It is feasible and effective to help patients with severe mental disorders uit smoking: An ecological pragmatic clinical trial with transdermal nicotine patches and varenicline

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Despite the proven association between smoking and high rates of medical morbidity and reduced life expectan-cy in people with severe mental disorders (SMD), their smoking rates do not decline as they do in the general population. We carried out a non-randomized, open-label, prospective, 9-month follow-up multicentre trial to investigate the clinical efficacy, safety and tolerability of a 12-week smoking cessation programme for patients with SMD in the community under real-world clinical conditions. Eighty-two adult outpatients with schizo-phrenic/bipolar disorder smoking ≥15 cigarettes/day were assigned by shared decision between doctors and patients to transdermal nicotine patches (TNP) [36(46.2%)] or varenicline [39(50%)]. *Short-term efficacy*: The 12-week 7-day smoking cessation (self-reported cigarettes/day = 0 and breath carbon monoxide levels ≤ 9 ppm) prevalence was 49.3%, without statistically significant differences between medications (TNP 50.0% vs varenicline 48.6%, chi-square = 0.015, $p = 1.000$). *Long-term efficacy*: At weeks 24 and 36, 41.3 and 37.3% of patients were abstinent, with no statistically significant differences between treatments. *Safety and Tolerability*: no patients made suicide attempts/required hospitalization. There was no worsening on the psycho-metric scales. Patients significantly increased weight [TNP 1.1(2.8) vs varenicline 2.5(3.3), $p = 0.063$], without significant changes in vital signs/laboratory results, except significant decreases in alkaline phosphatase and low-density lipoprotein-cholesterol levels in the varenicline group. Patients under varenicline more frequently presented nausea/vomiting ($p < 0.0005$), patients under TNP experienced skin reactions more frequently ($p = 0.002$). Three patients under varenicline had elevated liver enzymes. In conclusion, we have demonstrated that in real-world clinical settings it is feasible and safe to help patients with stabilized severe mental disorders to quit smoking.

1. Introduction

Recent evidence suggests that tobacco control policies and cessation interventions were less effective in individuals with mental illness than in the general population (Le Cook et al., 2014), demonstrating the failure of the recommendations in the 50th anniversary of the 1964 Surgeon General's report (Schroeder and Koh, 2014) in this population.

In people with severe mental disorders (SMD), the estimated prevalence of smoking is between 50–80% and 54–68% for schizophrenia and bipolar disorder, respectively (De Hert et al., 2011a). These exceptionally high prevalence rates have been shown to be associated with the high rates of medical morbidity and reduced life expectancy in this population (Bobes et al., 2010; Dickerson et al., 2016; Garcia-Portilla et al., 2010, Kelly et al., 2011;). Despite the emerging evidence showing that people with SMD are motivated to quit, that smoking cessation treatments in these people are about as effective as in the general population (Chengappa et al., 2014; Evins et al., 2001, 2005, 2007; George et al., 2002, 2008), and that, in stabilized patients, it does not worsen their mental state (De Hert et al., 2011b), a study in smoker patients with bipolar disorder found that only a third of clinicians advise their patients

about smoking cessation (Prochaska et al., 2011). The underlying reasons probably have more to do with negligence and old prejudices of psychiatrists, and medical stigma than with evidence-based decisions. Therefore, the European Psychiatric Association (Rüther et al., 2014) and the Schizophrenia Patient Outcomes Research Team (PORT) (Buchanan et al., 2010) published guidance on strategies for smoking cessation in people with mental illness for psychiatrists as a tool to help eradicate therapeutic nihilism in this area.

The superiority of varenicline compared to placebo for smoking cessation in patients with schizophrenia has been demonstrated in randomized clinical trials (Weiner et al., 2011; Williams et al., 2012) and described by the Cochran group (Tsoi et al., 2013). Although the meta-analysis of Kishi and Iwata (2015) raises doubts about the efficacy of varenicline, their serious methodological problems, highlighted by Evins et al. (2015) question their conclusions. There is less evidence in patients with bipolar disorder, but recent data show superiority of varenicline over placebo both in the acute (Chengappa et al., 2014) and maintenance-treatment (Evins et al., 2014) phases. Furthermore, varenicline has recently been associated with some beneficial cognitive effects (Smith et al., 2009; Hong et al., 2011; Shim et al., 2012) and with amelioration of abstinence-induced cognitive and affective adverse effects (Liu et al., 2011; Wing et al., 2013) in patients with schizophrenia or schizoaffective disorders. Psychiatrists' concerns about psychopathological exacerbations and suicidal behaviours induced by varenicline in people with SMD does not seem fully justified according to recent reviews (Cerimele and Durango, 2012; Gibbons and Mann, 2013; Kishi and Iwata, 2015; Roberts et al., 2015; Tsoi et al., 2013; Yousefi et al., 2011) and clinical trials (Anthenelli et al., 2016; Chengappa et al., 2014; Evins et al., 2014; Pachas et al., 2012; Weiner et al., 2011; Williams et al., 2012) despite previous case reports on the subject (Ahmed, 2011; Annagur and Bez, 2012; Freedman, 2007; Knibbs and Tsoi, 2011). However, Tofler (2015) recently questioned the supposed safety of varenicline and reported a completed suicide in a patient with unstable bipolar disorder.

Much less evidence-based information is available regarding the effects of transdermal nicotine patches (TNP) in this population. Concerning efficacy, Tsoi et al. (2013) concluded that although some studies have found a decrease in the number of self-reported cigarettes per day (CPD) or in the level of physical dependence, TNP failed to demonstrate a reduction in exhaled CO level in individuals with schizophrenia. With respect to safety and tolerability, TNP was well tolerated (Horst et al., 2005), with the exception of one patient who experienced an allergic reaction (Cather et al., 2013), and patients remained psychopathologically stable during treatment (Cather et al., 2013).

