



ORIGINAL ARTICLE

## Effectiveness and safety of varenicline and nicotine replacement therapy among mental health patients: A retrospective cohort study



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### KEYWORDS

Smoking;  
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### Abstract

**Objective:** To analyse the effectiveness and safety of two smoking cessation medications (varenicline and nicotine patches) in patients with controlled psychiatric disorders in daily practice in a Smoking Cessation Service.

**Methods:** This is a retrospective cohort study. It was carried on at a smoking cessation clinic in Madrid and used a convenience sampling strategy. We reviewed medical records of patients diagnosed with psychiatric disorders who attended a Smoking Cessation Service. All patients received similar treatment programme: a combination of pharmacological treatment (varenicline or nicotine replacement therapy) and intensive cognitive-behavioural therapy.

**Results:** The group included 349 patients (38.4% men). Mean age (SD) 49.6 (10.5) years. 28.3 (12.8) cigarettes per day. 156 subjects achieved 9–24 weeks continuous abstinence (44.7%), in 39% of those who used nicotine patches and in 53.7% of those who used varenicline. OR: 1.64 (95% CI: 1.03–2.61;  $p=0.036$ ). Success rates were higher in men; OR 1.85 (95% CI: 1.12–3.04;  $p=0.016$ ). High levels of CO and high daily cigarette use were associated with poorer success rates (OR: 0.98, 95% CI: 0.96–0.99,  $p=0.007$ ; and OR: 0.98, 95% CI: 0.96–1.00,  $p=0.045$ ), respectively. Nausea and pruritus were the most common adverse events. No cases of suicidal ideation or behaviour were found.

**Conclusions:** Varenicline and nicotine patches could be safe and effective smoking cessation treatments for patients with psychiatric disorders in daily clinical practice.

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## Introduction

Tobacco use is very common among patients with psychiatric disorders. One study found that tobacco use was two to four times higher in a group of patients with psychiatric disorders than in the general population.<sup>1</sup> More than 40% of patients with schizophrenia, depression, bipolar disorder, panic disorder or post-traumatic stress are smokers, with tobacco use by schizophrenic and depressed patients in particular peaking at almost 80%.<sup>1-3</sup> Furthermore, morbidity and mortality rates caused by smoking-related diseases are particularly high among individuals with psychiatric disorders.<sup>4</sup>

Several studies have concluded that smoking cessation treatments are less effective in patients with psychiatric disorders than in smokers from the general population. Abstinence rates for smokers with schizophrenia range from 13% to 26% when using nicotine patches<sup>5,6</sup> and increase to 28% when treated with a combination of patches plus bupropion.<sup>7</sup> Eagles' study analysed the safety and efficacy of different smoking cessation treatments in two patient cohorts<sup>8</sup>; psychiatric-cohort and non-psychiatric cohort. The results revealed that the various treatments were more effective, although not significantly, in the non-psychiatric cohort than in the psychiatric cohort.<sup>8</sup> 18.5% of healthy subjects treated with nicotine patches achieved sustained abstinence at six-months follow-up, compared to just 13% of patients in psychiatric cohort. Similarly, 18.8% and 22.5% of healthy subjects treated with bupropion and varenicline, respectively, achieved sustained abstinence at six month follow-up, vs just 13.7% and 18.3% of patients in the psychiatric cohort.<sup>8</sup> It is worth mentioning that this study found varenicline to be the most effective of all active treatments, and more effective than placebo, at both three and six months follow-up.<sup>8</sup>

Another important aspect to consider when treating tobacco use in patients with psychiatric disorders is the safety of the various smoking cessation drugs. The results of Eagles' study in this regard are conclusive.<sup>8</sup> Patients with controlled psychiatric disorders treated with either varenicline, nicotine patches or bupropion did not experience a greater number or more intense neuropsychiatric adverse effects than subjects treated with placebo.<sup>8</sup>

Eagles' findings in terms of the safety and efficacy of smoking cessation treatments in smokers with psychiatric disorders had been suggested in previous meta-analyses and reviews<sup>10,11</sup> and were confirmed by a recent meta-analysis.<sup>9</sup>

However, relatively few studies have analysed the effectiveness and safety of the various smoking cessation drugs in daily clinical practice in patients with controlled psychiatric disorders. Furthermore, very little is known about the effectiveness of the different drugs in patients with different psychiatric disorders.

