($r = .89$, $p < .001$). Table 1 summarizes the clinical and demographic differences between smokers and nonsmokers in the sample.

Compared to nonsmokers and former smokers, schizophrenic patients who currently smoked were significantly more likely to have a longer duration of schizophrenic illness and a greater number of previous hospitalizations despite their slightly younger age. Current smokers were also significantly more likely to have reported more days of alcohol use in the 30 days prior to admission. There were no significant differences between the two groups on demographic variables, typical and atypical antipsychotic dosages, number of urine screens positive for illicit drugs, those receiving anticholinergic medication, or history of head trauma. There were no significant differences between men and women with

TABLE 1
Comparison of Clinical and Outcome Variables between Smokers and Nonsmokers in Schizophrenia

Assessment	Subjects (n = 87) Smokers n = 66 Mean (SD)	Nonsmokers n = 21 Mean (SD)	χ^2/t
Age	39.1 (6.4)	41.5 (7.3)	ns
Male	59.1%	52.3%	ns
African-American	60.6%	66.6%	ns
Unemployed	93.9%	85.7%	ns
Education (highest grade)	10.4 (2.9)	11.37 (3.6)	ns
Schizophrenia			
Duration (yrs)	20.3 (6.9)	13.03 (4.1)	4.58*
Hospitalizations	6.8 (3.4)	3.2 (3.7)	4.13*
Paranoid subtype	57.5%	61.9%	ns
Family history	45.4%	38.1%	ns
Typical neuroleptic[a] (mg)	862.7 (942.2)	740.4 (826.3)	ns
Risperidone[a] (mg)	6.4 (3.2)	5.2 (2.8)	ns
Olanzapine[a] (mg)	18.6 (2.4)	17.4 (3.7)	ns
Anticholinergics	22.7%	28.6%	ns
Alcohol use[b]	7.4 (6.3)	5.1 (4.1)	2.36**
Positive urine drug screens	30.3%	14.3%	ns
Head Trauma	21.2%	14.3%	ns

* $p < .001$, ** $p < .05$, df = 85 for t tests
[a] represents mean doses for patients receiving the particular antipsychotic medication
[b] represent days of alcohol use in the previous 30 days

respect to duration of illness or number of hospitalizations ($t < 1.12$, $df = 85$, $p > .05$ in each case).

Relationship Between Smoking and Positive and Negative Symptoms

The average total positive symptom score for the sample was 27.7 (SD = 6.5), the average total negative symptom score was 23.1 (SD = 8.3), and the average total general psychopathology score was 54.1 (SD = 12.8). Correlations with the total scores and relevant subscales for the PANSS are shown in Table 2.

Significant positive correlations were found between FTND scores and the total negative symptom scores and scores on its subscales of blunted affect, social withdrawal, difficulty in abstract thinking, and stereotyped thinking. Although correlations with the other negative subscales (emotional withdrawal, poor rapport, and lack of spontaneity) did not reach significance, the results were in the expected direction. Because a trend was observed when correlations between total general psychopathology scores and FTND scores were examined ($p = .08$), further analyses were performed using subscale scores on this symptom cluster. A significant positive association was found between FTND scores and scores on subscales of unusual thought content, disorientation, poor attention, and poor impulse control. The other subscales on the general psychopathology cluster and the total positive symptom score did not show any significant correlations with FTND scores.

TABLE 2
Correlation between Smoking (FTND Scores) and Scores on the Positive and Negative Syndrome Scale (PANSS) in Patients with Schizophrenia (n = 87)

PANSS scales	Correlation coefficient r	p
Positive symptom scores[a]		
Total	−.11	ns
Negative symptom scores		
Total	.28	<.01
Blunted affect	.22	<.05
Emotional withdrawal	.20	<.10
Poor rapport	.20	<.10
Passive/apathetic social withdrawal	.22	<.05
Difficulty in abstract thinking	.26	<.01
Lack of spontaneity	.17	<.10
Stereotyped thinking	.25	<.05
General psychopathology scores[b]		
Total	.18	<.10
Unusual thought content	.22	<.05
Disorientation	.26	<.01
Poor attention	.23	<.05
Poor impulse control	.21	<.05

[a] no further subscale correlations performed.
[b] correlations with other subscales not significant.

Multiple Predictors of Smoking Among Schizophrenic Patients

In addition to PANSS scores, we examined the relationship between potentially important clinical variables and FTND scores. To determine the opti-

mal combination of predictors in each group, the variables that correlated significantly with FTND scores were entered into a multiple linear regression analysis (backward elimination method). The surviving variables that contributed to predicting smoking were total negative symptom scores ($t = 2.57$, $p < .01$), duration of schizophrenic illness ($t = 2.28$, $p < .05$), and history of alcohol use ($t = 1.84$, $p = .06$). The multiple correlation coefficient (R) in predicting smoking from a combination of these three variables was .48 ($p < .01$). This suggested that a combination of negative symptoms, duration of schizophrenia, and alcohol use enhanced the prediction of smoking among schizophrenic patients compared with the individual contribution of each of the three variables.

