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Dual diagnosis: a European perspective

Patología dual: una perspectiva europea

Marta Torrens*,**,***, Joan-Ignasi Mestre-Pintó**, Linda Montanari****, Julian Vicente****, Antònia Domingo-Salvany*****.

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The combination of harmful psychoactive substance use with other serious health problems is a key issue in national and international drug policies. For a long time attention has focused almost exclusively on infectious diseases, especially human immunodeficiency virus (HIV) infection and hepatitis C. One of the topics currently generating a great deal of interest and concern in the field of addiction is the detection and treatment of comorbidity between mental disorders in general and disorders related to psychoactive substance use. This combination, also called dual diagnosis, has become increasingly important in recent years as epidemiological and clinical studies have emerged revealing the high prevalence of such comorbidity, as well as the severity in both clinical and social terms associated with it, its poor prognosis and the high healthcare costs it generates (Lieb, 2015; Torrens, Gilchrist & Domingo-Salvany, 2011; Whiteford et al, 2013.).

Experience shows that users of substances of abuse with psychiatric comorbidity are admitted to emergency services more frequently, have higher rates of psychiatric hospitalizations and a greater prevalence of suicide than those without comorbid mental disorders. They also exhibit more risky behaviors that generate more medical problems (e.g., infections caused by HIV, HCV, etc.) and social problems (e.g., higher rates of unemployment, homelessness, etc.) and more violent or criminal behaviors. Moreover, clinical practice has shown that comorbid conditions are mutually interactive and cyclical, with a poor prognosis for both if not treated jointly (San et al., 2016). People who consume substances and have psychiatric comorbidity thus have an increased risk of chronicity, their treatment is more problematic and costly, and the chances of recovery are smaller. So, if we take into account the costs of caring for such dual patients to both health and legal systems, we can say that they represent a high economic cost for society and lead to great challenges not only for health professionals but also for health authorities and the legal field. Given this evidence, the European Monitoring Centre for Drugs (EMCDDA) decided to get involved by studying the issue and commissioned a publication for the 'Insights' series. The result is an insight into the state of affairs regarding the comorbidity of mental disorders among users of illicit drugs within the European Union (EU) (EMCDDA, 2015) (http://www.emcdda.europa.eu/publications/insights/comorbidity-substance-use-mental-disorders-europe). This publication also led to a brief report in the 'Perspectives on Drugs' (PODs) section (http://www.emcdda.europa.eu/topics/pods/comorbidity-substance-use-mental-disorders-europe).

To prepare the Insight report, the authors reviewed the definitions and concepts of comorbidity between substance use and mental disorders, and the instruments available to detect and assess the presence of psychiatric comorbidity in

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these people. They therefore carried out a review of epidemiological data and treatment approaches, mainly in terms of services, within the EU context. To this end, a comprehensive literature search was conducted on Medline, using the keywords 'comorbidity', 'dual diagnosis', 'treatment', 'epidemiology', 'health services' and 'diagnosis', combined in such a way as to cover the greatest possible range of published information, a review of the European guidelines published on the subject, a comprehensive review of the latest national reports from 2006 to 2013 (Réseau Européen d'Information sur les et les Drogues Toxicomanies-Reitox) available with information on this topic, and finally a number of key informants from different European countries were contacted in order to complete the full picture of the situation and the treatment of comorbidity between substance use and mental disorders in the European context. The information on the implementation of dual diagnosis services was reviewed by each country.

An initial conclusion, one which was to be expected, was that the epidemiological data available in the EU are very heterogeneous. Most studies were focused on a particular mental disorder (e.g., major depression, schizophrenia, first psychotic episode, bipolar disorder, attention deficit hyperactivity disorder, PTSD, etc.) or on the consumption of a specific psychoactive substance (e.g. opioids, stimulants, cannabis, etc.). Furthermore, the care environment in which studies of comorbidity were carried out are varied (primary care centers, treatment centers for use of specific drugs, emergency departments of general hospitals, psychiatric departments, prisons, the homeless, etc.). Likewise, the instruments and diagnostic criteria used to determine the presence of both the various mental disorders in general and the various substances, including the different consumption patterns (recreational, abuse, dependence), are diverse and often make any possible comparisons difficult to draw.

Finally, another key factor to be taken into account for a better understanding of the heterogeneity of the results concerning the prevalence of psychiatric comorbidity among consumers of psychoactive substances across Europe are the differences in the illegal markets among the different EU countries (e.g., amphetamines and heroin in northern European countries, cocaine in southern Europe). Despite the great heterogeneity of the available data, it is clear from the data that the prevalence of other mental disorders among substance users is higher than in the non-drug-using population.

As in the studies conducted in the US or Australia, the most common psychiatric comorbidity among substance users in the EU was major depression, with a prevalence ranging from 12% to 80%. Studies of this comorbidity also showed the lowest success rate in treatments and its association with a higher suicide rate (both attempted and completed) compared with patients affected by just a single disorder. Among individuals with a substance use disorder, major depression was more common in women than in men, and it was also found that women with substance use disorder were twice as likely to suffer major depression compared to women in the general European population, making this group of women an especially vulnerable population and a particularly sensitive target for treatment policies. Studies have also been conducted on comorbidity in anxiety disorders. In particular, links have been found between panic disorder and PTSD on the one hand and substance use on the other, with a prevalence of up to 35%.

Substance use comorbidity is more common in people with psychosis, including schizophrenia and bipolar disorder than in the general population. Among people with psychosis, those who are also substance abusers are at increased risk of relapse and hospitalization and higher mortality. In part, this is because the substances used can exacerbate psychosis or interfere with pharmacological or psychological treatments. Comorbidity between schizophrenia and substance use disorders is common, with rates of between 30% and 66%. Substances of use and abuse common among psychotic patients, besides tobacco, are alcohol and cannabis, and more recently cocaine. The relationship between schizophrenia and cannabis use among young people has been an area of particular interest, given the high prevalence of cannabis consumption among young people in the EU. The comorbidity rate of substance use and bipolar disorder ranges from 40% to 60%. During the manic phase of bipolar disorder, patients often consume large amounts of alcohol or other substances, particularly stimulants and cannabis. During the depression phase, substance use may also increase, and the data indicate that alcohol can exacerbate depression, and consumption of stimulants and cannabis may precipitate a manic episode or an episode of mixed symptoms. In any case, the presence of a substance use disorder indicates poorer social adjustment and poorer treatment outcomes in bipolar patients. Substance use is also often associated with personality disorders, especially antisocial and borderline disorder. Individuals with a personality disorder and a substance use disorder are more likely to indulge in risky behaviors that predispose them to both infections from blood-borne viruses (HCV, HIV) and medical and social complications (e.g., illegal behavior). Although these patients may have difficulties in remaining in treatment programs and in complying with treatment plans, treatment for substance use in people with personality disorders is linked to a reduction in substance use and also in criminal behavior. In recent years, there has been growing interest in comorbidity between attention deficit disorder and hyperactivity disorder (ADHD) and substance use. A recent study conducted in six European countries revealed that the prevalence of ADHD in substance users seeking treatment ranges from 5% to 33%.

Despite the importance of providing effective treatments for comorbid mental disorders among patients with substance use disorder, patients often have difficulty not only in identifying but also in accessing and coordinating mental health services and addiction services. Thus, with reference to where these dual patients are treated, an overview of the current situation in different European countries shows that treatment of mental disorders and substance use disorders is provided in different services, which in most cases correspond to different healthcare networks, and this hinders access to treatment for such individuals. Most EU countries have one healthcare network for mental health and another healthcare network treating substance use disorders, with a deficit in each of experts in treating both types of pathologies, with notable differences in therapeutic approach, as well as regulations and different funding sources.

Finally, based on their findings, the authors present a series of recommendations for the future, summarized below:

- Systematic screening and treatment of comorbid mental disorders in patients with substance use disorders is necessary.
- The use of validated instruments for both screening and diagnosis of psychiatric comorbidity in substances users is recommended.
- A therapeutic approach to dual pathology, either pharmacological, psychological or both, must take into account all disorders simultaneously and from the first point of contact in order to select the best option for each individual.
- A study is recommended which, across the whole EU, using it same methodology in all countries, allows for a better understanding of the prevalence and characteristics of psychiatric comorbidity in people consuming psychoactive substances.
- In order to improve expertise and therapeutic approaches, the report recommends that specific indicators of psychiatric comorbidity in patients with substance use disorder should be introduced into the treatment demand indicators of the European Monitoring Centre for Drugs.
- Studies should be conducted to improve therapeutic strategies based on the evidence in these dual patients.

Thus, given the high prevalence, clinical severity and social seriousness of the issue, the detection and appropriate treatment of mental disorders and comorbid substance use is one of the biggest challenges healthcare managers, professionals and doctors working in the field of addiction to psychoactive substances must tackle in the coming years.

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References

EMCDDA. (2015). *Comorbidity of substance use and mental disorders in Europe, EMCDDA Insights.* Luxembourg: Publications Office of the European Union.

EMCDDA. (2016). *Comorbidity of substance use and mental health disorders in Europe, EMCDDA Perspectives On Drugs.* Luxembourg: Publications Office of the European Union.

Lieb, R. (2015). Epidemiological Perspectives on Comorbidity Between Substance Use Disorders and Other Mental Disorders. En G. Dom & F. Moggi (Eds.), *Co-occurring Addictive and Psychiatric Disorders* (pp. 3–12). Berlin, Heidelberg: Springer Berlin Heidelberg. doi:10.1007/978-3-642-45375-5_1.

San, L., Arranz, B., Arrojo, M., Becoña, E., Bernardo, M., Caballero, L., … Zorrilla, I. (2016). Clinical guideline for the treatment of dual pathology in the adult population. *Adicciones, 28*, 3-5. doi:10.20882/adicciones.784.

Torrens, M., Gilchrist, G. & Domingo-Salvany, A. (2011). Psychiatric comorbidity in illicit drug users: Substance-induced versus independent disorders. *Drug and Alcohol Dependence, 113*, 147–156. doi:10.1016/j.drugalcdep.2010.07.013.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., … Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet, 382*, 1575–1586. doi:10.1016/S0140-6736(13)61611-6.

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.

Gender differences in success at quitting smoking: Short- and long-term outcomes

Diferencias de género en el éxito al dejar de fumar: resultados a corto y largo plazo

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Abstract

Smoking cessation treatments are effective in men and women. However, possible sex-related differences in the outcome of these treatments remain a controversial topic. This study evaluated whether there were differences between men and women in the success of smoking cessation treatment, including gender-tailored components, in the short and long term (> 1 year). A telephone survey was carried out between September 2008 and June 2009 in smokers attended in a Smoking Cessation Clinic. All patients who have successfully completed treatment (3 months) were surveyed by telephone to determine their long-term abstinence. Those who remained abstinent were requested to attend the Smoking Cessation Clinic for biochemical validation (expired CO ≤10 ppm). The probability of remaining abstinent in the long-term was calculated using a Kaplan-Meier survival analysis. The treatment success rate at 3-months was 41.3% (538/1302) with no differences by sex 89% (479/538) among those located in the telephonic follow-up study and 47.6% (256/479) were abstinent without differences by sex (p = .519); abstinence was validated with CO less than 10 ppm in 191 of the 256 (53.9% men and 46.1% women). In the survival analysis, the probability of men and women remaining abstinent in the long-term was not significant. There are no differences by sex in the outcome of smoking cessation treatment that included gender-tailored components in the short and long term (> 1 year).

Keywords: Smoking; smoking cessation; gender and health; women; survival analysis.

Resumen

Los tratamientos para dejar de fumar son eficaces en hombres y mujeres. Sin embargo, las posibles diferencias encontradas en los resultados del tratamiento aún son objeto de controversia. Este estudio analiza si existen diferencias entre hombres y mujeres en el éxito al dejar de fumar a corto y largo plazo (> 1 año) con un programa de tratamiento que incluye la perspectiva de género. Se realizó una encuesta telefónica en fumadores atendidos en una unidad de tabaquismo. Los pacientes que completaron con éxito el tratamiento (3 meses), fueron encuestados telefónicamente para determinar su abstinencia a largo plazo; se validó la abstinencia mediante cooximetría (CO espirado ≤10 ppm) en los que se mantenían abstinentes. La probabilidad de permanecer abstinentes a largo plazo se calculó utilizando un análisis de supervivencia de Kaplan-Meier. La tasa de éxito del tratamiento fue de 41,3% (538/1302), sin diferencias por sexo. El 89% (479/538) fue localizado por teléfono y el 47,6% (256/479) se mantenía abstinente sin diferencias por sexo (p = ,519); la abstinencia fue validada en 191 de 256 (53,9% hombres y 46,1% mujeres). En el análisis de supervivencia, la probabilidad de que los hombres y las mujeres mantuvieran la abstinencia a largo plazo no fue significativa. No hay diferencias por sexo en el resultado del tratamiento para dejar de fumar, que incluyan aspectos de género, a corto y largo plazo (> 1 año).

Palabras clave: Tabaquismo; cesación tabáquica; género y salud; mujeres; análisis de supervivencia.

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Smoking is the greatest public health problem in developed countries and an emerging problem in developing countries (López, Mathers, Ezzati, Jamison, & Murray, 2006). Worldwide, the prevalence of smoking is higher in men than in women, although the rate for young women is on the rise (Amos, Greaves, Nichter, & Bloch, 2012). As a consequence of these differences in the smoking prevalence by sex, so far the smoking related mortality has been higher among men. However, in some developed countries, the increase in the smoking habit among women has conditioned also a rise in related mortality in women compared with previous years. Thus, in many countries tobacco use is already a major public health concern for women (Croghan et al., 2009; Banegas et al., 2011; US Department of Health and Human Services, 2001).

Helping current smokers to quit is the single most important step to reduce morbidity and mortality associated with cigarette smoking (Peto et al., 2000). Smoking cessation treatments recommended in the main clinical practice guidelines have been found to be equally effective in men and women (Munafo, Bradburn, Bowes, & David, 2004; Perkins & Scott, 2008). However, possible sex-related differences in the outcome of these treatments remain a controversial topic.

First, in the beginning of the 1980s, a Surgeon General's report (US Department of Health and Human Services,1980) concluded that women had greater difficulties in stopping smoking, although subsequent studies suggested that this conclusion was perhaps premature (Whitlock, Vogt, Hollis, & Lichtenstein, 1997). Overall, studies which evaluated possible differences in the results of smoking treatment by sex showed different results. Thus, Whitlock et al. (1997) found no gender differences in a brief clinic-based smoking intervention and Croghan et al. (2009) neither found differences through a clinical treatment program. Likewise, in a meta-analysis of 11 clinical trials using Nicotine Replacement Therapy (NRT) for smoking cessation did not find gender differences between males and females smokers (Munafo et al., 2004). Conversely, Osler, Prescott, Godtfredsen, Hein, & Schnohr (1999) found worse results for women in spontaneous smoking cessation whereas Piper et al. (2010) observed that with pharmacotherapy of smoking cessation, women were less likely to quit smoking successfully than men. On the other hand, Cepeda, Reynoso, & Erath (2004), observed that smoking abstinence between males and females receiving NRT was mediated by intensity of behavioural support, (with higher intensity support for women) with poorer 1-year outcome in women vs. men, a similar result found by Perkins et al., (2008). Finally, Scharf & Shiffman (2004) concluded that women were less successful at quitting than men, regardless of treatment. Related to the follow-up, numerous studies have assessed the success of smoking cessation treatments by sex in the short and medium term (three and six months of abstinence), and even up to one year (Croghan et al., 2009; Puente et al., 2011), but very few have continued follow-up in the longer term, beyond 12 months (Bjornson et al., 1995; Osler et al., 1999; Wetter et al., 2004) also with contradictory findings.

As we can see, all these studies had many methodological differences which could partially explain the different results: differences in the treatment applied (with or without pharmacotherapy), different methodological criteria for determining abstinence (self-reported or biochemical measures), or a different time length of the follow-up period. All these differences make it difficult to draw reliable comparisons between studies.

The objective of this study was to determine whether there were differences between men and women as regards the success of smoking cessation treatment, in the short and long term, with a smoking cessation program which includes gender-tailored components.

Methods

Participants

A telephone survey was carried out in smokers attended in a Smoking Cessation Clinic between 2002 and 2007 (inclusive). The participants were smokers who requested treatment and had successfully quit at the end of the treatment. This unit is a public service that treats smokers who request a smoking cessation treatment or are referred by their primary care physician (general practitioner) or specialist. For access to treatment the inclusion criteria were being a smoker older than 18 years and voluntarily agreeing to start treatment and the exclusion criteria included having an uncontrolled psychiatric disorder, other active drug-dependence or, in the case of women, pregnancy. All participating gave their written informed consent to be included in the study.

Intervention

The smoking cessation program uses a group format of 60 minute sessions over the course of 3 months. The follow-up visits were arranged as follows: first session, the day before giving up smoking; second session, the day after giving up smoking; one booster visit every week during the first month; and at six, nine and twelve weeks of abstinence; in summary, nine sessions over three months. All those sessions were in group format (men and women mixed) and the day for giving up smoking was the same for all.

The smoking cessation treatment offered is a multicomponent intervention: cognitive and behavioural treatment in group with pharmacological treatment using the medications recommended in smoking cessation treatment guidelines, such as Nicotine Replacement Therapy (NRT), Bupropion and Varenicline (Fiore et al., 2008); the fulfillment of pharmacological treatment was carried out along the group sessions. It is led by health professionals with extensive experience in group therapy.

In the cognitive behavioural therapy, all participants received cessation counselling focused on preparing to quit, the benefits of cessation, coping with smoking urges and relapse prevention. Also were incorporated specific strategies for women as cognitive therapy to reduce weight/body image concerns, how to break the link between cues and smoking and strategies to cope with the negative affect.

Measures

During the first visit, and before smoking cessation treatment commenced, sociodemographics (sex, age, marital status, educational level, employment activity) and smoking-related variables, including number of cigarettes smoked per day, years as a smoker, number of previous quit attempts to stop smoking (0, 1 or 2, and 3 or more) and degree of nicotine dependence (Fagerström Test) (Fagerström & Scheneider, 1989) were collected from all participants. The baseline CO level was measured using a Mini Smokerlyzer cooximeter (Bedfont Scientific Ltd., Rochester, UK) (Jarvis, Russell, & Saloojee, 1980). Finally, a medical history (hypertension, cholesterol levels, cardiovascular disease, hyper- or hypothyroidism and cancer) was completed. Subjects were also asked about their previous history of anxiety and/or depression requiring pharmacological treatment. This information was collected using two variables: history of depression before the smoking cessation treatment, or during treatment. In this first visit the pharmacological treatment was prescribed according to individual profile of each smoker.

Continuous abstinence, in other words not smoking from the quit day until the end of the treatment (3 months), as validated by CO values of ≤ 10 ppm, was considered to indicate successful treatment. Expired-air CO was assessed at each of the follow-up visits. As the intention-to-treat criterion was used to assess the success percentage, the success rate was taken to be the proportion of abstinent subjects (continuous and CO validated abstinence) with respect to the total number of subjects who started treatment. Both these criteria (success and success rate) were established on the basis of the recommendations to communicate the outcome of smoking cessation treatment (Hughes et al., 2003). All subjects who failed to attend the final group treatment session (week 12) were considered to be smokers.

Follow-up

To analyze long-term abstinence (>1 year), a telephone survey of all subjects who were abstinent at the end of treatment (3 months) was carried out between September 2008 and June 2009. Trained interviewers called each subject a maximum of five times in two different time periods. As follow-up was phone-based, those subjects who reported not to have smoked again since receiving treatment were asked to attend the unit for biochemical validation of their abstinence.

Statistical analysis

A descriptive analysis was performed of the sample as a whole, with qualitative variables expressed as absolute frequencies and the equivalent proportion of each category and quantitative variables as means and standard deviations. The characteristics were compared using the two sample t-test for continuous variables and the chi-square test for categorical variables; the test used to compare short-term outcomes was the chi-square test. Two-sided p-values ≤0.05 were used to denote statistical significance in all cases.

In the phone-based follow-up study, the abstinence time was calculated as the number of months from the end of the treatment to the date of the interview. A survival analysis was performed using the Kaplan-Meier method to analyse the probability of remaining abstinent in the long term, with the Tarone-Ware test being used to study the possible differences in survival time between men and women (Hughes et al., 2003; Tarone & Ware, 1977). We employed the Tarone-Ware test to asses Kaplan-Meyer plots of different groups because this test is designed to have good power across a wide range of survival functions. Data were analysed using SPSS© version 15.0.

Results

A total of 1472 people, 768 men (52.2%) and 704 women (47.8%), completed a medical history. The mean age was 43.2 (SD = 10.3) years. Of these, 170 (11.5%) decided not to commence smoking cessation treatment, 90 (52.9%) men and 80 (47.1%) women. All subjects who decided not to start smoking cessation treatment (170) were excluded from the study and were therefore not included in the subsequent analyses.

The sample studied included 1302 people of whom 678 (52.1%) were male and 624 (47.9%) female. The mean age was 43.4 (SD = 10.2) years. The characteristics of the sample as a whole, and the male and female subgroups, can be found in Table 1. On average, male subjects were older than females (44.2 vs. 42.5 years) and were more likely to be married (73.6% vs. 58.8%), be working (87.9% vs. 77.6%), and to have a secondary education (47.3% vs. 38.9%), whereas women were more likely to have completed higher education (41.7% vs. 27.3% for men). As far as the smoking-related variables are concerned, men smoked more cigarettes per day than women (26.7 vs. 23.7), had been smoking for longer (27.9 vs. 24.9 years), had higher levels of CO (29.3 vs. 24.9) and 56.6% had attempted to stop smoking once or twice compared with 49.1% of women. All these differences were statistically significant ($p<0.05$).

Despite the different consumption patterns, no statistically significant differences were found between the sexes in terms of nicotine dependence (6.3 vs. 6.2 points; p=.431). Analysis of the different diseases studied showed that men were more likely to present cardiovascular risk factors such

Table 1. *Characteristics of the patients who initiated smoking cessation treatment (2002-2007) (N=1302)*

	Total % (N)	**Men** % (N)	**Women** % (N)	**p**
Sociodemographic				
Age (SD)	43.4 (10.2)	44.2 (10.4)	42.5 (9.9)	.002
Marital status %(N)				‹ .0001
Single	23.5 (306)	20.1 (136)	27.3 (170)	
Divorced or widowed	10.0 (130)	6.3 (43)	13.9 (87)	
Married	66.5 (866)	73.6 (499)	58.8 (367)	
Educational level %(N)				‹ .0001
Basic	22.5 (293)	25.4 (172)	19.4 (121)	
Secondary	43.3 (564)	47.3 (321)	38.9 (243)	
Higher	34.2 (445)	27.3 (185)	41.7 (260)	
Employment %(N)				‹ .0001
Not active	17.1 (222)	12.1 (82)	22.4 (140)	
Working	82.9 (1080)	87.9 (596)	77.6 (484)	
Consumption pattern				
No. cigarettes/day (SD)	25.3 (10.4)	26.7 (11.5)	23.7 (8.9)	‹ .0001
Years smoking (SD)	26.4 (10.1)	27.9 (10.7)	24.9 (14.8)	.003
Previous attempts %(N)				.019
0	26.5 (345)	23.9 (162)	29.3 (183)	
1-2	53 (690)	56.6 (384)	49.1 (306)	
3 or more	20.5 (267)	19.5 (132)	21.6 (135)	
Fagerström Test (SD)	6.2 (2.2)	6.3 (2.2)	6.2 (2.2)	.431
Baseline CO (SD)	27.2 (15.8)	29.3 (16.4)	24.9 (14.8)	.003
Medication prescribed %(N)				.007
None	0.2 (2)	0.1 (1)	0.2 (1)	
Nicotine replacement therapy	64.8 (844)	69.0 (468)	60.3 (376)	
Bupropion	31.1 (405)	27.9 (189)	34.6 (216)	
Varenicline	3.9 (51)	2.9 (20)	5.0 (31)	
Diseases %(N)				
Hypertension	10.2 (133)	12.1 (82)	8.2 (51)	.020
Cholesterol	9.8 (127)	12.7 (86)	6.6 (41)	‹ .0001
Cardiovascular	8.4 (109)	11.2 (76)	5.3 (33)	‹ .0001
Diabetes	3.5 (46)	4.9 (33)	2.1 (13)	.007
Hypo/Hyperthyroidism	3.1 (41)	0.7 (5)	5.8 (36)	‹ .0001
Cancer	1.5 (19)	0.9 (6)	2.1 (13)	.072
Anxiety or depression before treatment %(N)	35.7 (465)	24.5 (166)	47.9 (299)	‹ .0001
Anxiety or depression during treatment %(N)	10.4 (136)	5.9 (40)	15.4 (96)	‹ .0001

p ≤ ,05

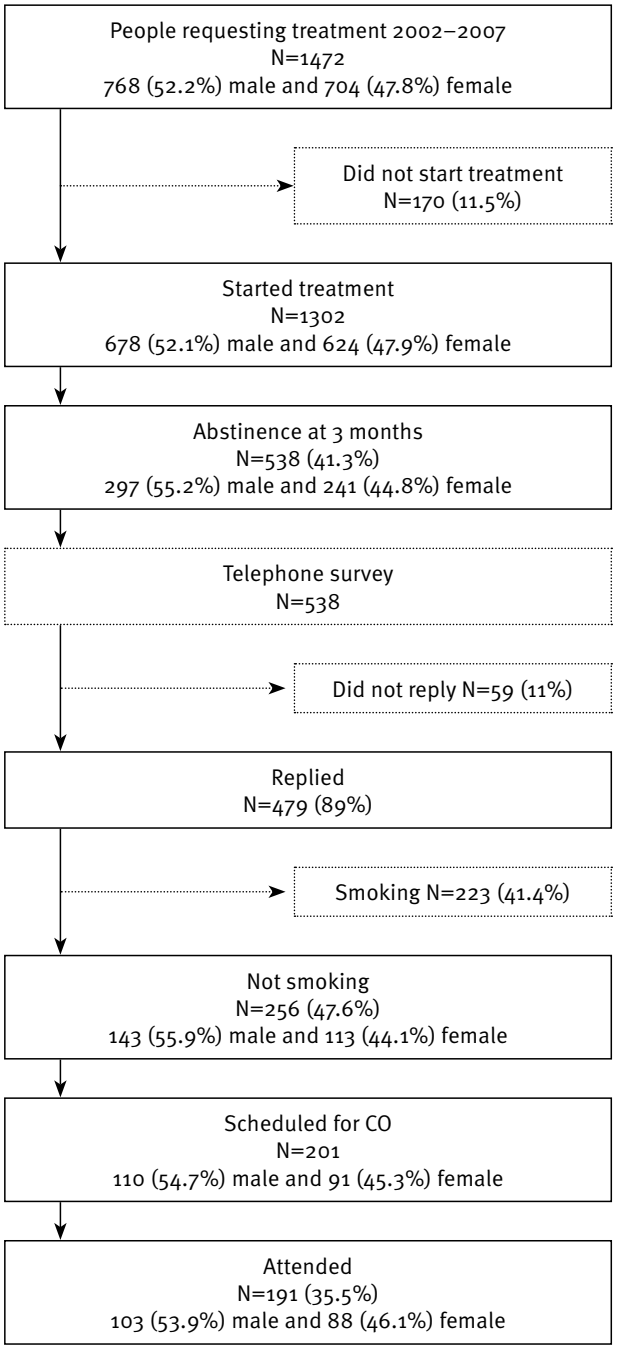
as hypertension, cholesterol and diabetes. In contrast, women were more likely to present a psychiatric-type disorder such as anxiety and/or depression requiring pharmacological treatment, either at the beginning of treatment or previously.

The three-month treatment success rate using the intention-to-treat criterion was 41.3% (538/1302). There were no statistically significant differences in success rate by sex, although the percentage of abstainers was higher for men than for women [43.8% (297/678) vs. 38.6% (241/624) respectively; p=.058].

A total of 479 of the 538 subjects who successfully completed the treatment were located during the phone-based follow-up study. Of the 59 who did not reply, 24 had changed phone number, 21 could not be located in the stipulated number of attempts, eight refused to respond to the questionnaire and six had died. Phone-based follow-up was therefore performed with 89% (479/538) of those subjects who successfully completed treatment, 47.6% (256) of whom had remained abstinent since the day they stopped smoking (the quit day); therefore it was 19.6% with respect to the total number of subjects who started treatment (256/1302). There were no statistically significant differences by sex (p=.519). Abstinence was validated in 191 (53.9% men and 46.1% women) of the 256 subjects who claimed to have stopped smoking, with CO values of less than 10 ppm; abstinence could not be validated in the remainder (65) as they failed to keep their appointment (see Figure 1).

When compared using the Tarone-Ware test, the differences detected in the survival analysis used to determine the probability of men and women remaining abstinent in the long-term were not significant (see Figure 2).

Figure 1. Study scheme

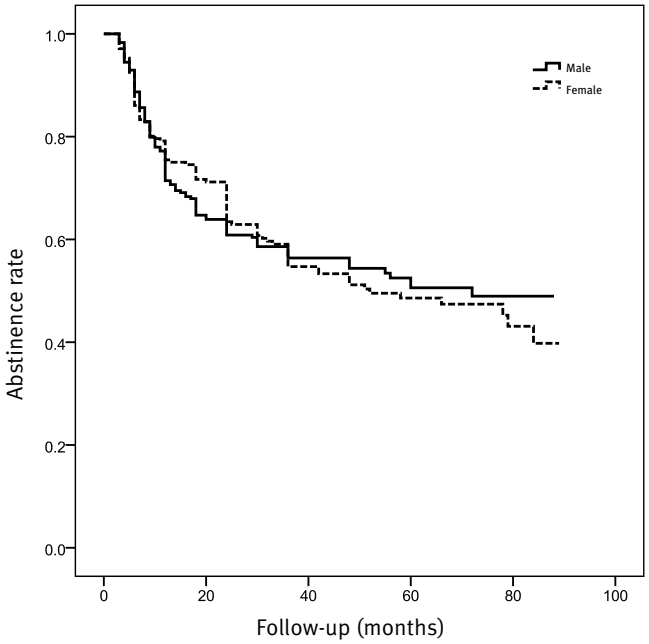


Discussion

Our results show that there are no gender differences in the short- and long-term success of smoking cessation treatment which includes gender-tailored components, with men and women having the same probability of remaining abstinent. However, we found sex-based differences in the sociodemographic variables of those people who commenced treatment in our unit. Thus, women tended to be younger, but were less likely to be married than men; these differences are similar to those described by other authors (Croghan et al., 2009; Ramon, Bruguera, Fernández, Sanz de Burgoa, & Ramírez, 2009). The higher percentage of working males reflects the general situation in Spain, where the employment rate for men is higher. Our study also highlights the predominance of women with higher educational qualifications with respect to the greater proportion of men with a secondary education, also found by Iliceto, Fino, Pasquariello, D´Angelo Di Paola, & Enea (2013) in Italy recently. This aspect corresponds, for women, with phase III of the epidemiological model proposed by López, Collishow & Piha (1994) and recently review by Thun, Peto, Boreham & Lopez (2012) in which countries like Spain or Italy are currently placed, whereby women with more educational qualifications tend to start smoking first but also decide to stop smoking first. Concerning the high number of women who requested treatment, other studies carried out in a similar setting (Smoking cessation Units) also showed high number of women, most of them with high educational level (Croghan et al., 2009; Fernández et al., 2006; Fidler, Ferguson, Brown, Stapleton & West, 2013)

In accordance with previous findings from our group (Marqueta, Nerín, Jiménez-Muro, Gargallo & Beamonte,

Figure 2. Long-term abstinence by sex



2013) and from other authors in recent studies (Chatkin et al. 2006; Iliceto et al. 2013), no statistically significant differences between men and women were found in terms of the degree of nicotine dependence measured by Fagerström Test. This "equality" reflects the increased consumption in women over the past few years and is in contrast to literature reports from the 1990s, which found a lower dependence in women (Bjornson et al., 1995; Ward, Klesges, Zbikowski, Bliss, & Garvey, 1997). Furthermore, this study was undertaken in a specialised Smoking Cessation Clinic where the men and women who request treatment are usually smokers with a moderate to severe dependence.