On the other hand, psychiatric patients are a group of smokers who attend frequently Smoking Cessation Services. The majority of Smoking Cessation Services are run by lung physicians, so lung physicians should know how to develop effective Smoking Cessation Strategies in this specific group of patients. In this paper, we present the experience of a Smoking Cessation Service run by lung physicians.

The aim of this study was to analyse the effectiveness and safety of two smoking cessation medications (varenicline

and nicotine patches) in patients with controlled psychiatric disorders in daily practice in a Smoking Cessation Service.

## Methodology

This is a retrospective cohort study. The medical records of all patients diagnosed with psychiatric disorders who attended our Smoking Cessation Service (Community based clinic that receives patients refer by primary care health-care professionals) with the intention of quitting smoking between January 2009 and January 2016 were reviewed. The subjects suffered from a range of psychiatric disorders: bipolar disorder, schizophrenia, depression, obsessive-compulsive disorder, borderline personality disorder and generalised anxiety disorder. They were admitted to receive treatment as long as they had not experienced psychiatric symptom exacerbation in the previous six months, were receiving stable treatment and had been recommended for smoking cessation treatment by a psychiatric specialist.

All patients received a very similar treatment programme, comprising a combination of pharmacological treatment and cognitive-behavioural therapy. Cognitive-behavioural therapy was administered over 10 individual sessions: one baseline visit and nine follow-up visits. The cognitive-behavioural therapy consists of the following activities: self-monitoring, identifying high-risk situations, coping strategies, and intra-treatment support. All the subjects received the same therapy.

The patients' medical records and smoking history were taken at the baseline visit. Patients received behavioural therapy and non-tailored self-help materials, and selected a day to quit. Pharmacological treatment was prescribed and patients were instructed on its correct use. The baseline visit lasted approximately 40–45 min.

During the follow-up visits, patients received additional cognitive-behavioural therapy to prevent relapses and to manage high-risk situations. The onset of adverse effects was monitored, regardless of the treatment administered, and patients were asked about any neuropsychiatric adverse effects. Sustained abstinence was measured between weeks 9 and 24 and was defined as no tobacco consumption of any kind between weeks 9 and 24. Patients' verbal declaration of abstinence was verified by measuring CO levels <4 ppm in exhaled air (we chose this cut off point in order to increase accuracy). Follow-up visits were conducted during weeks 1, 2, 4, 6, 8, 10, 12, 18 and 24 after the day of quitting. Each follow-up visit lasted between 20 and 25 min.

Pharmacological treatment consisted of nicotine patches or varenicline. 24-h nicotine patches at a dose of 21 mg/day were administered for 6 weeks, followed by 14 mg/day for 4 weeks and then 7 mg/day for 2 weeks. Patients were advised to use 4-mg nicotine gum sporadically to curb cravings. Subjects were instructed how to use the gum correctly. Varenicline was administered at 0.5 mg/day for the first three days, 0.5 mg/12 h for the next four days and 1 mg/12 h from day 8 onwards until treatment completion at 12 weeks. We did not use bupropion because bupropion can have several interactions with psychiatric medications.

The study was conducted according to the principles of the Declaration of Helsinki (last revision Washington 2002).

**Table 1** Variables included in the study.

Qualitative variables	Quantitative variables
<i>Gender</i> "Men" vs "Women" (Ref.)	Age FTND-score Level of CO in exhaled air (ppm)
<i>Time to smoking 1st cigarette</i> "<5 min" "From 5 to 30 min" ">30 min" (Ref.)	Number of cig./day Duration of tobacco use (years smoking) Accumulated consumption (pack-years)
<i>Type of psychiatric disorder<sup>a</sup></i> Bipolar Schizophrenia Depression Other psychiatric disorders	
<i>Treatment type</i> "Varenicline" vs "NRT" (Ref.)	
<i>Outcome</i> "Success" vs "Failure" (Ref.)	

NRT: nicotine replacement therapy. Ref.: indicates the reference category in the logistic regression model (table). cig./day: cigarettes/day.

<sup>a</sup> Type of psychiatric disorder: each disorder type is a variable with "Yes" vs "No" categories (Ref.).

Subjects gave their informed consent and the study was approved by the Spanish Respiratory Society committee on human research.

## Variables and statistical analysis

The variables included in the study are detailed in [Table 1](#). Qualitative variables are expressed as absolute value and percentage, while quantitative variables are expressed as means with their standard deviations (SD). The correlation between the "Outcome" variable ("success" vs "failure", with "failure" as reference category) and the "treatment type" variable ("varenicline" vs "NRT", with "NRT" as reference category) was studied using logistic regression.