In this study, we tried to avoid the drawbacks of previous studies and address the key issues of smoking cessation programmes for people with SMD. That is, (1) the trial was carried out in real-world clinical settings; (2) a specific programme was developed according to the smoking pattern and needs of persons with SMD; (3) patients were exhaustively evaluated; and, (4) patients were followed 6 months after the end of the acute treatment phase. We hypothesized that patients with SMD can be effectively treated for smoking cessation in real-world clinical settings.

The aim of this study was to investigate the clinical efficacy, safety and tolerability of a Multi-component Smoking Cessation Support Programme (McSCSP) (Garcia-Portilla et al., 2013) specifically designed for the treatment of patients with severe mental disorders under real-world clinical conditions.

2. Methods

2.1. Study design

This is a non-randomized, open-label, prospective, 9-month follow-up, multicentre study, conducted at 3 sites in Spain (Oviedo, Jaén and Vitoria) between March 2011 and June 2013. The Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo approved the study protocol (Ref. 64/2010). Written informed consent was obtained from all subjects prior to enrolment.

2.2. Subjects

Subjects were outpatients with a diagnosis of severe mental disorder. Inclusion criteria were: (1) DSM-IV diagnosis of schizophrenia, or schizoaffective or bipolar disorder, clinically stable (no hospitalization or acute exacerbation) in the 6 months prior to enrolment; (2) currently smoking ≥15 cigarettes/day without a period of smoking abstinence longer than 1 month during the previous year; (3) Fagerström Test for Nicotine Dependence (Becoña and Vazquez, 1998) score ≥ 4; (4) breath carbon monoxide (CO) level > 9 particles per million (ppm); (5) between 18 and 65 years of age; (6) no suicidal ideation; and (7) written informed consent to participate in the study.

Exclusion criteria were: (1) a total score > 70 on the Positive and Negative Symptoms Scale (Peralta and Cuesta, 1994) for patients with schizophrenia, or >14 on the Hamilton Depression Rating Scale (Bobes et al., 2003) or >6 on the Young Mania Rating Scale (Colom et al., 2002) for patients with bipolar disorder; (2) serious suicidal behaviour or thoughts in the last 6 months; (3) severe unstable somatic illness; (4) history of organic brain damage; (5) significant renal impairment (creatinine ≥1.5 mg/dL); and (6) liver function tests more than twice the upper limit of normal.

2.3. Assessments

All subjects were evaluated at baseline (before starting the motivational therapy phase), during the 12-week active treatment phase (weekly during the first 4 weeks and then biweekly), and at weeks 12 and 24 of the posttreatment follow-up phase.

The self-reported number of cigarettes smoked per day (CPD) was recorded and subjects were classified on this basis into three categories: light (self-reported CPD ≤ 10), moderate (between 11 and 20), and heavy smokers (>20). Breath CO level was measured with a portable piCOsimple™ Smokerlyzer® monitor (Bedfont Scientific Ltd., Kent, England). Since smokers have diurnal variations in CO, measurements were taken between 9.00 and 11.00 am. Nicotine dependence was evaluated using the Fagerström Test for Nicotine Dependence (Becoña and Vazquez, 1998) and the Glover-Nilsson Smoking Behavioral Questionnaire (Nerin et al., 2005).

Safety and tolerability were assessed using different sources: psychometric rating scales, anthropometric measures, vital signs, laboratory tests, and spontaneous patient self-reports. For further details see Garcia-Portilla et al. (2013).

2.4. Study treatment

The McSCSP consisted of 2 phases: (phase 1) prior to the active treatment phase, a weekly individual motivational therapy for 4 to 12 weeks and, (phase 2) a 12-week active treatment phase. During the active treatment phase, at each study visit, patients received a one- or two-week supply of medication with instructions on how to take it, in addition to specific intensive 12-week manualized group therapy on issues relevant for these patients (Garcia-Portilla et al., 2013).

2.4.1. Pharmacological treatment

The treatment drugs used in the study were those recently recommended by the European Psychiatric Association and the Food and Drug Administration, i.e. bupropion, nicotine or varenicline (Montoya and Vocci, 2007; Rüther et al., 2014). The choice of treatment for each patient was a shared decision between the clinician and the patient based on (1) the clinical characteristics of patient's mental disorder, (2) his/her smoking pattern and previous smoking cessation

experiences, (3) somatic comorbidities and their pharmacologic treatments, and (4) patient preferences.

Bupropion SR was given as recommended, i.e. 150 mg/day for the first 6 days and 150 mg twice daily for the remaining treatment period. Twenty-four-hour transdermal nicotine patches (TNP) were given to patients at doses of 14, 21, 28 or 35 mg based on their tobacco use during the last 12 weeks. Varenicline was given according to the usual schedule, i.e. 0.5 mg/day for the first 3 days, 0.5 mg twice daily on days 4–7, and 1 mg twice daily for the remaining 11 weeks.

2.5. Outcome measures and statistical analyses

The primary outcome measure was smoking cessation, a composite measure consisting of patient self-reported abstinence in the previous 7 days confirmed by breath CO levels ≤9 ppm at week 12. Also considered a main outcome measure was the proportion of subjects with at least a 50% reduction in the number of CPD over the last 7 days at week 12. Secondary outcome measures were safety, including changes in the symptoms of the primary illness and suicide attempts, and tolerability.

The statistical analysis was done using SPSS 17.0. The two-tailed level of significance used was 0.05. All analyses were performed according to an intention-to-treat approach. For dealing with missing data the last observation carried forward (LOCF) method was employed. The drug that the patient was taking at the last visit was used for the efficacy analysis. That is, 40 patients were in the TNP group (36 from the outset and 4 changed from varenicline) and 35 in the varenicline group. The chi-square test, Student's *t*-test, and paired *t*-test were used to determine statistically significant differences between treatment groups and to test for changes over time in efficacy, safety and tolerability outcomes between baseline and week 12.