Our analysis of reported diseases shows that, in accordance with previous studies (Killen, Fortmann, Varady, & Kraemer, 2002; Marqueta, Jiménez-Muro, Beamonte, Gargallo, & Nerín 2010), anxiety disorders and/or depression are more common in women, whereas a larger proportion of men present cardiovascular risk factors. Both these aspects have been reported in the general non-smoking population and may be due to gender differences arising from both psychosocial and hormonal effects (Borrell, García-Calvente, & Martí-Boscà, 2004; National Institute of Mental Health, 2009).

Concerning the success of the treatment of smoking cessation, although the success rate was higher in men than women we have found no short-term gender differences in the same way as other studies (Croghan et al., 2009; Killen et al., 2002; Puente et al., 2011; Raich et al., 2015; Whitlock et al., 1997;), whereas other authors, such as Bohadana, Nilsson, Rasmussen & Martinet, (2003), Wetter et al., (2004) and Bjornson et al., (1995), have found higher success rates in men and a higher probability of relapse in women (Iliceto et al., 2013; Swan, Ward, Carmelli, & Jack, 1993). The reasons used to justify the worse outcome of smoking cessation treatments in women include the suggestion that women perceive the act of smoking as a strategy to reduce negative affects (for example stress) and/or increase positive ones (Xu et al., 2008). It is well known that women smoke for different reasons than men, for example to reduce negative states (sadness, anxiety, etc.), and that they have different worries when stopping smoking, such as weight control and the appearance of depressive symptoms (Croghan et al., 2009; US Department of Health and Human Services, 2001; WHO, 2001); Therefore, it has been suggested that in women smoking behaviour might be more influenced by behavioural components and less by the nicotine dependence than in men, and accordingly the treatment should be appropriately tailored to women to increase their chances of abstinence (Bohadana et al., 2003). Some studies observed that the result in women of smoking cessation program was mediated by intensity of behavioural support, with higher intensity support for women, but they did not include any specific recommendation for women (Cepeda et al., 2004). In our study, we included strategies to prevent relapses that are specific to women, such as weight aspects, facing up to negative situations and how to handle stress, which could explain the lack of a difference between men and women as regards the outcome of smoking cessation treatment.

Moreover, Croghan et al. (2009), adjusting for the baseline characteristics of smokers, observed that the likelihood of abstinence did not differ by sex and suggested that observed differences in tobacco abstinence outcomes between female and male smokers may be explained by other characteristics (e.g., baseline smoking rate, history of depression etc.), which are different for women and men. In the same way, our group, using a similar methodology, found no differences in the outcome of smoking cessation programs by sex suggesting that the predictors of successful abstinence are different for females and males (Marqueta et al., 2013). In other words and as others authors have suggested previously the rate of success in smoking cessation is similar for both sexes, but the process for men and women is different (Whitlock et al., 1997). These findings support the importance of individualizing the treatment for smokers, depending on being a smoker woman or a smoker man.

In our study the long term success can be seen in Figure 1, and in agreement with the findings of Chatkin et al. (2006), men and women have the same probability of remaining abstinent in the long term. Knowing long term results highlights that men and women have the same success after undergoing a smoking cessation program, including gender-tailored components, and is consistent with the short term findings.

As limitations of our study, it should be noted that the study population is not representative of the general smoker

population as it only includes smokers who requested treatment in a specialised Smoking Cessation Clinic. Despite this, the sample of smokers is sufficiently large to allow the differences between men and women in terms of treatment success to be analysed and is therefore appropriate for the proposed objective. Besides, the studies carried out in Smoking Cessation Units usually analyze all patients treated and they do not use samples (Fernandez et al., 2006). Another limitation of our study could be the number of patients who said at the telephone survey that they were not smoker and did not attend to the biochemical validation (see figure 1). However, this situation is very common in studies which evaluate long term abstinence, where these patients are considered as smokers (Álvarez et al., 2015); this criterion was also applied in our study.

On the other hand, one of the strengths of the study is the large and clinical sample and the long-term follow-up assessment, unlike most other studies which tend to be clinical trials with shorter follow-up periods. Furthermore, we use continuous abstinence which is the most rigorous measure and considered by many to be the gold standard, since it requires a longer period of abstinence than other measures and thus is more likely to represent long-term abstinence; and we validated abstinence with CO. Also, according to the intention-to-treat criterion applied to assess the success percentage, all subjects who failed to attend were considered as smokers. Similarly, and as is recommended by the SRNT (2002) (Hughes et al., 2003), we used a survival analysis using the Kaplan-Meier method to analyse the probability of remaining abstinent in the long term. This method provides more detailed information than a simple cut-off point rate as it reflects the evolution in time and provides probability information, thereby more accurately reflecting the patient´s actual situation. Since smoking is not a static process in time (Prochaska & DiClemente, 1983), it appears more appropriate to use dynamic techniques, such as survival analysis, to assess such outcomes. In contrast, many studies evaluate the abstinence only with self-declaration in a sample cut-off point.

In summary, our study shows that there are no differences by sex in terms of the outcome of smoking cessation treatment when following the treatment recommended in clinical practice guidelines. These recommendations include tailoring the treatment on the basis of each smoker's characteristics. This means that is necessary to adapt smoking cessation treatment taking into account the different worries and needs for women and men.

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Conflicts of interests

The authors declare that there are no conflicts of interests.

References

Álvarez, F.J., Ferrer, M., Ruiz, A., Medina, J.F., Romero, B., Sáez, A., & Romero, A. (2015). Predictors of 10-year smoking abstinence in smokers abstinent for 1 year after treatment. *Addiction, 111*, 545-551. doi: 10.1111/add.13220

Amos, A., Greaves, L., Nichter, M., & Bloch, M. (2012). Women and tobacco: a call for including gender in tobacco control research, policy and practice. *Tobacco Control, 21*, 236-243. doi: 10.1136/tobaccocontrol-2011-050280.

Banegas, J.R., Díez-Gañán, L., Bañuelos-Marco, B., González-Enríquez, J., Villar-Álvarez, F., Martín-Moreno, J.M., …Jiménez-Ruiz, C. (2011). Smoking-attributable deaths in Spain. *Medicina Clínica, 136,* 97-102. doi: 10.1016/j.medcli.2010.03.039.

Bjornson, W., Rand, C., Connett, J.E., Lindgren, P., Nides, M., Pope, F., …O´Hara, P. (1995). Gender differences in Smoking Cessation after 3 Years in the Lung Health Study. *American Journal of Public Health, 85*, 223-230.

Bohadana, A., Nilsson, F., Rasmussen, T., & Martinet, Y. (2003). Gender differences in quit rates following smoking cessation with combination nicotine therapy: Influence of baseline smoking behavior. *Nicotine & Tobacco Research, 5*, 111-116.

Borrell, C., García-Calvente, M. M., & Martí-Boscà, J.V. (2004). La salud pública desde la perspectiva de género y clase social. *Gaceta Sanitaria, 18*,2-6.

Chatkin, J.M., Abreu, C.M., Blanco, D.C., Tonietto, R., Scaglia, N., Wagner, M.B., & Fritscher, C.C. (2006). No gender difference in effectiveness of smoking cessation treatment in a Brazilian real-life setting. *The International Journal of Tuberculosis and Lung Disease, 10,* 499-503.

Cepeda, A., Reynoso, J.T., & Erath, S. (2004). Meta-Analysis of the Efficacy of Nicotine Replacement Therapy for Smoking Cessation: Differences Between Men and Women. *Journal of Consulting and Clinical Psychology, 72,* 712-722.

Croghan, I.T., Ebbert, J.O., Hurt, R.D., Hays, J.T., Dale, L.C. Warner, N. & Schoroeder, D.R. (2009). Gender differences among smokers receiving interventions for tobacco dependence in a medical setting. *Addictive Behaviors, 34*, 61-67. doi: 10.1016/j.addbeh.2008.08.010.

Fagerstrom, K.O. & Schneider, N.G. (1989). Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *Journal of Behavioral Medicine, 12*, 159-182.

Fernandez, E., Schiaffino, A., Borrell, C., Benach, J., Ariza, C., Ramon, J.M., …Kunst, A. (2006). Social class, education, and smoking cessation: Long-term follow-up of

patients treated at a smoking cessation unit. *Nicotine & Tobacco Research, 8,* 29-36.

Fidler, J., Ferguson, S.G., Brown, J., Stapleton, J., & West, R. (2013). How does rate of smoking cessation vary by age, gender and social grade? Findings from a population survey in England. *Addiction, 108*, 1680-1685. doi: 10.1111/add.12241.

Fiore, M.C., Jaen, C.R., Baker, T.B., Baikey, W.C., Benowitz, N.L., Curry, S.J., ...Wewers, M.E. (2008). *Treating tobacco use and dependence. A report of the US Surgeon General* Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, 257p.

Hughes, J.R., Keely, J.P., Niaura, R.S., Ossip-Klein, D.J., Richmond, R.L, & Swan, G.E. (2003). Measures of abstinence in clinical trials: issues and recommendations. *Nicotine & Tobacco Research, 5,* 13-25.

Iliceto, P., Fino, E., Pasquariello, S., D´Angelo Di Paola, M.E., & Enea, D. (2013). Predictors of success in smoking cessation among Italian adults motivated to quit. *Journal of Substance Abuse Treatment, 44*, 534-540. doi: 10.1016/j.jsat.2012.12.004.

Jarvis, M.J., Russell, M.A., & Saloojee, Y. (1980). Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *British Medical Journal, 281,* 484-485.

Killen, J.D., Fortmann, S.P., Varady, A., & Kraemer, H.C. (2002). Do Men Outperform Women in Smoking Cessation Trials? Maybe, But Not by Much. *Experimental and Clinical Psychopharmacology, 10*, 295-301.

López, A.D., Collishow, H.E., & Piha, T. (1994). A descriptive model of the cigarette epidemic in developed countries. *Tobacco Control, 3,* 242-247.

López, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T., & Murray, C.J. (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet, 367,* 1747-1757.

Marqueta, A., Nerín, I., Jiménez-Muro, A., Gargallo, P., & Beamonte, A. (2013). Factores predictores de éxito según género en el tratamiento del tabaquismo. *Gaceta Sanitaria, 27,* 26-31. doi: 10.1016/j.gaceta.2011.12.011

Marqueta, A., Jiménez-Muro, A., Beamonte, A., Gargallo, P., & Nerín, I. (2010). Evolución de la ansiedad en el proceso de dejar de fumar en fumadores que acuden a una Unidad de Tabaquismo. *Adicciones, 22*, 317-324.

Munafo, M., Bradburn, M., Bowes, L., & David, S. (2004). Are there sex differences in transdermal nicotine replacement therapy patch efficacy? A meta-analysis. *Nicotine & Tobacco Research, 6,* 769-776.

National Institute of Mental Health, 2009. *Women and depression.* Retrieved from: http://www.nimh.nih.gov/health/publications/women-and-depression-discovering-hope/depression-what-every-woman-should-know.pdf

Osler, M., Prescott, E., Godtfredsen, N., Hein, H.O., & Schnohr, P. (1999). Gender and determinants of smoking cessation: a longitudinal study. *Preventive Medicine, 29,* 57-62.

Perkins, K.A. & Scott, J. (2008). Sex differences in long-term smoking cessation rates due to nicotine patch. *Nicotine & Tobacco Research, 10,* 1245-1251. doi: 10.1080/14622200802097506.

Peto, R., Darby, S., Deo, H., Silcocks, P., Whitley, E., & Doll, R. (2000). Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *British Medical Journal, 321*, 323-329.

Piper, M.E., Cook, J.W., Schlam, T.R., Jorenby, D.E., Smith, S.S., Bolt, D.M., & Loh, WY. (2010). Gender, race, and education differences in abstinence rates among participants in two randomized smoking cessation trials. *Nicotine & Tobacco Research, 12,* 647-657. doi: 10.1093/ntr/ntq067.

Prochaska, J.O. & DiClemente, C.C. (1983). Stages and processes of self change of smoking: toward an integrative model of change. *Journal of Consulting and Clinical Psychology, 51,* 390-395.

Puente, D., Cabezas, C., Rodriguez-Blanco, T., Fernández-Alonso, C., Cebrian, T., Torrecilla, M.,…& Martín, C. (2011). The role of gender in a smoking cessation intervention: a cluster randomized clinical trial. *BMC Public Health, 11,* 369. doi: 10.1186/1471-2458-11-369.

Raich. A., Martínez-Sánchez, J.M., Marquilles, E., Rubio, L., Fu, M., & Fernández, E. (2015). Smoking cessation after 12 months with multi-component therapy. *Adicciones, 27*, 37-46.

Ramon, J.M., Bruguera, E., Fernández, C., Sanz de Burgoa, V., & Ramírez, E. (2009). Motivos para dejar de fumar en España en función del sexo y la edad. *Gaceta Sanitaria, 23,* 539.e1-539.e6. doi: 10.1016/j.gaceta.2009.07.004.

Scharf, D. & Shiffman, S. (2004). Are there gender differences in smoking cessation, with and without bupropion? Pooled- and meta-analyses of clinical trials of Bupropion SR. *Addiction, 99*, 1462-1469.

SRNT Subcommittee on Biochemical Verification. (2002). Biochemical verification of tobacco use and cessation. *Nicotine & Tobacco Research, 4,* 149-159.

Swan, G.E., Ward, M.M., Carmelli, D., & Jack, L.M. (1993). Differential rates of relapse in subgroups of male and female smokers. *Journal of Clinical Epidemiology, 46,* 1041-1053.

Tarone, R.E. & Ware, J. (1977). On distribution-free tests for equality of survival distributions. *Biometrika 64*, 156-160.

Thun, M., Peto, R., Boreham, J., & Lopez, A.D. (2012). Stages of the cigarette epidemic on entering its second century. *Tobacco Control, 21*, 96-101. doi: 10.1136/tobaccocontrol-2011-050294.

US Department of Health and Human Services (USDHHS) (2001). *Women and Smoking: A report of the Surgeon*

General. Rockville, MD. Public Health Service, Office of the surgeon General.

US Department of Health and Human Services (USDHHS) (1980). *The health consequences of smoking for women. A report of the Surgeon General*. Rockville, MD. Public Health Service, Office of the surgeon General.

Ward, K., Klesges, R.C, Zbikowski, S.M., Bliss, R.E., & Garvey, A.J. (1997). Gender differences in the outcome of a unaided smoking cessation attempt. *Addictive Behaviors, 22,* 521-533.

Wetter, D.W., Cofta-Gunn, L., Fouladi, R.T., Cinciripini, P.M, Sui, D., & Gritz, E. (2004). Late relapse/sustained abstinence among former smokers: a longitudinal study. *Preventive Medicine, 39,* 1156-1163.

Whitlock, E.P., Vogt, M.T., Hollis, J.F., & Lichtenstein, E. (1997) Does gender affect response to a brief clinic-based smoking intervention? *American Journal of Preventive Medicine, 13,* 159-166.

World Health Organization. *Women and the tobacco epidemic. Challenges for the 21st century*. Geneva: WHO, 2001. Retrieved from:http://whqlibdoc.who.int/hq/2001/WHO_NMH_TFI_01.1.pdf

Xu, J., Azizian, A., Monterosso, J., Domier, C.P., Brody, A.L., Fong, T.W., & London, E.D. (2008). Gender effects on mood and cigarette craving during early abstinence and resumption of smoking. *Nicotine & Tobacco Research, 10*, 1653-1661. doi: 10.1080/14622200802412929.

Association between bullying victimization and substance use among college students in Spain

Asociación entre victimización por bullying y consumo de sustancias entre la población universitaria de España

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Abstract

The purpose of this study is to analyze the prevalence and association between victimization and substance use among the university population in the southeast of Spain in a sample of 543 randomly selected college students (405 females and 138 males with an average age of 22.6 years). As a cross-sectional study, data was collected through an anonymous survey to assess victimization and drug use over the last 12 months. Results indicated that 62.2% of college students reported bullying victimization and 82.9% consumed some type of psychoactive substance, and found a statistically significant association between both variables measured. Additionally, logistic regression analysis confirmed the association between psychoactive substance use and different types of victimization. Our findings confirm the need for prevention to prevent this relation between victimization and substance use.

Keywords: bullying, cyberbullying, substance use, cross-sectional study, college students.

Resumen

Este estudio tiene como objetivo analizar la prevalencia y la asociación entre victimización y consumo de sustancias psicoactivas entre la población universitaria en el sureste de España en una muestra de 543 estudiantes universitarios seleccionados aleatoriamente (405 mujeres y 138 hombres con una media de edad de 22,6 años). Estudio transversal analítico, la recogida de los datos se llevó a cabo por medio de una encuesta anónima que recogía información acerca de victimización y consumo de drogas durante los últimos 12 meses. Los resultados muestran que un 62,2% de los estudiantes había sufrido algún tipo de victimización y un 82,9% había consumido alguna sustancia psicoactiva, con una asociación estadísticamente significativa entre ambas variables analizadas. Además, el análisis de regresión logística mostró que el consumo de sustancias psicoactivas se relacionaba con diferentes tipos de victimización. Nuestros hallazgos confirman la necesidad de implementar programas para prevenir la relación entre victimización y consumo de sustancias.

Palabras clave: bullying, ciberbullying, consumo de sustancias, estudio transversal analítico, estudiantes universitarios.

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In societies where alcohol use and abuse is an integral part of social life and is largely unregulated by law it is especially important to understand the patterns linked of drinking and consumers behaviour (WHO, 2005). According to WHO (2011) 4.5% worldwide of the global burden of disease and injury can be attributable to alcohol and drug use. In the year 2013, approximately a quarter (22.3%) of college students were illicit drug users (Substance Abuse & Mental Health Services Administration, 2013) with higher rates of alcohol and drug use among male college students than among female (26% vs. 19%, respectively). These results are high despite the fact that previous studies have shown the detrimental effects on health among college population of alcohol and drug use and abuse (Hartzler & Fromme, 2003; Knight et al., 2002).

According to the most recent data from Monitoring the Future, in 2013 approximately a quarter of (25.1%) college students had used cannabis in the past year (Johnston, O'Malley, Bachman & Schulenberg, 2010). Another representative research conducted by McCabe and colleagues (2007) with a sample of approximately 5.000 college students in the United States found differences in drug use and abuse depending on gender and degree, and showed how male students were generally more likely to report drug use and abuse than female students. Previous investigations have also documented the prevalence of drug use among college students (Mohler-Kuo, Lee & Wechsler, 2003; O'Malley & Johnston, 2002). Indeed, during the last decade the illicit use of prescription drugs has become one of the most common causes of drug use among this collective (Johnston et al., 2010). Regarding this, also associations between illicit drugs were founded (McCabe, Knight, Teter & Wechsler, 2005; Teter, McCabe, Cranford, Boyd & Guthrie, 2005).

Bullying and Cyberbullying among college population

Bullying is defined as a form of aggressive behavior experienced in schools or colleges that is defined as repeated exposure to negative actions carried by one or more students (Olweus & Limber, 2010). Bullying can be produced through the following forms: physical (punching or kicking, seizing or damaging other people's belongings); verbal (ridiculing, insulting, repeatedly mocking at someone, saying racist remarks); relational (leaving people out of groups) and indirect (spreading rumours or gossip about a student). Bullying is one of the most significant health problems among adolescents, with the international prevalence ranging from 9% to 54% (Nansel, Overpech, Pilla, Ruan & Simons-Morton, 2001; Kim, Koh & Leventhal, 2004). In a representative study (Wang, Iannotti & Luk, 2012) conducted among approximately 7.500 U.S. adolescents students approximately 29% reported suffering verbal and/or social bullying. Moreover, a cross-national study conducted in 40 countries estimated frequencies of bullying ranging from 8.6 % to 45.2 % among boys, and from 4.8 % to 35.8 % among girls (Craig et al., 2009). A victimization survey developed in two universities in the East Midlands (United Kingdom) conducted by Barberet and colleagues (2004) examined the incidence of student victimization during the previous twelve months, finding that 31% of them had been the victim of a crime, stolen some personal property (27%). A recent research (Zhou et al., 2015) has shown that approximately 5.9% of college students in China have been victims of bullying.

Similar to the definitions of traditional bullying, cyberbullying is defined as the behavior followed by an offender in an aggressive way with the intention of causing harm to the victims (Kiriakidis & Kavoura, 2010). According to Tokunaga (2010), cyberbullying should be defined as a clearly intentional aggression or maybe as a hostile or harmful act carried out through an electronic device repeatedly over time. This behaviour establishes an imbalance of powers between the aggressor and the victim. Furthermore, recently several authors identify cyberbullying exclusively with cyber-aggression (Calvete, Orue, Estévez, Villardón & Padilla, 2010) or with cyber victimization (Müller, Pfetsch & Ittel, 2014), without giving attention to the dynamic existing between these roles. Also, criteria of intentionality, repetition and imbalance of powers takes place between victim and aggressor and sometimes are forgotten (Olweus, 2013). Cyberbullying might occur in several ways (Tokunaga, 2010), and specific features that may intensify its effects are the potential audience or the ability to attack at any time and place that internet has. Previous studies have found rates of cyberbullying victimization, ranging from 4% to 72% among young population (Juvonen & Gross, 2008; Yang & Salmivalli, 2013; Ybarra & Mitchell, 2004). Nevertheless, schools and colleges lack of information about the effects and consequences of these attacks not distinguishing such cases from traditional bullying cases.

Association between substance use and bullying victimization

Previous research have shown that bullying victims are more likely to have externalizing behaviours, such as substance use and violent behaviours (Niemelä et al., 2011; Stein, Dukes & Warren, 2007), however few studies have already distinguished between different subtypes of bullying behaviors. On one hand, research demonstrates that bullying victimization at school is a significant predictor of alcohol and other substances use among adolescents (Radliff, Wheaton, Robinson & Morris, 2012). In a study conducted by Mustaine and Tewksbury (1998) in 1500 students, using a survey as the main research instrument, found that alcohol use is a risk factor to become a victim of verbal and physical aggression. In fact, alcohol use and abuse has been associ-

ated with sexual victimization in previous studies in the college population (Testa, Vanzile-Tamsen & Livingston, 2007).

The European Monitoring Centre for Drugs and Drug addiction in a research about sexual assaults facilitated by drugs or alcohol (Olszewski, 2009) argued that most of the drugs implicated in cases of sexual victimization were central nervous system depressants, alcohol and benzodiazepines. This result has also been defended by other authors (Resnick et al., 2012; Resnick, Walsh, Schumacher, Kilpatrick & Acierno, 2013), adding marijuana use as another risk factor (Gilreath, Astor, Estrada, Benbenishty & Unger, 2014; Golder & Logan, 2014; Nowotny & Graves, 2013; Resnick, Acierno, Amstadter, Self-Brown & Kilpatrick, 2007). On the other hand, previous studies conducted among young, adolescents (Begle et al., 2011 ;McCart., 2011) and general population (Vaugnh et al., 2010) suggested that individuals with history of victimization are at heightened risk for falling in substance use and abuse as a consequence of victimization.

Therefore, further investigation of the association between bullying victimization and substance use and abuse should be developed.

Gaps in the Literature and purpose of the Current Study

This study is designed to address several limitations of previous research. Firstly, most of the research on substance use and college population victimization has been conducted in the United States. So that, there is very short information in other western countries, and especially in Spain. Thus, it is interesting to test whether co-occurrence of different subtypes of bullying is related to substance use. Secondly, although a positive association between substance use and victimization has been documented in recent researches (Dehart & Moran, 2015; Huebner, Thoma & Neilands, 2014; Redondo Rodriguez & Graña Gómez, 2015; Zinzow & Thompson, 2015) they are not usually focused on college population. College student substance use and victimization are two relevant problems that might further interfere with the learning environment in the campus, and for this reason were included in the present research.

The present study attempts to solve the gap in the literature about substance use and victimization problems among college students in Spain. Using data from a questionnaire survey, the present study aims to: 1) estimate the prevalence of substance use during the previous twelve months to the study; 2) estimate the prevalence of some types of victimization during the previous twelve months; 3) analyse the association between substance use a victimization (and *viceversa*) among college population in Spain. Based on the previous literature, it is expected that substance use participants show higher levels of victimization, compared to non-users.

Method

Participants

College students from the University of Murcia (Spain) studying Grades 2 to 6 were the target population of the survey. It contained questions about substance use and victimization referred to the previous twelve months. Thus, the students who were at first year of college were excluded from the research. The University of Murcia had approximately 25.000 full-time (65% women and 35% men) students and 5.000 part-time students (68% women and 32% men) during the 2013-2014 course. We performed a cross sectional study for the students by means of simple random sampling with a margin of error of ± 5% and 95% confidence level. The student response rate was 88.7%, for a total of 617 college students. 70 selected students refused to participate in the research for the following reasons: "there is nothing to be gained from the survey" (8.3%) and "I am leaving the University soon" (3%). Finally, 547 students aged 18 to 45 years, being 74.2% female students (with a mean age of 22.1) and 25.8% male students (with a mean age of 22.7) agreed to participate in the current study. Complete demographic descriptive data and college related characteristics of participants for the whole sample and separated by consumers and non-consumers are presented in Table 1.

Procedure

Data were collected through anonymous self-report questionnaires distributed in the classroom.The study protocol was reviewed and approved by the University of Murcia's Research Ethics Board. Information was collected throughout the university year 2013-2014, except during July and August (Spanish summer holidays). College students and teachers were notified in advance via email and given the opportunity to view the survey. Students were advised by the teachers about the day to be surveyed and those who did not want to participate were excused from going to the lesson. Research staff (3 interviewers), were trained at a central location and sent to the different faculties, to supervise the filling of the anonymous self-report questionnaire by the participants. An interviewer (from the Research staff of University of Murcia) remained in the classroom while college students responded to the survey to address questionnaire-related issues. If participants did not understand a specific question, the interviewer would re-read the question in order to make it more clear without leading them in any particular direction. An informed consent to the procedure according to the laws in force at the time was attached. Only anonymous data were used and the questionnaires were completed on a voluntary basis. No compensation was paid to participants for their participation in current research.

Measures

Demographic measures. Including age, gender, nationality, dating status, work situation and membership to a sports

club. At the end of demographics characteristics, and after adapting questions from previous research (Glaser, Van Horn, Arthur, Hawkins & Catalano, 2005) family economic situations were measured, specifically through the question: "Currently, does have your family economic difficulties?". Responses included "Yes" or "No".

Substance Use. Substance use in the previous 12 months was measured using four yes/ no questions adapted from the European School Survey Project on Alcohol and Other Drugs 1995, 1999, and 2003 (Hibell et al., 2004) and were also used another surveys such as Monitoring the Future Study (Johnston et al., 2010) showing a high degree of reliabilitya necessary condition for validity (O'Malley, Bachman & Johnston, 1983). Substance use was indicated with an affirmative answer to the following questions: "Have you consumed alcohol during the previous 12 months?", "Have you consumed tobacco during the previous 12 months?", "Have you consumed cannabis during the previous twelve months?" and "Have you consumed cocaine during the previous 12 months?". If a participant answered "Yes", information on frequency of use was obtained. The frequence choices for these items were (1) less than once a month, (2) 1 to 3 days a month, (3) 1 to 2 days a week, (4) 3 to 5 days a week, and (5) 6 to 7 days a week. However, in the current study, respondents who answered affirmatively were considered as consumers in the past twelve months, without differences according to the frequency of consumption. In the current study, the Cronbach's alpha estimate of internal consistency was 0.84 for the scores in the five items about substance use during the previous twelve months.

Bullying victimization items. Involvement in traditional bullying behaviors was measured using the Revised Olweus Bully/Victim Questionnaire (OBVQ) (Olweus, 1996). Prior studies showed that the OBVQ had satisfactory construct validity and reliability (Kyriakides, Kaloyirou & Lindsay, 2006) as well as its adapted version in Spanish (Ruiz, 1992) used among young Spanish population with adequate psychometric properties (Cronbach's alpha = 0.87) (Ruiz, López, Pérez & Ochoa, 2009). Students were asked about bullying and cyberbullying victimization in the previous twelve months. A definition of both ways of victimization was first provided. Thefts, verbal bullying, physical bullying, sexually bullying and cyber were included in the current study as different variables. Thefts were measured by the next item: "Have you been stolen any personal belongings?". Verbal bullying was measured by the next two items: "Have you been verbally abused?" and "Have you been threatened?". Physical bullying was measured by the next three items: "Have you been beaten kicked, or pushed?". Students who responded affirmatively to any one of the 3 questions were considered victims of physical victimization. The questions regarding sexual bullying victimization were adapted from the National Violence Against Women and Men Survey (Tjaden & Thoennes, 2000). Sexually bullying was measured by the next three items: "Have you ever been touched, felt, or grabbed in a way that you felt sexually threatened?". For the previous victimization questions if a participant answered positively, information on frequency of use was obtained: (1) less than once a month, (2) 1 to 3 days a month, (3) 1 to 2 days a week, (4) 3 to 5 days a week, and (5) 6 to 7 days a week. No frequency information was used in the present study, thus all the positive data was recoded in the same variable "yes". In the current study, the Cronbach's alpha estimate of internal consistency was 0.85 for scores of the items measuring bullying prevalence in the previous twelve months.

