Tobacco Smoking and Bipolar Disorder

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Background: We sought to determine whether tobacco smoking is associated with bipolar disorder.

Method: This case-control study carried out in Alava, in the north of Spain, included patients with a DSM-III-R diagnosis of bipolar disorder type I (N = 51) and a representative sample of the normal population (N = 517). Smoking history of bipolar patients was assessed with the Fagerstrom Test for Nicotine Dependence and was verified by family members of the patients.

Results: The frequencies of ever smoking and current daily smoking were, respectively, 63% (32/51) and 51% (26/51) for the bipolar patients and 45% (235/517) and 33% (169/517) for the control group (respective odds ratios [ORs] and 95% confidence intervals [CIs] were OR = 2.0, 95% CI = 1.1 to 3.8 and OR = 2.1, 95% CI = 1.2 to 4.0). The differences were significant (p = .03 and p = .042, respectively) for bipolar versus control males. Bipolar disorder (in both genders) was also significantly associated (OR = 4.4, 95% CI = 1.7 to 11.9, p = .0015) with heavy smoking (more than 1 pack per day).

Conclusion: Despite its small sample size, this study suggests that smoking may be more prevalent in bipolar patients than in the normal population. Since most patients started to smoke before the onset of illness, vulnerability to bipolar illness may make subjects vulnerable to become tobacco smokers.

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Hughes et al.[1] first reported that psychiatric patients have higher rates of tobacco smoking than the general population. Glassman[2] found that subjects with a history of major depression have more difficulties quitting smoking and have a greater frequency of smoking history. In a female twin study, Kendler et al.[3] suggested that genetic factors probably influence the liability to both smoking and major depression. When compared with other chronic mental illnesses, schizophrenia may be associated with smoking and heavy smoking.[4] Vulnerability to schizophrenia may also be associated with tobacco use.[5] However, information on smoking in bipolar patients is limited to reports on the difficulty of smoking cessation in 4 patients.[2,6]

This case-control study was conducted in Alava, a very small state in northern Spain (Basque country). It was developed to investigate whether smoking and heavy smoking, after correcting for confounding variables, are more frequent in patients with bipolar disorder type I (the last 51 cases of a larger survey of 148 patients) than in the normal population (a representative normal sample, N = 517). This study also explores what factors may be associated with smoking and heavy smoking in bipolar patients.

METHOD

Sample

Bipolar patients. A survey was conducted to establish the relationship between age at onset and family history of affective disorders of bipolar type I patients. From February 1994 to May 1996, all patients diagnosed as bipolar in the state of Alava were studied, after giving informed consent, at the 5 outpatient community mental health centers, the only long-term hospital, or the Santiago Apostol Hospital.[7] The Santiago Apostol Hospital receives all patients from the National Health System and has the only psychiatric unit for acute patients in the state. The diagnosis of bipolar disorder type I was confirmed by a research psychiatrist (A.G.-P.) using the Structured Clinical Interview for the DSM-III-R (SCID)[8] after discussion with another research psychiatrist, each patient's treating psychiatrist, a review of all medical records, and interviews with 2 family members.

The original sample included 148 patients. Information on smoking was collected only in the last 51 patients stud-

Table 1. Patients (Demographic and Clinical Information) and Controls (Demographic Information)

Characteristic	Bipolar Patients (N = 51) N	%	Controls (N = 517) N	%
Demographic information[a]				
Gender				
Male	23	45	230	45
Female	28	55	287	55
Socioeconomic class				
I. Upper	3	6	44	9
II. Upper-middle	7	13	36	7
III. Middle	5	10	72	14
IV. Lower-middle	26	51	213	41
V. Lower	10	20	152	29
Clinical information[b]				
History of suicide attempts	22	43		
History of psychotic symptoms	44	86		
Incongruent	28	55		
Congruent	16	31		
Alcohol use				
Never or infrequent	28	55		
Regular use (social drinkers)	8	16		
History of DSM-III-R alcohol abuse	8	16		
History of DSM-III-R alcohol dependence	7	13		
Drug use				
Never	47	92		
History of polysubstance abuse	2	4		
History of polysubstance dependence	2	4		
Current medications				
Lithium	27	53		
Antiepileptics	8	16		
Neuroleptics	24	47		
Antidepressants	5	10		

[a]Mean ± SD age (y) was 44.1 ± 13.8 (range, 16–72) for bipolar patients and 43.3 ± 17.6 (range, 16–85) for controls.
[b]Mean ± SD age at onset of illness (y) for bipolar patients was 28.6 ± 12.6 (range, 13–66); mean ± SD duration of illness (y) was 15.5 ± 11.9 (range, 0–45); and mean ± SD number of hospitalizations was 5.5 ± 5.9 (range, 0–31).

ied following a suggestion by the senior author (J.d.L.) to add the smoking questionnaire to the study. All 51 patients were white; other demographic and clinical information is described in Table 1.

