

Cigarette smoking and schizophrenia

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It has been recognised for many years that patients with psychiatric illnesses, especially schizophrenia, smoke to excess. However, recently there has been a resurgence of interest in the high prevalence of nicotine addiction in patients with schizophrenia. It has become increasingly clear that heavy cigarette smoking is intimately associated with the schizophrenic illness and that this may have implications for the underlying neurobiology of schizophrenia.

Rates of cigarette smoking

The number of patients with schizophrenia who smoke is very high (see Box 1). One study reported the prevalence to be 88%, nearly three times the rate in the general population and higher than the elevated rates of smoking in patients with other psychiatric illnesses. The increased prevalence persists even after adjustment for marital status, alcohol use and socio-economic status (Hughes *et al*, 1986).

A number of more recent cross-sectional studies from different countries have reported high rates of smoking in patients with schizophrenia (Goff *et al*, 1992; Chong & Choo, 1996). One large study of 360 state hospital in-patients, of whom 237 were diagnosed as having schizophrenia or schizoaffective disorder, found that the overall prevalence of smoking was 85%, and 93% in young male patients with schizophrenia (De Leon *et al*, 1995). Smoking occurs at much higher rates than other types of substance misuse or dependence, which have been shown also to be elevated among patients with schizophrenia.

In our own study (Kelly & McCreadie, 1999) we found that the average age when patients with schizophrenia started smoking was the same as in the general population, namely mid-teens; 90% of patients who smoked had started smoking before their illness began.

Patients with schizophrenia who smoke are also heavier smokers than those in the general population and those with other psychiatric disorders. In our own study, 68% of patients with schizophrenia who smoked were classed as heavy smokers (25 or more cigarettes daily) compared with only 11% of the general population who smoke. In another study (Olinicy *et al*, 1997), patients with schizophrenia who smoked had much higher levels of the nicotine metabolite cotinine in comparison with other smokers, confirming our finding. Excessive smoking tends to be a lifelong habit among patients with schizophrenia. The proportion of those who quit is lower than in the general population; in our study of a population of patients with schizophrenia, only 8% of males were ex-smokers, compared with 31% of males in a local general population.

Box 1 Rates of smoking in schizophrenia

The rate of smoking in people with schizophrenia is at least two to three times that in the general population

Patients who smoke, smoke at heavier rates than in the general population

Most patients start smoking in their teens, before the illness begins

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Why do patients with schizophrenia smoke?

Why do patients with schizophrenia smoke at these excessive rates? There are three possible explanations for the association: something about the illness leads patients to smoke; smoking is another risk factor for schizophrenia; or a third factor leads to both schizophrenia and smoking (see Box 2).

The first possibility has received most attention. It has been suggested that smoking may be a marker of a more severe illness process (De Leon, 1996). Smokers are more often young and male; they have an earlier onset of illness, increased numbers of hospital admissions and receive higher doses of neuroleptic medication (Goff *et al*, 1992; Ziedonis *et al*, 1994). In addition, smokers have more severe symptoms with higher scores on the Brief Psychiatric Rating Scale (Overall & Gorham, 1962) for positive and negative symptoms (Goff *et al*, 1992; Chong & Choo, 1996; Ziedonis *et al*, 1994).

Another suggestion is that patients smoke as a form of self-medication with nicotine, which may help regulate a dysfunctional mesolimbic dopamine system. It may increase dopamine release in the pre-frontal cortex and alleviate positive and negative symptoms (Lavin *et al*, 1996). Worsening of psychotic symptoms on nicotine withdrawal has been reported (Dalack & Meador-Woodruff, 1996). It has also been shown that nicotine administration enhances cognitive performance on a number of tasks. However, in general, patients with schizophrenia who smoke report similar reasons to other smokers ("addicted", "relaxation" and "to calm down"), with only 17% of patients reporting that smoking improved psychotic symptoms.

As we have found that most patients who smoke began to do so before psychotic aspects of the illness appeared, premorbid characteristics are perhaps important. It is noteworthy that in our study patients who smoked were as children more poorly adjusted socially than those who were not smokers.

