Psychiatry Research 195 (2012) 45–50

Contents lists available at SciVerse ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

# Psychosis and smoking cessation: Difficulties in quitting associated with sex and substance abuse

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ARTICLE INFO

*Article history:*
Received 22 November 2010
Received in revised form 4 August 2011
Accepted 10 August 2011

*Keywords:*
Tobacco
Female
Schizophrenia
Bipolar disorder
Psychotic disorders
Antipsychotic agents

ABSTRACT

No prospective studies of first psychotic episodes have explored sex differences in smoking cessation. The aim of this study was to determine the influence of sex and substance abuse on smoking cessation during an 8-year follow-up of patients after a first psychotic episode. Logistic regression modeling was used to identify factors associated with smoking cessation by sex. To examine for sex variable interactions, the following two methods were used: 1) for other clinical variables, mixed analyses were calculated; and 2) for use of other substances, logistic regression models were performed only in the substance users. At baseline, 79% of men and 84% of women were current smokers. Lower smoking cessation after 8 years was associated with female sex (odds ratio, OR = 0.30; 95% confidence intervals, CIs = 0.12–0.75) and treatment with typical antipsychotics (OR = 0.30, CIs = 0.10–0.93). In a logistic regression model of alcohol users, those who used alcohol continuously were less likely to stop smoking (adjusted OR = 0.22, CI = 0.05–1.0). Among patients who continued using cannabis, female sex was associated with significant lower smoking cessation (adjusted OR = 0.03, CI = 0.001–0.77). Sex may act as a moderator in smoking cessation after a first psychotic episode. Smoking cessation interventions in these patients should consider sex differences and comorbidity with alcohol and cannabis use.



## 1. Introduction

Schizophrenia and bipolar disorder are associated worldwide with higher rates of current and ever smoking than those observed in the general population or in patients with other severe mental illnesses (Gonzalez-Pinto et al., 1998; John et al., 2004; Aguilar et al., 2005; de Leon and Diaz, 2005; Diaz et al., 2009; Bobes et al., 2010). Moreover, patients with both schizophrenia and bipolar disorder appear to have more difficulties with smoking cessation than the general population (de Leon and Diaz, 2005; Baker et al., 2007; Diaz et al., 2009). Although it is not definitively established, smoking in schizophrenia (Aguilar et al., 2005) and bipolar disorder (Berk et al., 2008) may be associated with worse illness prognosis. It is not known whether comorbid substance abuse explains this poorer prognosis. In particular, tobacco and alcohol use are highly associated, and this association is universally found in the general populations of the developed countries (de Leon et al., 2007) and in patients with severe mental illnesses (de Leon et al., 2005).

In order to design useful treatments to help psychotic patients to quit smoking, it is important to identify factors associated with difficulties experienced by psychotic patients in quitting smoking (McCreadie and Scottish Comorbidity Study Group, 2002; Etter et al., 2004; Evins et al., 2007; Williams and Foulds, 2007; Culhane et al., 2008; Weinberger et al., 2008, 2009a; Williams et al., 2010). In the general population female smokers appear to have more difficulty with smoking cessation and permanent abstinence than male smokers (Bjornson et al., 1995; Escobedo and Pedicord, 1996; Wetter et al., 1999). This is a major concern because smoking might be especially harmful in fertile women, as it can have negative effects on the fetus (Zammit et al., 2009; Ekblad et al., 2010). In the general population, female sex and lack of success in quitting smoking have been associated with depression and other forms of negative emotional experience (Borrelli et al., 1996; Benjet et al., 2004; Rohrbaugh et al., 2009; Weinberger et al., 2009b). Less attention has been given to the association of cigarette smoking and the use of other substances in women. In fact, in recent years there have been few studies about substance use disorders among women with serious mental illness, although women with schizophrenia and bipolar disorder are also at high risk for drug abuse (de Leon et al., 2007). In a meta-analysis comparing schizophrenia with the general population (de Leon and Diaz, 2005), the association between schizophrenia and