Discussion

A significant finding in the present study is that severity of tobacco use was positively associated with negative symptoms and symptoms reflecting impairment in attention, orientation, and thinking in schizophrenia. These relationships appeared quite specific and emerged despite no significant differences between smokers and nonsmokers on demographic variables, medication doses, type of illness, family history of schizophrenia, and head trauma. With regard to psychopathology, the most impressive association of smoking seemed to be with negative symptoms. The global score, as well as scores on four of the seven subscales on this cluster, showed a significant positive association with severity of smoking. Moreover, among a variety of clinically significant variables, the total negative symptom score was found to be the strongest contributor to predicting smoking behavior. It is worth noting that no significant association was observed between positive symptoms and smoking, which indicates that, in a heterogeneous disorder like schizophrenia, it may be more appropriate to examine the relationship of smoking with specific symptom clusters rather than overall psychopathology. Although the results are consistent with some studies of chronic schizophrenic patients (Fukui et al., 1995; Hall et al., 1995), contrasting findings have also been reported with outpatient samples (Herran et al., 2000) and with different assessment of smoking (Ziedonis et al., 1994). In addition to methodological differences, several variables such as onset of illness, response to medication, and substance abuse can affect clinical symptoms in schizophrenia, and this may in part explain why the data from different studies have remained inconsistent.

The study also found that smoking was positively associated with subscales reflecting impaired cognition on the general psychopathology symptom cluster. Nicotine has been shown to improve cognition difficulties (Wesnes et al., 1983), and recent studies have implicated the nicotinic receptor dysfunction in learning and attention deficits in schizophrenia (Leonard et al., 2000). It is therefore possible that smoking could be an attempt to alleviate cognitive difficulties by schizophrenic patients (Sandyk, 1993). Because our hypothesis primarily addressed the relationship between positive and negative symptoms and smoking, extensive cognitive assessments were not performed in the study. However, in light of our findings, this issue seems worth exploring.

Our findings can be interpreted in several ways. First, patients with more negative symptoms could constitute a clinically and biologically distinct subgroup that may use nicotine as "self-medication" to treat their symptoms. This explanation is consistent with neurobiological effects of nicotine (Dalack et al., 1998). Also, responses indicative of a desire for relief of negative symptoms (*e.g.*, to increase energy, to increase emotions) have been reported as some of the reasons for smoking in schizophrenic patients (Glassman, 1993). Alternatively, nicotine use could have modified the clinical presentation by worsening negative symptoms. In this context, chronic nicotine exposure has been reported to desensitize nicotinic receptors and reduce cholinergic activity in the prefrontal cortex (Vezina et al., 1992); this may adversely affect negative symptoms. Finally, the possibility remains that, because patients with prominent negative symptoms may avoid social interactions or any meaningful activity as a part of their illness, smoking may be a way to simply fill time and avoid boredom (Hughes et al., 1986).

Additional findings from the study also deserve comment. The 76% prevalence of nicotine dependence attests to the widespread addiction to tobacco among schizophrenic patients observed in outpatient clinics and state hospitals (De Leon et al., 1995; Goff et al., 1992). Interestingly, tobacco use was associated with alcohol use but not with the use of illicit drugs in schizophrenic patients, unlike the association between illicit drugs and nicotine found in the general population. Smoking was also positively associated with duration of schizophrenia consistent with the relationship between tobacco use and age of onset and severity of schizophrenia reported in several studies (De Leon et al., 1995; Hughes et al., 1986, Kelly & McCreadie, 1999). Indeed, multiple regression analyses showed that negative symptoms, alcohol use, and duration of illness combined to best predict smoking, which suggests

that several clinical variables may contribute to smoking among the schizophrenic population.

Although smoking has been found to reduce blood levels of neuroleptics (Jaan et al., 1986) our study did not find any significant relationship between severity of smoking and dose of neuroleptics. Because we studied acutely decompensated patients, it is possible that the patients were noncompliant or not sufficiently stabilized on neuroleptics to observe any relationships between dose and smoking. Data in this area are inconsistent, and systematic studies on large stable samples using well-defined criteria to record medication dosages and assess nicotine dependence seem timely, particularly due to reports that smoking may interact with neuroleptics to increase the risk for tardive dyskinesias (Yassa et al., 1987).

The strengths of this study include its prospective design, use of standardized criteria to assess nicotine dependence, and blinded PANSS ratings. Also, the study setting and patient population may permit generalization of findings to acute inpatient units in urban areas in the United States. Moreover, the coherent profile of results seems to indicate a meaningful relationship. Nevertheless, interpretations of our findings are subject to certain methodological limitations. The study was cross-sectional in nature and precluded any analysis of causal relationships. Also, the sample included acutely decompensated patients, and the findings need to be replicated by extending such studies to outpatient treatment settings that traditionally involve a more stable patient population.

Conclusion

Tobacco smoking was found to be highly prevalent in acutely decompensated schizophrenic patients; moreover, it was strongly associated with negative symptoms, whereas positive symptoms showed no significant relationship to smoking. Although the cross-sectional nature of data limits definitive conclusions, clearly increased efforts are needed to systematically address nicotine dependence in this population. Also, as expected in a complex disorder such as schizophrenia, different variables were found to contribute to smoking, and better identification of these variables should be a focus of continuing research. Finally, longitudinal, prospective studies seem necessary to advance our understanding of the relationship and interaction between symptoms of this serious psychiatric illness and nicotine dependence.

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