

Nicotine dependence and symptoms in schizophrenia

Naturalistic study of complex interactions

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Background Smoking may have a beneficial effect on either schizophrenic symptoms or antipsychotic side-effects, but studies are hampered by the lack of control of confounding factors.

Aims To explore the self-medication hypothesis in a large sample of stable out-patients with schizophrenia.

Method Symptoms, assessed with the Positive and Negative Syndrome Scale (PANSS), and number of hospitalisations were compared in 250 out-patients with DSM-IV schizophrenia classified into three categories: highly dependent smokers, mildly dependent smokers and non-smokers. Log-linear analysis was used to control for potential confounding and interacting variables.

Results High PANSS total scores and positive symptoms were less frequent in mildly dependent smokers than in non-smokers or highly dependent smokers. The highly dependent smokers had the worst outcome.

Conclusions The data do not generally support the self-medication hypothesis but rather suggest a complex interaction between nicotine dependence and schizophrenic symptoms.

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Schizophrenia is associated worldwide with a higher rate of smoking than that observed among the general population or those with other severe mental illnesses (McCreadie, 2002; Llerena *et al*, 2003). This association persists after correcting for such confounding factors as antipsychotic medication, institutionalisation or alcohol and drug use (de Leon *et al*, 1995, 2002a; Llerena *et al*, 2003). Smoking might be a marker of a more severe illness or might have a beneficial effect in schizophrenia by improving its symptoms and/or decreasing extrapyramidal side-effects of antipsychotics – ‘the self-medication hypothesis’ (Lohr & Flynn, 1992; Ziedonis *et al*, 1994; Dalack *et al*, 1998). This study explores both the self-medication hypothesis and the hypothesis that severe forms of schizophrenia are associated with high levels of nicotine dependence.

METHOD

Patients

The study was located at two community mental health centres and their rehabilitation unit, covering the catchment area of the city of Granada (southern Spain). All participants received free psychiatric treatment from the national health system. The sample included the first 250 consecutive patients with a diagnosis of DSM-IV (American Psychiatric Association, 1994) schizophrenia who provided written informed consent after a complete description of the study (18 of 278 patients refused to participate; 10 additional excluded patients had a chart diagnosis of schizophrenia but did not meet the DSM-IV diagnosis). The diagnosis was made with the clinician version of a structured diagnostic interview (First *et al*, 1994). All 250 patients were Caucasians. The mean age was 36.1 (s.d.=9.5) years and the mean age at diagnosis was 21.9 (s.d.=6.0) years. There were 195 males (78%); this male

overrepresentation is typical of treatment samples from many countries (Hambrecht *et al*, 1993), including Granada (Salize *et al*, 1999).

Twenty per cent had not completed their primary education; 45% had completed primary, 25% secondary and 10% a university education. Most patients (94%, 236/250) were taking antipsychotics, with a mean dose of chlorpromazine equivalents of 550 mg/day (s.d.=459). The frequency of patients taking depot antipsychotics was 45% (113/250); risperidone, 33% (82/250); olanzapine, 6% (14/250); and clozapine, 4% (10/250). There is no reason to believe that the self-reported smoking of these patients was unreliable, because until recently smoking has been socially acceptable in Spain. Moreover, a reliable self-report of smoking or non-smoking status was provided by a subsample of 99 participants (of the 250 studied) whose cotinine in saliva was measured by radioimmunoassay.

Variables

All ratings were conducted by a research psychiatrist (M.C.A.). Table 1 describes the variables used in statistical analyses. In order to avoid bias in the assessment, the clinical evaluation was conducted first, and information concerning medication and substance use, including tobacco and nicotine dependence, was gathered afterwards.

All variables were dichotomised except nicotine dependence, which was given three categories. On the basis of the Fagerström Test for Nicotine Dependence (FTND), smokers were classified as very highly dependent (FTND >7; smoking a median of 40 cigarettes/day) or not very highly dependent (FTND ≤7; median of 20 cigarettes/day) (Fagerström *et al*, 1990). The three categories will be called highly dependent smokers, mildly dependent smokers and non-smokers. Schizophrenic symptomatology was assessed with the Spanish version of the Positive and Negative Syndrome Scale (PANSS; Peralta & Cuesta, 1994). The PANSS total scores were divided into high (≥45) and low scores. The negative, positive, disorganised, excited, anxious and depressed factors of the PANSS were calculated by adding the scores of the items with a loading higher than 0.50 in the factor (Peralta & Cuesta, 1994), and dividing by the number of those items. Subjects with a score ≥2 for a factor