A mixed between-within subject analysis of variance was conducted to assess the impact of the two pharmacological treatments (TNP and varenicline) on patient smoking and clinical variables over four time periods (pre-intervention, post-intervention and 3- and 6-month follow-up).

3. Results

In all, 82 patients were enrolled; 74.4% with schizophrenia or schizoaffective disorder and 25.6% with bipolar disorder. Four of them dropped out before the active treatment phase. Of the 78 patients who were included in the active treatment phase, 3 (3.8%) received bupropion SR, 36 (46.2%) TNP, and 39 (50%) varenicline. Fig. 1 shows patient disposition. Patients who received treatment with bupropion SR (n = 3) were excluded from the statistical analysis. Their mean age was 42.7 (sd = 9.0), 66.7% were male and all three had schizophrenia. The retention rates in the study were 61.3% at week 12, 48% at week 24 and 46.6% at week 36. There were no statistically significant differences in the retention rates among treatments. However, we found statistically significant differences in the retention rates among sites at weeks 24 and 36. In this respect, Oviedo and Jaén showed significantly higher retention rates than Vitoria (week 24: Oviedo 62.1%, Jaén 53.8%, Vitoria 20%, chi-square = 8.938, $p = 0.011$; week 36: Oviedo 62.1%, Jaén 50%, Vitoria 20%, chi-square = 8.595, $p = 0.014$).

3.1. Demographic, clinical and smoking characteristics

The demographic, clinical and smoking characteristics at baseline are given in Table 1. There were no statistically significant differences between treatment groups regarding demographic characteristics. Among patients with schizophrenia, those on varenicline had significantly more severe negative symptoms than those on TNP ($p = 0.039$). With respect to smoking history, patients on treatment with varenicline showed statistically significant greater physical dependence than patients on TNP ($p = 0.037$).

The percentage of patients with a history of suicide attempts was 38.7%, with no statistically significant differences between treatment

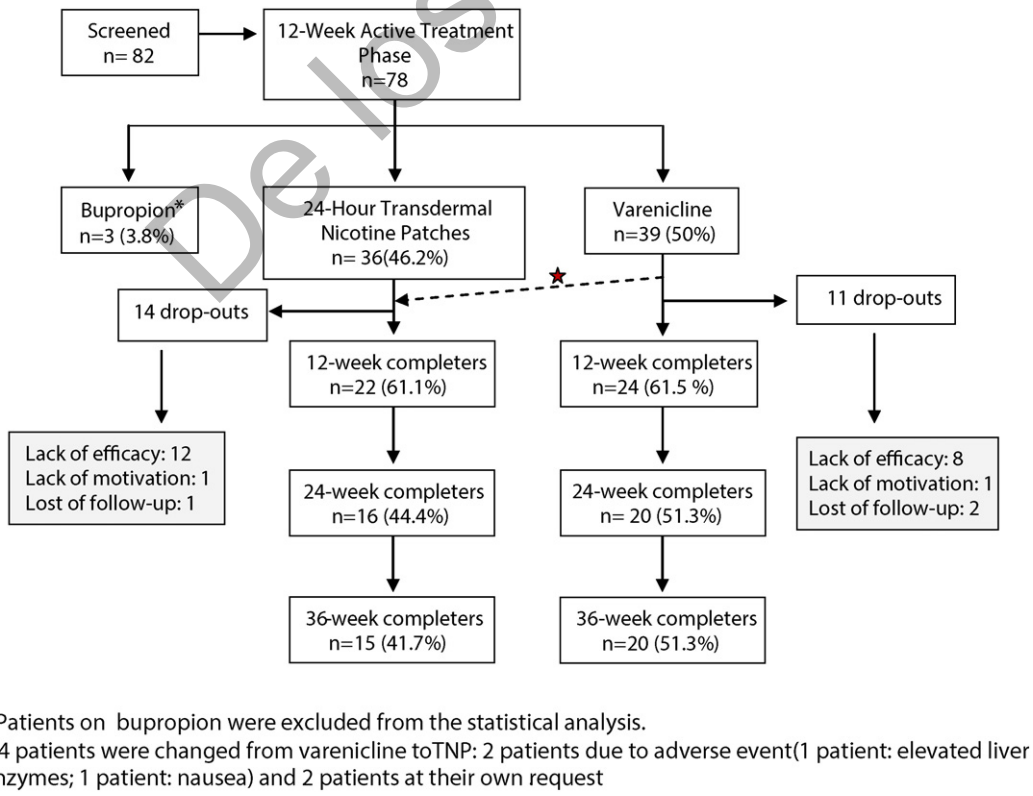


Fig. 1. Patient disposition. *Patients on bupropion were excluded from the statistical analysis. 4 patients were changed from varenicline to TNP: 2 patients due to adverse event (1 patient: elevated liver enzymes; 1 patient: nausea) and 2 patients at their own request.

Table 1
Patient demographic and baseline clinical and smoking characteristics for the total sample and for varenicline and transdermal nicotine patch (TNP) patients separately.