Box 2 Why do patients with schizophrenia smoke?

Aspects of the illness might lead more patients to smoke

Smoking might be an aetiological factor in schizophrenia

Genetic and/or environmental factors might lead both to nicotine addiction and to schizophrenia

Patients with schizophrenia may smoke heavily as a result of antipsychotic medication, which produces marked dopamine receptor blockade. Possibly, a very high level of smoking is necessary to overcome this blockade and produce the reward effects. It has been shown that, compared with baseline, patients with schizophrenia smoke more after starting haloperidol (McEvoy *et al*, 1995). It has also been shown in a placebo-controlled study that after a single dose of haloperidol, normal subjects smoked significantly more during the following hour, as measured by blood nicotine levels (Dawe *et al*, 1995).

A second explanation for the association between schizophrenia and smoking is that smoking acts as an aetiological risk factor for schizophrenia. It may be that repeated activation by nicotine of the mesolimbic system over a long time precipitates the onset of schizophrenia in vulnerable individuals. We found that the earlier the age of starting smoking, the earlier was the onset of psychotic illness in women (Kelly & McCreadie, 1999). Interestingly, nicotine acts like other drugs of addiction such as cocaine and amphetamine, activating the mesolimbic dopamine system (Pontieri *et al*, 1996); this effect appears to be of critical importance for the reinforcing and reward properties of the drug. Also, nicotine has been shown to increase burst activity in the dopamine neurons of the ventral tegmental area, a form of firing pattern of these cells that is physiologically associated with basic motivational processes underlying learning and cognition (Iversen, 1996).

Third, genetic and/or environmental factors might predispose individuals to develop both schizophrenia and nicotine addiction. Much work in the genetics of both schizophrenia (Maier & Schwab, 1998) and nicotine addiction (Clarke, 1998) has focused on the dopamine receptor system.

Consequences of smoking

Morbidity and mortality

Smoking remains the single greatest preventable cause of death in our society. It appears to engender both general and specific health risks for patients with schizophrenia. There is no doubt that cigarette smoking causes considerable morbidity and mortality, but there are no epidemiological data addressing smoking-related morbidity and mortality in schizophrenia. Previous work has shown that among people with schizophrenia life expectancy is estimated as being 20% less than in the general population. There is an increase in deaths from

natural causes and the most common causes are cardiovascular and respiratory disease, both smoking-related (Mortensen & Juel, 1993). The markedly elevated prevalence of smoking is clearly an important potential factor in explaining the elevated mortality in schizophrenia.

Medication and side-effects

Smoking has been shown to decrease plasma levels of neuroleptics by inducing hepatic microsomal enzymes (Salokangas *et al*, 1997). Therefore, patients who smoke require larger doses of drugs than non-smokers to achieve the same therapeutic effect (Lohr & Flynn, 1992). It has also been reported that smokers have been prescribed neuroleptics at twice the daily dose of non-smokers while exhibiting significantly less neuroleptic-induced parkinsonism. Spontaneous abnormal involuntary movements indistinguishable from tardive dyskinesia have also been reported in a general population sample of older males who smoke (Nilsson *et al*, 1997). It would seem likely, therefore, that there is an association between tardive dyskinesia and smoking in schizophrenia. However, in three previous studies, only one showed that tardive dyskinesia was more prevalent among smokers (Yassa *et al*, 1987); two found no relationship (Menza *et al*, 1991; Chiles *et al*, 1993).

Economic considerations

Cigarettes are not cheap. We have recently carried out some simple arithmetic in relation to smoking and schizophrenia (McCreadie & Kelly, 2000). Our patients smoke on average 26 cigarettes per day. At £2.79 per packet, this works out at £1300 per year. Very few of our patients work. We reckon that probably up to one-third of state benefits is spent on cigarettes. Of the cost of a packet of cigarettes, 87% is tax. Thus, patients, through their smoking habits, are contributing very substantially to the cost of their own care.