Table 1 Description of variables in 250 patients with schizophrenia, according to their nicotine dependence status: non-smokers (NS), mildly dependent smokers (MDS) and highly dependent smokers (HDS)

Variable	250 patients	77 NS	92 MDS	81 HDS	χ^2 (d.f.=2)
High total score on the PANSS (≥ 45)	115 (46%)	40 (52%)	32 (35%)	43 (53%)	7.4*
Presence of symptoms ¹					
Negative	93 (37%)	31 (40%)	29 (32%)	33 (41%)	2.0
Positive	76 (30%)	24 (31%)	18 (20%)	34 (42%)	10.3**
Disorganised	34 (14%)	10 (13%)	5 (5%)	19 (24%)	11.9**
Excited	49 (20%)	11 (14%)	12 (13%)	26 (32%)	11.9**
Anxious	117 (47%)	39 (51%)	38 (41%)	40 (49%)	1.8
Depressive	78 (31%)	30 (39%)	23 (25%)	25 (31%)	3.8
Vulnerability to extrapyramidal symptoms	172 (69%)	54 (70%)	57 (62%)	61 (75%)	3.6
Presence of akathisia	35 (14%)	13 (17%)	9 (10%)	13 (16%)	2.2
High antipsychotic dose (≥ 10 mg/kg per day of chlorpromazine equivalents)	50 (20%)	12 (16%)	12 (13%)	26 (32%)	11.1**
Use of typical antipsychotic	177 (71%)	48 (62%)	59 (64%)	70 (86%)	14.2***
Male gender	195 (78%)	49 (64%)	79 (86%)	67 (83%)	13.6**
Caffeine intake	147 (59%)	27 (35%)	54 (59%)	66 (82%)	35.1***
Alcohol intake	52 (21%)	7 (9%)	16 (17%)	29 (36%)	18.1***
High number of hospital admissions	88 (35%)	18 (23%)	26 (28%)	44 (54%)	19.6***

1. Presence of symptoms is defined as factor scores > 2 , except for the excited factor, which is > 1 .
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

were considered to have clinically significant symptoms (except for the excited factor, see Table 1 footnote). In summary, the presence of symptoms with regard to a factor (e.g. positive symptoms) in these clinically stable out-patients suggests that despite treatment they continue to have sufficient positive symptoms to be identified through a standardised assessment.

The Simpson & Angus (1970) Neurological Rating Scale was used to measure parkinsonian side-effects. Akathisia was assessed with the Barnes Akathisia Scale (Barnes, 1989). Some patients might have extrapyramidal side-effects previously corrected by antiparkinsonian drugs, therefore vulnerability to extrapyramidal side-effects was defined as the occurrence of at least one of the three following conditions: current treatment with antiparkinsonian medication; a score of > 0 on the neurological rating scale; or a score of > 0 on the Barnes Akathisia Scale (presence of akathisia).

A high antipsychotic dose was defined as a chlorpromazine equivalent of ≥ 10 mg/kg per day. Current alcohol and caffeine intake was assessed by interview and verified by chart review and collateral information from the family (with whom

most patients live in Spain). Owing to the small number of patients using illegal drugs (7%, 17/250), a drug-use variable was not included in the analysis.

Finally, a high number of hospitalisations after correcting for duration of illness was used for the longitudinal definition of the severity of psychiatric symptoms.

Statistics

The Statistical Package for the Social Sciences (version 11.0) was used for calculations (SPSS, 1997). Initially, the three groups were compared by univariate parametric or non-parametric tests, as appropriate. Then, log-linear analyses of the data were performed (Agresti, 1990; SPSS, 1997); the log-linear analyses had two main purposes: they tested the hypothesis of a significant association of nicotine dependence with schizophrenic symptomatology, as measured by either the PANSS total score (or each one of its factors) or the number of hospitalisations; and they described the strength and direction of such association across different combinations of levels of potential interacting variables such as gender, antipsychotic dose/type and caffeine and alcohol intake. Strength and direction of associations were measured with odds ratios and their 95% confidence intervals from cross-tabulations.

