Tobacco and cognitive performance in schizophrenia patients: the design of the COGNICO study

Tabaco y rendimiento cognitivo en pacientes con esquizofrenia: diseño del estudio COGNICO

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Abstract

People with schizophrenia constitute a substantial part of the people who still smoke. Regarding cognitive performance, the self-medication hypothesis states that patients smoke to improve their cognitive deficits based on the stimulating effects of nicotine. The aim of this paper is to describe in detail the methodology used in the COGNICO study. A quasi-experimental, observational, prospective, multicenter study with follow-ups over 18 months was conducted in three cities in northern Spain (Oviedo, Ourense and Santiago de Compostela). A total of 81 outpatient smokers with schizophrenia were recruited with a mean age 43.35 years (SD = 8.83), 72.8% of them male. They were assigned to 3 groups: a) control group (smokers); b) patients who quit smoking using nicotine patches; c) patients who quit smoking with Varenicline. The MATRICS neuropsychological battery was applied as a primary measure. In addition, a comprehensive assessment of patients was performed, including the number of cigarettes per day, physical and psychological dependence on nicotine and CO expired. Clinical evaluation (PANSS, HDRS, CGI, C-SSRS), anthropometric measurements and vital signs assessment was also performed. The aim is to identify the relationship between the pattern of tobacco use and cognitive performance by comparing scores on the neuropsychological battery MATRICS during the follow-up periods (3, 6, 12 and 18months). The importance of this study lies in addressing a topical issue often ignored by clinicians: the unacceptably high rates of tobacco use in patients with severe mental disorders

Keywords: Tobacco; schizophrenia; cognitive performance; Varenicline; nicotine patches.

Resumen

Las personas con esquizofrenia constituyen una parte sustancial de las personas que todavía fuman. La hipótesis de la automedicación en relación al rendimiento cognitivo mantiene que los pacientes fuman para mejorar su déficit cognitivo basándose en los efectos estimulantes de la nicotina. El objetivo de este artículo es describir la metodología del estudio COGNICO. Estudio cuasiexperimental, observacional, prospectivo, multicéntrico y con seguimiento a 3, 6, 12 y 18 meses. Fue llevado a cabo en tres ciudades del norte de España (Oviedo, Ourense y Santiago de Compostela). Se reclutaron 81pacientes con esquizofrenia fumadores (edad media de 43,35 años (DT=8,83). 72,8% varones). Se asignaron a 3 grupos: a) control: pacientes fumadores; b) pacientes que dejan de fumar mediante parches de nicotina; c) pacientes que dejan de fumar mediante vareniclina. Como medida primaria se aplicó la batería neuropsicológica MATRICS. Además, se llevó a cabo una evaluación comprehensiva de los pacientes, que incluía el número de cigarrillos por día, la dependencia física y psicológica a la nicotina y el CO expirado. También se realizó una evaluación clínica general (PANSS, HDRS, ICG, C-SSRS) así como un seguimiento de las medidas antropométricas y los signos vitales. Se pretende identificar la relación entre el patrón de consumo de tabaco y el rendimiento cognitivo mediante la comparación de las puntuaciones en la batería neuropsicológica MATRICS durante los períodos de seguimiento.

Palabras clave: Tabaco; esquizofrenia; rendimiento cognitivo; vareniclina; parches de nicotina.

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Despite the steady decline in tobacco consumption in the general population, people with serious mental disorders such as schizophrenia are an exception to this trend (García-Portilla et al., 2014). In fact, these patients constitute a significant proportion of people who still smoke (Lancet, 2013), with a rate of two to four times greater than among the general population (Lising-Enriquez & George, 2009), or - according to some very recent publications - even five times higher (Beck, Baker & Todd, 2015). In Spain, the prevalence of cigarette smoking among patients with schizophrenia is 54.4% (Bobes, Arango, García-García & Rejas, 2010). This is practically double the rate of the general Spanish population, estimated at 24.1% (Encuesta Nacional de Salud, 2011/12).

