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

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ABSTRACT

Despite the proven association between smoking and high rates of medical morbidity and reduced life expectancy 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 schizophrenic/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 psychometric 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., 2015; 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

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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

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