	Total sample n = 75	TNP n = 36	Varenicline n = 39	Statistical test, *p*
Mean age (sd)	45.3 (9.0)	45.7 (8.6)	45.0 (9.4)	-0.345[d], 0.731
Gender, males [n (%)]	49 (65.3)	25 (69.4)	24 (61.5)	0.517[e], 0.628
Marital status [n (%)]				0.152[e], 0.927
Never married	47 (62.7)	23 (63.9)	24 (61.5)	
Married or cohabiting	16 (21.3)	7 (19.4)	9 (23.1)	
Widowed or separated/divorced	12 (16.0)	6 (16.7)	6 (15.4)	
Educational level [n (%)]				1.826[e], 0.401
Primary school	32 (42.7)	16 (44.4)	16 (41.0)	
Secondary school	32 (42.7)	13 (36.1)	19 (48.7)	
University	11 (14.7)	7 (19.4)	4 (10.3)	
Work status [n (%)]				1.622[e], 0.655
Working (full/part-time)	7 (9.3)	3 (8.3)	4 (10.3)	
Disabled (temporary/permanent)	33 (44.0)	17 (47.2)	16 (41.0)	
Illness benefit	19 (25.3)	7 (19.4)	12 (30.8)	
Other[a]	16 (21.3)	9 (25.0)	7 (17.9)	
Diagnosis [n (%)]				2.259[e], 0.198
Schizophrenia	54 (72.0)	23 (63.9)	31 (79.5)	
Bipolar	21 (28.0)	13 (36.1)	8 (20.5)	
Length of illness, months [Mean (sd)]	209.2 (125.4)	197.0 (106.9)	220.4 (140.9)	0.805[d], 0.423
First episode, yes [n (%)]	10 (13.3)	6 (17.1)	4 (10.3)	0.748[e], 0.502
Comorbid SUD [n (%)]	10 (13.3)	3 (8.3)	7 (17.9)	1.498[e], 0.313
Suicidal attempts				
Yes [n (%)]	29 (38.7)	10 (27.8)	19 (48.7)	3.461[e], 0.096
Mean number (sd)	2.8 (1.8)	2.8 (2.0)	2.7 (1.7)	-0.088[d], 0.931
CGI-S [Mean (sd)]	3.5 (1.0)	3.5 (0.9)	3.6 (1.1)	0.279[d], 0.781
PANSS[b] [Mean (sd)]				
Positive	11.4 (3.8)	10.4 (3.6)	12.1 (3.9)	1.668[d], 0.101
Negative	14.9 (5.6)	13.1 (5.9)	16.3 (5.0)	2.122[d], 0.039
General psychopathology	27.2 (8.2)	25.6 (6.1)	28.3 (9.4)	1.205[d], 0.234
Total	52.2 (11.4)	49.1 (11.2)	55.4 (11.1)	1.731[d], 0.089
HDRS[c] [Mean (sd)]	5.1 (4.0)	5.8 (4.5)	3.9 (2.7)	-1.110[d], 0.281
YMRS[c] [Mean (sd)]	2.3 (2.5)	2.5 (2.4)	3.4 (2.9)	0.725[d], 0.477
Self-reported CPD [Mean (sd)]	30.1 (11.8)	28.8 (12.2)	31.3 (11.5)	0.903[d], 0.369
Smoking status				2.143[e], 0.158
Moderate (self-reported CPD 11–20)	27 (36.0)	16 (44.4)	11 (28.2)	
Heavy (self-reported CPD >20)	48 (64.0)	20 (55.6)	28 (71.8)	
Breath CO levels	27.3 (18.3)	26.4 (18.3)	28.0 (18.5)	0.359[d], 0.721
FTND score	6.3 (2.6)	5.6 (3.1)	6.9 (1.8)	2.134[d], 0.037
GN-SBQ score	17.8 (6.9)	16.5 (7.9)	19.1 (5.5)	1.589[d], 0.116

CGI-S: Clinical Global Impression - Severity; CO: carbon monoxide; CPD: cigarettes per day; FTND: Fagerström Test for Nicotine Dependence; GN-SBQ: Glover-Nilsson Smoking Behavioral Questionnaire; HDRS: Hamilton Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale; sd: standard deviation; SUD: substance use disorder; YMRS: Young Mania Rating Scale.

[a] Other includes unemployed, housewife, student, and retired.
[b] Data for PANSS are from patients with schizophrenia (n = 54).
[c] Data for HDRS and YMRS are from patients with bipolar disorder (n = 21).
[d] Student's *t*-test.
[e] Chi-square test.

groups (TNP 27.8% vs varenicline 48.7%, chi-square = 3.461, $p = 0.096$). Among those who had suicidal behaviours, the mean number of attempts was 2.8 (sd = 1.8), with no statistically significant differences between treatment groups [TNP 2.8 (sd = 2.0) vs varenicline 2.7 (sd = 1.7), Student's *t*-test = −0.088, $p = 0.931$].

3.2. Efficacy

3.2.1. Short-term efficacy

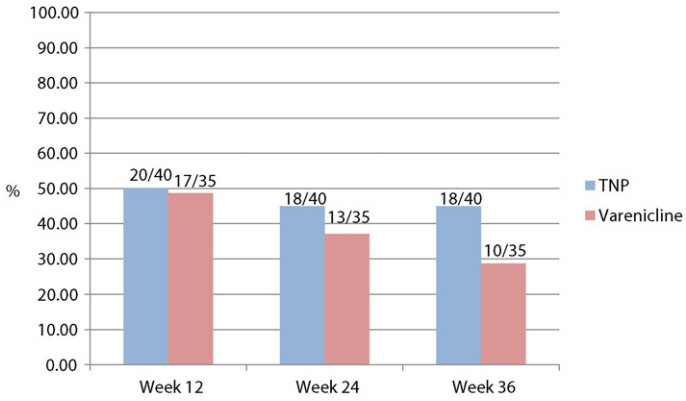
At the end of the 12-week active treatment phase, 53.3% of patients reported abstinence from smoking in the previous 7 days. This self-reported abstinence was confirmed by breath CO levels ≤9 ppm in 92.5% of the cases. Thus, the 12-week 7-day smoking cessation prevalence in the McSCSP was 49.3% (37 patients), with no statistically significant differences between medications (TNP 50.0% vs varenicline 48.6%, chi-square = 0.015, $p = 1.000$) (see Fig. 2).