It is currently difficult to open any scientific publication on the subject of cognitive performance in patients with psychotic disorders who also smoke without reading about the etiopathogenic aspects of this kind of consumption or references to possible causal explanations of the addictive disorder among this type of patient (Burda et al., 2010; Dervaux & Laquelille, 2008; Dolam et al., 2004; Sacco et al., 2005). This high prevalence has been noted in a variety of countries and cultures, which suggests that a hypothetical biological factor may be responsible for making these patients more susceptible to smoking (De Leon, Díaz, Aguilar, Jurado & Gurpequi, 2006). The self-medication hypothesis is an attempt to explain this potential mediating factor (Segarra et al., 2010).

On the one hand, numerous publications argue that people with schizophrenia smoke in order to reduce the adverse effects of antipsychotic medication. In fact, various studies have found that patients who smoke have lower prevalence and severity of extrapyramidal symptoms compared to patients who do not (Carrillo et al., 2003; De Leon et al., 2006; Dervaux & Laquelille, 2008). Nevertheless, a great deal of controversy surrounds this topic because the results have not always been consistent (De Leon et al., 2006). In addition, it appears that the attempt to relieve the negative effects of the treatment cannot by itself explain the high prevalence of tobacco consumption given that this is similar among both chronic patients and those suffering their first psychotic episodes. Studies by Beratis, Katrivanou and Gourzis (2001), and Kelly and McCreadie (1999) demonstrate that 86-90% of patients who smoke started doing so before being diagnosed with the disorder. Weiser et al. (2004) show that those at risk of developing schizophrenia also present risk factors for smoking onset.

Some authors therefore argue that the factor which mediates between tobacco consumption and the presence of a psychotic disorder has to be a characteristic inherent in the disorder, thus constituting a premorbid symptom. This factor could be cognitive deficit, which at present appears as a nuclear characteristic of the psychotic disorder prior to its manifestation (Andreou et al., 2015; Green & Harvey, 2014; Segarra et al., 2010).

The self-medication hypothesis with regard to cognitive performance holds that patients smoke in order to reduce their cognitive deficits on the basis of the stimulating effects of nicotine, which improves the visuospatial working memory and reduces the attentional deficits of these subjects (Depatie et al., 2002; Harris et al., 2004; Jacobsen et al., 2004; Sacco et al., 2005), as well as the deficits in sensory processing (Leonard & Adams, 2006). However, results in this area are also contradictory because such benefits have not been replicated in other research (Harris et al., 2004; Sacco et al., 2005), nor have these positive effects been found in other cognitive domains such as language production or executive functions (Harris et al., 2004, Sacco et al., 2005; Smith et al., 2006). In Spain, a study published by Segarra et al. (2010) and carried out with patients being treated for their first psychotic episode found that while smokers scored better in attention tasks and working memory after the initial stabilization of clinical symptoms, the scores of non smokers increased more quickly over the period studied so that both groups carried out the attention tasks and working memory tasks equally well after one year of treatment.

In any case, the beneficial effects of nicotine would not justify such a harmful habit as smoking, associated as it is with more than 4000 toxins and 60 carcinogenic substances. These drawbacks have led some authors in recent years to propose the use of nicotine (Levin & Rezvani, 2002; Piñeiro et al., 2014) as a way of modifying damaged cognitive function in patients (Smith et al., 2006; Barr et al., 2008).

For the above mentioned reasons we believe that a greater understanding of the role played by tobacco in cognitive performance of schizophrenia patients can contribute to a clarification regarding the questions outstanding on this topic and to open new ways of treating the neuropsychological deficits of these patients on the basis of neuronal nicotinic receptor mechanisms (Levin & Rezvani, 2006). Such mechanisms have been identified as a therapeutic objective by the NIMH's MATRICS program (*Measurement And Treatment Research to Improve Cognition in Schizophrenia*), which led to a consensus neuropsychological battery for the study of cognition in schizophrenia using a wide ranging scientific assessment of measures (Nuechterlein et al., 2008).

This article aims, therefore, to describe the methodology of the COGNICO study, the main objective of which is to identify the links between nicotine and cognitive performance in schizophrenia patients through the comparison of scores in the MATRICS neuropsychological battery over a monitoring period of 18 months.