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doi:10.1016/j.psychres.2011.08.005

higher current smoking was significantly higher in males (odds ratio [OD] = 7.2, 6.1–8.3) than in females (OR = 3.3, 3.0–3.6). Similarly, the association between schizophrenia and smoking cessation was significantly lower in males (OR = 0.10, 0.06–0.14) than in females (OR = 0.46, 0.23–0.69). There is no similar meta-analysis in bipolar disorder but Spanish (Gonzalez-Pinto et al., 1998) and US (Diaz et al., 2009) studies compared findings in men and women. The sex differences observed were not statistically significant and were in different directions in the two countries. After adjustment for confounding factors, the Spanish bipolar study found that the association between bipolar disorder and current smoking was lower in males (OR = 2.8, 1.1–7.0) than in females (OR = 3.7, 1.4–9.6), while the US bipolar study found the opposite (males: OR = 8.6, 3.6–21.0: females: OR = 4.8, 2.5–9.1). However, smoking cessation rates in smokers were lower in females in both studies (Spanish study: male rate= 25%, female rate = 5%; US study: male rate= 10%, female rate = 6%). In summary, sex differences in smoking cessation have been partly studied in schizophrenia, received limited attention in bipolar disorder and have not been studied in patients with a first psychotic episode. We therefore designed a study to determine smoking cessation in first psychotic episode patients. The aim of this study was to determine the influence of sex and substance abuse on smoking cessation during an 8-year follow-up of patients after a first psychotic episode. Our specific hypothesis was that females would have more difficulties in smoking cessation than males, and that substance abuse would be associated with difficulties in quitting tobacco use in both males and females.

## 2. Method

### 2.1. Subjects

First episode patients consecutively admitted to a general hospital with a psychiatric unit (Santiago Hospital) were recruited between February 1997 and January 1999 from the hospital catchment area. The catchment area is located around Vitoria in the Spanish Basque Country of northern Spain. This is the only psychiatric hospital for the area and provides free health care independent of socioeconomic status to all the catchment area population (approximately 320,000 people). Therefore, the study sample includes all patients with first psychotic episodes receiving hospitalization during that time and in that catchment area who were willing to sign an informed consent approved by the Institutional Review Board of the Santiago Hospital.

Criteria of inclusion included age 15 to 65 years and DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, atypical psychosis, bipolar disorder with psychotic symptoms, delusional disorder, brief psychotic disorder or major depressive disorder with psychotic symptoms. A first psychotic episode was defined as the first time a patient experienced positive symptoms such as delusions and/or hallucinations. Subjects with organic brain disorders, mental retardation or more than 6 months of positive symptoms were excluded, following criteria of previous studies (González-Pinto et al., 2010, 2011; Micó et al., 2011). The DSM-IV axis I diagnosis was made using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997).

### 2.2. Assessments

After admission, patients with first episode psychotic symptoms were assessed with a protocol that included the SCID-I and the following clinical scales: the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1960), the Phillips Permorbid Adjustment Scale (Harris, 1975), and the Global Assessment of Functioning (GAF) scale (Endicott et al., 1976). The GAF was used to assess general functioning. The original GAF instructions call for rating symptoms or functioning, but as symptoms were already evaluated with other scales, the raters were trained to focus on psychosocial functioning, as in some previous studies (Martínez-Arán et al., 2004). Other relevant clinical and demographic variables were also collected (i.e., sex, age, civil status, residency and comorbidity with alcohol, tobacco and drug abuse).

Tobacco use was defined according to DSM-IV using SCID-I and the Addiction Severity Index (ASI). The ASI and SCID-I were assessed at every visit (baseline, 1, 3, 5 and 8 years). The ASI is based on a 9-point scale (0–1, no real problem; 2–3, slight problem, substance abuse treatment probably not necessary; 4–5, moderate problem, some treatment indicated; 6–7, considerable problem, treatment necessary; and 8–9, extreme problem, treatment absolutely necessary). Using information obtained with these instruments from the patient, the key informant (usually a family member) and the medical record, we determined whether the patient had smoked, how often the patient had used tobacco, and when that use had occurred. The same method was used to establish use of, abuse of or dependence on other drugs and alcohol. The other drugs abused in this population were mainly cannabis, cocaine and amphetamines. Tobacco smoking behaviors were classified using epidemiological definitions (Diaz et al., 2009). Ever smoking included patients who had smoked at least occasionally (all ever smokers had smoked >100 cigarettes in their lifetime). Smoking cessation was defined as not smoking any cigarette for at least 1 year. Thus, ever smokers included those who had continued to smoke in the last year (current smokers) and those who had ceased smoking for at least 1 year (former smokers). Smoking cessation was defined by self-report but verified with family report. Other tobacco products are very rarely used in this catchment area (de Leon et al., 2007).

