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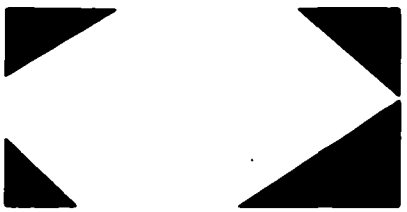
Smoking and Vulnerability for Schizophrenia

by José de Leon

At Issue



The At Issue section of the **Schizophrenia Bulletin** *contains viewpoints and arguments on controversial issues. Articles published in this section may not meet the strict editorial and scientific standards that are applied to major articles in the* **Bulletin**. *In addition, the viewpoints expressed in the following articles do not necessarily represent those of the staff or the Editorial Advisory Board of the* **Bulletin**.—The Editors.

Abstract

In several countries, the prevalence of smoking among schizophrenia patients is extraordinarily high (70% or greater). A State hospital survey demonstrated that after correcting for other factors, inpatients who have schizophrenia are more likely to be smokers than are persons in the normal population or even other chronic psychiatric inpatients. These findings suggest that neuroleptic treatment and the hospital environment cannot completely explain the high prevalence of smoking. The relationship between smoking and schizophrenia may be explained by a combination of three factors. One factor is the great difficulty for schizophrenia patients to quit smoking. Another is late onset: some schizophrenia patients start to smoke after the onset of psychosis. A third is increased early onset: schizophrenia patients may start daily smoking in greater numbers during adolescence (before the onset of their psychosis) than do persons in the normal U.S. population. Daily smoking is usually considered a sign of nicotine addiction and is used by epidemiological surveys to define the prevalence of smokers (most smokers smoke daily and very few smokers do not smoke every day). The increased early onset suggests that familial factors may increase the prevalence of smoking even among patients who have not yet shown psychotic symptoms. It is hypothesized that smoking among family members in families with genetic loading for schizophrenia may be a marker for those at risk of developing schizophrenia.

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Although the relationship between smoking and morbidity and mortality has been established, the relationship between smoking and psychiatric disorders is only now being explored (Glassman 1993). The frequency of smoking is higher for patients with schizophrenia than for persons in the normal population and for all psychiatric patients in general (Goff et al. 1992; Lohr and Flynn 1992). This appears to be true not only in the United States (O'Farrell et al. 1983; Hughes et al. 1986; Goff et al. 1992; Ziedonis et al. 1994), but in some other countries as well: Ireland (Masterson and O'Shea 1984), Italy (Calabresi et al. 1991), and Chile (Carvajal et al. 1989). In all these countries, patients suffering from schizophrenia appear to have an extraordinarily high prevalence of smoking. The prevalence appears to be 70 to 80 percent for schizophrenia outpatients and 80 percent or higher for schizophrenia inpatients. The current prevalence of smoking in the U.S. normal population is lower than 30 percent (Fiore et al. 1993).

The high frequency of smoking in schizophrenia patients has been

Reprint requests should be sent to Dr. J. de Leon, UK Mental Health Research Center, Eastern State Hospital, 627 West Fourth St., Lexington, KY 40508.

thought to be associated with the illness, with neuroleptic treatment, and/or with institutionalization. It has been suggested that smoking may be a form of self-treatment for patients with schizophrenia. Some researchers have hypothesized that nicotine may reduce negative symptoms (Lohr and Flynn 1992; Glassman 1993). Several studies reviewed by Lohr and Flynn (1992) have suggested that smoking may have a protective effect against the development of Parkinson's disease, but it has not been demonstrated that smoking reduces neuroleptic-induced extrapyramidal side effects. It has been shown that smoking can reduce blood levels of neuroleptics (Lohr and Flynn 1992); therefore, smokers need higher dosages to achieve the same effect. Factors associated with institutionalization in general and the use of cigarettes as reinforcement for good behavior have been linked to smoking in schizophrenia inpatients.

A survey in a State hospital confirmed that among schizophrenia inpatients, smoking is very prevalent (85%) and demonstrated that after correcting for other factors, being a schizophrenia patient increases the risk of being a smoker (by a factor of 2 in a logistic regression) even when compared with the rest of the chronic inpatients who display a high prevalence of smoking (67%) (de Leon et al. 1995*b*). These findings suggest that neuroleptic treatment, institutionalization, and the hospital environment cannot completely explain the high prevalence of smoking. Being a schizophrenia patient also increased the risk of being a heavy smoker (by a factor of 2) when compared to the rest of the chronic inpatients (prevalence was 38% vs. 19%) (de Leon et al. 1995*b*).