Method

Study design

This quasi-experimental, observational, prospective, multicenter study was carried out in three northern Spanish cities (Oviedo, Ourense and Santiago de Compostela)

between 2012 and 2015, with follow-ups at 3, 6, 12 and 18 months. The sample was recruited in two mental health centers in Oviedo (CSM Corredoria and CSM La Ería), the Conxo Psychiatric Hospital in Santiago de Compostela and the Addictive Behaviours Unit of the Ourense Hospital Complex. The participants were spread across three groups:

a. schizophrenia patients who smoke;
b. schizophrenia patients who quit smoking at the start of the study (after baseline assessment) using nicotine patches as substitution treatment;
c. schizophrenia patients who quit smoking at the start of the study (after baseline assessment) using methods which do not include nicotine substitution: Varenicline

This study was approved by the Regional Clinical Research Ethics Committee of the Principality of Asturias. All participants signed a letter of informed consent.

Participants

The participants are patients diagnosed with schizophrenia and under outpatients maintenance treatment. The initial recruitment target of 20 per group (n = 60) was exceeded, with a final total of 81participants with a mean age 43.35 years (SD = 8.83), 72.8% of which were men (n = 59). The control group was made up of 25 patients (30.9%), while 32 (39.5%) were assigned to the nicotine patch group and 24 (29.6%) to the varenicline group. Baseline mean daily cigarette consumption was as follows: control group = 29.76 (SD=13.13); nicotine patch group = 26.81 (SD=11.85); varenicline group = 27.63 (SD=12.13).

Patients were selected from those who had expressed a wish to give up smoking or other patients who smoked and wished to take part.

Inclusion criteria were: (1) diagnosis of schizophrenia according to ICD-10 criteria, being clinically stable for the previous six months in the eyes of the clinician (without hospitalizations or significant flare-ups in symptoms which required an intensification of psychiatric treatment), and receiving maintenance treatment; (2) smokers consuming at least ten cigarettes per day over the previous year without a period of abstinence longer than one month in the same year; (3) aged between 18 and 65; (4) currently no suicidal ideation and (5) signed letter of informed consent. Patients were excluded if they met one of the following criteria: (1) Scores above 70 points on the PANSS or above 20 points on the HDRS (Hamilton Depression Rating Scale); (2) presence of suicidal ideation or behavior in the previous six months; (3) history of organic brain damage, including epilepsy, tumors, head injuries with significant cognitive deterioration.

Variables and assessment instruments

All the assessments (see Table 1) were carried out by psychiatrists adequately trained for the purpose and imple-

Table 1. *Areas assessed and instruments used in the COGNICO study*

Assessment area		Assessment instruments / Biological parameters
Tobacco use	Pattern of use	Cigarettes smoked per day (CSD)
		Amount of carbon monoxide (CO) expired
	Nicotine dependence	Fagerström test of nicotine dependence (FTND) Glover-Nilsson questionnaire of psychological dependence (GNT)
Other substances	Caffeine	Daily consumption
	Others	Any consumption
Psychopathology	Schizophrenia	Positive and Negative Syndrome Scale (PANSS)
	Depression	Hamilton Depression Rating Scale (HDRS)
	Attempted suicide	Columbia-Suicide Severity Rating Scale (C-SSRS)
	Severity	Clinical Global Impression: Severity (CGI-S) and Change (CGI-C)
Biological assessment	Anthropometrics	Weight, height, BMI, waist circumference
	Vital signs	Blood pressure, pulse
Neuropsychological assessment	MATRICS Battery	Processing speed: *Verbal fluency* (FAS), *Brief Assessment of Cognition in Schizophrenia* (BACS), and *Trial Marking Test Part A (*TMT A) Attention and monitoring: *Test of Continuous Performance* and *Identical Pairs* (CPT-IP) Working memory: *Span tests letters, numbers* and *Wechsler Memory Scale* (WMS-III) Verbal learning: *Hopkins Verbal Learning Test* (HVLT) Visual memory: *Brief Visuospatial Memory Test* (BVMT) Reasoning and problem solving: *Neuropsychological Assessment Battery* (NAB) Social cognition: *Mayer-Salovey-Caruso Emotional Intelligence Test* (MSCEIT)

mented in each of the follow-ups (except sociodemographic and clinical data, which were only gathered at baseline).

Sociodemographic and clinical data

Data were collected on age, sex, marital status, level of education, occupation and employment situation. The following clinical data were gathered: primary diagnosis of schizophrenia (carried out by a psychiatrist), secondary diagnosis, duration of the disorder, first episode, previous suicide attempts, and current pharmacological treatment.