Patients were evaluated by direct interview with the same methodology at years 1, 3, and 5. The GAF evaluated psychosocial functioning from the last visit to the corresponding visit. Positive and negative symptoms were measured for each of the mentioned years by the PANSS positive and the PANSS negative subscale scores. All the information available in the emergency room, the hospital ward and the outpatient service was considered for this purpose. The first 5 years of follow-up ended in January 2004. Those patients who could not be contacted during this study period were considered lost to follow-up. At year 8, patients were re-interviewed and functional outcome, alcohol, tobacco and other drug use (SCID-I and ASI) were recorded. Additional information from clinical records, family informants and staff observations was incorporated into the rating process as in previous evaluations.

The pharmacological treatment included low doses of atypical antipsychotics (46%, 37/80); typical antipsychotics (10%, 8/80); both typical and atypical antipsychotics (16%, 13/80) and no treatment (28%, 22/80). The patients also received standard care at their community mental health center after discharge, usually with one visit per month. They received some family interventions if required, and psychological support. Hospitalization and emergency room care were available for all patients who required them. All patients were encouraged to reduce alcohol, drug and tobacco use. No formal treatment for smoking cessation was provided.

### 2.3. Patient classification

Based on tobacco use, patients were classified into two groups: those who stopped smoking during follow-up, and those who did not stop. To analyze the effect of alcohol on tobacco consumption, patients were classified into three groups depending on their use of alcohol: those who used it continuously, those who used it and stopped during follow-up, and those who had never used it. The same method was used for cannabis and other drugs. Thus, the respective percentages of ceasing substance use among users were 40% (31/78) for alcohol, 52% (23/44) for cannabis and 89% (25/28) for other drugs.

### 2.4. Statistical analyses

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) 18 and R 2.5.1 (R Development Core Team, 2007). Smoking cessation or lack of smoking cessation was the dependent variable for these analyses. For the baseline variables, sex comparisons were made using bivariate analysis. Mann-Whitney *U* tests were used for continuous variables and contingency tables for categorical variables ($\chi 2$ or Fisher's exact test if $n \leq 5$ per cell), all with significance defined as two-tailed ($p < 0.05$) at stated degrees-of-freedom (df). Odds ratios (ORs) were calculated for the significant variables using 95% confidence intervals (CIs). Survival analyses were performed to estimate the time until smoking cessation was reached for men and women.

To identify factors associated with smoking cessation in men and women, logistic regression modelling was used. To eliminate the effect of possible confounding variables, the regression models were adjusted by the sex variable and by those sociodemographic variables that were significantly different at baseline. These analyses took into account whether or not alcohol, cannabis or other drugs were used continuously. To analyze the influence of the evolution of the clinical variables, the variation between baseline and last visit was calculated. To examine sex variable interactions (at the same time adjusting for other significant clinical variables), the following two methods were used: 1) for other clinical variables, mixed analyses were calculated; and 2) for use of other substances, logistic regression models were performed only in the substance users. Data are presented as adjusted ORs with *p*-values and CIs.

## 3. Results

There were 127 patients with a first psychotic episode. Fifteen patients were excluded due to organic disease, diagnosis of drug-induced psychosis or not giving informed consent. Thus, the remaining 112 patients were enrolled at baseline. Ninety-two patients were followed for at least 5 years. Eighty-two patients were interviewed at year 8. After the first psychotic episode, the mean number of episodes per year was 0.49 (0.40).

### 3.1. Baseline description

The mean (SD) age of the patients at admission was 28.84 (10.26) years (range, 16–61 years) and 48% (54/112) were women. Rates of ever smoking were 79% (46/58) in males and 85% (46/54) in females, which does not represent a significant difference ($\chi^2 = 0.66$, $p = 0.42$). Respective ever smoking rates for the 82 patients followed for 8 years were similar: 79%, (31/39) and 84% (36/43), not significantly different between the sexes ($\chi^2 = 0.25$, $p = 0.62$). All ever smokers were current smokers at baseline and none of them had stopped smoking before the study started.