Smoking history was assessed by patient self-report during the euthymic phase using the 6-item Fagerstrom Test for Nicotine Dependence (FTND)[9] and was verified by family members. *Current smoking* was defined as currently smoking on a daily basis, *ever smoking* was defined as ever having smoked on a daily basis, and *heavy smoking* was defined as smoking more than 1 pack per day (20 cigarettes per pack). Family history of smoking was ascertained from subjects. Ever smoking was rare in the female cohorts born in Spain during the first half of the century, a finding that explains the low prevalence of smoking (N = 5, 10%) among mothers of patients in this study. Since history of smoking was more prevalent in the patients' fathers (33 of 51, 65%), the effect of this variable on the smoking practices of bipolar patients was studied.

Controls. The control group used in this study had been identified in a separate study that was sponsored by the Basque government. Alava is the smallest of 3 states in the Basque country. In 1992, the Basque government sponsored a survey to establish the health of the population; the population in each state was randomly sampled.[10] One of the authors (F.A.) supervised the survey in Alava, which included 517 subjects above the age of 15 years who were interviewed in their home about their health, including history of tobacco smoking (ever, current, and never smoking, and report of current smoking as measured in packs per day). Smoking history was not verified by family members; therefore, the smoking information on controls may not be as reliable as that determined for the bipolar patients. However, in Spain, there is almost no social pressure to quit smoking, and since there were no disagreements on smoking reports between bipolar patients and family members, the likelihood that the same level of agreement would exist with the controls was high. Moreover, although the data were available for analysis, the study of the controls was not carried out for this project. It is expected that a small number of controls may have had psychiatric disorders, since people with psychiatric disorders were not excluded from the study; the survey did not include psychiatric diagnostic interviews.

Statistics

The bipolar sample was compared with normal controls using odds ratios (ORs). The 95% confidence intervals (CIs) for the ORs were calculated. If the CI of the OR does not include 1, the difference will be significant ($p < .05$) in a 2-tailed chi-square test. The multivariant technique, logistic regression, was used to calculate the OR of smoking after correcting the effect of other independent variables. Demographic variables such as age, gender, and social class were included in the correction because they influenced smoking. Within the bipolar patients, smokers and nonsmokers were compared using chi-square and t tests. Significance levels were always 2-tailed.

RESULTS

The frequency of ever smoking was 63% (32/51) for the bipolar patients and 45% (235/517) for the control group. The significant OR was 2.0. When comparing respective controls, the difference was significant for bipolar males but not for females (Table 2). Differences tended to increase when the OR was corrected for effects of demographic variables (Table 2). Of the 32 bipolar patients who had ever smoked, 72% (23/32) started to smoke before the onset of illness, 9% (3/32) at the onset of illness, and 19% (6/32) after the onset. Therefore, in most patients, the association between smoking and bipolar illness cannot be explained by the illness, treatment, or hospitalizations.

Table 2. Comparison of Smoking Histories Between Bipolar Patients and Controls (Odds Ratios and Logistic Regression)*