Cyber bullying. Finally, with the same response options and time frame, two items measuring cyber bullying were included: "How many times has someone used the Internet, a phone, or other electronic communications to bully, tease, or threaten you in the past twelve months?". Data treatment was similar to that previously used in the item for substance use and bullying victimization. Cronbach's alpha in this study was 0.83 for the question referring to cyber bullying in the previous twelve months.

Data analysis

Statistical analyses were conducted on college students with no missing values for any of the variables studied. From a sample of 547 students, 543 (99.2% of the sample) were included in the analyses.With-and-without analyses showed that excluded missing data from the analyses did not have significant impact on the results. All the data analyses were conducted using the Statistical Package for the Social Sciences v.20 (SPSS, 2011).

The study was conducted in four steps. Firstly, descriptive statistics on socio-demographic characteristics were calculated and stratified by consumers and non-consumers in the previous twelve months. Chi-square tests of significance were used to identify bivariate relationships between these characteristics and reports of consumers. Secondly, univariate and bivariate analyses (whole sample and by gender) were conducted to know substance use characteristics in the previous twelve months, 95% confidence interval (CI) are presented. Thirdly, univariate and bivariate analyses (whole sample, consumers and no consumers and by gender) were conducted on every type of victimization in the previous twelve months, 95% confidence interval (CI) and are presented in table 3. Chi-square tests of significance were used to identify bivariate relationships between consumers and every type of victimization. Finally, we explored whether there were statistically significant associations between substance use and victimization. Thus, sequential logistic regression analysis was completed with every substance analyzed (alcohol, tobacco, cannabis and cocaine) and each of the five specific types of victimization (theft, verbal, physical victimization, sexual victimization and cyber) for the whole sample and by gender in the previous twelve months using Odds ratios (OR). Non-consumers in the previous twelve months were the reference group.

Results

Demographic characteristics by consumers

As shown in Table 1, the socio-demographic characteristics of the sample were examined to define the differences between consumers and non-consumers. Mean age of participants in the current sample was 22.6 years (SD = 6.12); consisting 25.4% of the sample of men. Regarding to nationality, 8.1% was foreigners, and finally over half of participants were currently in a relationship (53%).The associations between socio-demographic characteristics and substance use during the previous 12 months were examined using a chi-square test. The results identified a statistically significant association between nationality and substance use (p< 0.001) and between being a member of a sports club and substance use (p= 0.032).

Prevalence of substance use by gender

The prevalence of substance use among participants in the overlapping twelve months is shown in Table 2 by gender for the whole sample. During the twelve months reflection period, 82.9% (IC95%: 79.2-86.0) of participants indicated to use some type of substance use. Alcohol was the most common substance for both genders. No statistically significant association was found between gender and any substance use in the past twelve months (p= 0.669). There was a statistically significant association between cannabis use and gender (p= 0.002) with twice more men using cannabis than women (24.6%; CI 95%: 17.2-32.6 vs. 13.3%; CI 95%: 10.2-17.0, respectively).

Table 1. *Demographic characteristics of college students (whole sample and consumers and non-consumers).*

	Consumers (N = 450)	Non-Consumers (N = 93)	Whole sample (N = 543)	Consumers vs. non-consumers
	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Age	22.2 (5.54)	24.5 (8.14)	22.6 (6.12)	0.325
	n (%)	n (%)	n (%)	
Gender				0.669
Male	116 (25.8)	22 (23.7)	138 (25.4)	
Female	334 (74.2)	71 (76.3)	405 (74.6)	
Nationality				0.001
Spanish	424 (94.2)	75 (80.6)	499 (91.9)	
Non-Spanish	26 (5.8)	18 (19.4)	44 (8.1)	
With partner				0.543
Yes	247 (54.9)	41 (44.1)	288 (53.0)	
No	203 (45.1)	52 (55.9)	255 (47.0)	
Work situation				0.346
Working	43 (9.6)	6 (6.5)	49 (9.0)	
Notworking	407 (90.4)	87 (93.5)	494 (91.0)	
Member of sports club				0.002
Yes	100 (22.2)	15 (16.1)	115 (21.2)	
No	350 (77.8)	77 (83.9)	428 (78.8)	
Economic problems				0.126
Yes	158 (35.1)	25 (26.9)	183 (33.7)	
No	292 (64.9)	68 (73.1)	360 (66.3)	

Note. CI = Confidence interval

Table 2. *Prevalence of drug use in the past 12 months (whole sample and by gender)*

Substances used	Boys (N = 138)	Girls (N = 405)	Whole sample (N = 543)	
	% (95% CI)	% (95% CI)	% (95% CI)	p-value
None used	15.9 (9.7-22.6)	17.5 (14.1-21.5)	17.1 (14.0-20.8)	0.669
Any substance use	84.1 (77.4-90.3)	82.5 (78.5-85.9)	82.9 (79.2-86.0)	
Alcohol	80.4 (72.9-86.9)	80.7 (76.8-84.3)	80.7 (77.0-84.0)	0.937
Tobacco	23.9 (16.8-30.9)	26.9 (22.5-31.6)	26.2 (22.5-30.2)	0.488
Cannabis	24.6 (17.2-32.6)	13.3 (10.2-17.0)	16.2 (13.3-19.3)	0.002
Cocaine	5.1 (1.6-9.19	3.7 (2.0-5.6)	4.1 (2.4-5.7)	0.481

Note. CI = Confidence interval

Prevalence of victimization by gender

The percentages of each type of victimization in the previous year for the whole sample and for consumers and non-consumers are presented in Table 3. For all participants, cyber bullying victimization was the more common type of victimization (52.7%; CI 95%: 48.4-56.9) in contrast sexual victimization was the less common (3.9%; CI 95%: 2.2-5.5). No statistically significant associations were found between consumers and non-consumers participants in terms of victimization in the last twelve months. Among boys, during the twelve-month reflection period, 47.1% (CI 95%: 39.0-55.8) indicated to have suffered cyber bullying victimization with a larger proportion of men consumers compared to non-consumers (72.7% vs. 42.2%, respectively). There were no victims of sexual victimization among boys participants. Among girls, compared to their non-consumers counterparts, consumers participants were twice more likely to report sexual victimization (5.6%; CI 95%: 1.3-11.1 vs. 12.9%; CI 95%: 59.5-16.5, respectively).

Association between substance use and victimization by gender

No statistically significant association was found between consumers of any substance and the types of victimization analyzed in the previous year (Table 4). Alcohol consumers were more likely to be physically victimized (for all: OR 2.52; 95%: CI 1.12–5.68; and for girls only; OR 2.80; CI 95%: 1.07–8.05) and to suffer verbal aggressions for boys only (OR 2.39; CI 95% 1.11–5.63). Tobacco consumers were more likely to be stolen (for all: OR 2.47; CI 95: 1.65–3.68; for boys only; OR 3.55; CI 95: 1.55–8.13; and for girls only; OR 2.19; CI 95: 1.39–3.47) and to suffer cyber bullying victimization (for all: OR 2.22; CI 95: 1.49–3.31; and for girls only; OR 2.69; CI 95%: 1.67–4.32). For the whole sample, cannabis consumers were more likely to be physically (OR 2.00;CI 95%: 1.12–3.58) and sexually (OR 2.72;CI 95%: 1.06–6.95) victimized compared to non-consumers of cannabis. Finally, cocaine consumers were more likely to suffer oral aggressions (for boys only: OR 2.57; CI 95% 1.37–3.83), to be physically victimized (for boys only: OR 6.26; CI 95% 1.31–29.88) and to suffer cyber bullying victimization (for all: OR 1.15; CI 95%: 1.21–2.83; and for girls only; OR 1.89; CI 95% 1.72–2.07).

Discussion

In the current study, we found high rates of substance use (legal and illegal) and bullying victimization (and cyber bullying) among University students of Spain. Our results are in agreement with the results of previous studies that show how substance use among college population is a widespread phenomenon (Caldeira et al., 2009; Mohler-Kuo et al., 2003; McCabe et al., 2007) but also it is traditional bul-

Table 3. *Prevalence of every type of victimization among sample during the past 12 months (whole sample and consumers and by consumers)*

	Consumers (N = 450)	Non-Consumers (N = 93)	Whole sample (N = 543)	Consumers vs. non-consumers
Variables	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**p-value**
All (N = 543)				
Theft	30.4 (26.1-34.6)	29.0 (19.5-38.6)	30.2 (26.2-34.4)	0.787
Verbal	53.1 (48.3-57.4)	44.1 (34.7-54.0)	51.6 (47.5-55.6)	0.223
Physical	14.4 (11.4-17.7)	9.7 (4.2-16.8)	13.6 (10.9-16.8)	0.113
Sexual	4.0 (2.2-5.9)	3.2 (0.3-7.0)	3.9 (2.2-5.5)	0.724
Cyber	52.2 (48.4-56.9)	54.8 (44.0-65.5)	52.7 (48.4-56.9)	0.645
Boys (N = 138)				
Theft	31.8 (11.8-52.6)	26.7 (18.8-35.1)	27.5 (20.0-35.3)	0.624
Verbal	54.5 (33.3-75.0)	58.6 (49.6-67.0)	58.0 (49.4-66.0)	0.683
Physical	22.7 (5.9-42.9)	19.0 (12.1-26.9)	19.6 (13.4-27.0)	0.723
Sexual	-	-	-	-
Cyber	72.7 (54.2-91.3)	42.2 (33.3-51.3)	47.1 (39.0-55.8)	*0.*009
Girls (N = 405)				
Theft	31.7 (26.9-37.0)	28.2 (18.2-39.8)	31.1 (26.7-35.7)	0.555
Verbal	51.2 (46.0-56.4)	40.8 (29.2-52.0)	49.4 (44.5-54.2)	0.084
Physical	12.9 (9.5-16.5)	5.6 (1.3-11.1)	11.6 (8.6-15.1)	0.113
Sexual	5.4 (3.2-8.0)	4.2 (0.7-9.2)	5.2 (3.1-7.5)	0.688
Cyber	55.7 (50.6-61.2)	49.3(37.0-61.0)	54.6 (49.8-59.4)	0.326

Note. CI = Confidence interval

Table 4. *Summary of regression analyses examining substances use and types of victimization during the past 12 months (whole sample and consumers and by gender)*

	All (N = 543)		Boys (N = 138)		Girls (N = 405)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Consumers vs. non-consumers						
Theft	1.07 (0.65-1.74)	0.787	0.78 (0.29-2.09)	0.624	1.18 (0.65-2.08)	0.555
Verbal	1.43 (0.91-2.25)	0.113	1.18 (0.47-2.95)	0.723	1.51 (0.90-2.55)	0.113
Physical	1.57 (0.75-3.28)	0.223	0.79 (0.26-2.39)	0.683	1.43 (0.91-2.25)	0.084
Sexual	1.25 (0.36-4.33)	0.723	-	-	1.29 (0.37-4.50)	0.688
Cyber	0.90 (0.57-1.40)	0.645	0.27 (0.10-0.75)	0.009	1.29 (0.77-2.15)	0.326
Alcohol consumer vs. non-consumer						
Theft	1.23 (0.76-1.99)	0.380	1.86 (0.65-5.33)	0.242	1.10 (0.64-1.88)	0.073
Verbal	1.47 (0.95-2.25)	0.077	2.39 (1.11-5.63)	0.021	1.25 (0.76-2.05)	0.375
Physical	2.52 (1.12-5.68)	0.021	2.20 (0.61-7.95)	0.217	2.80 (1.07-8.05)	0.047
Sexual	1.45 (0.42-5.04)	0.550	-	-	1.45 (0.41-5.07)	0.553
Cyber	1.01 (0.66-1.55)	0.947	0.65 (0.28-1.52)	0.326	1.17 (0.71-1.93)	0.517
Tobacco consumer vs. non-consumer						
Theft	2.47 (1.65-3.68)	0.001	3.55 (1.55-8.13)	0.002	2.19 (1.39-3.47)	0.001
Verbal	1.57 (1.06-2.32)	0.021	0.83 (0.37-1.83)	0.648	1.95 (1.24-3.06)	0.003
Physical	1.64 (0.97-2.77)	0.058	2.25 (0.91-5.56)	0.075	1.47 (0.76-2.81)	0.241
Sexual	0.87 (0.31-2.44)	0.803	-	-	0.84 (0.30-2.35)	0.742
Cyber	2.22 (1.49-3.31)	0.000	1.26 (0.57-2.76)	0.056	2.69 (1.67-4.32)	0.000
Cannabis consumer vs. non-consumer						
Theft	1.31 (0.81-2.13)	0.262	1.95 (0.85-4.46)	0.108	1.12 (0.61-2.06)	0.705
Verbal	0.83 (0.52-1.31)	0.431	0.65 (0.29-1.41)	0.278	0.86 (0.48-1.54)	0.262
Physical	2.00 (1.12-3.58)	0.017	1.72 (0.68-4.29)	0.242	1.92 (0.89-4.15)	0.088
Sexual	2.72 (1.06-6.95)	0.030	-	-	3.58 (1.37-9.33)	0.006
Cyber	0.70 (0.44-1.12)	0.139	0.99 (0.45-2.16)	0.995	0.62 (0.35-1.11)	0.109
Cocaine consumer vs. non-consumer						
Theft	1.63 (0.68-3.90)	0.264	2.57 (1.37-3.83)	0.020	0.54 (0.15-1.95)	0.344
Verbal	0.52 (0.21-1.26)	0.145	1.86 (0.34-9.97)	0.459	0.24 (0.06-0.88)	0.020
Physical	1.95 (1.18-3.78)	0.204	6.26 (1.31-29.88)	0.010	0.53 (0.06-4.15)	0.543
Sexual	1.04 (1.02-1.06)	0.337	-	-	1.05 (1.03-1.08)	0.356
Cyber	1.15 (1.21-2.83)	0.001	1.08 (0.15-7.18)	0.936	1.89 (1.72-2.07)	0.000

Note. CI = Confidence interval. OR = odds ratio.

lying (Barberet et al., 2004; Wang et al., 2012;) and cyber bullying (Juvonen et al., 2008; Ybarra et al., 2004).

The results of this study show substance use differences depending on the gender of the student. These results agree with previous research (McCabe et al., 2007), which found higher rates of substance use among boys students. For example, we found a higher rate of cannabis use in male than in female students (24.4% vs. 13.3%) which is supported by previous work (Gledhill-Hoyt, Lee, Strote & Wechsler, 2000; Johnston et al., 2010). In the current research, the more common substance use was alcohol for both genders, finding a high proportion of consumers during the previous 12 months in the college, in consonance with previous studies (Gebreslassie, Feleke & Melese, 2013; Knight et al., 2002) that also reports the huge prevalence of alcohol use and abuse among college students.

Bullying reported prevalence in the current study was high; almost 62% of participants reported at least some kind of bullying victimization during the previous year. Several individual demographic and background characteristics emerged as significant related to the prevalence of bullying victimization as other authors showed previously. Gender differences in bullying prevalence might be partly explained because of the existence of differences in the types of bullying (e.g. sexual and physical victimization) to which girls and boys are exposed. Compared to boys (0%), a significant proportion of girls (5.4%) had been sexually victimized. However, similar to earlier research (Wang et al., 2012)

physical victimization is almost twice more present among boys than among girls (22.7% vs. 12.9%, respectively).

The current research also shares common findings with past studies, i.e. substance use was consistently associated with higher prevalence of bullying victimization (Gilreath et al., 2014; Resnick et al., 2007; Rospenda et al., 2013), as hypothesized. However, because of the cross-sectional nature of our data, we cannot determine whether substance increases the risk of bullying victimization or bullying victimization increases the use of substance use as a form of self-medication. To determine causality, a longitudinal study design with qualitative interviews would be required.

In this sense, analyzing the relationship between substance use and bullying victimization, we found support for our initial hypothesis that consumers-students would have a higher risk of becoming a victim than non-consumers. In addition, we found differences in this relationship according to the type of substance and victimization: sexual victimization is more common among consumers than among non-consumers (4% vs. 3.2%) which agrees with previous studies (Golder et al., 2014; Hughes, McCabe, Wilsnack, West & Boyd 2010; Reisner, Greytak, Parsons & Ybarra, 2014). According to Olszewski (2009) substance of abuse as alcohol might cause a reduction in physical and cognitive functions making them more vulnerable to sexual victimization, especially regarding to female young population.

Implications of findings for practice and policy

Several potential implications for the prevention of different types of bullying victimization could be extracted about student experiences of bullying victimization. There are established a few bullying prevention programs such as the Olweus Bullying Prevention program (see http://www.olweus.org/public/bullying_prevention_program.page) for use in adolescent context. However, in what refers to Spain, researchers need to be better communicated with educational institutions to reduce bullying victimization and consequence substance use (and *vice versa).* Universities could play an important role in identifying young people with substance use or victimization problems and should be an excellent manner to help them to find appropriate assistance. Like this, they would remain in contact with the University being exposed to the protective factors that schools can provide to the students, in order to reduce violence and consequencely to improve the health of its population.

Strengths and limitations

This study has a certain number of strengths. It contains for the first time data collected as part of an on-going study in adolescents in Spain, with rich data about the prevalence and risk factors of suffering victimization and substance use (and vice versa). Therefore it provides an opportunity to examine in the future the longitudinal predictors of victimization and substance use across different adolescent contexts, and especially among college students using a state-representative sample from Spain for substance use and bullying victimization prevalence differencing them by region of the country, type of college (e.g., public versus private), and living arrangements of students (e.g., off-campus versus on-campus).

On the other hand, interpretations of our findings should be constrained by several limitations. Firstly, it should be noted that this study only took place in a single city in Spain. If the findings could be generalized to other cities of Spain is still unknown. A second limitation is related to the type of study (cross-sectional), data on substance use patterns and victimization changes over time may provide new insights into their relationship. Thirdly, the present study was cross-sectional. Hence, the association between substance use and bullying and cyber bullying victimization could not be properly tested. For these reasons, future studies should use longitudinal designs in order to identify the time pattern, hence causality, between substance use and victimization. Given these limitations, our findings need to be replicated and refined in future studies. More longitudinal and qualitative research is necessary to examine further the direction of the link between substance use and victimization as well as to determine what protective and risk factors are provided in order to reduce drug use and violence among college population in Spain. Fourthly, the college bullying and substance use were self-reported, which may be subjectively biased or underestimate the associations between college bullying and substance use. Future studies should assess bullying behaviors using more objective measures. Finally, cyber bullying can occur at anytime and anywhere. However, in the current study we did not measure access factors that are likely to be particularly relevant to the longitudinal prediction of cyber bullying. Thus, future research should explore cyber bullying among college population in more robust ways.

Conclusions

This study is unique in Spain in examining the association between substance use and victimization among college population. Bullying among college students is a neglected public health issue. The current results underline the importance of further theoretical and conceptual development of victimization and the subtypes of victimization, and their relationship with legal and illegal substances as a complex. Demographic differences were found regarding to victimization, which may provide useful information to identify college students at risk of suffering victimization, especially among consumers. Then, this information can influence the development of prevention programs and strategies which aim to reduce victimization in Spain. These programs should have a special focus on at-risk students with substance use and abuse problems.

Conflicts of interest

The authors declare no conflict of interest concerning this article.

References

Barberet, R., Fisher, B., & Taylor, H. (2004). *University student safety in the East Midlands*. London: Home Office.

Begle, A. M., Hanson, R. F., Danielson, C. K., McCart, M. R., Ruggiero, K. J., Amstadter, A. B., ... & Kilpatrick, D. G. (2011). Longitudinal pathways of victimization, substance use, and delinquency: Findings from the National Survey of Adolescents. *Addictive behaviors, 36,* 682-689. doi: 10.1016/j.addbeh.2010.12.026.

Caldeira, K. M., Kasperski, S. J., Sharma, E., Vincent, K. B., O'Grady, K. E., Wish, E. D., & Arria, A. M. (2009). College students rarely seek help despite serious substance use problems. *Journal of Substance Abuse Treatment, 37,* 368-378. doi: 10.1016/j.jsat.2009.04.005.

Calvete, E., Orue, I., Estévez, A., Villardón, L., & Padilla, P. (2010). Cyberbullying in adolescents: Modalities and aggressors' profile. *Computers in Human Behavior, 26,* 1128–1135. http://dx.doi.org/10.1016/j.chb.2010.03.017.

Craig, W., Harel-Fisch, Y., Fogel-Grinvald, H., Dostaler, S., Hetland, J., Simons-Morton, B., … Pickett, W. (2009). A cross-national profile of bullying and victimization among adolescents in 40 countries. *International Journal of Public Health, 54,* 216-224. doi: 10.1007/s00038-009-5413-9.

DeHart, D. D., & Moran, R. (2015). Poly-victimization among girls in the justice system trajectories of risk and associations to juvenile offending. *Violence Against Women, 21,* 291-312. doi: 10.1177/1077801214568355.

Gebreslassie, M., Feleke, A., & Melese, T. (2013). Psychoactive substances use and associated factors among Axum university students, Axum Town, North Ethiopia. *BMC Public Health, 13,* 693-705. doi: 10.1186/1471-2458-13-693.

Gilreath, T. D., Astor, R. A., Estrada Jr, J. N., Benbenishty, R., & Unger, J. B. (2014). School victimization and substance use among adolescents in California. *Prevention Science, 15,* 897-906. doi: 10.1007/s11121-013-0449-8.

Glaser, R. R., Horn, M. L. V., Arthur, M. W., Hawkins, J. D., & Catalano, R. F. (2005). Measurement properties of the Communities That Care® Youth Survey across demographic groups. *Journal of Quantitative Criminology, 21,* 73-102. doi: 10.1007/s10940-004-1788-1.

Gledhill-Hoyt, J., Lee, H., Strote, J., & Wechsler, H. (2000). Increased use of marijuana and other illicit drugs at US colleges in the 1990s: results of three national surveys. *Addiction, 95,* 1655-1667.

Golder, S., & Logan, T. K. (2014). Violence, victimization, criminal justice involvement, and substance use among drug-involved men. *Violence and Victims, 29,* 53-72.

Hartzler, B., & Fromme, K. (2003). Cognitive–behavioral profiles of college risk-takers with Type II and psychopathic personality traits. *Addictive Behaviors, 28,* 315-326.

IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Hibell, B., Andersson, B., Bjarnason, T., Ahlström, S., Balakireva, O., & Kokkevi, A. (2004). *The Swedish council for information on alcohol and other drugs and the Pompidou Group at the Council of Europe*. The 2003 ESPAD Report.

Huebner, D. M., Thoma, B. C., & Neilands, T. B. (2014). School victimization and substance use among lesbian, gay, bisexual, and transgender adolescents. *Prevention Science, 17,* 734-743. doi: 10.1007/s11121-014-0507-x

Hughes, T., McCabe, S. E., Wilsnack, S. C., West, B. T., & Boyd, C. J. (2010). Victimization and substance use disorders in a national sample of heterosexual and sexual minority women and men. *Addiction, 105,* 2130-2140. doi: 10.1111/j.1360-0443.2010.03088.x

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2010). *Monitoring the Future: National Survey Results on Drug Use, 1975-2009*. Volume I: Secondary School Students. NIH Publication No. 10-7584. National Institute on Drug Abuse (NIDA).

Juvonen, J., & Gross, E. F. (2008). Extending the school grounds? Bullying experiences in cyberspace. *Journal of School Health, 78,* 496-505. doi: 10.1111/j.1746-1561.2008.00335.x.

Kim, Y. S., Koh, Y. J., & Leventhal, B. L. (2004). Prevalence of school bullying in Korean middle school students. *Archives of Pediatrics & Adolescent Medicine, 158,* 737-741.

Kiriakidis, S. P., & Kavoura, A. (2010). Cyberbullying: A review of the literature on harassment through the internet and other electronic means. *Family & Community Health, 33,* 82-93. doi: 10.1097/FCH.0b013e3181d593e4.

Knight, J. R., Wechsler, H., Kuo, M., Seibring, M., Weitzman, E. R., & Schuckit, M. A. (2002). Alcohol abuse and dependence among US college students. *Journal of Studies on Alcohol, 63,* 263-270.

Kyriakides, L., Kaloyirou, C., & Lindsay, G. (2006). An analysis of the Revised Olweus Bully/Victim Questionnaire using the Rasch measurement model. *British Journal of Educational Psychology, 76,* 781-801.

McCabe, S. E., & Teter, C. J. (2007). Drug use related problems among nonmedical users of prescription stimulants: A web-based survey of college students from a Midwestern university. *Drug and Alcohol Dependence, 91,* 69-76.

McCabe, S. E., Knight, J. R., Teter, C. J., & Wechsler, H. (2005). Non-medical use of prescription stimulants among US college students: Prevalence and correlates from a national survey. *Addiction, 100,* 96-106.

McCabe, S. E., Morales, M., Cranford, J. A., Delva, J., McPherson, M. D., & Boyd, C. J. (2007). Race/ethnicity and gender differences in drug use and abuse among

college students. *Journal of Ethnicity in Substance Abuse, 6,* 75-95. doi: 10.1300/J233v06n02_06.

McCart, M. R., Zajac, K., Danielson, C. K., Strachan, M., Ruggiero, K. J., Smith, D. W., ... & Kilpatrick, D. G. (2011). Interpersonal victimization, posttraumatic stress disorder, and change in adolescent substance use prevalence over a ten-year period. *Journal of Clinical Child & Adolescent Psychology, 40,* 136-143. doi: 10.1080/15374416.2011.533411.

Mohler-Kuo, M., Lee, J. E., & Wechsler, H. (2003). Trends in marijuana and other illicit drug use among college students: results from 4 Harvard School of Public Health College Alcohol Study surveys: 1993–2001. *Journal of American College Health, 52,* 17-24.

Müller, C. R., Pfetsch, J., & Ittel, A. (2014). Ethical media competence as a protective factor against cyberbullying and cybervictimization among German school students. Cyberpsychology, *Behavior and Social Networking, 17,* 644–651. http://dx.doi.org/10.1089/cyber.2014.0168.

Mustaine, E. E., & Tewksbury, R. (1998). Specifying the role of alcohol in predatory victimization. *Deviant Behavior, 19,* 173-199.

Nansel, T. R., Overpeck, M., Pilla, R. S., Ruan, W. J., Simons-Morton, B., & Scheidt, P. (2001). Bullying behaviors among US youth: Prevalence and association with psychosocial adjustment. *JAMA, 285,* 2094-2100.

Niemelä, S., Brunstein-Klomek, A., Sillanmäki, L., Helenius, H., Piha, J., Kumpulainen, K., & Sourander, A. (2011). Childhood bullying behaviors at age eight and substance use at age 18 among males. A nationwide prospective study. *Addictive Behaviors, 36,* 256-260. doi: 10.1016/j.addbeh.2010.10.012.

Nowotny, K. M., & Graves, J. L. (2013). Substance use and intimate partner violence victimization among White, African American, and Latina women. *Journal of Interpersonal Violence, 28,* 3301-3318. doi: 10.1177/0886260513496903.

Olszewski, D. (2009). Sexual assaults facilitated by drugs or alcohol. Drugs: *Education, Prevention and Policy, 16,* 39-52.

Olweus, D. (1996).The revised Olweus bully/victim questionnaire. Research Center for Health Promotion (HIMIL), University of Bergen; Bergen, Norway.

Olweus, D. (2013). School bullying: Development and some important challenges. In S. NolenHoeksema (Ed.). Annual review of clinical psychology (Vol. 9, pp. 751–780). Palo Alto: Annual Reviews.

Olweus, D., & Limber, S. P. (2010). Bullying in school: Evaluation and dissemination of the Olweus Bullying Prevention Program. *American Journal of Orthopsychiatry, 80,* 124-134. doi: 10.1111/j.1939-0025.2010.01015.x.

O'Malley, P. M., Bachman, J. G., & Johnston, L. D. (1983). Reliability and consistency in self-reports of drug use. *International Journal of the Addictions, 18,* 805–824.

O'Malley, P. M., & Johnston, L. D. (2002). Epidemiology of alcohol and other drug use among American college students. *Journal of Studies on Alcohol, 3,* 23-39.

Radliff, K. M., Wheaton, J. E., Robinson, K., & Morris, J. (2012). Illuminating the relationship between bullying and substance use among middle and high school youth. *Addictive Behaviors, 37,* 569-572. doi: 10.1016/j.addbeh.2012.01.001.

Reisner, S. L., Greytak, E. A., Parsons, J. T., & Ybarra, M. L. (2015). Gender minority social stress in adolescence: disparities in adolescent bullying and substance use by gender identity. *The Journal of Sex Research, 52,* 243-256. doi: 10.1080/00224499.2014.886321.

Resnick, H. S., Acierno, R., Amstadter, A. B., Self-Brown, S., & Kilpatrick, D. G. (2007). An acute post-sexual assault intervention to prevent drug abuse: Updated findings. *Addictive Behaviors, 32,* 2032-2045.

Resnick, H. S., Walsh, K., McCauley, J. L., Schumacher, J. A., Kilpatrick, D. G., & Acierno, R. E. (2012). Assault related substance use as a predictor of substance use over time within a sample of recent victims of sexual assault. *Addictive Behaviors, 37,* 914-921. doi: 10.1016/j.addbeh.2012.03.017.

Resnick, H. S., Walsh, K., Schumacher, J. A., Kilpatrick, D. G., & Acierno, R. (2013). Prior substance abuse and related treatment history reported by recent victims of sexual assault. *Addictive Behaviors, 38,* 2074-2079.

Redondo Rodríguez, N. , & Graña Gómez, J. L. (2015). Consumo de alcohol, sustancias ilegales y violencia hacia la pareja en una muestra de maltratadores en tratamiento psicológico. *Adicciones, 27,* 27-36.

Rospenda, K. M., Richman, J. A., Wolff, J. M., & Burke, L. A. (2013). Bullying victimization among college students: Negative consequences for alcohol use. *Journal of Addictive Diseases, 32,* 325-342. doi: 10.1016/j.addbeh.2012.12.010.

Ruiz, R. O. (1992, September). Violence in schools. Problems of bullying and victimization in Spain. Paper presented at the European Conference of Developmental Psychology, Seville.

Ruiz, D. M., López, E. E., Pérez, S. M., & Ochoa, G. M. (2009). Reputación social y violencia relacional en adolescentes: el rol de la soledad, la autoestima y la satisfacción vital. *Psicothema, 21,* 537-542.