There were no differences between patients followed or not followed with respect to the following baseline variables: age ($U = 1023$, $p = 0.62$), sex ($\chi 2 = 0.30$, $p = 0.58$), marital status (Fisher's exact test, $p = 0.69$), socioeconomic level (Fisher, $p = 0.27$), tobacco use (Fisher's exact test, $p = 0.53$) and typical antipsychotic use (Fisher's exact test, $p = 0.54$).

### 3.2. Bivariate analyses at 8 years of follow-up

Table 1 shows the bivariate analyses used to explore differences between groups. When comparing those who ceased smoking at 8 years of follow-up and those who did not, lower smoking cessation was associated with female sex ($\chi^2 = 5.72$, $p = 0.017$) and treatment with typical antipsychotics ($\chi^2 = 4.59$, $p = 0.032$).

**Table 1**
Comparing patients who stopped smoking versus smokers at 8 years of follow-up: Bivariate analyses.

| VARIABLE | Former smokers ($n = 34$) | Smokers ($n = 48$) | Statistic |
|---|---|---|---|
| GENDER | | | $\chi^2 = 5.72$, $p = 0.017$ |
| Men | 65% (22) | 35% (17) | |
| Women | 35% (12) | 65% (31) | |
| CIVIL STATUS | | | Fisher, $p = 0.14$ |
| Single | 82% (28) | 69% (33) | |
| Married | 18% (6) | 21% (10) | |
| Other | 0% (0) | 10% (5) | |
| SOCIOECONOMIC STATUS | | | Fisher, $p = 0.34$ |
| Low | 35% (12) | 21% (10) | |
| Medium | 56% (19) | 62% (30) | |
| High | 9% (3) | 17% (8) | |
| EDUCATIONAL LEVEL | | | Fisher, $p = 0.12$ |
| <high school | 29% (10) | 38% (18) | |
| High school | 68% (23) | 48% (23) | |
| College | 3% (1) | 15% (7) | |
| CANNABIS USE | | | $\chi^2 = 0.01$, $p = 0.91$ |
| No | 44% (15) | 48% (23) | |
| Yes | 56% (19) | 52% (25) | |
| ALCOHOL USE | | | $\chi^2 = 0.13$, $p = 0.72$ |
| No | 6% (2) | 4% (2) | |
| Yes | 94% (32) | 96% (46) | |
| OTHER DRUG USE | | | $\chi^2 = 0.003$, $p = 0.96$ |
| No | 65% (22) | 67% (32) | |
| Yes | 35% (12) | 33% (16) | |
| ATYPICAL ANTIPSYCHOTICS | | | $\chi^2 = 0.47$, $p = 0.49$ |
| No | 29% (10) | 40% (17) | |
| Yes | 71% (24) | 60% (26) | |
| TYPICAL ANTIPSYCHOTICS | | | $\chi^2 = 4.59$, $p = 0.032$ |
| No | 85% (29) | 64% (30) | |
| Yes | 15% (5) | 36% (17) | |
| | m ± SD | m ± SD | |
| AGE | 27.9 ± 8.5 | 30.5 ± 11.9 | $U = 764.5$, $p = 0.63$ |
| PANSS | | | |
| Positive | 24.1 ± 7.7 | 24.2 ± 6.2 | $U = 828.5$, $p = 0.91$ |
| Negative | 19.5 ± 9.4 | 18.8 ± 9.6 | $U = 864.5$, $p = 0.65$ |
| General | 42.6 ± 11.5 | 42.0 ± 11.4 | $U = 863$, $p = 0.66$ |
| HAMILTON | 18.8 ± 8.6 | 17.7 ± 8.4 | $U = 884.5$, $p = 0.55$ |
| PHILLIPS | 6.2 ± 2.9 | 5.17 ± 3.0 | $U = 988.5$, $p = 0.10$ |
| GAF | 51.9 ± 13.5 | 57.0 ± 11.7 | $U = 668.5$, $p = 0.16$ |

### 3.3. Survival analysis of smoking during 8 years of follow-up

The sex difference influenced the survival analysis. Only men had significant differences in current smoking from baseline to the end of the study (men: 79% at baseline versus 25% at year 8, Fisher's exact test, $p < 0.01$; women: 84% at baseline versus 58% at year 8, Fisher's exact test, $p = 0.26$). This was reflected in the rates of smoking cessation over time (Fig. 1); men ceased smoking significantly earlier than women. The median survival time for men was 8 years. In women, the median survival time could not be calculated since, at the end of the follow-up, more than 50% of the women continued smoking.