Subgroup	Bipolar Patients	Controls	OR (CI)	Chi-Square χ^2	Chi-Square p	Corrected for Demographics OR (CI)	Corrected for Demographics Wald Test χ^2	Corrected for Demographics Wald Test p	Further Corrected for Alcohol OR (CI)	Further Corrected for Alcohol Wald Test χ^2	Further Corrected for Alcohol Wald Test p
Ever smokers											
Both genders	63% (32/51)	45% (235/517)	2.0 (1.1 to 3.8)	5.6	.018[a]	2.3 (1.2 to 4.3)	6.4	.01[a]	2.7 (1.4 to 5.1)	8.6	.003[a]
Males	87% (20/23)	62% (142/230)	4.1 (1.1 to 18.2)	4.7	.03[a]	4.2 (1.2 to 14.7)	5.1	.023[a]	5.1 (1.4 to 18.5)	6.0	.015[a]
Females	43% (12/28)	32% (93/287)	1.6 (0.7 to 3.7)	1.3	.26	2.2 (0.87 to 5.4)	2.8	.096	2.4 (0.96 to 6.0)	3.5	.06
Current smokers											
Both genders	51% (26/51)	33% (169/517)	2.1 (1.2 to 4.0)	6.9	.009[a]	2.4 (1.3 to 4.5)	8.0	.005[a]	2.9 (1.5 to 5.5)	10.8	.001[a]
Males[b]	65% (15/23)	43% (99/230)	2.5 (0.93 to 6.7)	4.2	.042[a]	2.5 (0.93 to 6.7)	4.2	.042[a]	2.8 (1.1 to 7.0)	4.5	.034[a]
Females	39% (11/28)	24% (70/287)	2.0 (0.83 to 4.8)	3.0	.085	3.0 (1.2 to 7.6)	5.2	.023[a]	3.7 (1.4 to 9.6)	7.3	.007[a]
Heavy smokers											
Both genders	42% (11/26)	14% (24/169)	4.4 (1.7 to 11.9)	12.1	.0015[a]	5.1 (2.0 to 12.9)	11.9	.006[a]	5.1 (2.0 to 13.0)	11.7	.006[a]
Males	40% (6/15)	20% (20/99)	2.6 (0.72 to 9.5)	2.9	.10	3.5 (1.1 to 11.7)	4.5	.033[a]	3.5 (1.1 to 11.9)	4.2	.041[a]
Females[b]	45% (5/11)	6% (4/70)	13.8 (2.3 to 89.9)	11.4	.002[a]	13.8 (2.3 to 89.9)	11.4	.002[a]	12.3 (2.5 to 60.9)	9.4	.002[a]

*Abbreviations: CI = 95% confidence intervals, OR = odds ratio. df = 1 for chi-square and Wald test.
[a]Denotes statistically significant difference.
[b]No significant change in statistical results when corrected for demographics.

Table 3. Comparison in Bipolar Patients of Those Who Have Ever Smoked Versus Those Who Have Never Smoked

Variable	Ever Smokers	Never Smokers	OR (CI)	Statistic	df	p
Male gender	63% (20/32)	16% (3/19)	8.9 (1.8 to 48.7)	$\chi^2 = 8.7$	1	.003
Father who smoked	75% (24/32)	47% (9/19)	3.3 (0.86 to 13.4)	$\chi^2 = 4.0$	1	.046
Alcohol abuse or dependence	47% (15/32)	0% (0/19)	…[a]	$\chi^2 = 10.5$	1	.0012
Age, y (mean ± SD)	40.8 ± 10.8	49.6 ± 16.5		t = 2.1	27.2	.049

[a]It is not appropriate to calculate an OR for alcohol abuse or dependence because of the 0 in "never smokers."

The frequency of current tobacco smoking was 51% for the bipolar patients and 33% for the control group. When compared with current smoking in the respective controls, current tobacco smoking in bipolar patients also reached significance in males. After controlling for demographic variables, the differences persisted (Table 2).

The frequency of heavy smoking among current smokers was 42% for the bipolar patients and 14% for the control group (OR = 4.4). When compared with respective controls, bipolar males and females were more prone to be heavy smokers. After other variables were controlled for, the differences continued to be similar (Table 2).

The prevalence of those who had quit smoking tended to be lower in bipolar patients than in controls (6 [19%] of 32 vs. 66 [28%] of 235, p = .26), particularly in females (1 [8%] of 11 vs. 23 [25%] of 70, p = .36).

Among bipolar patients, there were 32 ever smokers. Two variables associated with history of smoking in the normal population, male gender and younger age, were also significantly associated with smoking in the bipolar sample (Table 3). There were no significant associations of history of smoking (or FTND scores) with illness and treatment variables (which are listed in Table 1). Among bipolar patients, ever smokers were significantly more likely than never smokers to have fathers who smoked (Table 3). However, this appears to be predominant in bipolar males (the frequencies of smoking fathers in males were 80% [16/20] of ever smokers vs. 0% [0/3] of never smokers and in females were 67% [8/12] vs. 56%[9/16]).

History of pathologic use of alcohol (DSM-III-R abuse or dependence) was significantly more frequent in those with a history of smoking (47% vs. 0%) (Table 3). This association was especially prominent in the males (65% [13/20] in male ever smokers vs. 0% [0/3] in male never smokers). However, tobacco use in bipolar patients cannot be completely explained by comorbidity with alcohol, since not all bipolar patients who smoked used alcohol.