We consider the "Outcome" variable ("success" vs "failure", with "failure" as reference category) as the dependent variable, and the "Treatment type" ("varenicline" vs "NRT", with "NRT" as reference category) as the independent variable. To build the logistic regression model that correlates the "Outcome" variable and the "Treatment type" variable, all possible models with all possible combinations of all remaining variables were built, considering them all to be confounding or adjustment variables. The measure of effect used to compare the groups of the variable "Type of treatment" ("varenicline" vs "TSN" with "TSN" as reference category), in relation to the variable "Result" Failure "with the category"

failure "as the reference category" was the OR (and its 95% CI) estimated by logistic regression. The analysis of the study was carried out by intention to treat. Once the final model had been obtained, several additional variables were retested individually, namely: "Age", "FTND-score", "Time to smoking 1st cigarette", "Duration of tobacco use (years smoking)" and "Accumulated consumption (pack-years)". None of these variables was statistically significant or modified the OR of the "Treatment type" fundamental variable by more than 10% such as to be retained in the model as means of adjusting this variable.<sup>12</sup> Finally, all possible first-order interactions between the "Treatment type" fundamental variable and all other variables selected in the final model were tested, as well as potential first-order interactions between these remaining adjustment or confounding variables themselves.<sup>13</sup> None of these interactions was statistically significant.

The entire analysis was performed using SPSS v.20,<sup>14</sup> MedCalc<sup>15</sup> and STATA/SE 12.1 for Windows.<sup>16</sup> A significance level of  $p < 0.05$  was considered, unless otherwise indicated.

## Results

### Socio-demographic and smoking characteristics of patients

The group comprised 349 patients (134 men [38.4%] and 215 women [61.6%]) with a mean age (SD) of 49.6 (10.5) years. They smoked a mean of 28.3 (12.8) cigarettes per day with a mean level of CO in exhaled air of 28.4 (16.2) ppm. The mean FTND- score was 7.5 (2.3) and 61% of patients smoked their first cigarette five minutes after getting up in the morning. Mean accumulated tobacco consumption was 44.4 (26.2) pack-years and mean duration of tobacco use was 32.2 (11.0) years. Distribution by psychiatric disorder was as follows: 39 (11.2%) were diagnosed with bipolar disorder, 53 (15.2%) with schizophrenia, 201 (60.2%) with depression and 42 (12.0%) with other psychiatric disorders (4 cases of obsessive-compulsive disorder, 9 of borderline personality disorder, 11 with depression and anxiety disorders and 19 with generalised anxiety disorder). Five subjects (1.4%) suffered from more than one psychiatric condition (3 men and 1 woman with bipolar disorder and schizophrenia and 1 man with depression and "other psychiatric disorders"). However, this did not influence the model as each psychiatric disorder was included individually, coded as "yes" vs "no".

### Treatment effectiveness

9–24 weeks continuous abstinence was achieved by 156 subjects (44.7%). 84 of the 215 patients (39%) who used nicotine patches achieved abstinence, compared to 72 of the 134 patients (53.7%) who used varenicline.

9–24 weeks continuous abstinence in each of the disorder groups was as follows: bipolar disorder 35.9%, schizophrenia 39.6%, depression 45.7% and other psychiatric disorders 57.1%. Of the 5 subjects with two psychiatric disorders, only the male patient with depression and "other psychiatric disorders" achieved abstinence at six months follow-up.

[Table 2](#) shows the logistic regression analysis results. The analysis found no significant differences between the

**Table 2** Logistic regression model that correlates the treatment outcome ("success" vs "failure", with "failure" as reference category) with the treatment.

Variable	OR (95% CI)	<i>p</i>
<i>Treatment type</i>		
"Varenicline" vs "NRT" (Ref.)	1.64 (1.03–2.61)	0.036
<i>Gender</i>		
"Men" vs "Women" (Ref.)	1.85 (1.12–3.04)	0.016
<i>Level of CO in exhaled air (ppm)</i>		
<i>Number of cig./day</i>	0.98 (0.96–1.00)	0.045
<i>Other psychiatric disorders</i>		
"Yes" vs "No" (Ref.)	1.96 (0.97–3.95)	0.059
Constant	1.33	

OR: odds ratio. 95% CI: 95% confidence interval for the OR. *p*: degree of significance. Ref.: reference category. cig./day: cigarettes/day.