At week 12, the prevalence of self-reported 50% or more reduction in the number of CPD over the previous 7 days was 81.3%. Again, there were no significant differences between treatment groups (TNP 80.0% vs varenicline 82.9%, chi-square = 0.100, $p = 0.776$).

3.2.2. Long-term efficacy

At 24 and 36 weeks, 41.3 and 37.3% of the patients in the study were abstinent (previous 7-day self-reported CPD = 0 and breath CO levels ≤ 9 ppm). There were no statistically significant differences between treatments (week 24: TNP 45.0% versus 37.1%, chi-square = 0.475, $p = 0.639$; week 36: TNP 45.0% versus 28.6%, chi-square = 2.153, $p = 0.159$) (see Fig. 2). Eight of 37 patients (21.6%) who were abstinent at week 12 had returned to smoking at week 24 (3 patients in the TNP group and 5 in the varenicline group) and 2 of 36 (5.3%) who were smokers achieved abstinence (1 from each drug group). At week 36, 3 of 31 patients (9.7%) who were abstinent at week 24 returned to smoking (all in the varenicline group). No patients quit smoking between weeks 24 and 36.

Seventy-three per cent of patients self-reported a 50% or more reduction in the number of CPD in the previous 7 days at week 24, and as did 74.7% in week 36. In both time periods, there were no statistically significant differences between treatment groups (week 24: TNP 72.5% vs varenicline 74.3%, chi-square = 0.030, $p = 1.000$, week 36: TNP 75.0% vs varenicline 74.3%, chi-square = 0.005, $p = 1.000$). Changes in breath CO levels in those with at least a 50% of self-reported reduction in the number of CPD were from 29.1 (19.5) at baseline to 9.75 (13.3) at



There were no statistically significant differences in efficacy rates between the two drugs at any time period.
Numbers represent: numerator: number of abstinent subjects at each timepoint; denominator: total number of subjects under this treatment (according to ITT).
[a] Patient self-reported abstinence in the previous 7 days confirmed by breath CO levels ≤ 9 ppm.

Fig. 2. Short- and long-term efficacy[a] for transdermal nicotine patches (TNP) and varenicline. There were no statistically significant differences in efficacy rates between the two drugs at any time period. Numbers represent: numerator: number of abstinent subjects at each timepoint; denominator: total number of subjects under this treatment (according to ITT). [a]Patient self-reported abstinence in the previous 7 days confirmed by breath CO levels ≤9 ppm.

week 12 ($t = 8.022$, $p \leq 0.0005$), to 5.9 (9.0) at week 24 ($t = 9.792$, $p \leq 0.0005$), and to 11.9 (14.5) at week 36 ($t = 7.874$, $p \leq 0.0005$).

3.3. Change of smoking variables over four time periods

There was a substantial main effect for time, with both treatment groups showing a reduction in self-reported CPD, breath CO levels and scores on the FTND and GN-SBQ over the time periods. The main effect comparing the two drugs was not significant for any of the variables, suggesting no difference in the efficacy of the two drugs (see Table 2). Furthermore, since patients under treatment with Varenicline had significantly greater scores on the FTND and PANSS-P scales at baseline than patients under TNP (see Table 1) we performed a one-way between-groups analysis of covariance including these two variables along with baseline CPD or CO levels as covariates. Again, we did not find statistical significant differences between the two groups in self-reported CPD [F = 0.257, $p = 0.614$, partial eta squared = 0.004] and breath CO levels [F = 0.187, $p = 0.667$, partial eta squared = 0.003] at week 12″.

Regarding smoking status, patients significantly moved towards less severe categories from week 12 onwards in both treatment groups (see Table 2).

3.4. Safety and tolerability

Concerning safety, during the 12-week active treatment no patients made suicide attempts or required hospitalization. One patient with bipolar disorder treated with varenicline reported low suicidal ideation but did not require any specific intervention for that.

With respect to other psychopathological exacerbations, there was no worsening in the scores on the different psychiatric rating scales. Furthermore, in patients with schizophrenia, statistically significant decreases were found in the PANSS positive, general psychopathology, and total scores in the varenicline group (see Table 3).

In both treatment groups, patients experienced significant increases in weight and BMI with no significant changes in vital signs or laboratory results, with the exception of significant decreases in ALP and LDL cholesterol levels in the varenicline group (see Table 3). There were no significant differences in the increase in weight [TNP 1.1 (2.8) vs varenicline 2.5 (3.3), $t = 1.889$, $p = 0.063$] or BMI [TNP 0.5 (0.9) vs varenicline 1.0 (1.3), $t = 1.596$, $p = 0.115$] between groups.

Regarding adverse events (Table 4), 58.3% of patients receiving TNP and 69.2% of those receiving varenicline experienced at least one treatment-emergent side effect. In two patients, varenicline had to be changed for TNP (one 21 mg/day and the other 14 mg/day), due to elevated liver enzymes (1 patient) and nausea (1 patient). Furthermore, the dosage was reduced from 2 mg/day to 1 mg/day in five patients before the end of treatment. The reasons were nausea (2 patients), elevated liver enzymes (2 patients) and somnolence (1 patient). In spite of this, two of these five patients were switched to TNP (14 mg/day) at their own request. In all other patients, adverse events were described as mild or moderate and transient. As can be seen in Table 4, patients in the varenicline group more frequently presented nausea/vomiting ($p < 0.0005$) while TNP group patients experienced skin reactions more frequently ($p = 0.002$).

4. Discussion

This non-randomized, open-label, prospective, 9-month follow-up, multicentre trial demonstrated the effectiveness of a Multi-component Smoking Cessation Support Programme specifically designed for patients with schizophrenia or bipolar disorder in real-world clinical settings. After 12 weeks of treatment with TNP or varenicline, combined with group therapy, a smoking cessation rate of 50% was achieved (smoking cessation was defined as patient self-reported abstinence in the previous 7 days confirmed by breath CO levels ≤9 ppm). As expected, this rate decreased with time, but 6 months after the end of the acute-treatment phase, 37% of patients in the trial remained abstinent. There were no differences in the dropout rates between the two drugs at any point in the study. Both pharmacological treatments were safe and generally well tolerated.