Stein, J. A., Dukes, R. L., & Warren, J. I. (2007). Adolescent male bullies, victims, and bully-victims: A comparison of psychosocial and behavioral characteristics. *Journal of Pediatric Psychology, 32,* 273-282.

Substance Abuse & Mental Health Services Administration. (2014). *Results from the 2013 National Survey on Drug Use and Health: national findings.* Rockville, MD: Office of Applied Studies, USDHHS.

Testa, M., VanZile-Tamsen, C., & Livingston, J. A. (2007). Prospective prediction of women's sexual victimization

by intimate and nonintimate male perpetrators. *Journal of Consulting and Clinical Psychology, 75,* 52-60.

Teter, C. J., McCabe, S. E., Cranford, J. A., Boyd, C. J., & Guthrie, S. K. (2005). Prevalence and motives for illicit use of prescription stimulants in an undergraduate student sample. *Journal of American College Health, 53,* 253-262.

Tjaden P, Thoennes N. *Full report of the prevalence, incidence, and consequences of violence against women: Findings from the national violence against women survey* (NCJ 183781) Washington, DC: National Institute of Justice and Centers for Disease Control and Prevention; 2000.

Tokunaga, R. S. (2010). Following you home from school: A critical review and synthesis of research on cyberbullying victimization. *Computers in Human Behavior, 26,* 277-287.

Vaughn, M. G., Fu, Q., Delisi, M., Beaver, K. M., Perron, B. E., & Howard, M. O. (2010). Criminal victimization and comorbid substance use and psychiatric disorders in the United States: Results from the NESARC. *Annals of Epidemiology, 20,* 281-288.

Wang, J., Iannotti, R. J., & Luk, J. W. (2012). Patterns of adolescent bullying behaviors: Physical, verbal, exclusion, rumor, and cyber. *Journal of School Psychology, 50,* 521-534. doi: 10.1016/j.jsp.2012.03.004.

WHO (2005). Alcohol, gender and drinking problems: perspectives from low and middle income countries. Geneva: WHO.

WHO (2011). *Global status report on alcohol and health.* Geneva: WHO.

Yang, A., & Salmivalli, C. (2013). Different forms of bullying and victimization: Bully-victims versus bullies and victims. *European Journal of Developmental Psychology, 10,* 723–738. http://dx.doi.org/10.1080/17405629.2013.793596.

Ybarra, M. L., & Mitchell, K. J. (2004). Online aggressor/targets, aggressors, and targets: A comparison of associated youth characteristics. *Journal of child Psychology and Psychiatry, 45,* 1308-1316.

Zhou, Y., Guo, L., Lu, C. Y., Deng, J. X., He, Y., Huang, J. H., … Gao, X. (2015). Bullying as a Risk for Poor Sleep Quality among High School Students in China. *PLoS One,* 10, e0121602-e0121602. doi: 10.1371/journal.pone.0121602.

Zinzow, H. M., & Thompson, M. (2015). A longitudinal study of risk factors for repeated sexual coercion and assault in US College men. *Archives of Sexual Behavior, 44,* 213-222. doi: 10.1007/s10508-013-0243-5.

Alcohol, poverty and social exclusion: Alcohol consumption among the homeless and those at risk of social exclusion in Madrid

Alcohol, pobreza y exclusión social: Consumo de alcohol entre personas sin hogar y en riesgo de exclusión en Madrid

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Abstract

The work analyzes different aspects related to alcohol consumption among homeless people and people at risk of social exclusion. The data was gathered from a representative sample of homeless people in Madrid (n = 188) and a sample of people at risk of social exclusion (n = 164) matched in sex, age, and origin (Spaniards vs. foreigners). The results showed that homeless people present a greater consumption of alcohol and have experienced more problems derived from its consumption than people at risk of social exclusion. Most of the homeless people who had alcohol-related problems had had them prior to their homelessness, and they stated they had poorer health and had experienced a greater number of homelessness episodes. Despite the relevance of problems related to alcohol among our sample, only a small percentage of the sample had participated in treatment programs for alcohol consumption.

Keywords: Alcohol; Homeless; Poverty; Social exclusion.

Resumen

El trabajo analiza diferentes aspectos relativos al consumo de alcohol entre personas en situación de pobreza y/o exclusión social. La información se recogió a partir de una muestra representativa de las personas sin hogar en Madrid (n = 188) y una muestra de personas en riesgo de exclusión social (n = 164) equiparada en sexo, edad y procedencia (españoles vs. extranjeros). Los resultados obtenidos indican que las personas sin hogar presentan un mayor consumo de alcohol y han padecido más problemas derivados de dicho consumo que las personas en riesgo de exclusión. La mayoría de personas sin hogar que tuvieron problemas con el alcohol padecieron estos de forma previa a encontrarse en la situación sin hogar, manifestaron tener peor salud y haberse encontrado en un mayor número de ocasiones en la situación sin hogar. Pese al importante problema que supone el consumo de alcohol entre los entrevistados, tan sólo un pequeño porcentaje había accedido a programas de tratamiento para problemas derivados del consumo de esta sustancia.

Palabras clave: Alcohol; Personas sin hogar; Pobreza; Exclusión social.

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The scientific literature has identified multiple personal and social variables involved in the genesis and maintenance of homelessness (Panadero, Guillén & Vázquez, 2015). Among these variables, alcohol abuse has been considered as one of the most relevant risk factors (Caton et al., 2005; Panadero & Vázquez, 2012). A survey of 29 developed countries estimated that the prevalence of alcohol dependence among homeless people was around 37.9% (Fazel, Khosla, Doll & Geddes, 2008). The prevalence of alcohol dependence is even higher among people who are chronically homeless (Kuhn & Culhane, 1998), with the resulting negative impact and neurocognitive deterioration (Soler González, Balcells Oliveró & Gual Solé, 2014).

In Spain, research on homeless people reveals different percentages of alcohol consumption, such that whereas various studies have reported a higher than 40% rate of alcohol dependence or abuse (Muñoz, Vázquez & Cruzado, 1995), the Instituto Nacional de Estadística (INE [National Institute of Statistics], 2012) indicated that 9.5% of homeless people admitted moderate alcohol consumption, and only 4.1% reported high or excessive consumption. Muñoz, Vázquez, and Vázquez (2003) noted that 43.1% of the homeless in Madrid and 23.5% of a risk group reported having drunk excessively at some time in their lives. In addition, most of the homeless people had prior problems with alcohol before they became homeless.

Table 1. *Differences in Sociodemographic Characteristics, Homelessness Chronicity, and Health Status between Homeless People who had drunk excessively at some time of their Lives and those who had not*

	Has drunk excessively at some time of his/her life		**t/x²**
	Yes (n = 83)	No (n = 100)	
Sex			7.751**
Male	59.1%	40.9%	
Female	31.0%	69.0%	
Age Mean years (SD)	46.74 (9.614)	48.23 (14.822)	0.788
Nationality			1.475
Spanish	56.6%	43.4%	
Foreign	50.9%	49.1%	
Completed studies			4.698
No studies or incomplete primary education	65.2%	34.8%	
Primary studies	65.1%	34.9%	
Secondary studies	49.5%	50.5%	
University studies	45.5%	54.5%	
Number of times he/she was homeless in his/her life			12.147**
1 time	44.7%	55.3%	
Between 1 and 5 times	66.7%	33.3%	
More than 5 times	76.9%	23.1%	
Time of homelessness, adding all the periods during which he/she was homeless Mean months (SD)	89.15 (104.381)	78.34 (99.919)	-0.700
Perceived general health status			11.680*
Very good	35.0%	65.0%	
Good	50.0%	50.0%	
Regular	68.9%	31.1%	
Bad	62.5%	37.5%	
Very bad	63.6%	36.4%	
Suffering from a medically recognized severe or chronic disease	64.0%	36.0%	4.190*

Note. *p ≤ .05; **p ≤ .01; ***p ≤ .001

The study aims to analyze different issues about alcohol consumption among homeless people and people who, although they still retain their home, were at risk of sliding into homelessness.

Method

The research was carried out using the data provided by persons belonging to two groups (Panadero et al., 2015):

Homeless people: a representative sample of the homeless in Madrid (n = 188). Of them, 84% were men and 16% women, with a mean age of 47.57 years (SD = 12.172), 71.6% were Spanish and 28.3% were of foreign origin.

People at risk of exclusion: a sample of people who retained their home but were in need of services oriented to the homeless (n = 164). This group was matched with the group of homeless people in sex (81.8% men, 18.9% women), age (mean age = 45.54 years, SD = 10.818) and origin (62.2% Spanish, 37.8% foreign).

To collect the data, we used a structured hetero-applied interview, made up of standardized instruments and questions designed by the authors, which allowed us to address a broad array of issues: socio-demographic characteristics, housing location, economic situation, employment status, social support, history of homelessness, substance consumption, health, use of resources, victimization and suffering from stressful life events, citizen participation, causal attributions of homelessness, stereotypes and meta-stereotypes of homelessness, and access to new technologies (Vázquez, Panadero, Martín, & Díaz-Pescador, 2015). Sample selection was carried out through stratified random sampling with proportional affixation. The sample selection strategy prevented the rejection rate, around 30%, from generating bias in the sample. The interviews were carried out anonymously, preserving at all times the respondents' privacy.

Results

Data on alcohol abuse (collected through the question *"Have you drunk too much at any time of your life?"*) indicated that 54.6% (n = 100) of the homeless and 32.5% (n = 57) of the people at risk of exclusion ($\chi 2$ = 13.122, p = .000) reported having consumed excessive alcohol at some time of their lives. The mean age at which they admitted having consumed excessive alcohol was around 25.31 years (SD = 10.998) among the homeless and 24.98 years (SD = 9.821) among the people at risk. There were no statistically significant differences between the two groups. Among the homeless who admitted having drunk excessively at some time of their lives, 75.0% (n = 72) reported having done so before becoming homeless. Table 1 presents some differences observed between homeless people who had consumed excessive alcohol at some point in their lives and homeless people who had not.

As shown in Table 1, among the men, those who had been homeless more frequently, those who considered that their general health status was worse, and those who suffered a serious or chronic illness admitted having drunk excessively at some time of their lives.

As regards daily alcohol consumption during the month prior to the interview, the homeless drank, on average, the equivalent of 5.66 glasses per day (SD = 11.667), compared to the 2.51 glasses (SD = 4.520) of people at risk (t = 3.287, p = .001). The homeless people who mainly slept in the street during the month prior to the interview (n = 42) consumed significantly more alcohol than those who had mainly slept in a shelter (n = 131): the former reported having consumed an average equivalent to 10.88 glasses of alcohol per day (SD = 9.486) compared to the 3.98 glasses (SD = 15.775) of the latter (t = 2.682, p = .010).

There were differences between the homeless and the people at risk in the frequency of alcohol consumption. Of the homeless, 30.6% (n = 56) reported drinking four or more times a week, compared to the 9.4% times (n = 15) of persons at risk ($\chi 2$ = 24.465, p = .000). Moreover, 17.6% (n = 32) of the homeless and 13.8% (n = 22) of the people at risk had received treatment for alcohol-related problems at some time, and 7.1% (n = 13) of the homeless people and 3.8% (n = 6) of the people at risk participated in some program aimed at quitting alcohol consumption at the time of the interview. There were no statistically significant differences between the two groups in these issues.

Conclusions and discussion

More than half of the homeless admitted having consumed excessive alcohol at some point in their lives, a percentage reaching 59% in the homeless males. Undoubtedly, excessive consumption of alcohol is a problem for this group. The majority of homeless people who had alcohol-related problems had had them before becoming homeless. This allows us to infer a frequent probable causal relationship in the genesis of homelessness. Unfortunately, the percentage of the homeless and of people at risk who consume excessive alcohol is higher than that observed a decade ago by Muñoz et al. (2003), which leads us to assume that this circumstance, far from decreasing, has become more severe over the past decade.

The homeless people interviewed reported drinking a daily average equivalent to five glasses of alcohol, and one in three stated they drank four or more times a week. These data relatively coincide with those obtained in similar studies carried out in Spain (Muñoz et al., 2003) and elsewhere in the world (Fazel et al., 2008). The people at risk reported drinking daily one half of the alcohol consumed by homeless people, and only one out of ten consumed alcohol four or more times per week. The data collected suggest that the high consumption of alcohol among the homeless is a major obstacle to their processes of normalization. The high con-

sumption of alcohol was especially marked among homeless people who slept in the streets, as they reported consuming the equivalent of ten glasses of alcohol per day. The difficulty of drinking alcohol in most of the housing facilities may influence heavier consumers to remain in the streets, and not go to the care facilities, with the health problems that this entails.

Homeless people who had experienced problems derived from alcohol consumption had been homeless more frequently. Although excessive alcohol consumption does not seem to clearly affect the chronicity of homelessness, it does seem to lead more frequently to repeatedly sliding into homelessness. Thus, not only alcohol consumption is a factor of vulnerability to slide into homelessness, but it also appears as a major handicap in the processes of overcoming this situation.

Excessive alcohol consumption, as well as negatively influencing the processes of normalization in the homeless, also appears to be related to their health status, such that a greater percentage of those who considered they had a worse health status also reported having drunk excessively at some point in their lives. Despite the major problem posed by the excessive consumption of alcohol among persons in situations of social difficulty and, especially among the homeless, these groups' access to treatment is clearly insufficient. In fact, despite the fact that more than half of the homeless and one third of the group at risk reported having consumed excessive alcohol, not even one fifth had had access to programs to alleviate the problems arising from alcohol consumption. Doubtless, the access of the homeless and of people at risk to treatment for alcohol consumption is much lower than required and, despite the relevance of this issue, at least for the last decade, no effective intervention strategies seem to have been developed to mitigate the problem. Thus, it is necessary to design and implement new intervention programs that are especially accessible to homeless people, a group that tends to present special difficulties to access services.

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Conflict of interest

None of the authors has any conflict of interest.

References

Caton, C.L., Dominguez, B., Schanzer, B., Hasin, D.S., Shrout, P.E., Felix, A.,… Hsu, E. (2005). Risk factors for long-term homelessness: Findings from a longitudinal study of first-time homeless single adults. *American Journal of Public Health, 95,* 1753-1759. doi:10.2105/AJPH.2005.063321.

Fazel, S., Khosla, V., Doll, H., & Geddes, J. (2008). The prevalence of mental disorders among homeless in western countries: Systemic review and meta-regression analysis. *Plos Medicine, 5,* e225. doi:10.1371/journal.pmed.0050225

INE (Instituto Nacional de Estadística) (2012). *Encuesta a las personas sin hogar. Año 2012.* Recuperado de: http://www.ine.es/jaxi/menu.do?L = 0&type = pcaxis&path = %2Ft25%2Fp454&file = inebase

Kuhn, R., & Culhane, D.P. (1998). Applying cluster analysis to test a typology of homes pattern of shelter utilization: Results from de analysis of administrative data. *American Journal of Community Psychology, 26,* 207-232. doi:10.1023/A:1022176402357.

Muñoz, M., Vázquez, C., & Cruzado, J.A. (1995). *Personas sin hogar en la Comunidad de Madrid. Informe psicosocial y epidemiológico.* Madrid: Comunidad Autónoma de Madrid.

Muñoz, M., Vázquez, C., & Vázquez, J.J. (2003). *Los límites de la exclusión: Estudio sobre los factores económicos, psicosociales y de salud que afectan a las personas sin hogar en Madrid.* Madrid: Editorial Témpora.

Panadero, S., & Vázquez, J.J. (2012). La investigación sobre las personas sin hogar y los recursos de atención al colectivo en España. Evolución, situación actual y retos futuros (pp. 87-107). En C. Zúñiga (ed.) *Psicología, sociedad y equidad: aportes y desafíos.* Santiago de Chile: Universidad de Chile.

Panadero, S., Guillén, A.I., & Vázquez, J.J. (2015). Happiness in the street. Overall happiness among homeless people in Madrid (Spain). *American Journal of Orthopsychiatry, 85,* 324-330. doi: dx.doi.org/10.1037/ort0000080.

Soler González, C., Belcells Oliveró, M., & Gual Solé, A. (2014). Alcohol related brain damage. State of the art and a call for action. *Adicciones, 26,* 199-207.

Vázquez, J.J., Panadero, S., Martín, R.M., & Díaz-Pescador, V. (2015). Access to new information and communication technologies among homeless people in Madrid (Spain). *Journal of Community Psychology, 43,* 338-347. doi: 10.1002/jcop.21682.

Methadone dosage and its relationship to quality of life, satisfaction, psychopathology, cognitive performance and additional consumption of non-prescribed drugs

Dosis de metadona y su relación con calidad de vida, satisfacción, psicopatología, rendimiento cognitivo y consumo adicional de sustancias no prescritas

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Abstract

The effectiveness of methadone maintenance treatment is beyond any doubt, but there remains some incertitude about the appropriate and effective dosage and the objectives that should be achieved by this therapy. Some authors maintain that only doses higher than 50-60 mg/day ought to be considered effective, since only these block all the opioid receptors. But others propose the use of doses adjusted to the needs of the patient, based on their recovery process. Quality of life, satisfaction with treatment, psychopathological symptoms, cognitive performance and additional intake of illegal and unprescribed drugs were evaluated in a representative sample of all patients treated with opioid agonists in the Addiction Institute of Madrid (N = 1898, n = 450) and the Junta de Extremadura (N = 100, n = 65). The results revealed a negative relationship between dose and quality of life, psychopathological symptoms and cognitive performance. Satisfaction with treatment, based on doses negotiated together by doctor and patient, was very high, regardless of the dose. To establish hypothetical causal dependencies among the studied variables structural equation modelling was performed. The results reject the need for high dosage if not required by the patient, and highlight the benefits of other psychosocial interventions that lead to recovery, despite the chronification that could imply the use of high doses. Whereas high dosage programmes provide better indicators of social control, the patient's quality of life must be one of the main indicators of a successful treatment, as in any other health problem.

Keywords: Methadone Maintenance; Dosage; Quality of Life; Addiction; Treatment.

Resumen

La efectividad de los tratamientos con metadona está fuera de toda duda, si bien persisten dudas sobre las dosis efectivas y los objetivos que debe perseguir un programa de mantenimiento. Algunos autores propugnan que sólo superiores a 50-60 mg/día deben ser consideradas efectivas, al bloquear los receptores opioides. Otros proponen dosis ajustadas a las necesidades del paciente, atendiendo prioritariamente a su recuperación. Se estudió una muestra representativa de todos los pacientes en tratamiento con agonistas del Instituto de Adicciones de Madrid (N=1898, n=450) y de la Junta de Extremadura (N=100, n=65). Se evaluaron calidad de vida, satisfacción con el tratamiento, sintomatología psicopatológica, rendimiento cognitivo y consumos adicionales. Los resultados muestran una relación negativa entre dosis y calidad de vida, sintomatología psicopatológica y rendimiento cognitivo. La satisfacción con el tratamiento, basado en dosis negociadas entre médico y paciente, fue muy elevada, con independencia de la dosis. Se formuló una ecuación estructural que relacionara todas las variables. Los resultados descartan la necesidad de utilizar dosis altas si el paciente no las precisa, y contar con otras intervenciones psicosociales que favorezcan la recuperación frente a la cronificación que supone el uso de dosis altas. Mientras los programas de altas dosis atienden prioritariamente a indicadores de control social, la calidad de vida del paciente debe ser uno de los principales indicadores de éxito del tratamiento, como en cualquier otro problema de salud.

Palabras clave: Mantenimiento con metadona; Dosis; Calidad de vida; Adicción; Tratamiento.

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The efficacy, effectiveness and efficiency of methadone maintenance treatment for heroin addiction is currently beyond any doubt (Mattick, Breen, Kimber & Davoli, 2009). Uncertainty persists, however, as to the most effective doses and the objectives of a maintenance programme.

The currently predominant approach advocates doses higher than 50-60 mg/day (90-100 mg on average), and has three primary objectives: (a) suppression of symptoms on withdrawal of exogenous opioids; (b) cessation of craving; (c) pharmacological blocking of the reinforcing capacity of heroin in the saturation of opioid receptors (Maremmani, Pacini, Lubrano & Lovrecic, 2003). The chief indicators of successful treatment are reduction of heroin and cocaine consumption, reduction of the seriousness of problems linked to consumption, and greater retention rates. This approach focuses primarily on the pharmacological effects of opioids and their capacity for blocking receptors (Pacini, Maremmani, Rovai, Rugani & Maremmani, 2010). Various studies (for example Adelson *et al.*, 2013; Faggiano, Vigna-Taglianti, Versino & Lemma, 2003; Farré, Mas, Torrens, Moreno & Camí, 2002) have found that higher doses correspond to longer treatment times and lower consumption of heroin and other drugs. Patients with comorbid psychopathology need higher doses, 150mg/day, compared to those presenting only opioid addiction, who require 100mg/day on average (Eiden, Leglis, Clarivet, Blayac & Peyrière, 2012). Other authors even advocate very high doses (from 100 to 780 mg/day) as "necessary" to prevent opioid consumption and control concurrent psychopathology (Maxwell & Shinderman, 1999).

The above approach has been criticised for ignoring other issues such as the perspectives of the patients themselves or the need to deal primarily with other problems and risks. It must be remembered that, along with other opioids (Katz, 2005; Benyamin *et al.*, 2008), methadone is not a drug devoid of any undesirable side effects (Bell & Zador, 2000; Bileviciute-Ljungar, Häglund, Carlsson & von Heijne, 2014; Chugh *et al.*, 2008; Grönbladh & Öhlund, 2011; Webster, 2013), which are all the more intense and likely to occur the higher the dose (Leavitt, 2003; Walker, Klein & Kasza, 2003). Grave complications are not uncommon at high doses (Krantz, Kutinsky, Robertson & Mehler, 2003), and even at more moderate doses (Krantz, Martin, Stimmel, Mehta & Haigney, 2009; Roy *et al.*, 2012). Among these side effects, deficiencies in neuropsychological performance are some of the most frequently encountered (Bracken *et al.*, 2012; Gruber *et al.*, 2006; Loeber, Kniest, Diehl, Mann & Croissant, 2008; Mintzer, Copersino & Stitzer, 2005; Mintzer & Stitzer, 2002; Rass *et al.*, 2014) and their frequency increases with the dose (Rass *et al.*, 2014). Patients under methadone treatment presented significant cognitive deficits, while those in prolonged opioid abstinence and without treatment performed significantly better (Verdejo, Toribio, Orozco, Puente & Pérez-García, 2005), even as controls (Darke, McDonald, Kaye & Torok, 2012).

Another approach has been the so-called low threshold programmes, the main objective of which is not necessarily to eliminate the use of illicit drugs entirely but rather to establish and maintain contact with opioid users with the aim of helping to stabilize and reduce some of the associated risks and develop the confidence necessary to help them aspire to more ambitious objectives in later treatment phases (Hartgers, van den Hoek, Krijnen & Coutinho, 1992). There is plenty of empirical evidence pointing to a substantial improvement in the quality of life of these patients and a reduction of the risk of serious complications, even though consumption is not completely stopped (e.g., Brugal *et al.*, 2005; Millson *et al.*, 2007; Torrens, Castillo & Perez-Sola, 1996; Villeneuve *et al.*, 2006). Some studies show that retention in this kind of programme is not lower than in others which use higher doses (Perreault *et al.*, 2007) and which can favour the incorporation of other modes of treatment as required (Schwartz *et al.*, 2006).

A third line of treatment is characterised by focusing on the improvement in the quality of life without special attention to the doses required to achieve this. When considering the patient's quality of life it is also necessary to bear in mind the need for psychosocial interventions to avoid the negative consequences of the treatments, for example stigmatisation, discrimination, methadone dependence and the paralysing effects of the drug on the emotions (De Maeyer, Vanderplasschen, Camfield *et al.*, 2011; Harris & McElrath, 2012). The success of the treatments depends of other factors, such as work, family relationships, availability of intimate relationships, scheduling daily activities and the change of habits related to health, among others (De Maeyer, Vanderplasschen, Lammertyn *et al.*, 2011; He *et al.*, 2011). These programmes are based on the assumption that response to treatment is a function of individual differences rather than a mere dose-response function (Padaiga, Subata & Vanagas, 2007). From this perspective it is not correct to speak about high or low doses, but rather adjusted or suitable doses which eliminate the need for (but not the possibility of) additional consumption. In general terms we can say that methadone maintenance treatments produce an immediate improvement in the quality of life which, however, does not increase sufficiently over time to reach that of the general population. It does not even reach the levels declared by patients with other serious psychopathological symptoms (Habrat, Chmielewska, Baran-Furga, Keszycka & Taracha, 2002; Karow *et al.*, 2011; Millson *et al.*, 2004; Nosyk, Marsh, Sun, Schechter & Anis, 2010; Nosyk *et al.*, 2011; Torrens, Domingo-Salvany, Alonso, Castillo & San, 1999), and, furthermore, the variables more closely linked to quality of life and the success of the programme are not associated with the drug itself but rather with psychosocial factors such as family support (Lina, Wu & Detels, 2011). The multiplicity of factors involved in

the severity of the addiction and the patient's self-perceived quality of life highlights the need to design programmes which attend to the many dimensions connected with the problem (Fernández Miranda, González García-Portilla, Sáiz Martínez, Gutiérrez Cienfuegos & Bobes García, 1999; Millson, *et al.*, 2006). And yet, quality of life is not one of the indicators used to measure the effectiveness of the treatments (Amato *et al.*, 2005; Fernández Miranda, 2000).

The repeated finding that high doses increase retention rates has been challenged by some authors, who find that the risk of abandonment is greater (1.3/1) when the dose exceeds 60 mg/day than with lower doses, with other factors predicting the success or failure of maintenance programmes (Mino, Page, Dumont & Broers, 1998). With regard to the consumption of non-prescription drugs, other studies also question the superiority of high dosage programmes, arguing that suitable psychosocial intervention accompanying low doses can obtain equal or better results than high doses (Banys, Tusel, Sees, Reilly & Delucchi, 1994). Contrary to the arguments proposed in favour of high dosage treatments, other studies have found that an increase in methadone doses above the adjusted levels can trigger a notable increase in craving and the consumption of heroin (Curran, Bolton, Wanigaratne & Smyth, 1999; Fareed *et al.*, 2010). Follow-up studies in the United States have shown that the minimum dose of methadone proposed by high dosage models (60 mg) is not considered necessary in clinical treatment, and that the growing trend among prescribing doctors is to take the opinions of the patients, rather than dosage policies, into account when establishing a suitable dose (D'Aunno, Folz-Murphy & Lin, 1999). Thus, listening to the patient in setting dosage improves results (Maddux, Desmond & Vogtsberger, 1995; Maddux, Prihoda & Vogtsberger, 1997). A study carried out in Spain with a representative national sample found that the average maintenance dose was 61.52 mg/day (SD = 49.14), which means that a large percentage of patients would have received doses below 60 mg/day (Roncero *et al.*, 2011). Other authors have found that the dosage is irrelevant in the achieving objectives and suggest that more attention should be paid to other aspects of the programme, such as interpersonal therapist-patient relationships (Blaney & Craig, 1999). Nevertheless, studies which explore variables related to doses lower than 90 mg/day are disappearing from the literature at the same time as guidelines are insistently recommending the prescription of high doses (D'Aunno, Pollack, Frimpong & Wuchiett, 2014).

Not many studies have attempted to discover patients' opinions, their perception of health in relation to the doses and the influence of their attitudes and other psychological variables in connection with the results of the treatment. A variety of studies report large discrepancies in the assessments of results as declared on the one hand by the professionals and perceived on the other by patients (Trujols *et al.*, 2013). While motivation is a key variable in achieving good treatment results independently of the dosage administered (Zeldman, Ryan & Fiscella, 2004), many studies concur in confirming that patients meet a variety of barriers to enter and remain in methadone maintenance programmes: the treatment they receive from the therapy team, being labelled "ill", long waiting times, the inflexibility in the prescription of the dosage, nondisclosure of the dosage received, the length of treatment, which is likely to be indefinite, the feeling that the dosage administered is too high, the lack of necessary participation in setting dosage levels, among others (e.g. Al-Tayyib & Koester, 2011; Deering *et al.*, 2011; Peterson *et al.*, 2010). Conversely, satisfaction with the treatment received, taking part in therapeutic activities, and the feeling that treatment has been beneficial are aspects which improve retention irrespective of the dosage received (Kelly, O'Grady, Brown, Mitchell & Schwartz, 2010; Montgomery, Sanning, Litvak & Peters, 2014; Vanderplasschen, Naert, Vander Laenen & De Maeyer, 2014). Satisfaction levels, therefore, are a more powerful predictor of retention than dosage levels (Kelly, O'Grady, Brown, Mitchell & Schwartz, 2011). The improvement in terms of quality of methadone maintenance treatments as biopsychological treatments with proven effectiveness and with adaptability to the different patient profiles and needs is an undeniable objective, as is the opinion of the patients themselves (Fernández Miranda, 2004; Rodríguez *et al.*, 2002).

The aim of the current study is to find empirical evidence which supports the use of high doses while taking the patient's perspective into consideration. To this end, the following hypotheses derived from the studies reviewed will be tested: (a) high doses are associated with higher self-perceived levels of quality of life; (b) the prescription of high doses corresponds to greater satisfaction with the treatment; (c) patients receiving high doses show lower levels of somatic and psychological distress; (d) high doses result in levels of cognitive performance equal to or better than low doses; (e) patients receiving high doses present reduced consumption of non-prescribed drugs in comparison to those on low doses. In addition, we attempt to discover the interactions between all these variables and the received dosage in a structural model which would suggest a causal hypothesis.

Method

Description of the health centres

The study was carried out on two samples, both obtained from specific public institutions: one from a large city (Madrid) and the other from small cities serving an urban and rural population (Extremadura). The Institute of Addiction is a public organism run under the auspices of Madrid City Council which attends to people with drug related problems or other addictive behaviours without the involvement of drugs in the Madrid city district (with a population of

approximately 3.2 million). The city is divided into seven sectors, each with its own Drug Addiction Centre (CAD), under the direct control of the public administration. In addition, there are three treatment centres (CCADs) run in conjunction with non-governmental organisations (Caritas and Red Cross) with public funding and independent management. These ten participating facilities have multidisciplinary treatment teams (doctors, nurses, psychologists, social workers, occupational therapists, and auxiliary staff). Patients may access these directly, on their own initiative, or through referral from other health services such as their general practitioner, mental health clinics or hospitals. The treatment provided is individualised, attending to the medical, psychological, occupational and social needs of each patient. In cases of active heroin consumption, a medical assessment and immediate initiation of methadone treatment may take priority, with the assessment of other aspects being delayed. Each centre has an Opioid Agonist Treatment Programme in which all professionals participate. The prescription of methadone or buprenorphine is at the discretion of the doctors, who are under no strict orders to follow dosage guidelines and can therefore prescribe the amounts they consider necessary based on their relationship with the patient and their own criteria. The patients have appointments with their doctors, as well as the other professionals, and can therefore describe their symptoms and state if they wish to raise or lower their doses, but the final decision as to dosage is taken by the medical professional and based on the characteristics and situation of the patient. The substance administered is methadone hydrochloride (there is a sub-programme with buprenorphine, which is not included in the present study) in solution or in tablet form, and take home doses are collected from the centre daily, twice a week or weekly.