Unfortunately, the relationship between smoking and schizophrenia has not been adequately explored. The relationship between major depression and smoking, however, has been examined in a landmark study using female twins (Kendler et al. 1993). A causal analysis suggested that the relationship is not a causal one (smoking did not cause major depression, and major depression did not cause smoking). Instead, the relationship appears to be mediated largely or entirely through familial factors—probably genetic—that influence the liability to both smoking and major depression.

The prevalence of smokers among depressive patients ranges from one-half to two-thirds. The twin study carried out by Kendler et al. (1993) suggests that genetic vulnerability may explain why depressive patients smoke approximately two times more frequently than the normal population (Goff et al. 1992; Glassman 1993). The prevalence of smoking appears to be even higher in schizophrenia patients, who may smoke almost three times more frequently than the normal U.S. population. Although major depression has little genetic relationship to schizophrenia, it is not difficult to speculate that the high prevalence of smoking in schizophrenia patients may also be explained by genetic factors. Indeed, twin studies in the normal population have shown that there are moderate genetic influences on the initiation and maintenance of cigarette smoking (Benowitz 1992).

Chronological Relationship Between Smoking and Schizophrenia

Twenty-six chronic schizophrenia patients hospitalized in a research unit at a State hospital were studied for nicotine addiction (de Leon et al. 1995*a*). These patients met the diagnostic criteria of *DSM–III–R* (American Psychiatric Association 1987) for schizophrenia or schizoaffective disorders. Their mean age was 45.8 years (standard deviation [SD] 9.6), and half of the patients were female. We found that 22 of the 26 patients (85%) were currently smokers, 13 (50%) were heavy smokers (≥ 1.5 packs/ day). These results are similar to those obtained in our previous, larger survey (de Leon et al. 1995*b*). Among smokers, the mean number of packs per day was 1.3 (SD 0.4). Of the four patients who were not currently smokers, two had never been daily smokers, and two had been able to quit.

In a pilot study using retrospective information provided by the patients, we found that of those 24 patients who had a history of smoking, 12 (50%) appeared to have started daily smoking before the onset of the schizophrenia psychosis. Of the other 12 patients (50%), regular smoking appeared to start after the onset of the psychosis (de Leon et al. 1995*a*).

If these preliminary results are confirmed in larger samples studied with more sound methodologies to verify age at onset of smoking and of schizophrenia, it would mean that the high prevalence of smoking in schizophrenia may be explained by a combination of three factors. One factor is the great difficulty schizophrenia patients have in quitting smoking (the percentage of patients who quit smoking was 8% in our pilot study and 7%–12% in previous studies by Goff et al. [1992] and Ziedonis et al. [1994]) when compared with the normal U.S. adult, in which more than 45% have been able to quit (Fiore et al. 1993). A second factor is late onset. Some patients may start daily smoking after the onset of schizophrenia,

suggesting that it is important to explore the influence of other patients and of the treatment environment. A third factor is increased early onset of illness. Adolescents and young adults who will develop schizophrenia may be more prone to present daily smoking than the adolescents and young adults in the normal population (46% vs. 20%) (Fiore et al. 1993).

The inability of schizophrenia patients to stop smoking may be explained by a combination of some illness factors, particularly the severity of the nicotine addiction and two types of barriers: (1) the impairments present in schizophrenia patients and (2) the lack of encouragement in some treatment settings.

The second factor, late onset, raises the issue that prophylactic measures should be incorporated into both inpatient and outpatient psychiatric treatment programs to prevent nonsmoking schizophrenia patients from becoming regular smokers. Although our cross-sectional survey in a State hospital did not find that the neuroleptic dosage in chlorpromazine equivalents influenced smoking or heavy smoking in schizophrenia patients, it is probable that neuroleptic treatment or its side effects may influence smoking behavior in some patients, making them more prone to become regular or heavy smokers.

Smoking and Vulnerability to Schizophrenia

The third factor, increased early onset, raises a more interesting issue—the possibility that familial factors may increase the prevalence of smoking even among patients who have not yet shown psychotic symptoms. Learned or genetic influences may explain these familial factors. If it is found that genetic factors make people who are at risk for schizophrenia more prone to become smokers, a new avenue of inquiry into the genetics of schizophrenia may have been opened.