In a first analysis, the association between nicotine dependence and PANSS total score was tested while controlling for gender, antipsychotic dose/type and caffeine and alcohol intake. This was performed by including the seven variables in a saturated log-linear model. Table 2 shows the significant interactions that were obtained. The significances of interaction were tested using partial χ^2 (SPSS, 1997). A significant interaction between two variables was interpreted as evidence that the two variables were associated, even when controlling for the other variables in

Table 2 Log-linear analysis focusing on the association between the Positive and Negative Syndrome Scale (PANSS) total score and nicotine dependence

Variables	Significant interactions	d.f.	χ^2	P
Group A¹				
PANSS total score	Nicotine dependence v. PANSS total score	2	7.4	0.03
Antipsychotic dose	Nicotine dependence v. antipsychotic dose	2	5.9	0.05
Antipsychotic type	Nicotine dependence v. antipsychotic type	2	8.1	0.02
Group B²				
Gender	Nicotine dependence v. gender	2	9.2	0.01
Caffeine intake	Nicotine dependence v. caffeine intake	2	21.9	< 0.01
Alcohol intake	Caffeine intake v. alcohol intake	1	16.5	< 0.01
	Gender v. alcohol intake	1	23.4	< 0.01

1. Group A: variables influencing the association between PANSS total score and nicotine dependence.

2. Group B: variables not influencing the association between PANSS total score and nicotine dependence.

Model including vulnerability to extrapyramidal side-effects: PANSS total score v. nicotine dependence $\chi^2=6.5$, d.f.=1, $P < 0.04$; PANSS total score v. vulnerability to extrapyramidal side-effects $\chi^2=8.7$, d.f.=1, $P < 0.01$; antipsychotic type v. vulnerability to extrapyramidal side-effects $\chi^2=9.7$, d.f.=1, $P < 0.01$.

Table 3 Log-linear analysis focusing on the association between corrected number of hospital admissions and nicotine dependence

Variables	Significant interactions	d.f.	χ^2	P
Group A				
Corrected number of hospital admissions	Nicotine dependence v. corrected number of hospital admissions	2	17.3	<0.01
Group B¹				
Antipsychotic dose	Nicotine dependence v. antipsychotic dose	2	5.9	0.05
Antipsychotic type	Nicotine dependence v. antipsychotic type	2	6.6	0.04
Gender	Nicotine dependence v. gender	2	7.8	0.02
Caffeine intake	Nicotine dependence v. caffeine intake	2	20.6	<0.01
Alcohol intake	Nicotine dependence v. alcohol intake	2	5.8	0.05
	Caffeine intake v. alcohol intake	1	16.3	<9.91
	Gender v. alcohol intake	1	23.4	<0.01
	Antipsychotic dose v. antipsychotic type	1	6.3	0.01

I. Group B: variables not influencing the association between corrected number of hospital admissions and nicotine dependence.

Model including disorganised symptoms: corrected number of hospital admissions v. nicotine dependence $\chi^2=14.7$, d.f.=2, $P<0.01$; corrected number of hospital admissions v. disorganised symptoms $\chi^2=5.7$, d.f.=1, $P<0.02$; disorganised symptoms v. nicotine dependence $\chi^2=7.1$, d.f.=1, $P<0.03$.

the model. Analyses similar to that of the PANSS total score were repeated for number of admissions (Table 3) and for negative, positive, disorganised, excited, anxious and depressed PANSS factors (results not presented).

A second purpose of the statistical analyses was to describe the association between nicotine dependence and schizophrenic symptomatology across different combinations of levels of other variables. One difficulty was that the relatively high number of variables considered in this study produced many possible combinations. Some variables represented a small sample size; for instance, the five dichotomous variables (gender, antipsychotic dose and type and caffeine and alcohol intake) produced $2^5=32$ possible combinations of levels. It is not practical or statistically advisable to perform so many cross-tabulations. Because odds ratios are rather inaccurate with small sample sizes, a systematic methodology that discarded irrelevant variables was used (SPSS, 1997). This methodology was based on the collapsibility conditions (Agresti, 1990); the rationale behind the collapsibility conditions is that variables that do not affect an association can be excluded from the analysis of that association (group B of variables in Tables 2 and 3), even if those variables have an effect on one of the variables involved in the association. The above analyses were repeated by including vulnerability to extrapyramidal side-effects as an additional variable.

RESULTS

Among the 250 patients there were 173 (69%) current smokers and 77 (31%) non-smokers (including 7 (4%) former smokers and 70 (27%) that had never smoked daily). As expected, the rate of smoking was higher in our sample than among the Spanish general population (Pinilla & González, 2001) for both males (75% v. 45%) and females (49% v. 27%).