The comparison sample (which we shall call sample B) was obtained from a variety of outpatient centres in Extremadura. These centres are run in a similar way to those in Madrid, but the population served in the small cities of Caceres and Badajoz (with 95.000 and 150.000 inhabitants respectively) and surrounding rural areas is noticeably different.

Participants

At the beginning of the study, a total of 1898 patients were receiving treatment in Madrid's 10 Institute of Addiction centres. These centres, serving Madrid city residents, are publicly financed and free for patients. For the present study, a maximum confidence interval of 4% was set (p=q=0.5), which required a sample of n = 450 individuals. The subjects were evaluated between January 2014 and January 2015, with a total of n = 538 cases, although after 80 cases were excluded on the grounds of errors in test completion or missing data, the final sample (sample A) was composed of n = 458 individuals. The criterion for inclusion was that patients needed to have been prescribed methadone for heroin addiction for at least 3 months in the corresponding centre. Exclusion criteria were: being diagnosed as dependent on a substance other than heroin, recent alcohol consumption, suffering from any kind of brain damage, acute psychotic symptomatology, receiving pharmaceutical treatment (antiretroviral or other) which would involve the modification of the methadone dosage, difficulties in understanding the Spanish language or any other which could jeopardise the adequate completion of the tests. Sample B was obtained in different public treatment centres in Extremadura. The total number receiving treatment at the start of the study was 100 individuals, with two thirds providing evaluations (n = 65). Despite this, the sample was representative, although with a higher margin of error (confidence interval of 7% for p=q=0.5).

Instruments

The World Health Organisation's Quality of Life Questionnaire, abbreviated version (*World Health Organization Quality of Life*, WHOQOL BREF; WHO, 2004), an instrument designed with the aim of providing a tool for the assessment of the quality of life applicable to all cultures. The full version consists of 100 items, while the short version, used here, has 26: two general questions (about the quality of life in general and satisfaction with health) and 24 items covering the four domains of physical, psychological, social and environmental health. Responses to the items are in the form of a five-point Likert type scale. Its psychometric properties have been analysed in transcultural studies (Skevington, Lotfy & O'Connell, 2004) and in the Spanish population (Lucas-Carrasco, 2012). The version used was provided by the Andalusian Health Service (2010). Internal consistency of the test in our sample was $\alpha = 0.89$, with a corrected item-test correlation of $0.30 < r_{it} < 0.63$.

The Methadone Treatment Satisfaction Scale, developed on the basis of the Verona Service Satisfaction Scale of 32 items (VSSS-32; Ruggeri *et al.*, 2000), validated in the Spanish clinical population (Trujols & Pérez de los Cobos, 2005), but modified to adapt it to the characteristics of the participating services (Appendix I). It consists of 13 items with five-option Likert type scales which evaluate aspects of treatment in general, and eight items asking whether specific type of care has been received, followed by an evaluation of such in the case of an affirmative response. In terms of scoring Treatment Satisfaction, the responses to the first 13 items are multiplied by 25, obtaining a scoring range of 0 to 100 points, with an average of 50. The internal consistency of the test was satisfactory, with $\alpha = 0.86$ for the 29 items and $\alpha = 0.91$ for the 13 first items, and a corrected item-test correlation of $0.70 < r_{it} < 0.88$.

Of the Symptoms Checklist-90 Revised (SCL-90-R, Derogatis, 1992), the Spanish version by González de Rivera *et al.* (1989) was used, with the analysis of it psychometric properties by De Las Cuevas *et al.* (1991). This is a questionnaire which asks the subject about the presence and intensity of 90 symptoms of psychological and psychosomatic distress,

scored on a Likert type scale from total absence (0) to maximum intensity (4). The theoretical items are grouped in nine scales, although the factor studies do not find that the items are grouped in these, representing rather symptoms of psychological distress both in the clinical population (De Las Cuevas *et al.*, 1991) and in the clinical population of substance abusers (Pedrero Pérez & López-Durán, 2005). It has three general indices: General Symptomatic Index (GSI, intensity of global psychological and psychosomatic suffering), Positive Symptoms Total (PST) and Positive Symptom Distress Index (PSDI, mean symptom intensity). In the present study, the SCL-90-R showed an internal consistency of $\alpha = 0.97$, with all items bar one (item 60) having a corrected item-test correlation of $0.30 < r_{it} < 0.71$.

Of the Montreal Cognitive Assessment scale (MoCA, Nasreddine et al, 2005), the Spanish version was used, proposed by the present authors and validated in the clinical population of substance abusers in Spain (Rojo-Mota, Pedrero-Pérez, Ruiz-Sánchez de León, Llanero-Luque & Puerta-García, 2013). This is a screening test which assesses ten cognitive domains using conventional neuropsychological tests which have been widely validated. The highest score is 30, although a weighting of two points is applied for individuals with less than nine years of schooling and one point for those with between 9 and 12 years of schooling (Chertkow, Nasreddine, Johns, Phillips & McHenry, 2011). Transcultural studies estimate a cut-off score of 26, with individuals at this level or higher being considered as performing normally, and lower scores suggesting cognitive deterioration or early dementia. The time required to administer the test is around ten minutes. The internal consistency of the test in the present study was $\alpha = 0.70$, with a corrected item-test correlation of $0.30 < r_{it} < 0.46$.

The ultraviolet-visible spectrophotometry method was used to determine the metabolites of opioids, cocaine, cannabis and benzodiazepines in urine. In the case of benzodiazepines, the result was considered positive only when none had been prescribed.

Clinical and sociodemographic data were obtained by consulting each subject's medical record. The time spent in the current programme was taken into account, as was age, sex, educational level and the methadone dosage prescribed at the time of assessment.

Procedure

The test administrators were given three training sessions before the assessment period began (one face-to-face session in the case of Extremadura), as well as ongoing support to resolve any doubts arising. Prior to the administration of the assessment protocol, posters in the dispensing offices announced the upcoming study and invited volunteers. Leaflets announcing the study were also distributed. From the start, patients were offered the possibility of taking part in the study when they came to the clinic to collect their doses (daily or weekly). If they did not have enough time on such occasions, they were offered the possibility of a scheduled appointment in the following days. A small percentage refused to participate (n = 70, 7%). Regarding the self-reports, the test administrator read out the questions and the patients signalled their responses on cards prepared with the different response types. The cognitive performance test was carried out *in situ* after the self-reports. If patients asked for a break, they were allowed to take one. The assessments took between 30 and 45 minutes, and was followed by the collection of a urine sample for toxicological analysis. Patients were told that a second sample would be taken one month later, independently of other samples routinely taken as part of their treatment. The completed protocols were sent by internal mail to the senior researcher who coordinated the data and configured the database. Badly completed protocols with missing data or unanswered questions (n = 80) were excluded. To study the connections with other variables the received dosage was considered as a linear variable, and the participants were also divided into groups, as follows: very low dosage (<30 mg/day), low dosage (30-59 mg/day), average dosage (60-90 mg/day) and high dosage (>90 mg/day).

All participants were provided with information about the objective of the tests and signed an informed consent form agreeing to anonymous use of the results. The study was approved by the ethical committees of Caceres and Badajoz.

Data Analysis

To compare categories χ^2_{gl} was applied. For comparisons between continuous variables, the Snedecor F_{gl} distribution was used by means of univariate and multivariate analysis. The proportion of variance explained by covariables was estimated by means of Wilks' lambda (λ). Linear and partial correlations were measured with Pearson's r. Stepwise linear regression analyses were carried out, and the proportion of explained variance (R^2) and the β coefficient reported. To measure effect size, the eta squared estimator was used (η^2, Cohen, 1973) and in order to interpret the results the rules of thumb suggested by the author (Cohen, 1988) were applied: small effect (0.01 - 0.06), moderate effect (0.06 - 0.13) and large effect (>0.13). For the category comparisons Cramer's V was applied as an estimator of effect size and for the mutual correlation coefficients (r^2). The statistical package SPSS 19 was used for all analyses except for η^2, which was calculated manually. The structural relationships between the variables was explored by means of the maximum verisimilitude method and the different models were compared through the quality of fit indices (ECVI, Hoelter), with subsequent application of absolute adjustment (χ^2 degrees of freedom), relative adjustment (CMIN/DF, RMSEA) and incremental adjustment (NFI, CFI, RFI, IFI, TLI), following the recommendations of Hooper, Coughlan and Mullen (2008), based on the information provided by the AMOS 18 software.

Results

Descriptive data

Table 1 shows the descriptive data for the main sample. The 4 to 1 ratio of men to women which can be observed is normal in all countries with a similar cultural background, and stable in time over decades. By sex, males have a significantly higher average age, although the effect size of these differences is insignificant (η^2= 0.01). There are also significant differences (albeit with similarly small effect size V = 0.003) in educational level, with women more frequently appearing in extreme groups (less than 9 or more than 15 years of schooling), while more than half of the males are found in the group with 9 to 12 years of schooling. There are no significant differences by sex in terms of prescribed methadone dosage (F_1 = 0.02; p = 0.89). There also appears to be no relation between prescribed dose and age of the patient (r = 0.06; p = 0.19), but there does seem to be one with the duration of treatment (r = 0.10; p < 0.05).

Sample B was composed of 57 men and 8 women, with an average age of 42,5 (SD = 7.1). With regard to years of schooling, 36.9% had less than 9 years, 44.6% between 9 and 12 years, 16.9% between 12 and 15 years, and 1.5% more than 15 years (there were no women in the last two categories, while 75% had less than 9 years of schooling).

Dosage

Doses smaller than 60 mg/day were received by 72.7% of the sample, with 37.3% taking less than 30 mg/day (M = 15.1; SD = 7.2) and 35.4% between 30 and 60 mg/day (M = 41.6; SD = 8.2). In terms of higher doses, 14.6% had between 60 and 90 mg/day (M = 73.1; SD = 9.7) and only 12.7% received more than 90 mg/day (M = 126.1; SD = 33.1).

Sample B had very different characteristics. Doses below 60 mg/day were received by 96.9%, with 78.5% taking less than 30 mg/day (M = 17.8; SD = 8.4) and 18.5% between 30 and 60 mg/día (M = 38.5; SD = 9.5). Between 60 and 90 mg/day was taken by 3.1% (M = 82.0; SD = 8.5) and nobody received more than 90 mg/day.

The relationship between dosage and self-perceived quality of life

The administered dosage correlated negatively and significantly with quality of life: in the physical domain (r = -0.24; p < 0.001; r^2 = 0.06), psychological (r = -0.14; p < 0.01; r^2 = 0.02), social (r = -0.10; p < 0.05; r^2= 0.01), environmental (r = -0.19; p < 0.001; r^2 = 0.04) and with the global score (r = -0.22; p < 0.001; r^2 = 0.05).

Table 2 shows the values obtained in the different domains of self-perceived quality of life by prescribed methadone dose. The scores demonstrated significant differences, both in the total quality of life score and in each of the domains, and always pointed to a worsening quality of life as doses increased. The effect size of these differences was low, but especially significant in the physical and environmental health domains, as well as in global quality of life. The *post hoc* tests revealed that the main differences between physical and environmental health were found among those who took very small doses and received a medium or high dosage; between extreme groups in the psychological domain; and between those who took very low doses and received a low dosage in the social relations domain.

Next, the possible effect of other variables on these differences was investigated. Neither sex (λ = 0.99; $F_{4;447}$ = 0.74; p = 0.56) nor length of time on the treatment programme (λ = 0.99; $F_{4;447}$ = 0.64; p = 0.63) explained a significant amount of the variance of the differences observed. The opposite was true however with age (λ = 0.98; $F_{4;447}$ = 2.47; p = 0.04; η^2 = 0.022) as well as educational level (λ = 0.96; $F_{4;447}$ = 5.13; p < 0.001; η^2 = 0.044). Age had a significant effect on the environmental (F_1 = 4.02; p < 0.05; η^2 = 0.009), and social

Table 1. *Descriptive data.*

	Men	Women	Total	*F*	*p*
n	364	94	458		
%	79.5	20.5			
Mean current age (SD) in years	47.6 (6.2)	46.1 (6.5)	47.3 (6.3)	3.97	‹ 0.05
Years of schooling	%			χ^2	*p*
‹ 9	28.8	36.2		9.1	‹ 0.05
9 - 12	51.1	34.0			
12 -15	16.5	24.5			
› 15	3.6	5.3			
				F	*p*
Mean dose (SD) in mg/day	47.4 (39.0)	45.7 (36.2)	47.0 (38.4)	0.14	0.71
Range	5 – 220	5 - 160	5 - 220		
Mean duration of treatment (SD) in months	93.3 (120.3)	89.5 (67.1)	92.5 (111.4)	0.09	0.77
Range in months	3 - 2011	3 - 281	3 - 2011		

domains ($F_1 = 7.86$; $p < 0.01$; $\eta^2 = 0.017$) as well as on the global score ($F_1 = 4.17$; $p < 0.05$; $\eta^2 = 0.009$), while educational level significantly affected the psychological and ($F_1 = 9.67$; $p < 0.01$; $\eta^2 = 0.021$) and environmental domains ($F_1 = 15.04$; $p < 0.001$; $\eta^2 = 0.032$), as well as the global score ($F_1 = 9.27$; $p < 0.01$; $\eta^2 = 0.020$). Controlling for educational level, age correlated significantly with social relations ($r = -0.13$; $p < 0.01$; $r^2 = 0.02$), with quality of environment ($r = -0.10$; $p < 0.05$; $r^2 = 0.01$) and with the global quality of life score ($r = -0.10$; $p < 0.05$; $r^2 = 0.01$); and controlling for age, educational level correlated significantly with psychological health ($r = 0.15$; $p < 0.01$; $r^2 = 0.02$), with quality of environment ($r = 0.19$; $p < 0.001$; $r^2 = 0.04$) and with the global score ($r = 0.15$; $p < 0.01$; $r^2 = 0.02$). Effect size was low in all cases.

On investigating the differences by prescribed dosage groups and controlling for variables previously showing interaction effects (age and educational level), significant differences appeared in all health domains (Table 2). While those receiving very low dosages (< 30 mg/day) displayed higher health levels, this went down among those groups receiving stronger doses. The effect size of these differences was moderate in the case of physical ($\eta^2 = 0.06$) and environmental health ($\eta^2 = 0.08$), as well as on the global quality of life score ($\eta^2 = 0.08$).

In sample B, dosage correlated negatively with quality of life and all its dimensions (physical, $r = -0.17$; psychological, $r = -0.23$; social $r = -0.07$; environmental health $r = -0.06$; and global score, $r = -0.16$), although statistical significance was not achieved in any of the cases.

The relationship between dosage/satisfaction and quality of life

The great majority (96.5%) declared that they were satisfied (50.2%) or very satisfied (46.3%) with the treatment they received, with only 3.5% declaring moderate dissatisfaction. There were no significant differences between the different groups in terms of prescribed methadone dosage ($F_3 = 1.94$; $p = 0.12$). When controlling for the effect of covariables, a significant relationship was found with sex ($F_7 = 5.43$; $p < 0.05$; $\eta^2 = 0.012$) and age ($F_7 = 10.86$; $p < 0.01$; $\eta^2 = 0.024$), but not with educational level nor duration of treatment. Women were found to be significantly more satisfied ($F_1 = 6.75$; $p < 0.05$; $\eta^2 = 0.015$) (M = 78.6; SD = 13.0) than men (M = 74.9; SD = 12.4). Age was negatively correlated with satisfaction ($r = -0.17$; $p < 0.001$; $r^2 = 0.03$), even when controlling for sex ($r = -0.16$; $p < 0.01$; $r^2 = 0.03$). When controlling for both variables, the differences among groups by dosage reached levels of significance, the lower the dosage of methadone administered, the higher satisfaction with treatment (Table 3).

Levels of satisfaction in sample B were similar: 96.9% were satisfied or very satisfied with their treatment. The satisfaction score correlated negatively with dosage ($r = -0.14$), without reaching statistical significance ($p = 0.27$).

The relationship between dosage and psychological distress

Table 4 shows that all the SCL-90-R indices display an increase parallel to the dosage of methadone prescribed. *Post hoc* tests revealed that only the group with the highest dosage manifested significant differences with the others, with more positive symptoms and a higher General Symptomatic Index. On investigating the possible effects of other variables on these differences, it was observed that only sex showed a significant interaction effect ($\lambda = 0.97$; $F_{3;448} = 2.47$; $p < 0.01$; $\eta^2 = 0.035$). This was not the case with age ($\lambda = 0.99$; $F_{3;448} = 2.21$; $p = 0.09$), educational level ($\lambda = 0.99$; $F_{3;448} = 2.12$; $p = 0.10$), nor duration of treatment ($\lambda = 0.99$; $F_{3;448} = 1.23$; $p = 0.30$). Women scored significantly higher than men in the three indices:

Table 2. *Quality of Life Domains (WHOQOL-BREF) and prescribed methadone dosage.*

	Dosage						
	very low	low	medium	high			(*)
WHOQOL	M (DT)				$F_{df=3}$	η^2	η^2
Physical health	24.35 (4.87)	23.15 (4.41)	22.28 (4.94)	20.98 (4.50)	8.63	0.054	0.055
Total	23.20 (4.79)						
Psychological health	18.96 (4.40)	18.62 (4.16)	18.52 (4.14)	17.05 (4.35)	2.94	0.019	0.042
Total	18.53 (4.30)						
Social health	9.19 (2.55)	8.41 (2.61)	8.64 (2.37)	8.21 (2.59)	3.52	0.023	0.041
Total	8.71 (2.57)						
Environmental health	26.52 (4.73)	25.35 (4.76)	24.54 (5.25)	23.62 (5.50)	6.17	0.039	0.077
Total	25.45 (5.00)						
Quality of life	79.01 (12.98)	75.53 (12.55)	73.99 (13.37)	69.86 (13.39)	8.05	0.051	0.075
Total	75.89 (13.24)						

Note. *Controlling for age and educational level (F df = 5).

General Symptomatic Index ($F_{gl=1}$ = 15.2; p < 0.001; η^2 = 0.032), Positive Symptoms Total ($F_{gl=1}$ = 8.3; p < 0.01; η^2 = 0.018) and Average Somatic Intensity ($F_{gl=1}$ = 14.5; p < 0.001; η^2 = 0.031). Table 4 shows that the relationship between dosage and distress is linear among males, but it is women taking medium-sized doses (60-90 mg/day) who present the highest indicators of distress.

A regression analysis was carried out of the SCL-90-R scores on the dosage of methadone received to investigate which symptom groups were linked to higher dosages. Among men, the Somatisation scale was the only one which displayed positive predictive capacity (R^2 = 0.06; β = 14.6), while among women this was the Phobic Anxiety scale (R^2 = 0.05; β = 13.6). When the same procedure was run with the SCL-90-R items (Table 5), models were found which explained a significant part of the dosage variance (12% in men, 17% in women), but none of the models were effective, generating excessive residues (Durbin-Watson < 1 in both cases).

In sample B, the dosage correlated negatively with all scales SCL-90-R and indices, without reaching statistical significance in any case.

The relationship between dosage and cognitive performance

Only 40% of the sample displayed normal cognitive performance (MoCA scores ≥ 26), while 41.5% presented mild cognitive impairment (between 21 and 25), and 18.5% were more severely affected (≤ 20). Taking the MoCA scores as a continuous variable, no differences were apparent between cognitive performance and dosage group ($F_{gl=3}$ = 1.96; p = 0.12), nor the effects of the variables sex ($F_{gl=1}$ = 0.00; p = 0.99), age ($F_{gl=1}$ = 0.08; p = 0.77) or duration of treatment ($F_{gl=1}$ = 0.57; p = 0.45). Educational level does not display any interaction effect when considering the corrected scores ($F_{gl=1}$ = 2.54; p = 0.11), while the opposite is the case with the uncorrected raw scores ($F_{gl=1}$ = 24.99; p < 0.001; η^2 = 0.055). However, when dosage is taken as a continuous variable, a significant and negative relationship is revealed between dosage and score obtained in the MoCA (r = -0.22; p < 0.001; r^2 = 0.05), which is maintained at the same levels when controlling for the remaining variables.

When subjects are classified according to performance on the MoCA (normal, mild and severe impairment), significant differences appear (Table 6). Only 25.9% of those taking more than 90 mg/day of methadone and 25.4% of those receiving 60-90 mg/day presented normal cognitive functioning, while this percentage rises to 50.3% for those taking very low doses and 40.1% for individuals receiving 30-60 mg/day doses.

In sample B, 32.3% of the subjects were found to have normal cognitive performance, while 50.8% had mild and 16.9% severe impairment. There was no significant corre-

Table 3. *Satisfaction with treatment scores by dosage of prescribed methadone, controlling for sex and age.*

	Dosage						
	very low	low	medium	high			
	M (DT)				$F_{gl=5}$	Sig.	η^2_p
Satisfaction	77.14 (12.89)	75.64 (11.65)	74.14 (13.25)	73.08 (13.05)	4.8	p< 0.001	0.051

Table 4. *SCL-90-R distress indices.*

	Dosage						
	very low	low	medium	high			
	M (SD)				$F_{gl=5}$	Sig.	η^2_p
General Symptomatic Index	0.75 (0.55)	0.785 (0.59)	0.91 (0.59)	1.10 (0.65)	5.93	p< 0.01	0.038
Positive Symptoms Total	35.74 (18.1)	37.60 (20.3)	42.93 (19.5)	47.66 (19.5)	6.83	p< 0.001	0.043
General Symptomatic Index	1.70 (0.59)	1.72 (0.53)	1.79 (0.54)	1.93 (0.57)	2.62	p= 0.51	0.017
	Men				$F_{gl=3}$	Sig.	η^2_p
General Symptomatic Index	0.71 (0.51)	0.73 (0.56)	0.79 (0.51)	1.10 (0.68)	6.13	p< 0.001	0.049
Positive Symptoms Total	34.7 (17.3)	36.4 (20.1)	39.9 (18.7)	47.3 (19.2)	5.58	p< 0.01	0. 044
General Symptomatic Index	1.68 (0.56)	1.64 (0.51)	1.68 (0.47)	1.93 (0.60)	3.28	p< 0.05	0.027
	Women				$F_{gl=3}$	Sig.	η^2_p
General Symptomatic Index	0.90 (0.65)	1.03 (0.67)	1.35 (0.69)	1.10 (0.57)	1.65	p= 0.18	0.052
Positive Symptoms Total	39.8 (20.6)	42.6 (20.9)	54.4 (18.5)	48.8 (16.2)	2.11	p= 0.10	0.066
General Symptomatic Index	1.80 (0.67)	2.02 (0.53)	2.17 (0.62)	1.93 (0.63)	1.48	p= 0.23	0.047

lation between the MoCA scores and the administered methadone dosage, neither was statistical significance found between these variables, not even when controlling for the remaining variables.

The relationship between dosage/consumption and non-prescribed substances.

At the time of assessment, 14.2% of subjects tested positive for opioids (other than methadone), 24.5% for cocaine, 34.9% for cannabis and 9.0% for non-prescribed benzodiazepines. One month or more after the assessment, 13.8% of those testing positive were for opioids, 23.1% for cocaine, 33.2% for cannabis and 9.6% for benzodiazepines. Taking both samplings, 81.9% of the subjects were heroin abstinent (8.3% tested positive on one occasion, and 9.8% in both), while 71.2% were cocaine abstinent (10.0% testing positive in one and 18.8. in both samplings), 60.0% were completely cannabis abstinent (11.8% were positive in one analysis, 28.2% in both), and 88.2% did not use non-prescribed benzodiazepines (5.0% found positive in one sampling and 6.8% in both). A total of 41.3% tested negative for all substances in both controls.

When dosage received was analysed, no significant differences were found (Table 7). Nor was there a significant difference between those testing positive for opioids when considering only the extreme groups with very low or very high doses in the first sampling ($\chi^2_1 = 3.56$; $p = 0.06$). However, the opposite was true in the second sampling ($\chi^2_1 = 5.96$; $p < 0.05$; $V = 0.02$), where positive results were significantly greater among those taking less than 30 mg/day than those on 90 mg/day of methadone. The number of subjects testing negative for opioids in both analyses was also greater in the high dosage group than in those taking less than 30 mg/day ($\chi^2_1 = 6.00$; $p < 0.05$; $V = 0.02$), in those taking between 30-60 mg/day ($\chi^2_1 = 6.00$; $p < 0.05$; $V = 0.02$) and among those subjects receiving 69-90 mg/day ($\chi^2_1 = 4.14$; $p < 0.05$; $V = 0.02$).

There was no significant difference in the case of the other drugs tested for in urine. Nor were significant differences found in relation to sex, years of schooling, duration of treatment or substances tested for.

In sample B, 27,7% were found to have traces of opioids other than methadone at the time of the assessment (26.2% in the second sampling), 27.7% had traces of cocaine (23.1% in the second test), 50.8% cannabis (same level in the follow-up test) and 15.4% benzodiazepines (13.8% in the later test). The proportion testing negative for all drugs en both samplings was 36.9%. No correlation with methadone dosage was found anywhere.

Structural model of the relationships between variables

Finally, on the basis of our results, various attempts were made to model the structural relationships between the different variables. The model achieving best fit (ECVI = 0.11; Hoelter = 914; p= 0.05) was that shown in Figure 1. All the indicators displayed a good fit to the data. ($\chi^2 = 6.3$; g.l. = 6; $p = 0.39$; CMIN/DF = 1.05; RMSEA = 0.01; NFI = 0.98; CFI = 0.99; RFI = 0.96; IFI = 0.99; TLI = 0.99).

Table 5. *SCL-90-R items with predictive capacity for methadone dosage.*

Ítem	Men	R^2x100	β
58	Heavy feelings in your arms and legs	4.67	5.96
75	Feeling nervous when you are left alone	2.99	8.54
12	Pains in heart or chest	1.32	5.35
24	Temper outbursts that you cannot control	1.65	-6.68
61	Feeling uneasy when people are watching or talking about you	1.52	5.07
	Women		
82	Feeling afraid you will faint in public	10.54	13.12
88	Never feeling close to another person	3.21	-9.75
33	Feeling fearful	2.86	6.58

Table 6. *Percentage of subjects by MoCA performance category and by methadone dosage.*

	Dosage					
	very low	low	medium	high		
MoCA	Percentage of subjects				χ^2_6	Sign.
Severe impairment	14.6%	19.1%	16.4%	31.0%	23.8	p< 0.01
Mild impairment	35.1%	40.7%	58.2%	43.1%		
Normal performance	50.3%	40.1%	25.4%	25.9%		

Discussion

Methadone maintenance is the therapy of choice in almost all cases in which a patient demands professional help for heroin addiction, but there are individual, pharmacological, social and cultural variables which can influence the way in which this treatment is provided. The objective of the present study is to explore the relationships between the methadone dosage administered and the range of associated variables; the final aim being to discover empirical evidence which can help prescribing doctors to provide the most suitable dosage.

The present study has found a linear relationship between higher prescribed methadone dosage and lower self-perceived quality of life, which affects all dimensions of subjective assessment. Especially those on doses above 60 mg/day estimate significantly lower levels of quality of life. The effect size of these differences was particularly significant both in the physical and environmental health domains, as in global quality of life. *Post hoc* analyses showed that the main differences in physical and environmental health were found between those taking very low and those receiving medium to high doses. In the psychological health domain, the main differences were in the extreme groups. When controlling for the remaining variables, the effect size of the differences was moderately high regarding the subjects' evaluation of environmental conditions, and also in quality of life as a whole.

Assessing the patients' satisfaction with their treatment is another way of evaluating the suitability of the programmes to their problems. Our results reveal an almost total overlap between the needs and expectations of the patients and the care offered by the specialised services participating in the study. Results exceed those obtained in the Spanish population in general regarding methadone treatment (Pérez de los Cobos *et al.*, 2004). Nevertheless, a negative relationship between dosage administered and degree of satisfaction is also found. These data appear to contradict the widespread belief that patients need higher doses than necessary in order to perceive the psychoactive effects of methadone. These results will be integrated below with those obtained for other variables.

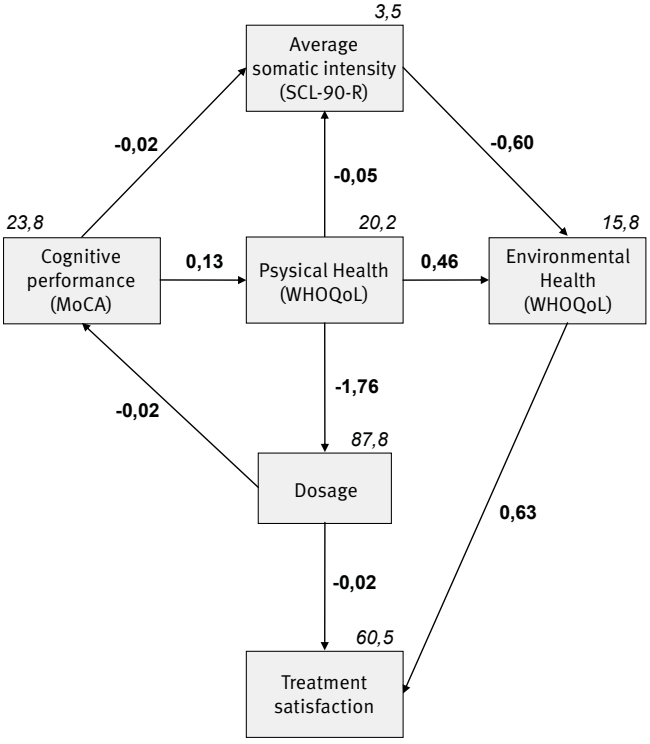

Figure 1. Structural model of the relationship between variables.