Genetic studies have suggested that the genotype for developing schizophrenia may manifest not only as a schizophrenia psychosis, but also as a personality disorder (Kendler and Diehl 1993), particularly schizotypal personality disorder. More recently, it has been suggested that neuropsychological deficits (Kremen et al. 1994) and structural brain abnormalities (Cannon and Marco 1994) in siblings of schizophrenia patients may be markers of vulnerability for schizophrenia. It is likely that smoking in individuals with high risk for schizophrenia may be a marker of the vulnerability for developing schizophrenia.

This speculation is based on two hypotheses: (1) our analogy with major depression is correct, and genetic vulnerability may contribute to the high prevalence of smoking in schizophrenia, and (2) the finding that smoking is more prevalent in adolescents who are going to develop schizophrenia is accurate. In individuals not at risk for schizophrenia, smoking may be related to other vulnerability factors. If our hypothesis is correct, smoking will not have the specificity of schizotypal personality disorder as a vulnerability factor for schizophrenia, but it would be similar to the cognitive deficits and structural abnormalities that are signs of vulnerability to schizophrenia only in situations of high risk for the illness, such as in families with genetic loading for schizophrenia.

The idea that smoking may be a sign of vulnerability to schizophrenia is a highly speculative hypothesis, but it is one that can be tested by two types of studies: (1) studies with people vulnerable for schizophrenia and (2) studies with first-onset patients. In studies with people vulnerable for schizophrenia, we should find that smoking is more frequent in families with heavy loading for schizophrenia, in people with schizotypal personality disorder, and in schizophrenia patients' relatives with schizotypal personality disorder and those with cognitive or structural brain abnormalities. To the best of my knowledge, these predictions have not yet been tested. It will, however, be easy to test them by assessing smoking in any of the many current studies of groups of people vulnerable to schizophrenia. Recent work from Freedman et al. (1994) suggests that the hypothesis of this article (the vulnerability for schizophrenia may be associated with a vulnerability for smoking) may have some basis. They believe that schizophrenia patients have a deficit in inhibitory gating and that this deficit also can be found in family members. Nicotine might normalize this gating defect by stimulating a specific type of low-affinity nicotine receptor in the hippocampus. If our hypothesis is correct, the relatives of patients with schizophrenia who have these sensory gating deficits but who do not have schizophrenia should smoke more heavily than do persons in the general population who do not have such deficits.

Prospective studies of first-onset schizophrenia provide an opportunity to obtain a more accurate determination of the onset of smoking behavior. Longitudinal studies will also help to determine the effect of neuroleptic treatment on the initiation and maintenance of regular and heavy smoking.

Schizophrenia is a heterogeneous disorder with a variety of manifesta-

tions. Few traits or markers can be found in more than 80 percent of patients. In spite of its high prevalence among schizophrenia patients, smoking has not been explored either as a familial behavior or as a marker of schizophrenia vulnerability. A better understanding of nicotine addiction among patients with schizophrenia may help to identify the pathophysiological and etiological factors involved in schizophrenia that have thus far eluded researchers' inquiries.

If nicotine addiction can be associated with vulnerability to schizophrenia, clues may well be uncovered about the neglected subject of the neuropharmacology of vulnerability to schizophrenia. Nicotine receptors and the effect of nicotine neurons in dopamine release have been discussed in the literature relating nicotine addiction to schizophrenia. The number of hippocampal interneurons with a specific type of nicotine receptor that can be labeled by alpha-bungarotoxin and have a low affinity for nicotine may be smaller in the brains of schizophrenia patients. Freedman et al. (1994) believe that this neuronal deficit may be associated with the schizophrenia gating deficits and may be present in family members with this gating deficit who have not developed schizophrenia. Nicotine releases dopamine in the nucleus accumbens, and this dopamine system may be impaired in schizophrenia patients (Lohr and Flynn 1992; Glassman 1993). Nornicotine—another of the tobacco alkaloids and a metabolite of nicotine—may also be important. In an animal model, Dwoskin et al. (1993) demonstrated that nornicotine induces significantly more dopamine release than nicotine, and unlike nicotine, there is no desensitization to the dopamine release.

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The Author

José de Leon, M.D., is Research Assistant Professor, Medical College of Pennsylvania, Philadelphia, PA, and Medical Director of the Clinical Research Center, Norristown State Hospital, Norristown, PA.

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