Table 1 shows the variable distribution across the three groups of nicotine dependence. There were no significant differences in current age, age at diagnosis or educational level. The mean (s.d.) PANSS total score was 45.7 (10.7) for non-smokers, 41.7 (9.2) for mildly dependent smokers and 47.9 (14.1) for highly dependent smokers (Kruskal-Wallis $\chi^2=12.0$, d.f.=2, $P<0.01$); had this comparison been made between smokers and non-smokers, no significant difference would have been found: 44.6 (12.1) v. 45.7 (10.7) (Mann-Whitney $\chi^2=1.3$, d.f.=1, $P=0.25$). The mean (s.d.) number of hospital admissions was 2.8 (4.0) for non-smokers, 3.0 (3.0) for mildly dependent smokers and 6.4 (6.3) for highly dependent smokers (Kruskal-Wallis $\chi^2=27.9$, d.f.=2, $P<0.0001$). The levels (median) of cotinine (ng/ml) in saliva in the 99 participants for whom it was determined were: 551 in highly dependent smokers ($n=31$), 423 in mildly dependent smokers ($n=29$) and 0.6 in non-smokers ($n=29$).

Symptom score and nicotine dependence

Table 2 shows results from the log-linear model that included nicotine dependence and the variables listed in the first column. The interaction between nicotine dependence and PANSS total score was significantly different from zero, indicating that these two variables were significantly associated when controlling for the other variables (gender, antipsychotic dose and type, caffeine and alcohol intake). Nicotine dependence was significantly associated with other variables (gender, antipsychotic dose and type, and caffeine intake). Two groups of variables can be identified from Table 2: group A, comprising PANSS total score and antipsychotic dose and type; and group B, comprising gender and caffeine and alcohol intake. Nicotine dependence was associated significantly with all the variables of group A and some variables of group B. However, the variables of group A were not associated with the variables of group B. In fact, no significant interactions simultaneously involving variables of A and variables of B were found. By virtue of the collapsibility conditions, the strength and direction of the association between PANSS total score and nicotine dependence do not vary across the levels of caffeine or alcohol intake, gender or across combinations of those levels. Thus, this association can be studied by controlling only for antipsychotic dose and type.

The association between PANSS total score and nicotine dependence was therefore studied with cross-tabulations for each of the four combinations of antipsychotic doses and types. The association was most significant among those on a low dose of typical antipsychotics (Fig. 1). In these subjects, mildly dependent smokers included the lowest number of subjects with clinically meaningful symptoms in the total PANSS. Among those on a low dose of a typical antipsychotic, non-smokers have an odds ratio of 2.7 of having a high PANSS total score when compared with mildly dependent smokers (Fig. 1). In other words, the percentage of patients with high total scores was significantly lower in mildly dependent smokers than among non-smokers or highly dependent smokers.

When vulnerability to extrapyramidal side-effects was also included in the log-linear model, the significant interactions were the same as in Table 2; additionally,

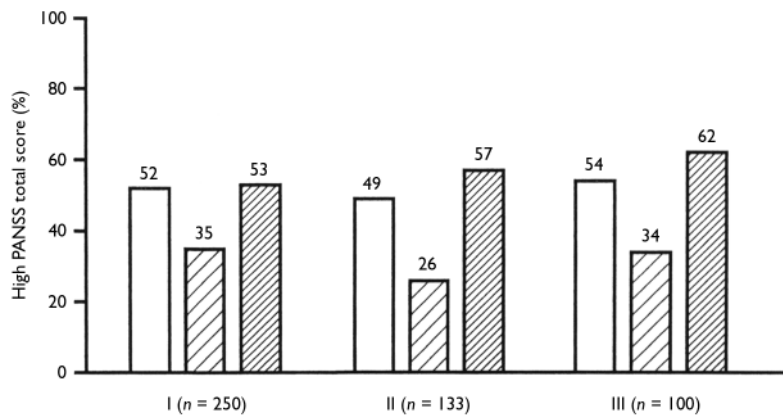


Fig. 1 High Positive and Negative Syndrome Scale (PANSS) total score (≥ 45 , presence of symptoms) among non-smokers (NS, □), mildly dependent smokers (MDS, ▨) and highly dependent smokers (HDS, ▩). Numbers above bars indicate percentages. Group I, all participants. Significance of simultaneous comparisons of the three dependence groups: $\chi^2=7.4$, d.f.=2, $P<0.02$. Odds ratio (95% CI): 2.0 (1.1–8.4) for NS v. MDS; 2.1 (1.9–3.9) for HDS v. MDS. Group II, participants with a low dose of typical antipsychotics: $\chi^2=9.9$, d.f.=2, $P=0.007$. Odds ratio (95% CI) 2.7 (1.1–6.6) for NS v. MDSS; 3.7 (1.6–8.9) for HDS v. MDS. Group III, participants with a low dose of typical antipsychotics and vulnerability to extrapyramidal symptoms: $\chi^2=5.8$, d.f.=2, $P=0.06$.