### 3.4. Relationship between clinical variables and smoking cessation at 8 years and sex variable interactions

The changes in negative symptoms (PANSS negative subscale) or GAF between baseline and year 8 were not significantly associated with smoking cessation, and their interaction with the sex variable was not significant. Change in positive symptoms (PANSS positive subscale) was not significantly associated with smoking cessation, but the interaction with the sex variable was significant (adjusted OR = 1.14, CI = 1.01–1.28, $p = 0.04$) after controlling for the effect of typical antipsychotics. Fig. 2 describes the differences of the positive symptoms by sex based on the effect of smoking cessation and shows that among patients with smoking cessation, females tend to have lower positive scores than males.

The change in depressive symptoms between baseline and the 8th year was not significantly associated with smoking cessation and its interaction with the sex variable was not significant.

To estimate the interaction between substance use and sex, logistic regression models were calculated using only the sample that was positive for substance use. In the 78 patients with history of alcohol use, those who used alcohol continuously were less likely to stop smoking (adjusted OR = 0.22, CI = 0.05–1.0, $p = 0.05$) after controlling for the effect of typical antipsychotics. However, the interaction between the sex variable and alcohol was not significant.

In the 44 patients with history of cannabis use, continuous cannabis use was not significantly associated with smoking cessation, but there was a significant interaction with the sex variable (Fig. 3); women who continued to use cannabis were less able to stop smoking than men (adjusted OR = 0.03, CI = 0.001–0.77, $p = 0.03$).

## 4. Discussion

### 4.1. Female sex was associated with lower smoking cessation rates

The major finding of this study is the association between difficulties in smoking cessation and female sex. Men were three

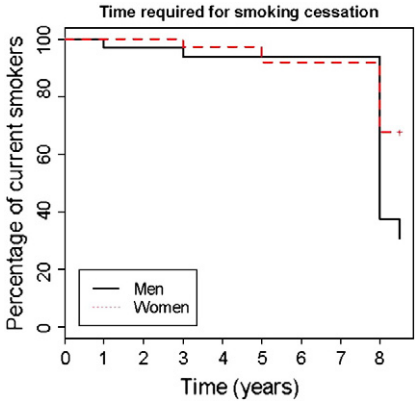


**Fig. 1.** Time required for smoking cessation.

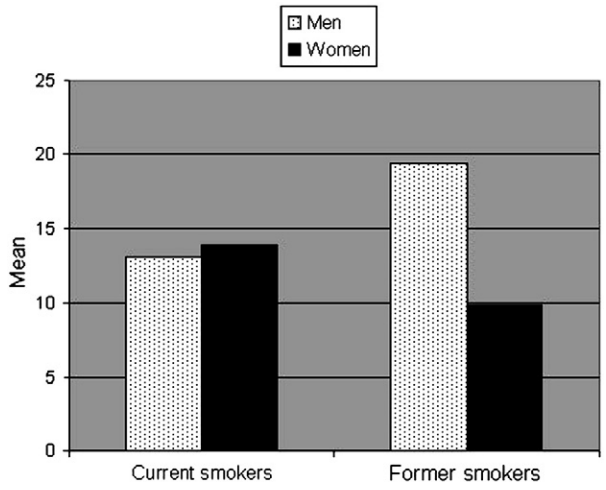


**Fig. 2.** Smoking cessation related to positive symptoms (PANNS positive subscale score) by sex at 8-year of follow-up.

times more frequently able to stop smoking than women, and also were able to do it earlier in the course of psychosis. In this sense, the sex variable may act as a moderator in smoking cessation. The rates of smoking were similar among men and women at baseline and higher in females at the follow-up, due to the higher rate of smoking cessation in men. In the general population of Vitoria the prevalence of smoking cessation was also greater in males than in females in 1996 (de Leon et al., 2007). In schizophrenia patients, as indicated in the introduction, male sex may be associated with lower cessation rates (de Leon and Diaz, 2005), but studies in bipolar patients provided non-significant and conflicting results (Gonzalez-Pinto et al., 1998; Diaz et al., 2009).