Smoking cessation

Smoking cessation rates are poor in heavy smokers and even lower in those with psychiatric illness. Attempts to get patients with schizophrenia to stop smoking have met with only limited success. There is often a perception that it will be unsuccessful and will deprive individuals of one of their few pleasures. This view is inherently discriminatory. In our own study (Kelly & McCreadie, 1999) a third of patients reported that they wanted to quit for health reasons.

Box 3 Management issues

Smoking must be implicated in the increased mortality in schizophrenia

Smokers require higher doses of antipsychotic medication

A substantial proportion of the income of smokers with schizophrenia is spent on cigarettes

Patients with schizophrenia have the right to be offered treatment for their nicotine addiction

Clearly, smokers with schizophrenia have a severe nicotine addiction, and pharmacological and psychological support with smoking cessation needs to be addressed.

There have been few studies that have looked at cessation methods (reviewed by Lavin *et al*, 1996). Smoking bans on in-patient psychiatric units have generated naturalistic reports; usually the most severely addicted patients are extremely resourceful and continue to smoke. Smoking cessation groups, nicotine gum, nicotine patches and clonidine patches have all been tried with both in-patients and out-patients, with poor results. For example, the six-month cessation rate was only 12–13% with group therapy alone (Addington *et al*, 1998) or in combination with nicotine reduction therapy (Ziedonis & George, 1997). Outcome studies are urgently necessary to evaluate the effectiveness of smoking cessation programmes (e.g. in-patient *v.* out-patient programmes, nicotine replacement, behavioural techniques and so on). For the severely addicted, the following combinations may be tried: combined gum and patch therapy; bupropion and nicotine patch; nicotine nasal spray; or nicotine inhaler (details available from the author upon request).

The use of bupropion is interesting. In normal subjects, sustained-release bupropion, an antidepressant, alone or in combination with a nicotine patch, resulted in significantly higher long-term rates of smoking cessation (30.3 and 35.5%, respectively) than use of either the nicotine patch alone (16.4%) or placebo (15.6%) (Jorenby *et al*, 1999). In a recent case report (Evins & Tisdale, 1999), sustained-release bupropion was successfully used with a chronically ill male patient with schizophrenia. Why might an antidepressant such as bupropion be helpful in smoking cessation? It has been suggested that long-term administration of bupropion and nortriptyline, adrenergic antidepressants, produces a significantly increased responsiveness to stimulation of the ventral tegmental dopamine cells. This is not seen with selective serotonin reuptake

inhibitors (SSRIs). This may be why bupropion and nortriptyline but not SSRIs increase smoking abstinence. For a fuller comment on this possibility, see Glassman (1998).

We have recently reported (Scottish Schizophrenia Research Group, 2000) that the prevalence of smoking in first-episode patients is just as high as in chronic patients, but that the number of cigarettes smoked per day is no higher than that in smokers in the general population. Perhaps it is at this early stage that attempts to help patients to stop smoking should be made.

In conclusion, despite the often limited resources of patients with schizophrenia, they commonly view cigarette smoking as a necessity. Most patients with schizophrenia smoke at high rates and few manage to stop. This dramatically elevated prevalence of smoking among individuals with schizophrenia raises the intriguing possibility that nicotine use and schizophrenia have some shared underlying neurobiology.

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Multiple choice questions

- Patients with schizophrenia who smoke:
 - smoke at rates higher than those with other psychiatric conditions
 - in the early stages of the illness smoke more cigarettes daily than general population smokers
 - start smoking at a later age than general population smokers
 - quit at the same rates as general population smokers.
- Nicotine may:
 - regulate a dysfunctional mesolimbic dopamine system
 - improve psychiatric symptoms on withdrawal
 - impair cognitive performance
 - prevent relapse.

3. Smoking cessation in schizophrenia:
- a can be achieved more readily than in other psychiatric conditions
 - b is unwanted by more than two-thirds of patients themselves
 - c should probably be attempted at the early stages of the illness
 - d might include combined nicotine gum and patch therapy.

MCQ answers

1	2	3
a T	a T	a F
b F	b F	b F
c F	c F	c T
d F	d F	d T



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