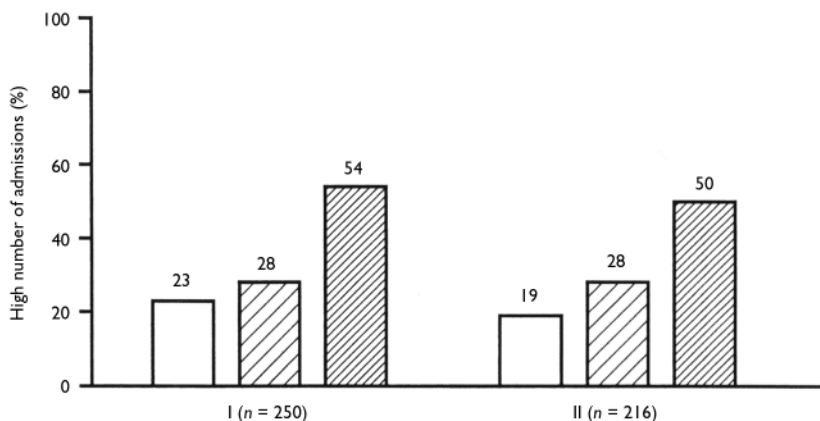


Fig. 2 High number of hospital admissions among non-smokers (NS, □), mildly dependent smokers (MDS, ▨) and highly dependent smokers (HDS, ▩). Numbers above bars indicate percentages. Group I, all participants. Significance of simultaneous comparisons of the three dependence groups: $\chi^2=19.6$, d.f.=2, $P<0.01$. Odds ratio (95% CI) 3.9 (2.0–7.7) for HDS v. NS; 3.0 (1.6–5.7) for HDS v. MDS. Group II, participants without disorganised symptoms: $\chi^2=15.0$, d.f.=2, $P<0.01$. Odds ratio (95% CI) 4.2 (1.9–9.1) for HDS v. NS; 2.6 (1.3–5.2) for HDS v. MDS.

a significant interaction between antipsychotic type and vulnerability to extrapyramidal side-effects, and a significant interaction between PANSS total score and vulnerability to extrapyramidal side-effects were found (see footnote to Table 2). The association between PANSS total score and nicotine dependence was close to significant for those on a low dose of typical antipsychotic medication who showed vulnerability to

extrapyramidal side-effects (Fig. 1); among these, mildly dependent smokers included the lowest number with clinically meaningful symptoms in the PANSS total score.

The analysis of the positive factor was very similar to the analysis of the PANSS total score and supported the self-medication hypothesis for those on a low dose of typical antipsychotics who are mildly dependent smokers.

Negative, depressive or anxious symptoms were not significantly associated with nicotine dependence (Table 1). Thus, the analyses of these symptoms did not support the self-medication hypothesis. Neither the disorganised nor the excited PANSS factor, after analysis, supported the self-medication hypothesis. Moreover, disorganised residual symptoms were associated with heavy smoking (see next section).

Number of admissions and nicotine dependence

Table 1 shows that highly dependent smokers had the highest proportion of hospital admissions compared with mildly dependent smokers (odds ratio=3.0) and non-smokers (odds ratio=3.9) (see also Fig. 2).

When the disorganised symptom variable was considered in the analysis, the association between nicotine dependence and number of admissions was significant only for those without disorganised symptoms (Fig. 2).

DISCUSSION

The self-medication hypothesis of smoking in schizophrenia

There is a discrepancy in the literature, with numerous animal studies suggesting that nicotine should help negative symptoms but scarce clinical data suggesting that this may be true in those with schizophrenia (Hughes, 2000). Two main sub-hypotheses are usually included in the self-medication hypothesis: smoking reduces the side-effects of antipsychotics; and nicotine may improve schizophrenic symptoms, particularly the negative, cognitive and/or depressive symptoms (Taiminen *et al*, 1998).