Although the association between smoking and psychosis in general is consistent between countries (de Leon et al., 2002), differences in the methodology of studies can influence the results of specific smoking behaviors, such as smoking cessation. In that sense, it is important to acknowledge that the long duration of our follow-up may have contributed to the significant sex differences in smoking cessation. In analysis of another first psychotic episode sample recruited from children and adolescents in the same catchment area, tobacco use did not decrease after 2 years of follow-up (Baeza et al., 2009). An Australian first episode psychosis study demonstrated a baseline current smoking rate (77%) similar to our rate (76%) and no smoking cessation at the 15-month follow-up (Wade et al., 2006). In our study only men stopped smoking at a significant rate, and this was seen only after at least 5 years of follow-up. An analysis at 15 months, like the one performed in the Australian study, would show no significant cessation in smoking.

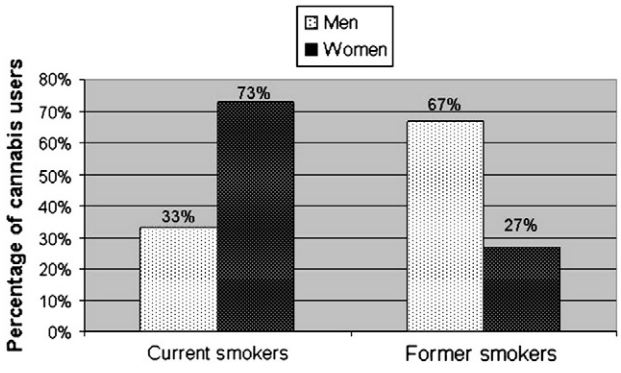


**Fig. 3.** Smoking cessation by gender at 8-year follow-up according to cannabis use.

Smoking cessation rates in this longitudinal study were higher than in cross-sectional studies. In our sample, 79% (31/39) of men were current smokers at baseline, compared with 26% (10/39) after 8 years of follow-up. In the same sample, 84% (36/43) of women were current smokers at baseline compared with 58% (25/43) after 8 years. The smoking cessation rates in male ever smokers versus female ever smokers were 71% (22/31) and 33% (12/36), respectively. In a cross-sectional US study (de Leon et al., 2005) of patients with severe mental illness and with an average duration of psychiatric treatment of more than 26 years, the smoking cessation within ever smokers appeared to be much lower, respectively, 8% in males and 13% in females. Both studies shared the lack of formal smoking treatments and similar alcohol cessation rates (40% in this study versus 44% in the US study). Other characteristics were different, including the characteristics of the health system and the inclusion in the US study of additional diagnoses besides psychosis and longer duration of treatment.

### *4.2. Other variables associated with low rates of smoking cessation in the whole sample*

Use of typical antipsychotics was associated with lower smoking cessation in the whole sample. The use of typical antipsychotics was also associated with lower smoking cessation in a schizophrenia clinical trial (George et al., 2000).

Persistent alcohol use was associated with lower smoking cessation rates. The strong association between alcohol and tobacco use has been found both in the general population (de Leon et al., 2007) and in patients with severe mental illnesses (de Leon et al., 2005). Lower smoking cessation rate has been associated with alcohol or other drug abuse, raising the question of the difficulties in abandoning only one drug when several substances are abused (de Leon et al., 2005; de Leon and Diaz, 2005; González-Pinto et al., 2010).