The retention rates in our study were slightly lower than in other studies (Chengappa et al., 2014; Evins et al., 2014) despite the fact that our programme was specifically designed for patients with SMD. Most dropouts occurred during the acute-treatment phase (almost 40% for each drug). Although four patients on varenicline had to be switched to TNP due to adverse events and in three the dose was reduced from 2 to 1 mg/day for the same reason, these seven patients did not withdraw from the study.

Contrary to the retention rates, our varenicline 12- and 24-week cessation rates were superior to those previously reported for patients with schizophrenia (Williams et al., 2012) and bipolar disorder (Chengappa

Table 2
Smoking characteristics for transdermal nicotine patches (TNP) and varenicline treatments over four time periods.

	TNP				Varenicline				Statistical test		
	Baseline	W12	W24	W36	Baseline	W12	W24	W36	Interaction effect (Time * Drug)	Main effect for Time	Main effect for Drug
									Wilks' Lambda, F^b, p	Wilks' Lambda, F, p	F, p
[mean (sd)]											
CPD	28.7 (11.9)	7.1 (9.7)	9.1 (10.5)	8.7 (10)	31.7 (11.7)	7.3 (10.5)	10.8 (11.7)	10.4 (10.5)	0.976, (3.71) 0.577, 0.632	0.267, (3.71) 64.889, <0.0005	0.716, 0.400
Breath CO level	26.0 (17.4)	11.0 (13.1)	11.4 (13.4)	11.8 (13.9)	28.7 (19.4)	11.5 (14.9)	11.4 (13.4)	11.8 (13.9)	0.948, (3.68) 1.239, 0.302	0.542, (3.68) 19.148, <0.0005	0.735, 0.394
FTND scores	5.6 (2.9)	2.5 (3.1)	2.6 (3.1)	2.7 (3.1)	7.0 (1.8)	2.4 (3.1)	3.1 (3.3)	3.7 (3.1)	0.890, (3.71) 2.916, 0.040	0.413, (3.71) 33.639, <0.0005	1.668, 0.201
GN-SBQ scores	16.3 (7.6)	9.5 (9.6)	9.3 (9.8)	9.4 (9.7)	19.7 (5.4)	7.3 (6.8)	9.2 (8.0)	10.5 (8.4)	0.785, (3.69) 6.317, 0.001	0.377, (3.69) 37.957, <0.0005	0.125, 0.725
									Between treatments chi-square, p	Within treatment chi-square, p TNP	Varenicline
Smoking[a] *[n (%)]*											
Abstinent		22 (55.0)	19 (47.5)	19 (47.5)		18 (51.4)	14 (10.0)	12 (34.3)	Base: 3.013, 0.097		
Mild		6 (15.0)	5 (12.5)	6 (15.0)		6 (17.1)	4 (11.4)	8 (22.9)	W12: 0.210, 0.976	Base-W12: 44.308, <0.0005	Base-W12: 42.30, <0.0005
Moderate	18 (45.0)	8 (20.0)	10 (25.0)	11 (27.5)	9 (25.7)	8 (22.9)	13 (37.1)	11 (31.4)	W24: 1.333, 0.721	W12–24: 0.933, 0.818	W12–24: 2.233, 0.525
Heavy	22 (55.0)	4 (10.0)	6 (15.0)	4 (10.0)	26 (74.3)	3 (8.6)	4 (11.4)	4 (11.4)	W36: 1.540, 0.673	W24–36: 0.539, 0.910	W24–36: 1.654, 0.647

Base: baseline; CO: carbon monoxide; CPD: cigarettes per day; FTND: Fagerström Test for Nicotine Dependence; GN-SBQ: Glover-Nilsson Smoking Behavioral Questionnaire; TNP: transdermal nicotine patches; sd: standard deviation; W: week.
[a] Smoking self-reported status: Abstinent: self-reported CPD 0, Mild: self-reported CPD 1–10, Moderate: self-reported CPD 11–20, Heavy: self-reported CPD >20.
[b] F is presented as: (Hypothesis df, Error df) F value.

et al., 2014). We think that this may be related to the design of the study. That is, regular clinical context, shared decisions about pharmacological treatment, and adjunctive treatment with specific intensive 12-week manualized group therapy. Furthermore, the self-reported 50% or more reduction rate in the number of CPD over the previous 7 days was very high and remained virtually constant throughout the study, with no statistically significant differences between treatment groups. We consider this finding of great interest as it raises the possibility that more intensive interventions (pharmacological treatment for 24 weeks, monthly booster group therapy sessions after the intensive 12-week sessions, etc.) may improve the transition of these patients to total abstinence. As in other studies, we also found a significant temporal trend for reduction in CPD and breath CO level with both varenicline (Pachas et al., 2012) and TNP. Scores on physical and psychological dependence scales followed the same significant trend.

The relapse rate of our study is quite modest. We think that this may be due to different factors including the high dropout rate (almost 40%) in the first 12 weeks of the study, the design and the setting of the study [(1) regular clinical context, that means that at each site the patients' psychiatrist was also researcher, (2) relatively small mental health centres with specific catchment areas and coordination with general practitioners], the informal positive reinforcement made to the patients by the staff of the centres (nurses, secretaries, …), and the relatively short follow-up period (3 and 6 months after the end of the acute phase of the study).