In the normal sample, regular use of alcohol was associated with smoking. When the effects of alcohol use were controlled, the OR between bipolar illness and ever smoking increased in the total, male, and female samples (Table 2). Correcting for the effects of alcohol had a similar effect in the analyses of current smokers but no effect in those of heavy smokers. There were no data on DSM-III-R alcohol abuse and dependence in the normal sample.

DISCUSSION

These results are limited by small sample size. Moreover, several of the findings are in the upper end of the significance ranges, and a few associations have a p value between .05 and .10. Nonetheless, these results suggest that bipolar disorder type I, like other psychiatric disorders, may be associated with both smoking and heavy smoking. In this small sample, the association of bipolar disorder

type I with smoking is more clear and consistently significant in males, while the association of bipolar disorder type I with heavy smoking appears to be significant in both sexes.

The association between bipolar disorder and smoking is not likely to be explained by chance, since measures of smoking were always higher in bipolar patients than in controls and many reached significance levels. Reverse causality (smoking causing bipolar illness) cannot explain this association.

The relationship between smoking and bipolar illness type I is probably complex and needs to be understood in the context of other severe mental illnesses such as major depression (with smoking prevalence among patients twice that in the U.S. population) and schizophrenia (with a prevalence 3 times that in the U.S. population).[5] Smoking and heavy smoking (which may be associated with intense nicotine dependence) may have different patterns of association with severe mental illnesses.

The higher number of current smokers with severe mental illness reflects (1) the inability of patients with severe mental illness to quit and (2) the increased onset of daily smoking among these patients. The severely mentally ill appear to have greater difficulties in quitting.[5] Glassman[2] found that patients with a history of major depression (including some bipolar patients) may become severely depressed when they cease to smoke.

Severe mental illness appears to be associated with an increase in the number of people who start smoking daily (ever smokers). A subgroup with a late onset of smoking may be influenced by seeing other patients. Patients with early onset, who start to smoke before the illness begins, suggest that vulnerability to severe mental illness is associated with vulnerability for nicotine dependence.[5] In this bipolar sample, the majority (72%) of patients began smoking before the development of the illness, a fact which suggests that *vulnerability* for bipolar disorder (not the illness itself) makes many bipolar subjects vulnerable to becoming smokers. In a landmark study using female twins, Kendler et al.[3] suggested that familial factors, probably genetic, influenced the liability to both smoking and major depression. It is also possible that liability to smoking and liability to become schizophrenic may be associated.[5] Freedman et al.[11] have described a genetic neurophysiologic abnormality in patients with schizophrenia and their relatives that is temporarily corrected by a high peak of nicotine. This abnormality is due to a dysfunction of a specific hippocampal nicotine receptor (α_7).

The higher prevalence of heavy smokers (with intense nicotine dependence) in severe mental illnesses may be linked to the "self-medication" hypothesis (that is, that smoking may alleviate the symptoms of mental illness or the side effects of psychiatric medications). In addition, nicotine may have antidepressant properties.[12] It has been proposed that smoking may alleviate negative symptoms or cognitive deficits in schizophrenia,[2] but it is difficult to conduct appropriate studies (on/off smoking) to prove it.

Smoking has been proposed to decrease neuroleptic-induced side effects. Although this may be true for some patients, it must not be forgotten that the most consistent finding of naturalistic studies among patients taking neuroleptics is that smokers receive higher doses. Therefore, if patients reduce the side effects of neuroleptics by smoking, in return, psychiatrists inadvertently treat them with higher doses. Two mechanisms have been implied in the reduction of side effects: a release of dopamine by administration of nicotine (supported by acute administration in animal models) and a decrease of blood levels through enzymatic induction. Some of the smoke compounds induce cytochrome P450 (CYP) isoenzymes, particularly CYP1A2 (important for clozapine and tricyclic antidepressant metabolism).[13]

New cross-sectional studies (including larger samples of bipolar patients, other psychiatric patients, relatives of patients, and normal controls, with information on age at smoking onset and careful assessments of use of other substances) as well as long-term longitudinal studies of bipolar type I patients and subjects at risk may be required to definitively prove that smoking is more prevalent in biplolar patients than in the normal population and that vulnerability to bipolar illness may make subjects vulnerable to become tobacco smokers.

Drug name: clozapine (Clozaril).

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