A linear relationship is also found between methadone dosage and psychological distress, especially in the case of people receiving high doses (>90 mg/day). Symptoms most frequently associated with such doses are of a somatic and indistinct character, or of anxiety in women. There does not seem to be a symptomatological pattern which fits specific

Table 7. *Percentage of positive toxicological tests for each drug. in relation to prescribed methadone dosage.*

	Dosage					
	very low	low	medium	high		
1st Sampling	% positives				χ^2_3	Sig.
Opioids	17.00	13.60	14.90	6.90	3.70	p= 0.30
Cocaine	21.60	26.50	26.90	24.10	1.33	p= 0.72
Cannabis	32.20	39.50	31.30	34.50	2.45	p= 0.48
Benzodiaz.	7.60	9.30	11.90	8.60	1.14	p= 0.77
2nd Sampling						
Opioids	15.80	16.00	11.90	3.40	6.70	p= 0.08
Cocaine	21.60	24.10	22.40	25.90	0.56	p= 0.91
Cannabis	31.60	36.40	34.30	27.60	1.82	p= 0.61
Benzodiaz.	6.40	11.10	11.90	12.10	3.23	p= 0.36

diagnostic categories, but rather a non-specific discomfort, as has been reported by prior studies (De Las Cuevas *et al.*, 1991; Pedrero Pérez & López-Durán, 2005). The question arises as to whether this discomfort is attributable to the side effects of methadone or rather to the fact that subjects experiencing greater levels of distress ask for higher doses of methadone to alleviate them. If the latter were the case, the results of the present study would point to the inefficacy of the method, which therefore makes it more likely that the discomfort is actually due to the increase in side effects accompanying increased doses of methadone. Nevertheless, the small effect size in almost all cases shows that the link between dosage and psychological distress is of little relevance.

Only 40% of patients were found to have normal cognitive functioning, according to the suggested cut-off points of the MoCA. This figure is lower than that obtained in studies using the same instrument with patients on high doses, which yielded 62% (Copersino *et al.*, 2012). Nevertheless, the figure is higher than that (29.1%) found in the same care context when subjects were assessed at the start of their treatment for addiction to a range of drugs (Rojo-Mota *et al.*, 2013). What these statistics suggest is that methadone maintenance improves the cognitive performance which could be expected at the base line, when factors such as the stress involved in drug consumption behaviour are relevant, but that treatment does not manage to raise the performance of a significant number of patients to population levels, not even to the levels of those who are completely abstinent of all opioids, including methadone, after a period of addiction (Darke *et al.*, 2012). Additionally, the mild cognitive impairment associated with methadone maintenance is linear with dosage, as the results of the present study indicates: around 40-50% on doses below 60 mg/day function normally, which is double the number of those taking more than 60 mg/day. There are no studies available to which these figures could be compared, mainly due to the fact that most programmes have adopted high dosage policies, ignoring the link between dosage and cognitive impairment in favour of other indicators.

As in all published research, a high percentage of subjects in methadone maintenance programmes persist in substance use. In the present study show, 60% tested positive for cocaine, cannabis or heroin when the assessment was carried out. Comparing results with other studies is difficult since the methods used vary, with self-reports of consumption frequently employed. Figures above 70% for consumption of any non-prescribed drugs in the previous month are reported in some cases, with 67% having used heroin in the previous week (Curran *et al.*, 1999). The current study cannot reflect the temporal dimension of consumption, given that drug use is only sampled at the time the assessment is administered. Nevertheless, figures found so far for the consumption of non-prescribed drugs are considerably higher than 60% (Darke *et al.*, 2012; Dobler-Mikola *et al.*, 2005).

Metabolites of opioids different to methadone were found in 18.1% of patients in both samplings. We can therefore consider that 80% of the patients sampled are not using heroin continuously or are abstinent. This figure is noticeably lower than that found in other studies, although the different methods used do not permit a perfect comparison (Keen, Oliver, Rowse & Mathers, 2003; Musshoff, Trafkowski, Lichtermann & Madea, 2010). What can clearly be observed, however, is that those receiving the highest dosage present significantly lower heroin consumption than those on doses below 90 mg/day. With regard to cocaine, no differences related to dosage were found. These results differ from those found in other studies, which revealed lower heroin and higher cocaine consumption at higher methadone doses, and the opposite at lower doses (Baumeister *et al.*, 2014).

While all indicators so far suggest that the lower the prescribed doses the better, the results regarding heroin consumption point in the opposite direction. The negative relationship between dose and risk of death from overdose is a repeated finding in earlier research (Liao *et al.*, 2013; Liu *et al.*, 2013; Van Ameijden *et al.*, 1999), but this is only confirmed when heroin is consumed by injection in addition to the administration of methadone. In such cases, the effects of both substances on the opioid receptors is cumulative, which does not happen when consumption is via inhalation or intranasal.

These results are worthy of reflection. Firstly, there appears to be no rationale for the prescription of high doses, other than in the case of persistent consumption of heroin by injection. In recent years we have seen certain institutions and research groups insistently proposing doses of around 100 mg/day, independently of variables other than mere opioid dependence (individual, environmental, therapeutic, etc.). To reach this conclusion, a host of studies were carried out which showed that certain indicators improved with a high dosage: rates of retention on the programmes, reduction of criminal activity, and reduction in the consumption of other drugs (Lingford-Hughes, Welch & Nutt, 2004). Nevertheless, far fewer studies have investigated variables relative to the patient, such as quality of life, satisfaction with treatment, returning to work, or relapse. When reviewing highest level research, not enough studies were found which explored the patient's perspective (Amato *et al.*, 2005; Fernández Miranda, 2001), and this is a rarity in the field of health care. Ignoring the perspectives and the opinions of the patient is unacceptable in any other health issue. The reasons for this contempt are to be found in the predominance of a model of the mental illness of addiction which converts an addict into a person who is unable to take appropriate decisions or make rational judgements because the brain has been taken hostage by the drug (Leshner, 1997). Some concerns have been voiced, however, with medical services being accused of enacting social control over

these patients, who are incapable of regulating their own behaviour. High-dosage policies have favoured the chronification of the disorder and its treatments, converting the patient into a mere recipient of the intervention (Harris & McElrath, 2012). Thus, stigmatisation is exacerbated and many people under treatment are forced to live in a state of sedation and powerlessness, with physical and psychological discomfort, and unable to participate actively in the day-to-day life of their community .

The model of mental illness has recently come under strong attack because none of its objectives are shown to have been met, while social stigmatisation is increased and the vast majority of substance dependent patients have had to endure doses which would only have made sense for the few cases of greatest severity (Hall, Carter & Forlini, 2015; Hammer *et al.*, 2013). The chemical blocking of receptors hands control to the physician and ignores treatments which could help the patients to regain control over their own behaviour. When the dosage does not cause lethargy, continued substance consumption or the success of the treatment are dependent on psychological variables (Senbanjo, Wolff, Marshall & Strang, 2009; Zeldman *et al.*, 2004), the patient's satisfaction with treatment is the best predictor of results (Kelly *et al.*, 2011), the results depend to a greater extent on the provision of psychosocial services as a complement to the pharmacological treatment (Mino *et al.*, 1998), certain psychotherapeutic interventions reduce the necessary dosage (Preston, Umbricht & Epstein, 2000), low doses are shown to be as useful as higher doses when combined with psychosocial treatments (Langendam, Van Brussel, Coutinho & Van Ameijden, 2001), and patients are able to self-administer their doses over and above the impositions of the programmes (Harris & Rhodes, 2013). Such an approach corresponds to an ethos of care where the focus is on recovery rather than medical/social control (White & Mojer-Torres, 2010).

As is common with similar research which has been consulted, our study has several limitations. It is impossible to attend to all variables involved in a treatment in a natural environment. Many patients, for example, though not all, receive psychoactive medicines as a complement to reduce psychopathological problems. These medicines may have positive or negative effects on the quality of life, satisfaction with treatment, and cognitive performance. While alcohol dependence has been controlled for, chronic alcohol consumption has not, and this can seriously interfere with cognitive performance (Chen *et al.*, 2011). The same applies to benzodiazepines, which were only controlled for when not prescribed, but could be taken in larger doses than those prescribed. In general, the consumption of substances other than methadone was restricted to the moment of assessment and a point one month later, but this does not report the intensity, chronicity, and variety of consumption patterns, although it is true that patients with proven dependence on any drug were excluded from the study. Treatments other than the purely medical (psychological, occupational, social and work integration, nursing care), are available to all participants, but not all make the same use of them nor stay on the treatments for the same amount of time and therefore the impact of each of these or the role they played in the results obtained cannot be quantified.

In conclusion, our data support the use of doses adjusted to the individual needs of each patient, via doctor-patient negotiation and a dynamic assessment of each case. With this approach, complete abstinence is not achieved, but neither is this the case in high-dosage programmes, as has been seen in the review of the literature, despite this being one of the strongest justifications for this kind of treatment, with its aim of achieving abstinence by a complete blocking of opioid receptors. Nevertheless, the consumption of non-prescribed substances is lower than in other studies, although it persists in the majority of cases. Self-perceived levels of quality of life are acceptable and at least comparable to those obtained in programmes with a different focus, although the fact of taking part in a treatment is a barrier to reaching the normal levels in the patients' normal environment. Patient satisfaction is scarcely improvable, thus indicating full acceptance of the individualised model aimed at recovery. The perception of physical health and the link to environmental health are essential in understanding the need for lower doses and satisfaction with the treatment received. Cognitive performance is unstable and negatively associated with dosage, and the repercussions of this on everyday life can lead to serious problems of integration. Reasons for recommending high doses are only apparent in those patients who persist in injecting heroin in order to reduce the likelihood of this type of consumption to the point of stabilisation. Future research should analyse in detail the role of each of the variables involved in the process of recovery and normalisation of the lives of these people. Quality programmes are needed which address not only the pharmacological issues related to addiction, but also the intrapersonal variables and environmental conditions which can favour the success of the programme and the normalisation of patients' lives, or conversely the breach of therapy and continuation of addiction. Methadone maintenance programmes should be oriented progressively towards individuals, valuing their opinions, encouraging their active participation in the process and improving the levels of quality of life, so that addressing their problems is done in the same way as in any other question of health.

Conflict of interest

The authors declare no conflict of interest.

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References

Adelson, M., Wilson, H. W., Celeste, V. Y., Linzy, S., Kreek, M. J. & Peles, E. (2013). Methadone maintenance treatment experience in Macao. Prospective follow-up for initial 4.5 years. *Journal of Psychoactive Drugs, 45*, 313-321. doi:10.1080/02791072.2013.825032

Al-Tayyib, A. & Koester, S. (2011). Injection drug users' experience with and attitudes toward methadone clinics in Denver, CO. *Journal of Substance Abuse Treatment, 41*, 30–36. doi:10.1016/j.jsat.2011.01.009

Amato, L., Davoli, M., Perucci, C. A., Ferri, M., Faggiano, F. & Mattick, R. P. (2005). An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Ttreatment, 28*, 321-329. doi:10.1016/j.jsat.2005.02.007

Banys, P., Tusel, D. J., Sees, K. L., Reilly, P. M. & Delucchi, K. L. (1994). Low (40 mg) versus high (80 mg) dose methadone in a 180-day heroin detoxification program. *Journal of Substance Abuse Treatment, 11*, 225-232. doi:10.1016/0740-5472(94)90079-5

Baumeister, M., Vogel, M., Dürsteler-MacFarland, K. M., Gerhard, U., Strasser, J., Walter, M., ... Petitjean, S. A. (2014). Association between methadone dose and concomitant cocaine use in methadone maintenance treatment: a register-based study. *Substance Abuse Treatment, Prevention, and Policy, 9*, 46. doi:10.1186/1747-597X-9-46

Benyamin, R, Trescot, A. M., Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., … Vallejo, R. (2008). Opioid complications and side effects. *Pain Physician, 11*, S105-S120.

Bell, J. & Zador, D. (2000). A risk-benefit analysis of methadone maintenance treatment. *Drug Safety, 22*, 179-190. doi:10.2165/00002018-200022030-00002

Bileviciute-Ljungar, I., Häglund, V., Carlsson, J. & von Heijne, A. (2014). Clinical and radiological findings in methadone-induced delayed leukoencephalopathy. *Journal of Rehabilitation Medicine, 46*, 828-830. doi:10.2340/16501977-1820

Blaney, T. & Craig, R. J. (1999). Methadone maintenance: does dose determine differences in outcome? *Journal of Substance Abuse Treatment, 16*, 221-228. doi:10.1016/S0740-5472(98)00031-2

Bourgois, P. (2000). Disciplining addictions: The bio-politics of methadone and heroin in the United States. *Culture, Medicine and Psychiatry, 24*, 165-195. doi:10.1023/A:1005574918294

Bracken, B. K., Trksak, G. H., Penetar, D. M., Tartarini W. L., Maywalt, M. A., Dorsey, C. M. & Lukas, S. E. (2012). Response inhibition and psychomotor speed during methadone maintenance: impact of treatment duration, dose, and sleep deprivation. *Drug and Alcohol Dependence, 125*, 132-139. doi:10.1016/j.drugalcdep.2012.04.004

Brugal, M. T., Domingo-Salvany, A., Puig, R., Barrio, G., García de Olalla, P. & de la Fuente, L. (2005). Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction, 100*, 981-989. doi:10.1111/j.1360-0443.2005.01089.x

Bourgois, P. (2000). Disciplining addictions: The bio-politics of methadone and heroin in the United States. *Culture, Medicine and Psychiatry, 24*, 165-195.

Chen, I. C., Chie W. C., Hwu, H. G., Chou, S. Y., Yeh, Y. C., Yu, C. Y. & Tan, H. K. L. (2011). Alcohol use problem among patients in methadone maintenance treatment in Taiwan. *Journal of Substance Abuse Treatment, 40*, 142-149. doi:10.1016/j.jsat.2010.09.004

Chertkow, H., Nasreddine, Z., Johns, E., Phillips, N. & McHenry, C. (2011). The Montreal Cognitive Assessment (MoCA): Validation of alternate forms and new recommendations for education corrections. *Alzheimer's & Dementia, 7*, S157. doi:10.1016/j.jalz.2011.05.423

Chugh, S. S., Socoteanu, C., Reinier, K., Waltz, J., Jui, J. & Gunson, K. (2008). A community-based evaluation of sudden death associated with therapeutic levels of methadone. *American Journal of Medicine, 121*, 66-71. doi:10.1016/j.amjmed.2007.10.009

Cohen, J. (1973). Eta-squared and partial eta-squared in fixed factor ANOVA designs. *Educational and Psychological Measurement, 33*, 107-112. doi:10.1177/001316447303300111

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2ª ed.)*. Hillsdale, NJ: Erlbaum.

Copersino, M. L., Schretlen, D. J., Fitzmaurice, G., Lukas, S. E., Faberman, J., Sokoloff, J. & Weiss, R. D. (2012). Effects of cognitive impairment on substance abuse treatment attendance: predictive validation of a brief cognitive screening measure. *American Journal of Drug and Alcohol Abuse, 38*, 246-250. doi:10.3109/00952990.2012.670866

Curran, H. V., Bolton, J., Wanigaratne, S. & Smyth, C. (1999). Additional methadone increases craving for heroin: a double-blind, placebocontrolled study of chronic opiate users receiving methadone substitution treatment. *Addiction, 94*, 665-674. doi:10.1046/j.1360-0443.1999.9456654.x

Darke, S., McDonald, S., Kaye, S. & Torok, M. (2012). Comparative patterns of cognitive performance

amongst opioid maintenance patients, abstinent opioid users and non-opioid users. *Drug and Alcohol Dependence, 126*, 309-315. doi:10.1016/j.drugalcdep.2012.05.032

D'Aunno, T., Folz-Murphy, N. & Lin, X. (1999). Changes in methadone treatment practices: results from a panel study, 1988-1995. *American Journal of Drug and Alcohol Abuse, 25*, 681-699. doi:10.1081/ADA-100101886

D'Aunno, T., Pollack, H. A., Frimpong, J. A. & Wuchiett, D. (2014). Evidence-based treatment for opioid disorders: A 23-year national study of methadone dose levels. *Journal of Substance Abuse Treatment, 47*, 245-250. doi:10.1016/j.jsat.2014.06.001

Deering, D., Sheridan, J., Sellman, J., Adamson, S., Pooley, S., Robertson, R. & Henderson, C. (2011). Consumer and treatment provider perspectives on reducing barriers to opioid substitution treatment and improving treatment attractiveness. *Addictive Behaviors, 36*, 636-642. doi:10.1016/j.addbeh.2011.01.004

De Las Cuevas, C., Gonzalez de Rivera, J. L., Henry Benitez, M., Monterrey, A. L., Rodriguez-Pulido, F. & Gracia Marco, R. (1991). Análisis factorial de la versión española del SCL-90-R en la población general. *Anales de Psiquiatria, 7*, 93-96.

De Maeyer, J., Vanderplasschen, W., Camfield, L., Vanheule, S., Sabbe, B. & Broekaert, E. (2011). A good quality of life under the influence of methadone: A qualitative study among opiate-dependent individuals. *International Journal of Nursing Studies, 48*, 1244-1257. doi:10.1016/j.ijnurstu.2011.03.009

De Maeyer, J., Vanderplasschen, W., Lammertyn, J., van Nieuwenhuizen, C., Sabbe, B. & Broekaert, E. (2011). Current quality of life and its determinants among opiate-dependent individuals five years after starting methadone treatment. *Quality of Life Research, 20*, 139-150. doi:10.1007/s11136-010-9732-3

Derogatis, L. R. (1992). *SCL-90-R: Administration, scoring and procedures manual for the R (evised) version and other instruments of the psychopathology rating scale series*. Towson: Clinical Psychometric Research.

Dobler-Mikola, A., Hattenschwiler, J., Meili, D., Beck, T., Boni, E., Modestin, J. (2005). Patterns of heroin, cocaine, and alcohol abuse during long-term methadone maintenance treatment. *Journal of Substance Abuse Treatment, 29*, 259-265. doi :10.1016/j.jsat.2005.08.002

Eiden, C., Leglis, Y., Clarivet, B., Blayac, J. P. & Peyrière, H. (2012). Co-morbidités psychiatriques associées à des fortes posologies de méthadone (>100 mg/j): analyse rétrospective d'une cohorte de patients traités. *Thérapie, 67*, 223-230. doi :10.2515/therapie/2012025

Faggiano, F., Vigna-Taglianti, F., Versino, E. & Lemma, P. (2003). Methadone maintenance at different dosages for opioid dependence. *Cochrane Database of Systematic Reviews, 3*, CD002208. doi:10.1002/14651858.CD002208

Fareed, A., Vayalapalli, S., Stout, S., Casarella, J., Drexler, K. & Bailey, S. P. (2010). Effect of methadone maintenance treatment on heroin craving, a literature review. *Journal of Addictive Diseases, 30*, 27-38. doi:10.1080/10550887.2010.531672

Farré, M., Mas, A., Torrens, M., Moreno, V. & Camí, J. (2002). Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. *Drug and Alcohol Dependence, 65*, 283-290. doi:10.1016/S0376-8716(01)00171-5

Fernández Miranda, J. J. (2001). Efectividad de los programas de mantenimiento con metadona. Una revisión de los resultados de los estudios de evaluación. *Medicina Clínica (Barcelona), 116*, 150-154.

Fernández Miranda, J. J. (2004). Calidad asistencial y cronicidad en los programas de mantenimiento con agonistas opiáceos. *Adicciones, 16*, 109-116.

Fernández Miranda, J. J., González García-Portilla, M. P., Sáiz Martínez, P.A., Gutiérrez Cienfuegos, E, Bobes García, J. (1999). Calidad de vida y severidad de la adicción en heroinómanos en mantenimiento prolongado con metadona. *Adicciones, 11*, 43-52.

González de Rivera, J. L., Derogatis, L. R., de las Cuevas, C., Gracia Marco, R., Rodríguez-Pulido, F., Henry-Benítez, M. & Monterrey, A. L. (1989). *The Spanish version of the SCL-90-R. Normative data in the general population.* Towson: Clinical Psychometric Research.

Grönbladh, L. & Öhlund, L. S. (2011). Self-reported differences in side-effects for 110 heroin addicts during opioid addiction and during methadone treatment. *Heroin Addiction and Related Clinical Problems, 13*, 5-12.

Gruber, S. A., Tzilos, G. K., Silveri, M. M., Pollack, M., Renshaw, P. F., Kaufman, M. J. & Yurgelun-Todd, D. A. (2006). Methadone maintenance improves cognitive performance after two months of treatment. *Experimental and Clinical Psychopharmacology, 14*, 157-164. doi:10.1037/1064-1297.14.2.157

Hall, W., Carter, A. & Forlini, C. (2015). The brain disease model of addiction: is it supported by the evidence and has it delivered on its promises? *Lancet Psychiatry, 2*, 105-110. doi:10.1016/S2215-0366(14)00126-6

Hammer, R., Dingel, M., Ostergren, J., Partridge, B., McCormick, J. & Koenig, B. A. (2013). Addiction: Current criticism of the brain disease paradigm. *American Journal of Bioethics Neuroscience, 4*, 27-32. doi:10.1080/21507740.2013.796328

Habrat, B., Chmielewska, K., Baran-Furga, H., Keszycka, B. & Taracha, E. (2002). Subjective Quality of Life in opiate-dependent patients before admission after six months and one-year participation in methadone program. *Przegl Lek, 59*, 351-354.

Harris, J. & McElrath, K. (2012). Methadone as social control: Institutionalized stigma and the prospect

of recovery. *Qualitative Health Research, 22*, 810–824. doi:10.1177/1049732311432718

Harris, M. & Rhodes, T. (2013). Methadone diversion as a protective strategy: the harm reduction potential of 'generous constraints'. *International Journal of Drug Policy, 24*, e43-e50. doi:10.1016/j.drugpo.2012.10.003

Hartgers, C., van den Hoek, A., Krijnen, P. & Coutinho, R. A. (1992). HIV prevalence and risk behavior among injecting drug users who participate in 'Low-Threshold' methadone programs in Amsterdam. *American Journal of Public Health, 82*, 547-551. doi:10.2105/AJPH.82.4.547

He, Q., Wang, X., Xia, Y., Mandel, J. S., Chen, A., Zhao, L., … Ling, L. (2011). New community-based methadone maintenance treatment programs in Guangdong, China, and their impact on patient quality of life. *Substance Use & Misuse, 46*, 749-757. doi:10.3109/10826084.2010.534124

Hooper, D., Coughlan, J. & Mullen, M. R. (2008). Structural equation modelling: Guidelines for determining model fit. Electronic *Journal of Business Research Methods, 6*, 53- 60.

Karow, A., Verthein, U., Pukrop, R., Reimer, J., Haasen, C., Krausz, M. & Schäfer, I. (2011). Quality of life profiles and changes in the course of maintenance treatment among 1,015 patients with severe opioid dependence. *Substance Use & Misuse, 46*, 705-715. doi:10.3109/10826084.2010.509854

Katz, N. (2005). The impact of opioids on the endocrine system. *Pain Management Rounds, 1*, 1-6. doi:10.1097/AJP.0b013e3181850df6

Keen, J., Oliver, P., Rowse, G. & Mathers, N. (2003). Does methadone maintenance treatment based on the new national guidelines work in a primary care setting? *British Journal of General Practice, 53*, 461-467.

Kelly, S. M., O'Grady, K. E., Brown, B. S., Mitchell, S. G. & Schwartz, R. P. (2010). The role of patient satisfaction in methadone treatment. *American Journal of Drug and Alcohol Abuse, 36*, 150–154. doi:10.3109/00952991003736371

Kelly, S. M., O'Grady, K. E., Brown, B. S., Mitchell, S. G. & Schwartz, R. P. (2011). Predictors of methadone treatment retention from a multi-site study: A survival analysis. *Drug & Alcohol Dependence, 117*, 170-175. doi:10.1016/j.drugalcdep.2011.01.008

Krantz, M. J., Kutinsky, I. B., Robertson, A. D. & Mehler, P. S. (2003). Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy, 23*, 802-805. doi:10.1592/phco.23.6.802.32186

Krantz, M. J., Martin, J., Stimmel, B., Mehta, D. & Haigney, M. C. P. (2009). QTc interval screening in methadone treatment. *Annals of Internal Medicine, 150*, 387-395. doi:10.7326/0003-4819-150-1-200903170-00104

Langendam, M. W., Van Brussel, G. H., Coutinho, R. A. & Van Ameijden, E. J. (2001). The impact of harm-reduction-based methadone treatment on mortality among heroin users. *American Journal of Public Health, 91*, 774-780. doi:10.2105/AJPH.91.5.774

Leavitt, S. B. (2003). Methadone dosing & safety in the treatment of opioid addiction. *Addiction Treatment Forum, 12*, 1-8.

Leshner, A. I. (1997). Addiction is a brain disease, and it matters. *Science, 278*, 45-47. doi:10.1126/science.278.5335.45

Liao, D. L., Chen, P. C., Chen, C. H., Hsieh, C. J., Huang, Y. F., Shih, W. Y. & Cheng, J. J. (2013). Higher methadone doses are associated with lower mortality in patients of opioid dependence in Taiwan. *Journal of Psychiatric Research, 47*, 1530-1534. doi:10.1016/j.jpsychires.2013.07.001

Lina, C., Wu, Z. & Detels, R. (2011). Family support, quality of life and concurrent substance use among methadone maintenance therapy clients in China. *Public Health, 125*, 269-274. doi:10.1016/j.puhe.2011.01.009

Lingford-Hughes, A. R., Welch, S. & Nutt, D. J. (2004). Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology, 18*, 293-336. doi:10.1177/0269881104048516

Liu, E., Rou, K., McGoogan, J. M., Pang, L., Cao, X., Wang, C., ... & Wu, Z. (2013). Factors associated with mortality of HIV-positive clients receiving methadone maintenance treatment in China. *Journal of Infectious Diseases, 208*, 442-453. doi:10.1093/infdis/jit163

Loeber, S., Kniest, A., Diehl, A., Mann, K. & Croissant, B. (2008). Neuropsychological functioning of opiate-dependent patients: A nonrandomized comparison of patients preferring either buprenorphine or methadone maintenance treatment. *American Journal of Drug and Alcohol Abuse, 34*, 584–593. doi:10.1080/00952990802308239

Lucas-Carrasco, R. (2012). The WHO quality of life (WHOQOL) questionnaire: Spanish development and validation studies. *Quality of Life Research, 21*, 161-165. doi:10.1007/s11136-011-9926-3

Maddux, J. F., Desmond, D. P. & Vogtsberger, K. N. (1995). Patient-regulated methadone dose and optional counseling in methadone maintenance. *American Journal on Addictions, 4*, 18-32. doi:10.1111/j.1521-0391.1995.tb00255.x

Maddux, J. F., Prihoda, T. J. & Vogtsberger, K. N. (1997). The relationship of methadone dose and other variables to outcomes of methadone maintenance. *American Journal on Addictions, 6*, 246–255. doi:10.1111/j.1521-0391.1997.tb00404.x

Maremmani, I., Pacini, M., Lubrano, S. & Lovrecic, M. (2003). When "enough" is still not "enough": effectiveness of high-dose methadone in the treatment of heroin

addiction. *Heroin Addiction & Related Clinical Problems, 5*, 17-32.

Mattick, R. P., Breen, C., Kimber, J. & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews, 3*, CD002209. doi:10.1002/14651858.CD002209.pub2

Maxwell, S. & Shinderman, M. (1999). Optimizing response to methadone maintenance treatment: use of higher-dose methadone. *Journal of Psychoactive Drugs, 31*, 95-102. doi:10.1080/02791072.1999.10471730

Millson, P., Challacombe, L., Villeneuve, P. J., Strike, C. J., Fischer, B., Myers, T., ... Hopkins, S. (2006). Determinants of health-related quality of life of opiate users at entry to low-threshold methadone programs. *European Addiction Research, 12*, 74-82. doi:10.1159/000090426

Millson, P. E., Challacombe, L., Villeneuve, P. J., Fischer, B., Strike, C. J., Myers, T., … Pearson, M. (2004). Self-perceived health among Canadian opiate users: a comparison to Canadian the general population and to other chronic disease populations. *Canadian Journal of Public Health, 95*, 99-103.

Millson, P., Challacombe, L., Villeneuve, P. J., Strike, C. J., Fischer, B., Myers, T., … Hopkins, S. (2007). Reduction in injection–related hiv risk after 6 months in a low-threshold methadone treatment program. *AIDS Education and Prevention, 19*, 124–136. doi:10.1521/aeap.2007.19.2.124

Mino, A., Page, D., Dumont, P. & Broers, B. (1998). Treatment failure and methadone dose in a public methadone maintenance treatment programme in Geneva. *Drug and Alcohol Dependence, 50*, 233-239. doi:10.1016/S0376-8716(98)00035-0

Mintzer, M. Z., Copersino, M. L. & Stitzer, M. L. (2005). Opioid abuse and cognitive performance. *Drug and Alcohol Dependence, 78*, 225–230. doi:10.1016/j.drugalcdep.2004.10.008

Mintzer, M. Z. & Stitzer, M. L. (2002). Cognitive impairment in methadone maintenance patients. *Drug and Alcohol Dependence, 67*, 41-51. doi:10.1016/S0376-8716(02)00013-3

Montgomery, L. T., Sanning, B., Litvak, N. & Peters, E. N. (2014). Preliminary findings on the association between clients' perceived helpfulness of substance abuse treatment and outcomes: Does race matter? *Drug and Alcohol Dependence, 139*, 152-158. doi:10.1016/j.drugalcdep.2014.03.026

Musshoff, F., Trafkowski, J., Lichtermann, D. & Madea, B. (2010). Comparison of urine results concerning co-consumption of illicit heroin and other drugs in heroin and methadone maintenance programs. *International Journal of Legal Medicine, 124*, 499-503. doi:10.1007/s00414-009-0361-8

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I.… Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*, 695-699. doi:10.1111/j.1532-5415.2005.53221.x

Nosyk, B., Guh, D. P., Sun, H., Oviedo-Joekes, E., Brissette, S., Marshd, D. C., … Anis, A. H. (2011). Health related quality of life trajectories of patients in opioid substitution treatment. *Drug and Alcohol Dependence, 118*, 259-264. doi:10.1016/j.drugalcdep.2011.04.003

Nosyk, B., Marsh, D. C., Sun, H., Schechter, M. T. & Anis, A. H. (2010). Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996–2006. *Journal of Substance Abuse Treatment, 39*, 22-31. doi:10.1016/j.jsat.2010.03.008

Notley, C., Blyth, A., Maskrey, V., Pinto, H. & Holland, R. (2015). Exploring the concepts of abstinence and recovery through the experiences of long-term opiate substitution clients. *Substance Abuse, 36*, 232-239. doi:10.1080/08897077.2014.941085

Pacini, M., Maremmani, A. G. I., Rovai, L., Rugani, F. & Maremmani, I. (2010). Treating heroin addicts. Blocking dosages and stimulation-stabilization of opioidergic system. *Heroin Addiction & Related Clinical Problems, 12*, 41-48.