Two mechanisms have been implicated in the reduction of antipsychotic side-effects: a release of dopamine resulting from the administration of nicotine, a notion supported by both acute administration of nicotine in animal models (Drew *et al*, 2000) and *in vivo* human studies (Salokangas *et al*, 2000); and a decrease in antipsychotic blood levels through enzymatic induction. Individuals with schizophrenia who smoke tend to receive consistently higher doses of antipsychotics than non-smokers (Ziedonis *et al*, 1994; de Leon *et al*, 1995, 2002a). The inductive effect of smoking in antipsychotic metabolism therefore is inadvertently corrected by psychiatrists, because smokers

tend to be treated with higher daily doses of antipsychotics than non-smokers. When compared with others with severe mental illness in three epidemiological studies in psychiatric hospitals, the effect of antipsychotic medication did not explain the association between schizophrenia and smoking (de Leon *et al*, 1995, 2002a; Llerena *et al*, 2003). Some cross-sectional studies have suggested that smoking reduces antipsychotic side-effects and others have not (Dalack *et al*, 1998); yet all of these studies are hampered by the lack of control for confounding factors. Longitudinal studies with small samples suggest that, when compared with atypical antipsychotics, typical antipsychotics are associated with increased smoking in some individuals (McEvoy *et al*, 1995) and with a greater difficulty for quitting smoking (George *et al*, 2000). Anticholinergic medication was not associated significantly with smoking in this or in previous studies (de Leon *et al*, 1995, 2002a,b).

In spite of the hypothesis from animal studies (Drew *et al*, 2000), very limited clinical data support an association between smoking and a reduction in negative symptoms (Dalack *et al*, 1998). Data indicating that nicotine may improve sensory gating abnormalities and smooth pursuit eye movements in schizophrenia or cognitive abnormalities induced by antipsychotics are somewhat stronger. Nicotine may have antidepressant qualities in individuals with depression (Salin-Pascual *et al*, 1996), but this is not well established in those with schizophrenia.

The literature appears to suggest that those with severe forms of schizophrenia may smoke more frequently, and more heavily, than those with less severe forms (Lohr & Flynn, 1992). The possible beneficial effect of nicotine (and smoking) on schizophrenic symptoms and antipsychotic side-effects may be obscured by this association between smoking and severe forms of schizophrenia. In summary, a critical reading of the literature lends very limited support to the self-medication hypothesis, but this effect may be obscured by the association between severe forms of schizophrenia and heavy smoking.

Limitations and strengths of this study

The limitations of the cross-sectional design make it impossible to prove definitively or to deny that smoking has beneficial effects

on schizophrenia. It is not ethical to conduct long-term studies by (ideally) randomising patients to heavy or mild smoking. However, our study – involving a great number of stable out-patients with schizophrenia – like other naturalistic studies, may help to select which individuals are more likely to improve their schizophrenic symptoms and/or extrapyramidal side-effects using nicotine patches or other nicotine agonists. Because experimental designs with randomisation (to different levels of smoking and lack of smoking) are not admissible, other naturalistic studies with large samples, refined assessments and sophisticated statistical techniques to control for confounders are needed to confirm these findings.

Our findings suggest that nicotine dependence and schizophrenic symptomatology might be statistically dependent in out-patients with schizophrenia, but the data imply a complex interaction between these two variables. Our large sample size and the use of a sophisticated statistical technique, log-linear analysis, made it possible to control for potential confounding and interacting variables (Agresti, 1990). In contrast with other statistical techniques such as multiple linear or logistic regression, the log-linear methodology provides a clearer way to identify and deal with multiple interactions among several variables. In addition, as explained in the statistics section, the methodology used allows the systematic identification of variables affecting the association between nicotine dependence and schizophrenic symptoms, and the identification of subgroups where this association exists. Finally, the log-linear methodology does not imply the assumption of linear relationships among the variables analysed. The results of this study in stable out-patients with low levels of symptoms suggest that such an assumption is unsustainable. One apparent drawback of log-linear methodology is the need to transform continuous variables into categorical ones. Nonetheless, the amount of information that a log-linear analysis produces compensates for the possible loss of some information in the transformation (Agresti, 1990).

One may argue that the association between increased frequency of hospitalisation and high nicotine dependence may be partly explained by institutionalisation. However, this is not likely. Our cross-cultural studies suggest that, although the prevalence of current smoking in the general population is influenced by social

pressure, high nicotine dependence among smokers with severe psychiatric illness appears to be similar across countries and remarkably resistant to social pressure (de Leon *et al*, 2002b).