With respect to safety, in patients with schizophrenia under treatment with varenicline, improvements were observed in all scales of the PANSS, with the exception of the negative scale. Pachas et al. (2012) also reported significant improvement in ratings of psychosis, and Evins et al. (2014) found more than twice the psychiatric hospitalizations in the placebo group compared with varenicline. In the EAGLES study, Anthenelli et al. (2016) did not found significant differences in neuropsychiatric adverse events among varenicline, bupropion, TNP and placebo. However, one case of exacerbation of schizophrenia was reported (Freedman, 2007), and several case reports have described manic (Ahmed, 2011; Knibbs and Tsoi, 2011) and psychotic symptoms (Annagur and Bez, 2012) in patients with bipolar disorder on varenicline. These data indicate that, although infrequent, psychopathological exacerbations may occur, so that smoking cessation programmes should be led by psychiatrists and good clinical practices must be followed. In our study, suicidal ideation was not a significant problem (only one patient with bipolar disorder treated with varenicline reported low suicide ideation). In this sense, most studies have not found significant differences in suicidal ideation rates between varenicline and placebo during the acute-treatment phase (Chengappa et al., 2014; Evins et al., 2014; Gibbons and Mann, 2013; Weiner et al., 2011; Williams et al., 2012). On the other hand, it is necessary to point out that tobacco smoking was found to be a predictor of suicidal ideation and behaviour in patients with bipolar disorder (Ostacher et al., 2009) and a predictive factor of natural mortality in schizophrenia (Dickerson et al., 2016). Although the issue of suicide is of great concern, the Tofler's (2015) requirement that patients with bipolar disorder be hospitalized for smoking cessation may represent a step backwards and a handicap in the fight against nicotine dependence. We have demonstrated that stable patients with SMD may be safely helped to quit smoking in outpatient clinics with adequate monitoring.

Weight and BMI significantly increased in both treatments. The average weight increase was 1.1 and 2.5 kg for TNP and varenicline, respectively. The weight increase with varenicline was similar to the findings of Chengappa et al. (2014) and Pachas et al. (2012). TNP did not produce any significant change in laboratory results. By contrast, varenicline produced clinically significant increases in liver function tests in five of the 39 patients treated with it, although no statistically significant changes were observed in the total sample. In addition, statistically significant decreases in total bilirubin and HDL-cholesterol levels were observed. To our knowledge, there are no studies reporting changes either in liver function tests or in lipid profile, and the few

Table 3
Safety in the transdermal nicotine patches (TNP) and varenicline treatment groups.

	TNP			Varenicline		
	Baseline	Week-12	Paired *t*-test, *p*	Baseline	Week-12	Paired *t*-test, *p*
	Mean (sd)	Mean (sd)		Mean (sd)	Mean (sd)	
PANSS						
PANSS-Positive	10.8 (3.6)	10.5 (3.6)	1.382, 0.179	11.9 (4.0)	10.1 (3.6)	2.872, 0.008
PANSS-Negative	13.6 (5.8)	14.2 (6.8)	-0.851, 0.403	16.1 (5.3)	15.1 (5.4)	1.805, 0.082
PANSS-General Psychopathology	26.0 (6.3)	24.9 (7.1)	1.134, 0.267	28.3 (9.6)	23.6 (5.4)	2.594, 0.015
PANSS-Total	50.5 (11.4)	49.5 (13.2)	0.581, 0.567	53.8 (11.3)	48.9 (10.6)	2.217, 0.035
HDRS	5.6 (4.5)	5.5 (5.5)	0.053, 0.959	4.7 (2.7)	3.3 (4.3)	1.061, 0.337
YMRS	2.5 (2.3)	2.1 (3.9)	0.497, 0.628	4.2 (2.9)	3.0 (5.0)	0.636, 0.553
CGI-S	3.5 (0.9)	3.5 (1.0)	0.422, 0.676	3.5 (1.1)	3.4 (1.0)	1.000, 0.324
Weight (kg)	86.0 (12.9)	87.1 (12.7)	-2.337, 0.025	85.9 (21.8)	88.4 (21.9)	-4.339, <0.0005
BMI (kg/m^2)	30.4 (4.5)	31.0 (4.7)	-3.254, 0.003	31.1 (6.8)	32.0 (6.8)	-4.407, <0.0005
Heart rate (bpm)	81.6 (16.3)	81.2 (18.6)	0.155, 0.878	84.6 (15.5)	82.7 (15.5)	0.931, 0.359
Blood pressure						
Diastolic (mm Hg)	72.2 (10.6)	74.0 (10.4)	-1.177, 0.247	78.3 (11.8)	79.8 (9.9)	-0.935, 0.357
Systolic (mm Hg)	112.7 (12.3)	115.4 (15.2)	-1.538, 0.134	118.9 (19.7)	123.5 (18.5)	-1.037, 0.307
Creatinine (mg/dL)	0.8 (0.2)	0.8 (0.1)	1.409, 0.168	0.8 (0.2)	0.8 (0.2)	-0.210, 0.835
Urea (mg/dL)	31.1 (8.7)	31.2 (8.7)	-0.076, 0.940	31.0 (9.2)	31.1 (9.4)	-0.144, 0.887
Glomerular filtration rate (mL/min per 1.73 m^2)	100.4 (13.1)	99.4 (13.2)	0.578, 0.569	99.7 (24.1)	97.7 (21.9)	0.886, 0.393
AST (U/L)	19.2 (6.9)	20.5 (7.5)	-1.630, 0.113	21.3 (9.6)	22.3 (9.8)	-0.892, 0.379
ALT (U/L)	23.5 (11.6)	25.5 (13.6)	-1.460, 0.153	27.6 (17.8)	32.6 (24.2)	-1.530, 0.135
GGT (U/L)	34.1 (21.4)	36.6 (24.1)	-1.718, 0.095	42.3 (31.9)	41.8 (29.9)	0.320, 0.751
Total bilirubin (mg/dL)	0.5 (0.2)	0.5 (0.2)	0.648, 0.522	0.4 (0.2)	0.4 (0.2)	-0.093, 0.926
ALP (U/L)	71.6 (23.6)	71.6 (23.8)	-0.026, 0.980	74.5 (16.9)	71.3 (15.5)	2.205, 0.034
Cholesterol (mg/dL)	208.8 (42.5)	205.0 (45.2)	0.758, 0.454	205.2 (42.1)	199.6 (39.7)	1.766, 0.085
HDL cholesterol (mg/dL)	42.6 (9.5)	44.1 (10.4)	-2.011, 0.052	45.9 (13.8)	46.1 (13.5)	-0.242, 0.810
LDL cholesterol (mg/dL)	136.4 (35.2)	131.8 (34.9)	1.249, 0.221	129.8 (39.0)	122.2 (39.8)	2.515, 0.017
Triglycerides (mg/dL)	170.2 (107.1)	186.7 (108.9)	-1.467, 0.152	167.7 (128.5)	177.5 (145.9)	-0.928, 0.359