Padaiga, Z., Subata, E. & Vanagas. G. (2007). Outpatient methadone maintenance treatment program. Quality of life and health of opioid-dependent persons in Lithuania. *Medicina (Kaunas), 4*, 235-241.

Pedrero Pérez, E. J. & López-Durán, A. (2005). Autoinformes de sintomatología depresiva en drogodependientes: nivel de coincidencia del BDI, SCL-90-R & MCMI-II. ¿Depresión o malestar inespecífico? *Adicciones, 17*, 215-230.

Pérez de los Cobos, J., Fidel, G., Escuder, G., Haro, G., Sánchez, N., Pascual, C.,… , Trujols, J. (2004). A satisfaction survey of opioid-dependent clients at methadone treatment centres in Spain. *Drug and Alcohol Dependence, 73*, 307-313. doi:10.1016/j.drugalcdep.2003.11.001

Perreault, M., Héroux, M. C., White, N. D., Lauzon, P., Mercier, C. & Rousseau, M. (2007). Treatment retention and evolution of clientele in a low threshold methadone substitution treatment program in Montreal. *Canadian Journal of Public Health, 98*, 33-36.

Peterson, J. A., Schwartz, R. P., Mitchell, S. G., Reisinger, H. S., Kelly, S. M., O'Grady, K. E.… Agar, M. H.. (2010). Why don't out-of-treatment individuals enter methadone treatment programmes? *International Journal of Drug Policy, 21*, 36-42. doi:10.1016/j.drugpo.2008.07.004

Preston, K. L., Umbricht, A. & Epstein, D. H. (2000). Methadone dose increase and abstinence reinforcement

for treatment of continued heroin use during methadone maintenance. *Archives of General Psychiatry, 57*, 395-404. doi:10.1001/archpsyc.57.4.395.

Rass, O., Kleykamp, B. A., Vandrey, R. G., Bigelow, G. E., Leoutsakos, J. M., Stitzer, M. L., … Mintzer, M. Z. (2014). Cognitive performance in methadone maintenance patients: effects of time relative to dosing and maintenance dose level. *Experimental and Clinical Psychopharmacology, 22*, 248-256. doi:10.1037/a0035712

Rodríguez, M., Jiménez-Lerma, J. M., Iraurgi, I., Murua, F., Bacigalupe, L., Chavarri, M. R., & Balsategi, B. (2002). Evaluación de la satisfacción con el tratamiento en un centro ambulatorio de drogodependencias a través del Treatment Perceptions Questionnaire (TPQ). *Adicciones, 14*, 1-8.

Rojo-Mota, G., Pedrero-Pérez, E. J., Ruiz-Sánchez de León, J. M., Llanero-Luque, M. & Puerta-García, C. (2013). Cribado neurocognitivo en adictos a sustancias: la evaluación cognitiva de Montreal. *Revista de Neurología, 56*, 129-136.

Roncero, C., Fuste, G., Barral, C., Rodríguez-Cintas, L, Martínez-Luna, N., Eiroa-Orosa, F. J., Casas, M, on behalf of the PROTEUS study investigators. (2011). Therapeutic management and comorbidities in opiate-dependent patients undergoing a replacement therapy programme in Spain: the PROTEUS study. *Heroin Addiction and Related Clinical Problems, 13*, 5-16.

Roy, A. K., McCarthy, C., Kiernan, G., McGorrian, C., Keenan, E., Mahon, N. G. & Sweeney, B. (2012). Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. *Addiction, 107*, 1132-1139. doi:10.1111/j.1360-0443.2011.03767.x

Ruggeri, M., Lasalvia, A., Dall'Agnola, R., Van Wijngaarden, B., Knudsen, H.C., Leese, M., ... & The Epsilon Study Group (2000). Development, internal consistency and reliability of the Verona Service Satisfaction Scale - European Version. *British Journal of Psychiatry, 177*, s41-s48. doi:10.1192/bjp.177.39.s41

Schwartz, R. P., Highfield, D. A., Jaffe, J. H., Brady, J. V., Butler, C. B., Rouse, C. O., … Breteler, M. M. B. (2006). A randomized controlled trial of interim methadone maintenance. *Archives of General Psychiatry, 63*, 102-109. doi:10.1001/archpsyc.63.1.102.

Senbanjo, R., Wolff, K. I. M., Marshall, E & Strang, J. (2009). Persistence of heroin use despite methadone treatment: Poor coping self-efficacy predicts continued heroin use. *Drug and Alcohol Review, 28*, 608-615. doi:10.1111/j.1465-3362.2009.00064.x

Servicio Andaluz de Salud (2010). *Desarrollo de Programas de Tratamiento Asertivo Comunitario en Andalucía. Documento marco. Anexo 3.1.* Granada: Área de Dirección de Organizaciones Sanitarias de la Escuela Andaluza de Salud Pública.

Skevington, S. M., Lotfy, M. & O'Connell, K. A. (2004). The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Quality of life Research, 13*, 299-310. doi:10.1023/B:QURE.0000018486.91360.00

Skevington, S. M., Sartorius, N., Amir, M., and THE WHOQOL Group. (2004). Developing methods for assessing quality of life in different cultural settings. *Social Psychiatry and Psychiatric Epidemiology, 39*, 1-8. doi:10.1007/s00127-004-0700-5

Torrens, M., Castillo, C. & Perez-Sola, V. (1996). Retention in a low threshold methadone maintenance program. *Drug and Alcohol Dependence, 41*, 55-59. doi:10.1016/0376-8716(96)01230-6

Torrens, M., Domingo-Salvany, A., Alonso, J., Castillo, C. & San, L. (1999). Methadone and quality of life. *Lancet, 353*, 1101. doi:10.1016/S0140-6736(05)76462-X

Trujols, J., Portella, M. J., Iraurgi, I., Campins, M. J., Siñol, N. & Pérez de los Cobos, J. (2013). Patient-reported outcome measures: Are they patient-generated, patient-centred or patient-valued? *Journal of Mental Health, 22*, 555-562. doi:10.3109/09638237.2012.734653

Trujols, J. & Pérez de los Cobos, J. (2005). La perspectiva de los usuarios sobre los tratamientos de mantenimiento con metadona: una revisión centrada en la satisfacción con el tratamiento. *Adicciones, 17,* s181-s204.

Van Ameijden, E. J., Langendam, M. W. & Coutinho, R. A. (1999). Dose-effect relationship between overdose mortality and prescribed methadone dosage in low threshold maintenance programs. *Addictive Behaviours, 24*, 559-563. doi:10.1016/S0306-4603(98)00083-5

Vanderplasschen, W., Naert, J., Vander Laenen, F. & De Maeyer, J. (2015). Treatment satisfaction and quality of support in outpatient substitution treatment: opiate users' experiences and perspectives. *Drugs: education, prevention, and policy, 22*, 272-280. doi:10.3109/09687637.2014.981508

Verdejo, A., Toribio, I., Orozco, C., Puente, K. L. & Pérez-García, M. (2005). Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug and Alcohol Dependence, 78*, 283-288. doi:10.1016/j.drugalcdep.2004.11.006

Villeneuve, P. J., Challacombe, L., Strike, C. J., Myers, T., Fischer, B., Shore, R., Hopkins, S. & Millson, P. E. (2006). Change in health-related quality of life of opiate users in low-threshold methadone programs. *Journal of Substance Use, 11*, 137-149. doi:10.1080/14659890500256945

Walker, P. W., Klein, D. & Kasza, L. (2003). High dose methadone and ventricular arrhythmias: a report of three cases. *Pain, 103*, 321-324. doi:10.1016/S0304-3959(02)00461-X

Wang, P. W., Wu, H. C., Yen, C. N., Yeh, Y. C., Chung, K. S., Chang, H. C. & Yen C, F. (2012). Change in quality of

life and its predictors in heroin users receiving methadone maintenance treatment in Taiwan: An 18-month follow-up study. *American Journal of Drug and Alcohol Abuse, 38*, 213-219. doi:10.3109/00952990.2011.649222

Webster, L. R. (2013). Methadone side effects: Constipation, respiratory depression, sedation, sleep-disordered breathing, and the endocrine system. En Cruciani, R. A. & Knotkova H., *Handbook of Methadone Prescribing and Buprenorphine Therapy* (pp. 39-49). New York: Springer.

White, W. & Mojer-Torres, L. (2010). *Recovery-oriented methadone maintenance*. Chicago (IL): Great Lakes Addiction Technology Transfer Center, Philadelphia Department of Behavioral Health and Mental Retardation Services and Northeast Addiction Technology Transfer Center.

WHO (2004). *The World Health Organization Quality of Life (WHOQOL)-BREF World Health Organization*. Recuperado de http://www.who.int/substance_abuse/research_tools/whoqolbref/en/.

Zeldman, A., Ryan, R. M. & Fiscella, K. (2004). Motivation, autonomy support, and entity beliefs: Their role in methadone maintenance treatment. *Journal of Social and Clinical Psychology*, 23, 675-696. doi:10.1521/jscp.23.5.675.50744

Appendix I. *Satisfaction scale used.*

1. What is your general impression of the efficacy of the Drug Addiction Centre in dealing with your problems?
2. What is your general impression of the capacity of the professionals in the Drug Addiction Centre to listen to you and understand your problems?
3. What is your general impression of the behaviour of the Drug Addiction Centre staff and their personal treatment of you?
4. What is your general impression of the capacity of the Drug Addiction Centre staff to cooperate, when necessary, with your family doctor or other specialists?
5. What is your general impression of the all the services that you have received in the Drug Addiction Centre?
6. What is your general impression of the efficacy of the centre in helping you improve your relationship with your closest relatives?
7. What is your general impression of the efficacy of the centre in helping your closest relatives to find out about and understand your problems better?
8. What is your general impression of the Drug Addiction Centre staff's knowledge of your problems, past and present?
9. What is your general impression of the information you have received about your diagnosis and the possible development of your addiction?
10. What is your general impression of the efficacy of the centre in helping you to improve your relationships with people outside your family environment (friends, neighbours, workmates)?
11. What is your general impression of the clarity and precision of the instructions received about what you had to do between appointments?
12. What is your general impression of the efficacy of the centre in helping you to improve your ability to look after yourself (e.g. personal hygiene, diet, accommodation, etc.)?
13. What is your general impression of the help you have received when suffering side-effects and discomfort caused by your medicines?

Response options: 1 Very bad; 2 Generally unsatisfactory; 3 Not bad, not good; 4 Generally satisfactory; 5 Excellent.

Methadone for the treatment of Prescription Opioids Dependence. A retrospective chart review

Metadona para el tratamiento de la dependencia de opioides de prescripción médica. Una revisión retrospectiva de historias clínicas

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Abstract

Prescription opioids (PO) addiction is increasing to an epidemic level. Few studies exist regarding its treatment. Although buprenorphine has been the mainstay so far, other treatment options might be considered, such as methadone. We conducted a retrospective assessment of all patients admitted to a psychiatry ward for PO detoxification using methadone between 2010 and 2013. The assessment and description was carried out during a 3-month follow-up period after their discharge. Although this is a retrospective chart review, our exploration included sociodemographic and treatment variables in addition to the abstinence rates for the whole sample. Eleven patients were included, mostly women (81.8%), with a median age of 50 years. The median duration of dependence was 8 years. Dependence on other substances and psychiatric comorbidities were high. Eight patients were monitored during three months. Of these, 7 (87.5%) were abstinent after that period. The results suggest that methadone deserves further exploration as a potentially efficacious treatment option for PO dependence.

Keywords: Prescription opioids; Methadone; Detoxification; Day Hospital.

Resumen

La adicción a opioides de prescripción médica (OPM) está incrementado a niveles epidémicos. Los pocos estudios que existen hasta la fecha sobre su tratamiento se basan principalmente en el uso de buprenorfina. Sin embargo, la metadona puede considerarse como otra opción. El objetivo de nuestro estudio fue revisar las historias clínicas de todos los pacientes ingresados en una unidad de psiquiatría para la desintoxicación de OPM usando metadona entre el 2010 y el 2013. El periodo de evaluación finaliza a los 3 meses desde el alta médico. Pese a ser una revisión de historia clínicas, se evaluaron las características sociodemográficas de la muestra, así como las variables relacionadas con el tratamiento y la tasa de abstinencia durante el estudio. Se incluyeron 11 pacientes, mayoritariamente mujeres (81,8%), con una mediana de edad de 50 años. La mediana de duración de la dependencia fue de 8 años. Hubo una alta prevalencia de adicción a otras sustancias así como de comorbilidades psiquiátricas. Ocho pacientes fueron seguidos durante al menos 3 meses. De estos, 7 (87,5%) estuvieron abstinentes hasta el final del periodo evaluado por el estudio. Los resultados sugieren la necesidad de estudios de mayor rigor metodológico para la correcta evaluación de la metadona como un tratamiento potencialmente eficaz para la dependencia de los OPM.

Palabras clave: Opioides de Prescripción Médica (OPM); Metadona, Desintoxicación; Hospital de día.

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Opioids, used medically for pain relief, have analgesic and central nervous system depressant effects as well as the potential to cause euphoria. Activation of endogenous mu opioid receptors results in the prototypic opioid effects of reward, withdrawal, and analgesia (Camí & Farré, 2003).

Despite not being a recent phenomenon (Tennant & Rawson, 1982), in recent years, there has been a dramatic increase in the prescription and abuse rates of prescription opioids (PO). In the US, the number of adults abusing prescription opioids increased from 4.9 million in 1992 to almost 12.5 million in 2012 and the rate of treatment receipt for prescription opioid use disorders is now second only to alcohol (Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013). In Europe, emerging abuse of prescription opioids is of concern in Western and Central Europe, with treatment demand for abuse of opioids other than heroin increasing. Opioid-related deaths have decreased overall in Western and Central Europe, but the proportion of deaths attributable to fentanyl and methadone has increased (International Narcotics Control Board, 2014). Moreover, healthcare costs associated with opioid dependence have been found to exceed one billion dollars in the United States annually (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction,1998).

Given its recent epidemic level, little research exists regarding its treatment. To date, there exists only a large randomized controlled trial (Potter et al., 2015), which followed PO dependent patients for 40 months, using a buprenorphine-naloxone strategy. While results for the 18 month follow-up were promising, recently available data for the 40 month follow up (Weiss et al., 2015) suggest that, despite a clear overall improvement from baseline, there remains a large subset of patients with a worsening course, who initiate heroine use or opioid injection. All this has urged affected countries to set up educational and prevention policies, with moderate success, therefore arguing that the development of specific treatments for PO dependence is critically needed (Brady, McCauley & Back, 2015).

Given all that, other treatment strategies should be considered for prescription opioids addiction. Such is the case of methadone, a well-established substitutive therapy for opioids use disorders. A previous comparative study between buprenorphine and methadone found similar outcomes in both groups, with methadone being better at preventing relapse (Neumann et al., 2013). Other retrospective studies, not specifically focused on PO dependent patients, have also suggested methadone might be an appropriate treatment strategy (Brands, Blake, Sproule, Gourlay & Busto, 2004; Sander & Hays, 2005). Actually, in spite of its greater toxicity when compared to buprenorphine or its more frequent and costly interactions (Roncero et al., 2015), methadone has consistently shown better outcomes in opioid dependent patients (Mattick, Breen, Kimber & Davoli, 2014; Barnett, Rodgers & Bloch ,2001). Here, we report the results of a small retrospective chart review of prescription opioids dependent patients receiving substitutive treatment with methadone. Some illustrating cases will be described, and also, an exploratory description of the whole sample will be conducted.

Method

Patients and setting

We conducted a retrospective assessment and description of all patients admitted between 2010 and 2013 to the Acute Psychiatric Ward of a tertiary hospital for prescription opioids detoxification. Patients were eligible if they met criteria for prescription opioids dependence according to DSM-IV (American Psychiatric Association, 2000), were at least 18 years old, had a stable residence, had no severe or disabling physical or psychiatric conditions and were detoxified using methadone. The study was approved by the corresponding ethics committee.

Measures

An exploration of descriptive statistics for the whole sample was conducted. At baseline, sociodemographic variables and psychiatric comorbidities were collected from patients' medical chart. A follow-up period of 3 months was established. Variables regarding prescription opioids dependence and methadone treatment were also collected. A special focus was placed on abstinence during the study period, defined as having taken no other opioids besides the prescribed methadone. Urine toxscreen and patient self-reports were used to verify this information.

Study procedures

All patients underwent the same procedures. Upon admission, they underwent a blood analysis, an ECG, a urine toxscreen and an initial psychiatric evaluation. Once assessed, according to patients' self-reports on their prescription opioids dose, the daily morphine equivalent dose was calculated. Then, a methadone conversion ratio, seen in table 1 (Ripamonti et al., 1998), was used to establish the adequate dose of methadone. However, it is well known that due to its long half-life (up to 7 days) and wide inter-individual pharmacodynamics (Ferrari, Coccia, Bertolini & Sternieri, 2004), methadone has a high risk among opioids of overdose and accumulation during initial titration to effect (as steady state levels are approached). Therefore, it is recommended that once the conversion to methadone has been established, the initial dose be reduced to a half and then dosed one third every 8 hours, and never exceed 30 mg the first day (Mancini, Lossignol & Body, 2000). However, it is the prescriber decision and personal experience that ultimately guide and prevail in choosing the initial dose of methadone.

Table 1. *Methadone conversion rates according to morphine doses.*

Oral MEDD (mg/day)	Methadone Dose Conversion Ratio
0 to 99	4:1
100 to 299	8:1
300 to 499	12:1
500 to 999	16:1
>1000	20:1

Note. MEDD: Morphine equivalent daily dose

Table 2. *Sociodemographic and treatment variables.*

Sample characteristics	
Sex: females n (%)	9 (81.8%)
Age: median (IQR)	50 (18)
Duration of hospital stay in days: median (IQR)	16 (6)
Duration of prescription opioids dependence in years: median (IQR)	8.3 (10.9)
Duration of follow up in days: median (IQR)	258 (446)
Expected methadone dose in mg: median	30
Maximum methadone dose in mg: median (IQR)	22.5 (15)
Methadone dose at discharge in mg: median (IQR)	10 (15)
Duration of methadone treatment in days: median (IQR)	77 (68.5)
Patients taking other psychotropic drugs at intake: n (%)	8 (73%)
Patients taking no prescription opioids previously: n (%)	1 (9%)
Patients with dependence to other substances: n (%)	6 (54.5%)
Benzodiazepines	3 (27.3%)
Alcohol and benzodiazepines	2 (18.2%)
Alcohol, benzodiazepines and heroine	1 (9.1%)
Lost to follow up: n (%)	2 (18.2%)
Patients relapsing during detoxification: n (%)	1 (9.1%)
Prescription opioid: n (%)	
codeine	3 (27.3%)
fentanyl	6 (54.5%)
oxycodone	1 (9.1%)
meperidine	1 (9.1%)
Psychiatric comorbidity: n (%)	5 (35.5%)
Affective disorder	4 (36.4%)
Anxiety disorder	1 (9.1%)

Note. IQR: interquartile range

A stop start approach was used (Mercadante et al., 2001; Mercadante, Ferrera, Villari & Casuccio, 2005), where prescription opioids were suppressed on the first day of admission, and methadone was started according to the rule explained before. After a few weeks of inpatient detox, the process continued in our psychiatric day hospital, which mainly focuses on the aftercare of addictions, where patients were followed for the rest of their treatment.

Both in the inpatient and day hospital settings, patients received daily individual therapy as well as twice a week non-directive group therapy. Once in the day hospital, patients received methadone in a daily, single morning dose. Urine toxscreens were conducted on a random basis to verify patient self-reports.

Statistical analysis

For continuous variables, given the small sample size, robust measures were selected. Therefore we used the median and the interquartile range to describe them. Dichotomous variables are presented with their respective percentages. As this is small sample size, mainly descriptive study, no adjusted analyses were conducted.

Results

First, summary statistics regarding all cases are presented. Next, a description of the most representative cases is outlined.

Summary statistics

Table 2 shows sociodemographic and treatment variables for the whole sample.

Eleven patients were identified, meeting the inclusion criteria. Eight of them could be followed for at least 3 months in the day hospital. All of them took prescription opioids for pain related diagnoses, except for one patient, who started taking codeine because of cough. The sample was composed mainly of women with a median age of 50 years. The duration of dependence was relatively long, with a median of 8 years. Of all the patients completing the study period, only one relapsed. The two patients lost to follow-up were abstinent in the last assessment conducted. Of note, more than half of the patients were on psychotropic medication upon admission, more than half had dependence to other substances, and nearly half of them had psychiatric comorbidities diagnosed at the time of the study.

Methadone doses were relatively low, even lower than expected. Again, it highlights the necessity of a slow and careful titration when using methadone, and although indicative algorithms might be consulted, it is ultimately the clinician experience the one determining the appropriate dose. Regarding severe adverse events related to methadone treatment, none was observed during the time covered by the study.

Case 1

A 55 year-old woman was admitted to the psychiatry ward due PO addiction. The patient had a history of fibromyalgia and cervical disc herniation for which she had received analgesic treatment with oral oxycodone for 14 years. During this time, the patient developed dependence, with in-

creasing doses until a daily dose of 60 mg. Methadone was initially started up to 20 mg per day, then gradually reduced during her hospitalization, reaching 9 mg per day when discharged. He was also started on paracetamol and amitriptiline. During 10 weeks in the day hospital, a gradual reduction of dose was carried out. Finally, the patient was out of methadone, having shown no signs of withdrawal.

Case 2

A 52 year-old woman was admitted to the psychiatry ward due to PO addiction. The patient had a history of fibromyalgia for which she had received analgesic treatment with tramadol and fentanyl for 3 years. During this time, increasing doses were given, up to the habitual dose of tramadol 300 mg daily and fentanyl 25 µg daily. The patient suffered also from benzodiazepine dependence of about 15 years duration and a depressive syndrome. Methadone was started up to 20 mg daily then gradually reduced during the hospital stay, reaching 5 mg daily at hospital discharge. The outpatient control was conducted during 8 weeks in the day hospital, where methadone was finally suppressed, with no withdrawal signs or adverse effects observed.

Case 3

A 45 year-old man was admitted to the psychiatry ward due to transmucosal fentanyl dependence. The patient had a past history of chronic rectal pain due to radiotherapy of 3 years duration, the same time he had been receiving fentanyl for pain control. The habitual dose of transmucosal fentanyl was about 600 µg per day. Upon admission, methadone up to 90 mg per day was started. The patient did not present withdrawal signs o adverse effects. He also received duloxetine, pregabaline and carbamazepine as part of his routine pharmacological schedule. During 2 weeks, methadone was tapered to 70mg daily. He was then discharged to the day hospital, where during 12 weeks methadone was further tapered until total suppression. No withdrawal symptoms were observed.

Case 4

A 61 year-old woman was admitted to the psychiatry ward due to codeine addiction. The patient had a history of chronic arthropathy for which he had been receiving analgesic treatment with oral codeine for 16 years. Increasing doses had been given, until the present use of codeine at about 900 mg per day. The patient suffered also from benzodiazepine and alcohol addiction of long duration. Methadone was initially started up to 25 mg per day, and then gradually reduced during her two-week admission, reaching 15 mg per day at hospital discharge. The following 4 weeks she was in the day hospital, where a progressive reduction in methadone was carried out. The patient, however, moved to another city before a total suppression of methadone could be carried out.

Discussion

Overall, and despite being a small retrospective chart review, with a short follow-up period, the results obtained in this study are encouraging. Patient retention during methadone treatment was relatively high, a fact that has been observed for PO dependent patients in previous studies (Banta-Green, Maynard, Koepsell, Wells & Donovan, 2009). Of those being assessed for at least 3 months, only one patient relapsed. It should be taken into account that it was a patient with a previous history of heroin dependence, which has been shown to be associated with poorer outcomes (Potter et al., 2015).

Interestingly, psychiatric comorbidities as well as previous addictions were common in our sample. This fact, and given the increasing rate of prescription opioids addiction, implies that it is of vital importance to conduct an appropriate assessment before prescription opioids are initiated, and it calls for a close monitoring and supervision during treatment.

Although it is not possible to extract firm conclusions given the methodological shortcomings of this study, two elements should be mentioned. First, methadone as the medication used in the detoxification process. An extensive literature exists supporting its use for illicit opioids dependence (Marsch, 1998; Joseph, Stancliff & Langrod, 2000) which justifies and warrants research for its application in the field of prescription opioids. In our study, methadone doses were relatively low, no related severe adverse events were observed, and abstinence rates were high. Second, both inpatient and day hospital settings were the main sites of treatment, which allow for a close and daily monitoring of patients and its process of detoxification and dishabituation. This fact might have facilitated the good results of the study in interaction with methadone.

Being an inpatient sample which was subsequently transferred to a day hospital might mean it was a relatively selected group between the whole group of prescription opioids addicted patients: the most severely dependent. Whether buprenorphine might have been equally effective in a sample like this one remains to be determined.

Our approach with these patients was that of medically supervised withdrawal. It means methadone doses were slowly reduced until total suppression. The complementary approach would have been a maintenance paradigm. Heroine related literature suggests that a maintenance approach might be better suited for those patients. However, as previous studies suggest, one could consider whether PO dependent persons may differ from prior cohorts of heroin dependent patients and might be better candidates for medically supervised withdrawal to abstinence. Our data could suggest that supervised withdrawal is indeed a feasible approach with PO addicted patients.

Finally, it should be noted the relatively long duration of the dependence our patients had. It is the nature of addic-

tion itself that imposes a long time on patients before action towards change is taken, but it should also warn physicians prescribing opioids to try to detect early signs of a developing dependence and thus take the necessary steps to address it.

Limitations

Several limitations should be taken into account when interpreting the findings of this study. First, retrospective chart reviews offer evidence of poor quality, with no control group, small sample sizes and no analytic analysis. Also, we covered a short follow-up period. The descriptive and retrospective nature of the study remains also a relevant limitation. Therefore, no firm conclusions can be drawn from this study.

Conclusions

In conclusion, although methadone has some complexities regarding its prescription, which might limit its usefulness (Merrill et al., 2005), and despite the relevant methodological limitations of the present work, we believe methadone should remain an option when considering treatment for prescription opioids dependent patients. Further larger, randomized, comparative trials are warranted.

Declaration of interest

Pablo Barrio has received honoraria from Lundbeck S.A.. The rest of authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper. No financial issues to disclose for any of the authors.

References

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision.* Washinton, DC: American Psychiatric Press.

Banta-Green, C. J., Maynard, C., Koepsell, T. D., Wells, E. A., & Donovan, D. M. (2009). Retention in methadone maintenance drug treatment for prescription-type opioid primary users compared to heroin users. *Addiction*, *104*, 775–783. doi:10.1111/j.1360-0443.2009.02538.x

Barnett, P.G., Rodgers, J.H., & Bloch, D.A. (2001). A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction*, 96,683-90. doi:10.1080/09652140020039053.

Brady, K. T., McCauley, J. L., & Back, S. E. (2015). Prescription Opioid Misuse, Abuse, and Treatment in the United States: An Update. *The American Journal of Psychiatry*, appiajp201515020262. doi:10.1176/appi.ajp.2015.15020262.

Brands, B., Blake, J., Sproule, B., Gourlay, D., & Busto, U. (2004). Prescription opioid abuse in patients presenting for methadone maintenance treatment. *Drug and Alcohol Dependence*, *73*, 199–207.

Camí, J., & Farré, M. (2003). Drug addiction. *The New England Journal of Medicine*, *349*, 975–986. doi:10.1056/NEJMra023160

Ferrari, A., Coccia, C. P. R., Bertolini, A., & Sternieri, E. (2004). Methadone–metabolism, pharmacokinetics and interactions. *Pharmacological Research: The Official Journal of the Italian Pharmacological Society*, *50*, 551–559. doi:10.1016/j.phrs.2004.05.002

International Narcotics Control Board 2014.. *Report of the International Narcotics Control Board for 2013*. Retrieved from: www.incb.org

Joseph, H., Stancliff, S., Langrod J.(2000). Methadone maintenance treatment (MMT): a review of historical and clinical issues. *Mount Sinai Journal of Medicine*, 67, 347-364.

Mancini, I., Lossignol, D. A., & Body, J. J. (2000). Opioid switch to oral methadone in cancer pain. *Current Opinion in Oncology*, *12*, 308–313.

Marsch, L.A.(1998) The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction*, 93, 515-532.

Mattick, R.P., Breen, C., Kimber, J., Davoli, M. (2014). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane database Syst Rev.* 2014; doi:10.1002/14651858.CD002207.pub4.

Merrill, J. O., Jackson, T. R., Schulman, B. A., Saxon, A. J., Awan, A., Kapitan, S., … Donovan, D. (2005). Methadone medical maintenance in primary care. An implementation evaluation. *Journal of General Internal Medicine*, *20*, 344–349. doi:10.1111/j.1525-1497.2005.04028.x

National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction,1998. Effective medical treatment of opiate addiction. *JAMA, 280*, 1936-1943.

Neumann, A. M., Blondell, R. D., Jaanimägi, U., Giambrone, A. K., Homish, G. G., Lozano, J. R., & Azadfard, M. (2013). A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *Journal of Addictive Diseases*, *32*, 68–78. doi:10.1080/10550887.2012.759872.

Potter, J. S., Dreifuss, J. A., Marino, E. N., Provost, S. E., Dodd, D. R., Rice, L. S., … Weiss, R. D. (2015). The multi-site prescription opioid addiction treatment study: 18-month outcomes. *Journal of Substance Abuse Treatment*, *48*, 62-69. doi:10.1016/j.jsat.2014.07.009

Roncero, C., Domínguez-Hernández, R., Díaz, T., Fernández, J.M., Forcada, R., Martínez, J.M., ... Oyagüez, I. (2015). Manejo de pacientes dependientes de opiáceos: comparación del coste asociado al uso de buprenorfi-

na/naloxona o metadona, y sus interacciones con tratamientos concomitantes para comorbilidades infecciosas o psiquiátricas. *Adicciones, 27*, 179-189.

Ripamonti, C., Groff, L., Brunelli, C., Polastri, D., Stavrakis, A., & De Conno, F. (1998). Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *16*, 3216–3221.

Sander, S. C. E., & Hays, L. R. (2005). Prescription opioid dependence and treatment with methadone in pregnancy. *Journal of Opioid Management*, *1*, 91–97.