Support for the self-medication hypothesis in mildly dependent smokers

The analysis of the PANSS total score, as well as the analysis of its positive symptom factor, supported the self-medication hypothesis for mildly dependent smokers, especially for those taking low doses of typical antipsychotics. Those with low levels of total symptoms are overrepresented among mildly dependent smokers compared with non-smokers. It may be that mild levels of smoking were associated with a reduction of schizophrenic symptoms, especially among those taking a low dose of typical antipsychotics (and particularly those showing vulnerability to extrapyramidal side-effects). The differential effect of typical and atypical antipsychotics on smoking behaviour is consistent with other studies with different designs suggesting that those with schizophrenia on typical antipsychotics may smoke more (McEvoy *et al*, 1995) and have more difficulties in quitting smoking (George *et al*, 2000).

The possible alleviation of positive symptoms by *chronic* nicotine administration could be explained by a potential correction of the cortical–subcortical dissociation of dopamine activity, which may be associated with schizophrenia (Dalack *et al*, 1998). However, in certain cases of schizophrenia (perhaps the most severe), ‘self-medication’, even with higher amounts of nicotine – as in our highly dependent smokers – would not be effective.

In summary, if there is any beneficial effect of nicotine it may be restricted to mildly dependent smokers, and particularly to those on low dosages of typical antipsychotics who are sensitive to the extrapyramidal side-effects. Such a benefit appears to affect only certain symptoms. Our study does not support the self-medication hypothesis for highly dependent smokers, who have poorer outcomes despite their heavy smoking.

Other symptom differences do not support the self-medication hypothesis

In contrast to the positive symptoms, the analyses of negative, anxious and

depressive symptoms in our sample do not support the self-medication hypothesis. This does not necessarily refute the hypothesis; the assessment may not have been sensitive enough or the effect size too small to be apparent with the statistical power in our sample. Taiminen *et al* (1998) similarly found no differences in negative symptoms according to smoking behaviour. Although these two naturalistic studies do not rule out the possibility of beneficial effects of nicotine on negative symptoms, they certainly suggest that the alleviation of other schizophrenic symptoms is more likely. Ziedonis *et al* (1994) described lower levels of negative symptoms in heavy smokers (and higher levels of positive symptoms), in comparison with light smokers and non-smokers with schizophrenia. Goff *et al* (1992) found higher levels of both negative and positive symptoms in smokers than in non-smokers, whereas Kelly & McCreadie (1999) were not able to demonstrate significant differences between smokers and non-smokers.

The presence of disorganised symptoms was associated with a high dependence on nicotine in our sample and did not support the self-medication hypothesis.

Poor outcome and heavy smoking

Our results suggest that severe forms of schizophrenia with poor outcome, manifested by either residual disorganised symptoms or a greater number of hospital admissions without residual disorganised symptoms, were associated with heavy smoking. Certainly if nicotine has some beneficial influence in schizophrenia, it is not evident in those with a poor outcome. There are no clear-cut theories to explain the association between highly dependent smoking and poor long-term outcome in schizophrenia. The most likely underlying reason is that these individuals may have vulnerability to both high nicotine dependence and schizophrenia with poor outcome.

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CLINICAL IMPLICATIONS

- In out-patients with schizophrenia, smoking behaviour may be related to symptoms, dose and type of medication and vulnerability to extrapyramidal side-effects.
- This study provided very limited support for a beneficial effect of nicotine (a beneficial effect is possible in total and positive symptoms in mildly dependent smokers when compared with non-smokers).
- High nicotine dependence is associated with poor-outcome schizophrenia.

LIMITATIONS

- The limitations of the cross-sectional design make it impossible to prove definitively or to deny a beneficial effect of smoking on schizophrenia.
- Although the interviewer made every effort to avoid bias, including the assessment of nicotine dependence at the end of the interview, she was not always blind regarding the smoking status of the patient.
- Nicotine dependence assessment was based on patient self-reporting.