Anthropometric measures and vital signs

Height, weight (excluding jackets, coats and shoes), and waist circumference was measured and BMI (body mass index) was calculated. Pulse and blood pressure (both measured after a few minutes of rest) were the vital signs recorded.

Pattern of tobacco use

The pattern of tobacco use was measured using the following parameters: number of cigarettes smoked per day, amount of carbon monoxide expired and level of physical and psychological dependence on nicotine. The presence of possible nicotine withdrawal symptoms was assessed using DSM-IV-TR criteria.

- *Number of cigarettes smoked daily* (CSD): daily cigarette consumption can be considered a valid measure of nicotine dependence. Given the lack of consensus in terms of classifying smokers into low and high level users, it was decided for the purposes of this study to classify them into groups according to the criteria of García-Portilla et al., 2014: low (CSD = < 10), moderate (CSD = 11-20), and high (CSD = > 20).
- *Level of carbon monoxide expired* (CO): this was measured using a piCOsimpleTM Smokerlyzer®. The cut point for the criteria "current smoker" was 6ppm (following manufacturer's instructions). CO measurements were always carried out in the early morning.
- *Fagerström Test for Nicotine Dependence* (FTND) (Becoña & Vazquez, 1998). This test includes six items which assess the degree of physiological dependence. The total score ranges from 0 to 10 points and smokers are categorized as having low (0-3), moderate (4-7) and high (8-10) dependence.
- *Glover-Nilsson Test* (GNT) (Nerin et al., 2005). This test is composed of 11 items which assess the degree of psychological and behavioral dependence on nicotine. Depending on their scores, participants are classified into four levels of dependence: low (0-11), moderate (12-22), high (23-33) and very high (34-44).

Substance use

The consumption of caffeine, alcohol, cannabis, cocaine and other substances was assessed.

Neuropsychological assessment

In order to assess neuropsychological functioning, the MATRICS Consensus Cognitive Battery (*Measurement and Treatment Research to Improve Cognition in Schizofrenia*) (Nuechterlein et al., 2008) was used. See Table 1 for a more detailed description.

Psychopathological assessment

The instruments used for clinical assessment included the following scales:

- P*ositive and Negative Syndrome Scale* (PANSS) (Peralta & Cuesta, 1994), which measures the severity of schizophrenia symptoms (positive, negative and general psychopathology). Each item has a range of 0-7 points (total score between 30 and 120). Higher scores indicate greater symptom severity.
- *Hamilton Depression Rating Scale* (HDRS) (Bobes et al., 2003), which consists of 17 items to assess the symptomatological profile and measure the severity of the depression. It generates a global score between 0 and 52 points. The higher the score, the greater the severity.
- *Columbia-Suicide Severity Rating Scale* (C-SSRS) (Al-Halabí et al., in press), a semistructured interview which assesses both suicide ideation and behavior. No global scoring scale is used and there are no specified cut points.
- *Clinical Global Impression, severity and change versions* (CGI-S and CGI-C) (Guy, 1976) assessing the global severity of the disorder (schizophrenia in this case). Each item is measured on a 7-point Likert scale (from normal to extremely ill).

Smoking cessation treatment

The choice of smoking cessation method was made on the basis of the availability of the treatment, previous experiences of the patients and their preferences, and their clinical assessment. The pharmacological treatments used in this study were those approved and considered to be the first option by the Public Health Service of the USA (Guideline Update Panel, 2008). Similarly, the European Psychiatric Association (EPA) includes nicotine patches and varenicline in the pharmacological treatments to stop smoking for all patients with some type of mental disorder (Rüther et al., 2014). Dosages were implemented following the usual protocol (García-Portilla et al., 2014). In the case of psychopathological decompensation or serious side effects it was planned to suspend treatment and exclude the patient from the study. In addition, all patients who started treatment to stop smoking received nutritional counseling, stimulus control techniques (to eliminate stimuli which induce the urge to smoke), and suggestions for acquiring healthy habits.

Statistical plan

The descriptive statistics for all clinical and sociodemographic variables and will be obtained and the potential

prior differences between the groups will be analyzed. The main measurement will be the changes in the mean scores of the MATRICS battery at each stage of the assessment (3, 6, 12 and 18 months). Cognitive performance will be analyzed to discover differences between patients who smoke and those who stop. At the same time, we attempt to observe if there are differences between those who stop smoking by using nicotine substitutes and those who use other methods. In addition, as a secondary outcome, changes in the mean scores on the clinical assessment scales (PANSS, HDRS, C-SSRS, CGI) will be examined. Before the statistical analyses are run, the distribution characteristics of the sample and the presence of outliers will be examined. The bilateral level of statistical significance is set at a confidence interval of 95%.