**Table 3** Adverse effects.

	Nicotine patches	Varenicline
No. of patients	215	134
Nausea	4 (1.8%)	40 (30%)
Abnormal dreams	32 (15%)	27 (20%)
Pruritus	60 (28%)	–
Insomnia	30 (14%)	12 (9%)
Headache	20 (9.5%)	11 (8.3%)

No.: number. Some patients experienced more than one adverse effect.

bipolar disorder, depression and schizophrenia groups. The same result was found in subjects with "other psychiatric disorders" OR 1.96 (95% CI: 0.97–3.95; *p* = 0.059).

Subjects treated with varenicline were 1.64 times more likely to successfully quit (95% CI: 1.03–2.61; *p* = 0.036) than subjects treated with nicotine patches. Men were more likely to quit smoking than women, OR 1.85 (95% CI: 1.12–3.04; *p* = 0.016). The higher the level of CO in exhaled air, the lower the likelihood of successfully quitting, OR: 0.98 (95% CI: 0.96–0.99; *p* = 0.007); likewise, the more cigarettes smoked per day, the increased tendency to lower probability of quitting, OR: 0.98 (95% CI: 0.96–1.00, *p* = 0.045).

## Safety

General adverse effects and neuropsychiatric adverse effects that occurred during the pharmacological treatment phase and up to one month after treatment completion were studied.

### General adverse effects

General adverse effects were reported in 139 subjects (39.8%). Frequency of adverse effects ranged from 39% for nicotine patches (84 subjects out of 215) to 41% for varenicline (55 subjects out of 134). Table 3 lists the adverse effects experienced in each patient group by treatment used. Most adverse effects were mild or moderate. Treatment only had to be discontinued in four nicotine patch

users (1.8%); two due to intense pruritus and two due to headache. Treatment was also suspended in three subjects who used varenicline (2.2%), all as a result of nausea and vomiting.

### Neuropsychiatric adverse effects

Neuropsychiatric adverse effects were experienced by 22 of the 349 subjects who received treatment (6.3%). Frequency of onset of neuropsychiatric adverse effects ranged from 6% for nicotine patches (13 subjects out of 215) to 6.8% for varenicline (9 subjects out of 134).

Of the 13 nicotine patch users who suffered neuropsychiatric adverse effects, 7 experienced agitation, 4 aggression and 2 anxiety. Treatment had to be withdrawn in just two cases due to the severity of the adverse effect; one case of agitation and one of aggression. No cases of suicidal ideation or behaviour were found.

Of the 9 varenicline users who suffered neuropsychiatric adverse effects, 6 experienced agitation, 2 aggression and 1 depression. Treatment had to be withdrawn in just two cases due to the severity of the adverse effect; one case of agitation and one of depression. No cases of suicidal ideation or behaviour were found.

## Discussion

We present the results of a real-life smoking cessation programme using varenicline and nicotine patches in a group of 349 patients with controlled psychiatric disorders. The results show that 44.7% of patients had successfully quit at six months follow-up and that the likelihood of quitting was reduced in patients who had high levels of CO in exhaled air and tends to decrease in patients who smoked a high number of cigarettes per day. Varenicline users were more likely to be successful than nicotine patch users (OR: 1.64; 1.03–2.61; *p* = 0.036). Both nicotine patches and varenicline were found to be safe. Pharmacological treatment only had to be withdrawn due to severe adverse effects in isolated cases, and no cases of suicidal ideation or behaviour were found.

More patients achieved abstinence at six months follow-up in our study than in other studies conducted under clinical trial conditions.<sup>8–10</sup> There are a number of factors that could explain this result: (a) all patients were intensely followed-up for six months by a multidisciplinary medical team of smoking cessation treatment experts; (b) all subjects who attended the service were extremely motivated to quit smoking; (c) before being admitted for treatment, the stability of the patient's psychiatric disorder had to be confirmed by a psychiatric specialist; (d) the pharmacological treatment was prescribed free of charge in many cases; and (e) there could have been potential for selection bias, since the study was conducted in only one clinical centre.