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CGI-S: Clinical Global Impression - Severity; GGT: gamma glutamyl transferase; HDL: High-density lipoprotein; HDRS: Hamilton Depression Rating Scale; LDL: low-density lipoprotein; TNP: transdermal nicotine patches; PANSS: Positive and Negative Syndrome Scale; sd: standard deviation; YMRS: Young Mania Rating Scale.

available studies (Chengappa et al., 2014; Williams et al., 2012) did not find significant changes.

There are potential limitations to this study. First, the sample size of 78 patients with SMD and the dropout rate (nearly 40% at week 12) limit the statistical power to accurately detect rare serious adverse events, although the ITT approach to statistical analysis was used. Secondly, the efficacy and safety of bupropion could not be tested in this study since only 3 patients were receiving this treatment, and we decided to exclude them from the analysis. Third, the total PANSS score exclusion criteria is quite low and may limit the generalizability of our results to only the mild-moderate patients.

The most important strength of our study is that it can be considered an ecological pragmatic clinical trial. Such studies have the advantage over randomized controlled trials that, with similar internal validity, they have greater external validity as they are conducted in the community, in real-world clinical settings under real-world clinical conditions. The extensive and exhaustive psychopathological and physical evaluations done in the study also add value to our data.

In conclusion, it is feasible and safe to help patients with stabilized severe mental disorders to quit smoking either with varenicline or with transdermal nicotine patches in combination with specific intensive group therapy in real clinical settings. Further studies with larger samples should be done in order to determine the comparative efficacy of these two drugs in this population.

Table 4
Adverse events for transdermal nicotine patches (TNP) and varenicline treatments.

	TNP (n = 36)	Varenicline (*n* = 39)	Chi-square, *p*
At least one AE [n (%)]	21 (58.3)	27 (69.2)	0.965, 0.326
Switched drug due to AE [n (%)]	0 (0.0)	4 (10.2)	3.900, 0.116
Dose reduced due to AE [n (%)]	0 (0.0)	3 (7.8)	2.885, 0.241
Adverse event [n (%)]			
Abnormal/vivid dreams	9 (25.0)	4 (10.3)	2.840, 0.092
Agitation	0 (0.0)	1 (2.6)	0.936, 0.333
Constipation	5 (13.9)	9 (23.1)	1.041, 0.308
Depressed mood	5 (13.9)	3 (7.7)	0.754, 0.385
Dizziness	1 (2.8)	2 (5.1)	0.269, 0.604
Dry mouth	0 (0.0)	1 (2.6)	0.936, 0.333
Fatigue/weakness	5 (13.9)	4 (10.3)	0.234, 0.629
Headache	5 (13.9)	3 (7.7)	0.754, 0.385
Insomnia	1 (2.8)	5 (12.8)	2.565, 0.109
Nausea/vomiting	0 (0.0)	12 (30.8)	13.187, <0.0001
Skin rash/skin redness around patch site	10 (27.8)	1 (2.6)	9.509, 0.002
Suicidal ideation	0 (0.0)	1 (2.6)	0.936, 0.333
Tachycardia or palpitation	1 (2.8)	0 (0.0)	1.098, 0.295

AE: adverse event.

Conflict of interest

Julio Bobes has received research grants and served as consultant, advisor or speaker for the companies: AB-Biotics, Adamed, Almirall, AstraZeneca, Bristol-Myers Squibb, Ferrer, Glaxo- Smith-Kline, Hoffman La Roche, Janssen-Cilag, Lilly, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Sanofi-Aventis, Servier, Shering-Plough and Shire, research funding from the Spanish Ministry of Economy and Competiveness – Centro de Investigación Biomedica en Red area de Salud Mental (CIBERSAM) and Instituto de Salud Carlos III-, Spanish Ministry of Health, Social Services and Equality - Plan Nacional sobre Drogas- and the 7th Framework Program of the European Union.

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Fernando Sarramea has served as advisor to: Bristol-Myers Squibb, Janssen and Lundbeck; and as speaker to: Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Lundbeck, Otsuka, Pfizer, and Wyeth.

All other researchers report no biomedical financial interests or potential conflicts of interests.

Contributors

Drs. Bobes and García-Portilla designed the study. Drs. Elizagarate, Iglesias and Sarramea, Susana Al-Halabí, Eva Diaz-Mesa, Gonzalo Galvan, and Leticia Garcia-Alvarez assisted in carrying out the study. Dra. Saiz and Teresa Bobes-Bascaran assisted in the analysis of the data. Dra. Garcia-Portilla and Leticia Garcia-Alvarez wrote the first draft of the study. All authors aided in the interpretation of the data and reviewed and commented on the manuscript.

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The funding source had no role in the collection of the data, the interpretation of the data, or the preparation of the manuscript.

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