Discussion

This article has described in detail the methodology designed and used in the COGNICO study, the aim of which is to identify the relationship between nicotine and cognitive performance in schizophrenia patients. To this end, a comparison of scores obtained by the participants on the MATRICS neuropsychological battery over a period of follow-ups at 3, 6, 12 and 18 months will be carried out.

The importance of this study lies in the fact that it addresses an issue that has all too frequently been ignored by mental health professionals: the alarmingly high level of tobacco use among patients suffering from schizophrenia (Bachiller et al., 2015; García-Portilla et al., 2014). In this regard, the European Psychiatric Association (EPA) stresses the need to make greater efforts in this area, as well as to discover the impact tobacco dependence has on our patients (Rüther et al., 2013). Our study is designed to fit exactly into this research framework. Despite the situation outlined above, only a few studies have examined the efficacy and safety of smoking cessation programs among patients with mental disorders (García-Portilla et al., 2014).

Far from shedding light on this topic, one of the last publications published in the field (Asahre, Falcones & Lerman, 2014) makes it clear that the issue is a complex one which is yet to be resolved. These authors point out that giving up nicotine is linked to neurocognitive deficits in sustained attention, working memory and inhibition responses, for example. They add that "what is clear from our review is that the effects of nicotine withdrawal on cognitive function are more complex than initially theorized". According to Boggs, Carlson, Cortes-Briones, Krystal and D'Souza (2014), a greater understanding of the nicotinic system is necessary to determine whether we have a new therapeutic target which would lead to an improvement in cognitive performance.

One of the strengths of the study is its external validity and the generality of the results. The inclusion and exclusion criteria used have allowed us to recruit "real" patients. Our objective is to study what happens to our patients when they stop smoking, without needing to resort to sophisticated laboratory methods to measure the *mgs* of nicotine or other experimental conditions which are not very feasible in everyday practice. A further positive aspect is sample size. Although a total of 81 patients is not particularly ambitious, the majority of published studies work with smaller samples (García-Portilla et al., 2014). In addition to the above, we would like to highlight the fact that each patient was subject to a thorough assessment, not only with the application of the MATRICS and the reporting of the number of cigarettes smoked, but also because other aspects inherent in the pattern of tobacco use were taken into account, such as physical and psychological dependence and CO. A general clinical assessment was also carried out, including suicide ideation, with valid and reliable instruments, and the anthropometric measures and vital signs were also recorded, which all contribute to making the study more valuable.

There are, nevertheless, some limitations. The most serious of these is the lack of a control group with patients who were not smokers previously but began smoking just after the baseline assessment. The obvious difficulties in finding subjects for such a sample are of an empirical and ethical nature. A further limitation is the fact that the treatment for smoking cessation is naturalistic, not controlled. Nevertheless, such limitations, inherent in such open studies, guarantee a greater similarity to everyday clinical practice.

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Conflict of interests

None declared.

References

Al–Halabí, S., Sáiz, P.A., Burón, P., Garrido, M., Benabarre, A., Jiménez, E., … Bobes, J. (in press). Validation of a Spanish version of the Columbia-Suicide Severity Rating Scale (C-SSRS). *Revista de Psiquiatría y Salud Mental.*

Andreou, C., Schneider, B.C., Balzan, R., Luedecke, D., Roesch-Ely, D., Moritz, S. (2015). Neurocognitive deficits are relevant for the jumping-to-conclusions bias, but not for delusions: A longitudinal study. *Schizophrenia Research: Cognition, 2*, 8–11. doi:10.1016/j.scog.2015.02.001.

Ashare, R.L., Falcones, M., & Lerman, C. (2014). Cognitive function during nicotine withdrawal: Implications for

nicotine dependence treatment. *Neuropharmacology, 76,* 581–591. doi:10.1016/j.neuropharm.2013.04.034.