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REFERENCES

- Agresti, A. (1990) *Categorical Data Analysis*. New York: Wiley.
- American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). Washington, DC: APA.
- Barnes, T. R. E. (1989) A rating scale for drug-induced akathisia. *British Journal of Psychiatry*, **154**, 672–676.
- Dalack, W., Healy, D. & Meador-Woodruff, J. H. (1998) Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *American Journal of Psychiatry*, **155**, 1490–1501.
- de Leon, J., Davdand, M., Canuso, C., *et al* (1995) Schizophrenia and smoking: an epidemiological survey in a state hospital. *American Journal of Psychiatry*, **152**, 453–455.
- de Leon, J., Tracy, J., McCann, E., *et al* (2002a) Schizophrenia and tobacco smoking: a replication study in another US psychiatric hospital. *Schizophrenia Research*, **56**, 55–65.
- de Leon, J., Becoña, E., Gurpegui, M., *et al* (2002b) The association between high nicotine dependence and severe mental illness may be consistent across countries. *Journal of Clinical Psychiatry*, **63**, 812–816.
- Drew, A. E., Derbez, A. E. & Werling, L. L. (2000) Nicotinic receptor-mediated regulation of dopamine transporter activity in rat prefrontal cortex. *Synapse*, **38**, 10–16.
- Fagerström, K. O., Heatherton, T. F. & Kozlowski, L. T. (1990) Nicotine addiction and its assessment. *Ear Nose and Throat Journal*, **69**, 763–765.
- First, M. B., Spitzer, R. L., Gibbon, M., *et al* (1994) *Structured Clinical Interview for DSM-IV Axis I Disorders (Clinician Version)*. Washington, DC: American Psychiatric Association.
- George, T. P., Ziedonis, D. M., Feingold, A., *et al* (2000) Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *American Journal of Psychiatry*, **157**, 1835–1842.
- Goff, D. C., Henderson, D. C. & Amico, E. (1992) Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. *American Journal of Psychiatry*, **149**, 1189–1194.
- Hambrecht, M., Maurer, K. & Hafner, H. (1993) Evidence for a gender bias in epidemiological studies of schizophrenia. *Schizophrenia Research*, **8**, 223–231.
- Hughes, J. F. (2000) Evidence for and against the self-medication hypothesis for smoking. *International Journal of Neuropsychopharmacology*, **3** (suppl. 1), S58–S59.

- Kelly, C. & McCreadie, R. G. (1999)** Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *American Journal of Psychiatry*, **156**, 1751–1757.
- Llerena, A., de la Rubia, A., Peñas-Lledó, E. M., et al (2003)** Schizophrenia and tobacco smoking in a Spanish psychiatric hospital. *Schizophrenia Research*, **60**, 313–317.
- Lohr, J. B. & Flynn, K. (1992)** Smoking and schizophrenia. *Schizophrenia Research*, **8**, 93–102.
- McCreadie, R. G., on behalf of the Scottish Comorbidity Study Group (2002)** Use of drugs, alcohol and tobacco by people with schizophrenia: case–control study. *British Journal of Psychiatry*, **181**, 321–325.
- McEvoy, J. P., Freudenreich, O., Levin, E. D., et al (1995)** Haloperidol increases smoking in patients with schizophrenia. *Psychopharmacology*, **119**, 124–126.
- Peralta, V. & Cuesta, M. (1994)** Psychometric properties of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia. *Psychiatry Research*, **53**, 31–40.
- Pinilla, J. & González, B. (2001)** Profile of the population of Spain with respect to the smoking habit, period 1993–1997. *European Journal of Public Health*, **11**, 346–351.
- Salin-Pascual, R. J., Rosas, M., Jimenez-Genchi, A., et al (1996)** Antidepressant effect of transdermal nicotine patches in nonsmoking patients with major depression. *Journal of Clinical Psychiatry*, **57**, 387–389.
- Salize, H. J., Küstner, B. M., Torres-Gonzalez, F., et al (1999)** Needs for care and effectiveness of mental health care provision for schizophrenic patients in two European regions: a comparison between Granada (Spain) and Mannheim (Germany). *Acta Psychiatrica Scandinavica*, **100**, 328–334.
- Salokangas, R. K., Vilkkumäki, H., Ilonen, T., et al (2000)** High levels of dopamine activity in the basal ganglia of smokers. *American Journal of Psychiatry*, **157**, 632–634.
- Simpson, G. M. & Angus, J. W. S. (1970)** A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*, **212** (suppl.), 11–19.
- SPSS (1997)** *SPSS Advanced Statistics 7.5*. Chicago, IL: SPSS Inc.
- Taiminen, T. J., Salokangas, R. K., Saarijärvi, S., et al (1998)** Smoking and cognitive deficits in schizophrenia: a pilot study. *Addictive Behaviors*, **23**, 263–266.
- Ziedonis, D. M., Kosten, T. R., Glazer, W. M., et al (1994)** Nicotine dependence and schizophrenia. *Hospital and Community Psychiatry*, **45**, 204–206.