Varenicline's superior efficacy over nicotine patches as an aid to quitting smoking in this group of patients had already been demonstrated by the results of Eagles' study,<sup>8</sup> which had an OR of 1.51 (95% CI: 1.19–1.93), compared to 1.64 (95% CI: 1.03–2.61) in our study. Although all patients who received nicotine patches were advised to use nicotine gum to curb any cravings, it is important to note that this drug was seldom used and in no case for longer than four weeks.



It should also be noted that men were more likely to quit than women, while patients who smoked a higher number of cigarettes per day and with higher levels of CO in exhaled air were less likely to quit. The reasons for these findings could be as follows: (a) numerous studies have found nicotine patches to be ineffective in women<sup>17</sup>; the majority of our patients were women and nicotine patches was the most common treatment; (b) smoking a high number of cigarettes each day leads to higher levels of CO in exhaled air; smoking a high number of cigarettes each day is indicative of a high degree of physical dependence on nicotine, which reduces the efficacy of smoking cessation medications<sup>18</sup>; and (c) there may be other factors associated with gender and high success rate that may cause confounding, since important determinants of cessation were not included in the multifactorial analyses.

Another noteworthy finding in this study is the fact that no significant differences in terms of treatment effectiveness were found between the different psychiatric disorders. However, it is worth pointing out that effectiveness was higher in the group of patients with less severe psychiatric disorders (the "other psychiatric disorders" group) than in the rest of the patients, and was on the cusp of reaching statistical significance. Numerous studies have analysed the efficacy and safety of smoking cessation treatments in patients with depression, schizophrenia or other psychiatric disorders and all have found both varenicline and nicotine replacement therapy to be effective and safe.<sup>8,19–21</sup> However, to date no results from controlled studies that compare treatment efficacy between various psychiatric disorders have been published. In our study, the less severe psychiatric disorders suffered by patients in the "other psychiatric disorders" group could explain the higher effectiveness of smoking cessation treatment in this group.

The general safety data obtained from our study are similar to the findings of the Eagles' study.<sup>8</sup> Nausea and abnormal dreams were the most common adverse events reported in the varenicline group, while pruritus, insomnia and abnormal dreams were the most prevalent in the nicotine patch group. Most were mild to moderate in intensity and treatment only had to be suspended in seven cases due to the severity of these adverse effects. The type of adverse effects experienced by both varenicline users as well as nicotine patch users are similar to those reported in other studies conducted on the general population.<sup>10,22,23</sup>

The number of neuropsychiatric adverse effects found in our study is similar to that found by Eagles' study.<sup>8</sup> It is noteworthy that 6.3% of subjects suffered neuropsychiatric adverse effects, with no significant differences found between nicotine patch users and varenicline users. Furthermore, treatment only had to be suspended in four cases due to the severity of these adverse effects. An important aspect of our study is that no cases of suicidal ideation or behaviour were found. The safety data obtained in this study are comparable to the data obtained by Raich et al., who conducted a study with similar characteristics to ours in daily clinical practice. The study, which followed 90 patients with addiction or neuropsychiatric disorders, found that abnormal dreams were experienced by 27.8% of patients, and nausea by 22%.<sup>24</sup> As with our study, the onset of neuropsychiatric adverse effects was minimal.<sup>24</sup>

Our study has the following limitations: (a) it is a retrospective, non-random and uncontrolled study; (b) the appropriate instruments to detect neuropsychiatric adverse effects were not used; the study was based on the analysis conducted by the expert clinician during the visit; whilst this method is widely accepted, it is not without its limitations<sup>25</sup>; (c) we do not have data on social determinants of smoking, and other main determinants of smoking cessation such as "living with a smoker" or "being exposed to Second Hand Smoke"; (d) the number and severity of general and neuropsychiatric adverse effects were not collected in a controlled manner; and (e) the psychiatric disorders of all patients were being controlled at the time of uptake of smoking cessation treatment.

Whilst bearing these limitations in mind, it is also important to acknowledge the strengths of our study: (a) a high number of patients with various psychiatric disorders; (b) it was conducted in real-life conditions; and (c) although the results of Eagles' study confirm the safety and efficacy of smoking cessation treatment in patients with psychiatric disorders, studies such as ours that analyse the effectiveness and safety of smoking cessation drugs in patients with controlled psychiatric disorders in daily clinical practice are also necessary.

In conclusion, our study shows that varenicline and nicotine patches could be safe and effective smoking cessation treatments for patients with psychiatric disorders in daily clinical practice.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work centre on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

## Conflicts of interest

Authors declare do not have conflict of interest.

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