### *4.3. Variables associated with decreased smoking cessation only in the female subsample*

Two variables (positive symptoms and cannabis use) were significantly associated with smoking cessation rates in females when compared with males, indicating a sex interaction. Lower positive symptoms at follow-up were associated with smoking cessation in females. The association was significant, although weak (adjusted OR = 1.14, CI = 1.01–1.28). Continuous cannabis use was particularly detrimental for smoking cessation in women, with a significant and strong association (adjusted OR = 0.03, CI = 0.001–0.77). Cannabis use may need to be considered when designing programs for smoking cessation in psychotic women (Patel et al., 2006). In fact, of the 12 women that quit tobacco, 5 had used cannabis and almost all of them (83%, 4/5) had ceased cannabis use before quitting smoking. In Western countries, cannabis use and tobacco use appear to be associated in adolescents of both sexes (Chabrol et al., 2006; Degenhardt et al., 2010).

Although it is not clear why women have more difficulties in quitting tobacco use than men, some hypotheses can be considered. In our female sample, a low rate of smoking cessation was associated with cannabis use and higher positive symptoms. This result may appear unusual since it is generally considered that cannabis use and positive symptoms are less prominent in women with psychosis. Our study suggests that this may only be true for non-smoking psychotic women; in smoking psychotic women smoking may be another sign of the severity of the psychosis. A schizophrenia study (Aguilar et al., 2005) and a bipolar study (Berk et al., 2008) have reported that tobacco smoking may be associated with worse illness prognosis. Thus, our study may indicate that the association between smoking and poor psychosis prognosis may be particularly strong in women.

### 4.4. Limitations and strengths

This study has some limitations. A small number of patients were not followed up due to dropping out of the study. All patients were hospitalized at admission, so patients not needing hospitalization are not represented in the study. Nevertheless, in our catchment area the majority of patients with a first psychotic episode are hospitalized and <20% might have been lost. As the hospital treats all patients in Vitoria, and all first psychotic patients were included, the results can be generalized to our state. Due to the lack of other studies, it is not known whether the results can be generalized to other Spanish states or other countries.

Another limitation is that this is a naturalistic study and no smoking cessation treatments were provided. In our catchment area, formal smoking cessation programs for psychotic patients started in 2011. No biochemical verification of smoking cessation was performed, but there was no obvious reason for the patient to lie and the information was verified by a family member. Future studies will benefit from the use of biochemical verification and the collection of other smoking data including the number of cigarettes per day and the time to first cigarette in the morning, which may influence smoking cessation.

In conclusion, women were less prone to quit smoking than men during long-term follow-up after the development of psychosis. Factors that have usually been considered mediators of the difficulties in smoking cessation, such as cannabis use and positive symptoms, were linked to continued tobacco use in women but not in men. If our results are replicated by other studies this would indicate a sex difference for the treatment of nicotine dependence in psychotic patients. Treatment for psychotic women who want to quit smoking should probably be more supportive and intensive than that for men. This will improve longitudinal outcomes in women with psychosis, especially those with comorbid cannabis abuse. New treatment studies of patients with first episode psychosis, including pharmacological and psychological interventions for substance abuse of tobacco, cannabis and alcohol, are needed. Our current study indicates that these new studies should incorporate long-term follow-up and consider sex differences.

#### Acknowledgements

Preparation of this article was supported by Health Research Funds from the Spanish Government (PS09/02002, PI08/90439; PI08/90224; PI081213; PI081536; PI08/0873; EC07/90435; EC07/90666; CD08/00269; CM08/00213), CIBER Network (which is an initiative of ISCIII CB07/09/0024; P91A; P91E), European Regional Development Funds (FEDER), and by local grants (GV20009111047; BIO09/EM/010; BIOEF09 and EHU08/54). Dr González Pinto is responsible for a specific collaborative agreement between the Spanish Government (SCIII) and the Basque Government to stabilize and intensify research in the National Health System (Boe no. 68 19, March 2010).). These institutions had no further role in the study design, data collection, analysis and interpretation, writing of the report, or in the decision to submit the paper for publication. No pharmaceutical company or commercial organization had any role in the writing of this paper for publication. In the last 12 months, Dr. de Leon was co-investigator with Genomas in a National Institutes of Health grant.

The authors would like to thank the mental health professionals who helped with this research. The authors take full responsibility for the content of the paper, but thank Lorraine Maw, MA, at the Mental Health Research Center at Eastern State Hospital and Deirdre Elmhirst, PhD, for their assistance in editing the manuscript.

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