Bachiller, D., Grau–López, L., Barral, C., Daigre, C., Alberich, C., Rodríguez–Cintas, L., … Roncero, C. (2015). Grupo motivacional en unidad hospitalaria desintoxicación, su influencia en mantenimiento de la abstinencia y retención al tratamiento tras alta. *Adicciones, 27,* 09–118.

Barr, R.S., Culhane, M.A., Jubelt, L.E., Mufti, R.S., Dyer, M.A., Weiss, A.P., … Evins, A.E. (2008). The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology, 33*, 480–490.

Beck, A.K., Baker, A.L., & Todd, J. (2015). Smoking in schizophrenia: cognitive impact of nicotine and relationship to smoking motivators. *Schizophrenia Research: Cognition, 2,* 26–32. doi:10.1016/j.scog.2014.12.001.

Becoña, E., & Vazquez, F.L. (1998). The Fagerstrom test for nicotine dependence in a Spanish sample. *Psychological Report, 83*, 1455–1458.

Beratis, S., Katrivanou, A., & Gourzis, P. (2001) Facotrs affecting smoking in schizophrenia. *Comprehensive Psychiatry, 42*, 393–402.

Bobes, J., Arango, C., García–García, M., & Rejas, J. (2010). Healthy lifestyle habits and 10–year cardiovascular risk in schizophrenia spectrum disorders: an analysis of the impact of smoking tobacco in the CLAMORS schizophrenia cohort. *Schizophrenia Research, 119*, 101–109. doi: 10.1016/j.schres.2010.02.1030.

Bobes, J., Bulbena, A., Luque, A., Dal–Ré, R., Ballesteros, J., e Ibarra, N. (2003). A comparative psychometric study of the Spanish versions with 6, 17, and 21 items of the Hamilton Depression Rating Scale. *Medicina Clínica, 120*, 693–700.

Boggs, D.L., Carlson, J., Cortes-Briones, J., Krystal, J.H., & D'Souza, D.C. (2014). Going up in smoke? A review of nAChRs-based treatment strategies for improving cognition in schizophrenia. *Current Pharmaceutical Design, 20,* 5077-5792.

Burda, K., Czubak, A., Nowakowska, E., Kus, K., Metelska, J., & Nowakowska, A. (2010). Interactions of nicotine and drugs used in the treatment of mental illnesses with respect to cognitive functions. *Arzneimittelforschung, 60*, 527–543. doi: 10.1055/s–0031–1296322.

Carrillo, J.A., Herraiz, A.G., Ramos, S.I., Gervaisni, G., Vizcaíno, S., & Benítez, J. (2003). Role of the somoking–induced cytochrome P450 (CYP) 1ª2 and polymorphic CYP2D6 in steady–state concentration of olanzapine. *Journal of Clinical Psychopharmacology, 23*, 119–127.

Depatie, L., O'Driscoll, G.A., Holahan. A.L., Atikson, V., Thayundayil, J.X., Kin, N.N., & Lal, S., (2002). Nicotine and behavioral markers of risk for schizophrenia: a double–blind, placebo–controlled, cross–over study. *Neuropsychopharmacology, 27*, 1056–1070.

De Leon, J., Díaz, F.J., Aguilar, M.C., Jurado, D., & Gurpequi, M. (2006). Does somoking reduce akathisia? Testing a narrow version of the self–medication hypothesis. *Schizophrenia Research, 86*, 256–268.

Dervaux, A., & Laquelille, X. (2008). Tobacco and schizophrenia: epidemiological and clinical features. *Encephale, 34*, 299–305. doi: 10.1016/j.encep.2007.04.003.

Dolam, S.L., Sacco, K.A., Termine, A., Seyal, A.A., Dudas, M.M., Vessicchio, J.C., … George, T.P. (2004). Neuropsychological deficits are associated with smoking cessation treatment failure in patients with schizophrenia. *Schizophrenia Research, 70*, 263–275.

Encuesta Nacional de salud 2011/2012. Recuperado con fecha 28 de octubre de 2015 de http://www.msssi.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2011.htm.

García–Portilla, M.P., García–Álvarez, L., Saiz, P.A., Díaz–Mesa, E., Galván G., Sarramea, F., … Bobes, J. (2014). Effectiveness of a multi–component smoking cessation support programme (McSCSP) for patients with severe mental disorders: study design. *International Journal of Environmental Research and Public Health, 11*, 373–389.

Green, M.F., & Harvey, P.D. (2014). Cognition in schizophrenia: Past, present, and future. *Schizophrenia Research: Cognition, 1*, 1-9. doi:10.1016/j.scog.2014.02.001.

Guideline Update Panel, Liaisons, and Staff (2008). Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. *Respiratoty Care, 53*, 1217–1222.

Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology – Revised.* Rockville, MD: U.S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH.

Harris, J.G., Kongs, S., Allensworth, D., Martin, L., Tregellas, J., Sullivan B., & Freedman, R. (2004). Effects of nicotine on cognitive deficit in schizophrenia. *Neuropsychofarmacology, 29*, 1378–1385.

Jacobsen, L.K., D'Souza, D.C., Mencl, W.E., Pugh, K.R., Skudlarski, P., & Krystal, J.H. (2004). Nicotine effects on brain function and functional connectivity in schizophrenia. *Biological Psychiatry, 55*, 850–858.

Kelly, C., & McCreadie, R.G. (1999) Smoking habits, currents symptoms, and premorbid characteristics of schizophrenic patients in Nitthsdale, Scotland. *American Journal of Psychiatry, 156*, 1751–1757.

Lancet, E. (2013) Smoke alarm: Mental illness and tobacco. *Lancet, 381*, 1071.

Leonard. S., & Adams, C.E. (2006). Smoking cessation and schizophrenia. *American Journal of Psychiatry, 163*, 1877.

Levin, E.D., & Rezvani, A.H. (2002). Nicotinic treatment for cognitive dysfunction. *Current Drug Targets. CNS and Neurological Disorders, 4*, 423–431.

Levin, E.D., & Rezvani, A.H. (2006). Nicotinic–antipsychotic drug interactions and cognitive function. *Experientia Supplementum, 98*, 125–205.

Lising–Enriquez, K., & George, T.P. (2009). Treatment of comorbid tobacco use in people with serious mental illness. *Journal of Psychiatry and Neuroscience, 34*, E1–E2.

Nerin, I., Crucelaegui, A., Novella, P., Beamonte, A., Sobradiel, N., Bernal, V., Gargallo, P. (2005) Assessment of behavioral dependence with the glover–nilsson test in smoking cessation treatment. *Archivos de Bronconeumología, 41*, 493–498.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., … Marder, S.R. (2008) The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *American Journal of Psychiatry, 165*, 203–213.

Peralta, V., & Cuesta, M.J. (1994). Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatric Research, 53*, 31–40.

Piñeiro,B., López–Durán, A., Fernández del Río, E., Martínez, U., Brandon, T.H., & Becoña, E. (2014). Craving and nicotine withdrawal in a Spanish smoking cessation sample. Craving y abstinencia de la nicotina en fumadores españoles en un tratamiento para dejar de fumar. *Adicciones, 26*, 230–237.

Rüther, T., Bobes, J., De Hert, M., Svensson, T., Mann, K., Batra, A., … Möller, H.J. (2014). EPA—Position statement on smoking and strategies for smoking cessation in people with mental illness. *European Psychiatry, 29*, 65–82. doi:10.1016/J.EURPSY.2013.11.002.

Sacco, K.A., Termine, A., Seyal, A., Dudas, M.M., Vessichio, J.C., Krishnan–Sarin, S., & George, T.P. (2005). Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Archives of General Psychiatry, 62*, 649–659.

Segarra, R., Zabala, A., Eguíluz, J.I., Ojeda, N., Elizagarate, E., Sánchez, P., … Gutiérrez, M.(2010). Cognitive performance and smoking in first–episode psychosis: the self–medication hypothesis. *European Archives of Psychiatry Clinical Neuroscience, 261*, 241–250. doi:10.1007/s00406–010–0146–6.

Smith, R.C., Warner–Cohen, J., Matute, M., Butler, E., Kelly, E., Vaidhyanathaswamy, S., & Khan, A. (2006). Effects of nicotine nasal spray on cognitive function in schizophrenia. *Neuropsychopharmacology, 31*, 637–643.

Weiser, M., Reichenberg, A., Grotto, I., Yasvitzky, B., Rabinowitz, J., Lubin, G., … Davidson, M. (2004). Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical–prospective cohort study. *American Journal of Psychiatry, 161*, 1219–1223.