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2001-2011. State Admissions to Substance Abuse Treatment Services. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013. Tennant, F. S., & Rawson, R. A. (1982). Outpatient treatment of prescription opioid dependence: comparison of two methods. *Archives of Internal Medicine*, *142*, 1845–1847.

Weiss, R. D., Potter, J. S., Griffin, M. L., Provost, S. E., Fitzmaurice, G. M., McDermott, K. A., … Carroll, K. M. (2015). Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug and Alcohol Dependence*, *150*, 112–119. doi:10.1016/j.drugalcdep.2015.02.030

Cognitive impairment induced by benzodiazepine use disorder and its reversibility: a case report

Deterioro cognitivo secundario a trastorno por uso de benzodiacepinas y su reversibilidad: a propósito de un caso

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Dear Director,

In our country, benzodiazepine use disorder (BZD) is a widespread problem. Anxiolytics and hypnotics, used for treating insomnia and anxiety, are among the most-prescribed drugs in recent years (Hollingworth & Siskind, 2010). Between 2003 and 2010, the use of these drugs in Spain has registered an increase of 34.5%, surpassing other EU countries (Vicente et al., 2013). Possibly, current society's low frustration to tolerance together with its pace of life have transformed BZDs into one of the most highly demanded drugs in Primary Care and Psychiatry consultations.

However, these medications are no panacea. Long-term efficiency is questionable and, in any case, the risk-benefit balance is poor (Baldwin, Woods, Lawson & Taylor, 2011), reasons for which international clinical guidelines do not recommend their prolonged use (NICE, 2011). In addition to the well-known risk of tolerance, abuse and dependence, we have wanted to especially focus on their cognitive effects. Long-term effects on memory continue to be debated, though many studies have observed a greater risk of dementia and/or cognitive impairment (CI) in chronic users of BZDs (Billioti de Gage et al., 2012). However, are these alterations reversible? Evidence points out that, given improvement, it is only partial (Barker, Greenwood, Jackson & Crowe, 2004).

Our study presents the case of a 48-year-old woman with a history of BZD abuse who was hospitalised in the Addictive Behaviours Unit of the Clínic Hospital in Barcelona for detoxification. At the age of 44, she was diagnosed an Adaptation Disorder and began using BZDs. Upon admission, she claimed to take 8-10 mg of clonazepam and 10-15 mg of Diazepam daily, together with 20 mg of Paroxetine, and displayed moderate, fluctuating somatic anxiety, irritability and frequent forgetfulness. Only her smoking habit is worth highlighting from her background. An MRI of her brain two years earlier due to cephalea reported a mild predominantly frontal cortical atrophy. While hospitalized, she underwent detoxification by gradually reducing clonazepam, under medical supervision, from a dose of up to 8 mg/day through to its suspension, and with pregabalin of 75 mg/day as an adjuvant, an alternative drug for detoxification treatment (Oulis & Konstantakopoulos, 2012). Paroxetine was also replaced with 15 mg/day of escitalopram. A clinical analysis suggested CD, wherefore the Neurology Department was contacted and advised Positron Emission Tomography with Fluorodeoxyglucose (FDG-PET) to exclude central metabolic alterations, without any pathological findings. Other complementary analyses (including a blood test to detect thyroid problems, serology test to identify viruses, vitamin B12 and folic acid) were normal. Upon discharge, she was referred to the Alzheimer and other Cognitive Disorders Unit. A neuropsychological evaluation revealed that her executive processes were affected and that her information processing was slightly delayed, a performance-related profile that is compatible with dysfunctional dorsolateral prefrontal areas. During follow-up, the patient's treatment included 15 mg/day of escitalo-

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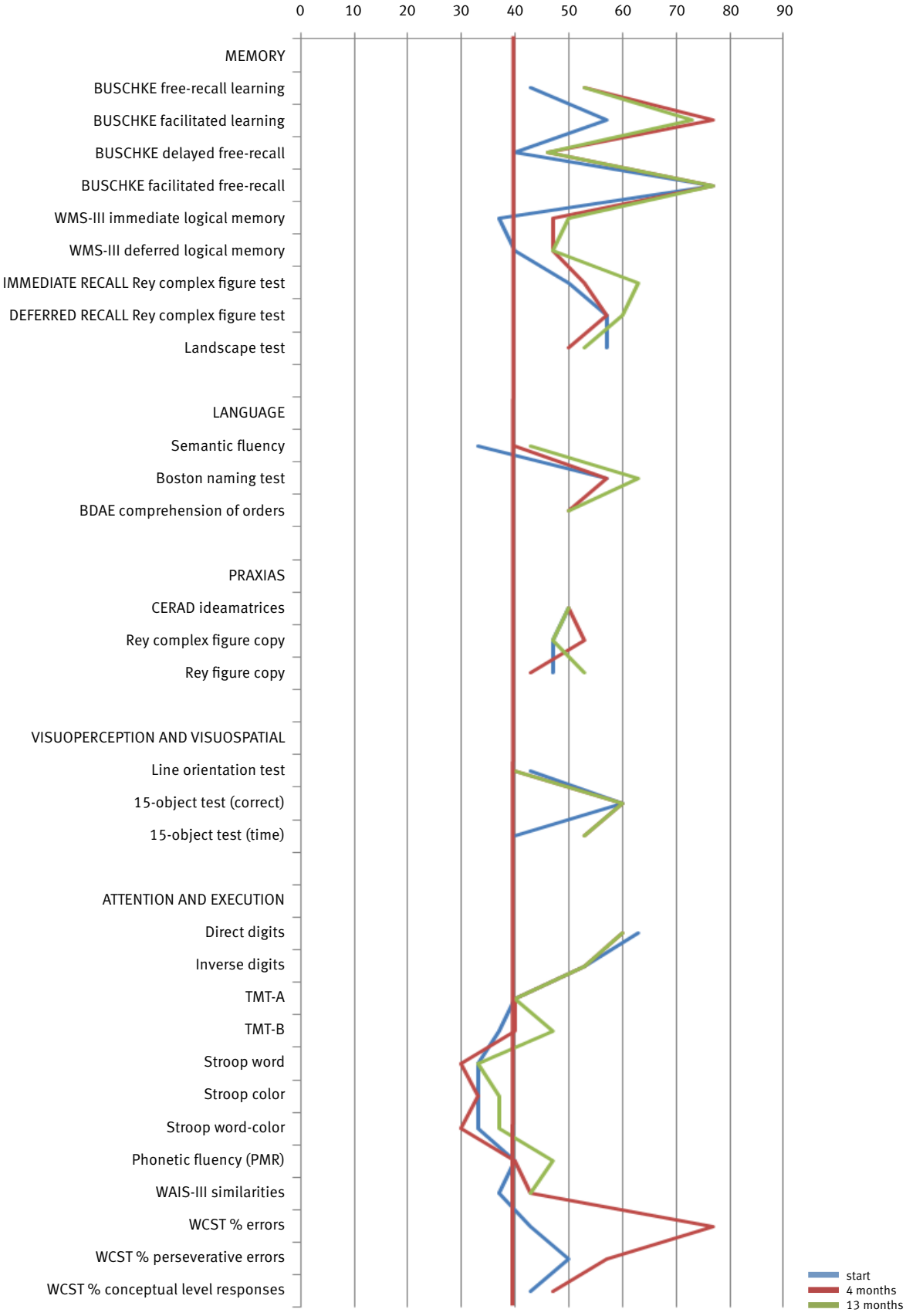

Figure 1. Comparative neuropsychological evaluation at start, 4 and 13 months after abstinence. Observed improvement in several of the different cognitive areas evaluated

pram and 50 mg/day of pregabalin. New evaluations were completed 4 and 13 months later, maintaining abstinence from BZDs (verified by weekly urine tests). Significant improvement was observed in attention and executive processes as well as in logical-verbal memory (Figure 1), an improvement that was also subjectively perceived by the patient and her family, who reported greater functionality and quality of life.

A cause-effect relationship has been suggested by the improvement in our patient's neuropsychological tests up to one year after the withdrawal of BZDs, as well as by the normality of complementary tests. An early withdrawal from chronic treatments with BZDs, especially in high-risk patients or in those with emerging signs of CD, may help to significantly improve quality of life and functionality across several areas, including basic tasks like job performance or driving a vehicle (Álvarez, González-Luque & Seguí-Gómez, 2015), as well as prevent irreversible deficits. Authors like Lader (Lader, 2012) have made their final appeal for reducing the risks related with BZDs, underlining the importance of adhering to clinical guidelines, limiting their use to 2-4 weeks for anxiety and 1-2 weeks for insomnia, informing users correctly, and using other first-line drugs, such as SSRIs or pregabalin (Hadley, Mandel & Schweizer, 2012) and, in more serious cases, opting for a harm reduction strategy, as used in other types of substance addictions. Beyond this scope, we also consider that awareness-raising of healthcare professionals, both those specialized in Mental Health as well as Primary Care, plays a very important role, as they must correctly opt for long-term management and security, as opposed to immediate alleviation of symptoms.

Conflict of interests

The authors declare the inexistence of conflicts of interest.

References

Álvarez, F. J., González-Luque, J. C. & Seguí-Gómez, M. (2015). Drogas, Trastorno por Uso de Sustancias y Conducción: La intervención de los profesionales que trabajan en adicciones. *Adicciones, 27,* 161-167.

Baldwin, D., Woods, R., Lawson, R. & Taylor, D. (2011). Efficacy of drug treatments for generalised anxiety disorder; systematic review and meta-analysis. *British Medical Journal, 342,* d1199. doi:10.1136/bmj.d1199.

Barker, M. J., Greenwood, K. M., Jackson, M. & Crowe, S. F. (2004). Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Archives of Clinical Neuropsycholy, 19,* 437-454.

Billioti de Gage, S., Bégaud, B., Bazin, F., Verdoux, H., Dartigues J. F., Pérès, K.,... Pariente, A. (2012). Benzodiazepine use and risk of dementia: prospective population based study. *British Medical Journal, 345,* e6231. doi:10.1136/bmj.e6231

Hadley, S. J., Mandel, F. S. & Schweizer, E. (2012). Switching from long-term benzodiazepine therapy to pregabalin in patients with generalized anxiety disorder: a double-blind, placebo-controlled trial. *Journal of Psychopharmacology, 26,* 461-470. doi:10.1177/0269881111405360.

Hollingworth, S. A. & Siskind, D. J. (2010). Anxiolytic, hypnotic and sedative medication use in Australia. *Pharmacoepidemiology and Drug Safety, 19,* 280-288. doi:10.1002/pds.1899.

Lader, M. (2012). Benzodiazepine harm: how can it be reduced? *British Journal of Clinical Pharmacology, 77,* 295-301. doi:10.1111/j.1365-2125.2012.04418.x

NICE. (2011). Anxiety. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. *Clinical Guideline 113.*

Oulis, P. & Konstantakopoulos, G. (2012). Efficacy and safety of pregabalin in the treatment of alcohol and benzodizepines dependence. *Expert Opinion on Investigational Drugs, 21,* 1019-1029. doi:10.1517/13543784.2012.685651.

Vicente, M. P., Sánchez, V., Macías, D., de la Fuente, C., González, D., Montero, D., & Catalá, F. (2013). Evolución del uso de medicamentos ansiolíticos en España durante el período 2000-2011. *Revista Española de Salud Pública, 87,* 247-255.

Desde el año 2012 sólo se admite la normativa APA.

Ante la preparación de un artículo de cara a su publicación se deben revisar y aplicar las normas extensas, que pueden ser consultadas en www.adicciones.es

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Papel. La revista Adicciones está impresa en papel estucado fabricado con pastas libres de cloro (TCF).

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Autoría. Es muy importante que únicamente se consideren autores aquellos que han hecho sustanciales contribuciones: 1) a la concepción y diseño, adquisición de datos, o el análisis e interpretación de datos; 2) a la redacción del artículo o a su revisión crítica; y 3) que ha dado su aprobación de la versión que se publicará. Los autores deben asegurarse de que partes significativas del material aportado no ha sido publicado con anterioridad. En caso de que puedan tener dudas sobre el cumplimiento de esta norma, deberán presentar copias de lo publicado o de lo presentado para publicación a otras revistas antes de poder ser considerado el artículo para su revisión. En caso de dudas sobre alguno de los aspectos anteriores los autores deben consultar el acuerdo de Farmington al que está adherida la revista Adicciones (Anexo 1), las normas de "Sponshorship, authorship, and accountability" del International Committee of Medical Journal Editors (www.icmje.org/sponsor.htm) o las normas de publicación de la American Psychological Association, 6ª edición (2010) (www.apastyle.org). El editor de la revista puede dirigirse a los autores del artículo para que especifiquen cual ha sido la contribución de cada uno de ellos.

Preparación de manuscritos. Los autores deben seguir exclusivamente para la presentación de sus manuscritos las Normas de Publicación de la American Psychological Association (6ª edición, 2010; http://www.apastyle.org). Las excepciones a esta regla son mínimas y dependen sólo de las diferencias que puede haber en el uso del español y del inglés. Por ejemplo, los ingleses utilizan en la bibliografía el signo '&' antes del último autor, mientras que en español dicho signo se corresponde exactamente con la 'y' (por tanto los artículos en español utilizarán solo la 'y'); otra diferencia puede ser en los títulos de los artículos, puesto que en inglés se pone en mayúscula la primera letra de muchas de las palabras, mientras que en español sólo ponemos la primera…

NO existe un límite exacto de palabras para los trabajos que se presenten. Pero deberá cuidarse mucho que toda la información que se incluya sea estrictamente la necesaria.

Es importante que los artículos sean interesantes para la comunidad científica del campo de las adicciones. Se evitarán trabajos que se refieran a realidades muy concretas –a menos que precisamente en ello resida su interés-, o que sean básicamente descriptivos –a menos, nuevamente, que se trate de algo novedoso.

Artículos originales. Serán preferentemente trabajos de investigación clínicos o experimentales sobre el campo de las drogodependencias o las adicciones. Pero también pueden ser aceptados trabajos teóricos o de otro tipo.

Informes breves. En esta sección se considerarán los trabajos de investigación que por sus características especiales (series con número reducido de observaciones, casos clínicos, trabajos de investigación con objetivos y resultados muy concretos, estudios epidemiológicos descriptivos, primeros resultados de un estudio amplio, etc.) pueden ser publicados de forma abreviada y rápida.

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Cartas al Director. Tendrán normalmente un máximo de 800 palabras, 10 referencias y una tabla o figura. Pueden consistir en una presentación breve sobre algo novedoso, una investigación original, o la contestación o matización a un artículo publicado en la revista. Cuando sea éste el caso la carta tendrá que recibirse dentro de las 6 semanas subsiguientes a la publicación del artículo en el número de la revista

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Envío electrónico. La forma más rápida y preferente de enviar artículos para su revisión editorial es a través de www.adicciones.es. Allí encontrará todas las instrucciones a seguir y la forma de adjuntar el original. Todo el seguimiento del proceso de revisión y editorial se realizará a través de la web (a través de la plataforma de RECYT). Ésta es la única forma prevista para envío de artículos (pero si tiene alguna duda puede comunicarse con secretaria@adicciones.es). Será muy útil para facilitar el proceso de revisión que en el momento del envío del artículo proporcione a través de la misma plataforma información sobre por lo menos dos posibles revisores para su artículo (nombre, institución y correo electrónico). Estos revisores deberán ser expertos en el tema y no estar ligados a la investigación que se desarrolla en el trabajo presentado. Tampoco podrán pertenecer al actual Comité de Redacción o Editorial. La revista se reserva la decisión de utilizar o no dichos revisores propuestos. El editor señalará además normalmente otros revisores. Recordar que el proceso de revisión es anónimo para los autores. Caso de que no fuese posible por alguna razón o tuviese algún problema con el envío del artículo a través de la web, le agradeceremos que se ponga en contacto con secretaria@adicciones.es o al teléfono (+34) 971727434 o a Editor de Adicciones. Rambla, 15, 2ª, 3ª. 07003 Palma de Mallorca.

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Todas las hojas deberán ir numeradas correlativamente en la parte superior derecha. Cada parte del manuscrito empezará una página en el siguiente orden:

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- Precedidos por un asterisco o los que fuesen necesarios –según el punto anterior– se indicarán el nombre/s del centro/s donde se ha realizado el trabajo o donde trabajan los autores.

Al final de la primera página (no como 'nota al pie') se colocará este texto: "Enviar correspondencia a: ...", indicando el nombre, la dirección postal, correo electrónico u otra información mediante la cual el autor elegido podrá ser contactado. Este será

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2. La *segunda hoja* del artículo incluirá un resumen del trabajo presentado, tanto en español como en inglés. Dicho resumen tendrá alrededor de 250 palabras. Siguiendo las normas de publicación internacional ya citadas, el resumen debe especificar los objetivos del estudio o investigación; la metodología fundamental utilizada; los principales resultados; y las conclusiones más importantes y/o novedosas. El resumen debe redactarse en uno o varios párrafos siguiendo las normas de publicación de la APA, sin atender a las divisiones de antecedentes, método, etc.

Después del resumen se incluirá un listado de alrededor de 5 Palabras clave en español y luego en inglés (Key words) en minúsculas y separadas por comas que, a ser posible, se adapten a las normalmente utilizadas en los índices al uso (ej., Index Medicus, Psychological Abstracts, Índice Médico Español).

3. La *tercera hoja* dará inicio al texto del artículo. Se recomienda la redacción del texto en impersonal. Conviene dividir claramente los trabajos en apartados, siguiendo, siempre que sea posible por las características del estudio, el esquema general siguiente: Introducción (no obstante la palabra introducción no se pondrá, pues se da por supuesta), Método, Resultados, Discusión, Reconocimientos, Conflicto de intereses y Referencias.

Introducción. Será breve y deberá proporcionar sólo la explicación necesaria para que el lector pueda comprender el texto que sigue a continuación. No debe contener tablas ni figuras, a menos que sean imprescindibles para la comprensión del texto. Debe incluir un último párrafo en el que se exponga de forma clara el o los objetivos del trabajo. Siempre que se pretenda publicar una observación muy infrecuente, debe precisarse en el texto el método de pesquisa bibliográfica, las palabras claves empleadas, los años de cobertura y la fecha de actualización.

Métodos. Se describirá claramente la metodología empleada (selección de la muestra, como se recogieron los datos, instrumentos de recogida de datos o de evaluación, temporalización,… Se deben identificar los métodos, instrumentos de evaluación, tratamientos, fármacos utilizados, aparatos, sistema de evaluación, pruebas estadísticas si son novedosas, métodos nuevos, etc. Debe especificarse el tipo de estudio (descriptivo, epidemiológico, experimental, ensayo clínico, etc.), sistema de asignación de los sujetos a grupos, aleatorización, etc. Cuando haya un protocolo debe citarse. Cuando los experimentos son realizados con animales o el ensayo es experimental en humanos debe especificarse explícitamente que se han seguido las normas éticas deontológicas, de investigación y que se han cumplido los convenios internacionales de experimentación animal o humana. Debe especificarse el tipo de análisis estadístico que se va a utilizar, describirlo cuando éste sea nuevo o poco conocido, e indicar el paquete estadístico que se va a utilizar. Se valorará positivamente si se ha conseguido la aprobación del estudio por algún comité ético o se podrá exigir cuando el estudio realizado lo requiera.

Resultados. Los resultados deben presentarse en una secuencia lógica en el texto, tablas y figuras. Utilice sólo aquellas tablas y figuras estrictamente necesarias, que expresen claramente los resultados del estudio. No duplique los datos en tablas y figuras. No repita en el texto todos los datos de las tablas y figuras, sólo los más importantes. Enfatice y resuma sólo las observaciones más importantes. Adicciones adopta el sistema convencional del 5% como valor para la significación estadística y no acepta tener en cuenta las tendencias para valores menores.

Los ensayos clínicos aleatorizados deben adecuarse a las guías CONSORT (www.consort-statement.org) y los estudios con diseños no experimentales a las guías TREND (www.trend-statement.org/asp/trend.asp) para la mayor claridad de los lectores y revisores del trabajo. Igualmente, se presentarán los estadísticos del tamaño del efecto.

Discusión. Enfatizará los aspectos nuevos e importantes del estudio y las conclusiones que se derivan del mismo. No repita en detalle los resultados que ha presentado en la sección anterior ni en la introducción. Destaque lo más importante y controvertido y relacionelo con otros estudios relevantes sobre el tema. No haga suposiciones si no se ven apoyadas por los datos. Cuando sea apropiado pueden incluirse recomendaciones. Indique las implicaciones de sus hallazgos y sus limitaciones (estas preferiblemente formarán un párrafo al final del artículo).

Reconocimientos. Este apartado se situará al final del texto del artículo y justo antes del apartado de Referencias. Cuando se considere necesario se citará a las personas, centros o entidades que hayan colaborado o apoyado la realización del trabajo. Pueden incluirse todas aquellas personas que hayan ayudado en la preparación del artículo, pero no con la intensidad requerida para ser considerados autores. Si el trabajo ha sido financiado se indicará la entidad financiadora.

Conflicto de intereses. Todos los artículos, editoriales, comentarios, opiniones, reseñas de libros y cartas que se publican en la revista estarán acompañados por una declaración sobre los posibles o reales conflictos de interés o una declaración de que los autores no tienen conflictos de intereses que declarar.

Referencias. Seguirán de forma estricta las normas de la American Psychological Association [American Psychological Association (2010). Publication Manual of the American Psychological Association (6th ed.). Washington, DC. http://www.apastyle.org

Tablas y figuras. Irán al final del texto, numeradas, y cada una en una página distinta, siguiendo el diseño propio de la APA.

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- Una copia del manuscrito revisado.
- Otro documento en donde se exponga de forma detallada las principales modificaciones efectuadas, así como sus propios comentarios sobre los principales aspectos de la revisión, con los que obviamente puede estar en desacuerdo.

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TREVICTA®
palmitato de paliperidona
suspensión inyectable de liberación prolongada

1. NOMBRE DEL MEDICAMENTO. TREVICTA 175 mg suspensión inyectable de liberación prolongada. TREVICTA 263 mg suspensión inyectable de liberación prolongada. TREVICTA 350 mg suspensión inyectable de liberación prolongada. TREVICTA 525 mg suspensión inyectable de liberación prolongada. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** 175 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 273 mg de palmitato de paliperidona equivalentes a 175 mg de paliperidona. 263 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 410 mg de palmitato de paliperidona equivalentes a 263 mg de paliperidona. 350 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 546 mg de palmitato de paliperidona equivalentes a 350 mg de paliperidona. 525 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 819 mg de palmitato de paliperidona equivalentes a 525 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACEUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). **4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas.** TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a TREVICTA. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de paliperidona inyectable mensual (±7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de paliperidona inyectable mensual, utilizando una dosis 3,5 veces más alta como se indica en la tabla siguiente:

Dosis de TREVICTA en pacientes tratados adecuadamente con palmitato de paliperidona inyectable mensual

Si la última dosis de palmitato de paliperidona inyectable mensual es de	TREVICTA se iniciará en la dosis siguiente
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

No se ha estudiado la dosis de TREVICTA equivalente a la dosis de 25 mg de palmitato de paliperidona inyectable mensual. Después de la dosis inicial de TREVICTA, este medicamento se administrará mediante inyección intramuscular una vez cada 3 meses (± 2 semanas, ver también la sección Dosis omitidas). Si es necesario, se puede ajustar la dosis de TREVICTA cada 3 meses en incrementos dentro del intervalo de 175 a 525 mg en función de la tolerabilidad del paciente y/o de la eficacia. Debido a la acción prolongada de TREVICTA, la respuesta del paciente al ajuste de la dosis puede no ser evidente hasta que han transcurrido varios meses (ver sección 5.2). Si el paciente sigue presentando síntomas, se le tratará conforme a la práctica clínica. *Cambio desde otros medicamentos antipsicóticos.* TREVICTA se debe usar solo después de que el paciente haya sido tratado adecuadamente con la formulación inyectable mensual de palmitato de paliperidona preferiblemente durante cuatro meses o más. *Cambio desde TREVICTA a otros medicamentos antipsicóticos.* Si se suspende la administración de TREVICTA, se deben tener en cuenta sus características de liberación prolongada. *Cambio desde TREVICTA a palmitato de paliperidona inyectable mensual.* Para cambiar desde TREVICTA a palmitato de paliperidona inyectable mensual, este se administrará en el momento en que se debe administrar la dosis siguiente de TREVICTA, dividiendo la dosis por 3,5 según se indica en la tabla siguiente. No es necesaria la dosis de inicio según se describe en la ficha técnica de palmitato de paliperidona inyectable mensual. El palmitato de paliperidona inyectable mensual se seguirá administrando una vez al mes tal como se describe en su ficha técnica.

Dosis de palmitato de paliperidona inyectable mensual en los pacientes que cambian desde TREVICTA

Si la última dosis de TREVICTA es de	Iniciar palmitato de paliperidona inyectable mensual 3 meses después en la dosis siguiente
175 mg	50 mg
263 mg	75 mg
350 mg	100 mg
525 mg	150 mg

Cambio desde TREVICTA a los comprimidos diarios de liberación prolongada de paliperidona oral. Para cambiar desde TREVICTA a los comprimidos de palmitato de paliperidona de liberación prolongada, se debe iniciar la administración diaria de los comprimidos 3 meses después de la última dosis de TREVICTA y continuar el tratamiento con los comprimidos de paliperidona de liberación prolongada según se describe en la tabla siguiente. La tabla siguiente indica las pautas recomendadas de conversión de los dosis para que los pacientes previamente estabilizados con diferentes dosis de TREVICTA obtengan una exposición a paliperidona similar con los comprimidos de paliperidona de liberación prolongada.

Dosis de los comprimidos de paliperidona de liberación prolongada para los pacientes que cambian desde TREVICTA*

	Tiempo transcurrido desde la última dosis de TREVICTA		
	de la semana 12 a 18, incluida	de la semana 19 a la 24, incluida	desde la semana 25 en adelante
Última dosis de TREVICTA (semana 0)	Dosis diaria de los comprimidos de paliperidona de liberación prolongada		
175 mg	3 mg	3 mg	3 mg
263 mg	3 mg	3 mg	6 mg
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

*Todas las dosis de los comprimidos de paliperidona de liberación prolongada diarios se debe adaptar siempre al paciente individual, teniendo en cuenta variables como los motivos del cambio, la respuesta al tratamiento previo con paliperidona, la gravedad de los síntomas psicóticos y/o la tendencia a presentar efectos adversos.

Dosis omitidas. *Margen de administración.* TREVICTA se debe inyectar una vez cada 3 meses. Para no omitir una dosis de TREVICTA se puede administrar a los pacientes la inyección hasta 2 semanas antes o después del momento en que se cumple el trimestre.

Dosis omitidas

Si se ha omitido la dosis programada y el tiempo transcurrido desde la última inyección es de	Medida
> 3 meses y medio a 4 meses	Se administrará la inyección lo antes posible y a continuación se reanudará el calendario de inyecciones trimestrales.
de 4 meses a 9 meses	Se seguirá la pauta de reanudación recomendada que se indica en la tabla siguiente.
> 9 meses	Se reanudará el tratamiento con palmitato de paliperidona inyectable mensual según se describe en la ficha técnica del producto. Se podrá reanudar la administración de TREVICTA después de que el paciente haya sido tratado adecuadamente con la formulación inyectable mensual de palmitato de paliperidona preferiblemente durante cuatro meses o más.

Pauta recomendada de reanudación del tratamiento después de 4 a 9 meses de interrupción de TREVICTA

Si la última dosis de TREVICTA fue de	Se administrarán dos dosis de palmitato de paliperidona inyectable mensual con un intervalo de una semana (en el deltoides)		A continuación se administrará TREVICTA (en el deltoides o el glúteo)
	Día 1	Día 8	1 mes después del día 8
175 mg	50 mg	50 mg	175 mg
263 mg	75 mg	75 mg	263 mg
350 mg	100 mg	100 mg	350 mg
525 mg	100 mg	100 mg	525 mg

[a] Ver también la *Información reservada para médicos y profesionales sanitarios* donde se describe la selección de la aguja para inyección en el deltoides en función del peso corporal.

Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia ni la seguridad en la población mayor de 65 años. En general, la dosis de TREVICTA recomendada en pacientes de edad avanzada con función renal normal es la misma que para los adultos más jóvenes con función renal normal. Dado que los pacientes de edad avanzada pueden presentar una reducción de la función renal, ver debajo en *Insuficiencia renal* las recomendaciones de dosificación para pacientes con insuficiencia renal. *Insuficiencia renal.* TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal (ver sección 5.2). En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se debe ajustar la dosis y se estabilizará el paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min). *Insuficiencia hepática.* No se ha estudiado el uso de TREVICTA en pacientes con insuficiencia hepática. Según la experiencia con paliperidona oral no es necesario ajustar la dosis en pacientes con insuficiencia hepática leve o moderada. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, por lo que se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y eficacia de TREVICTA en niños y adolescentes menores de 18 años. No se dispone de datos. Forma de administración. TREVICTA está indicado para administración intramuscular únicamente. No se debe administrar por ninguna otra vía. Cada inyección se administrará solo por un profesional sanitario, que administrará la dosis completa en una sola inyección. Se debe inyectar lenta y profundamente en el músculo deltoides o en el glúteo. Si aparecen molestias en el lugar de inyección, se considerará el cambio del glúteo al deltoides (y *viceversa*) en sucesivas inyecciones (ver sección 4.8). TREVICTA se debe administrar usando únicamente las agujas de pared fina que se facilitan en el envase de TREVICTA. Para la administración de TREVICTA no se utilizarán las agujas que se facilitan en el envase de la inyección mensual de palmitato de paliperidona ni otras agujas comercialmente disponibles (ver *Información reservada para médicos o profesionales sanitarios*). Se inspeccionará visualmente el contenido de la jeringa precargada para descartar la presencia de cuerpos extraños o decoloración antes de la administración. Es importante agitar enérgicamente la jeringa con la punta hacia arriba y la muñeca relajada durante al menos 15 segundos para garantizar una suspensión homogénea. TREVICTA debe ser administrado dentro de los 5 minutos siguientes a la agitación. Si transcurren más de 5 minutos antes de la inyección, agitar otra vez enérgicamente durante al menos 15 segundos para resuspender el medicamento (ver *Información reservada para médicos o profesionales*). *Administración en el deltoides.* El tamaño especificado de la aguja para administración de TREVICTA en el músculo deltoides está determinado por el peso del paciente. • En pacientes de peso ≥90 kg, se debe utilizar la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm). • En pacientes de peso <90 kg, se debe utilizar la aguja de pared fina de 22 G 1 (0,72 mm x 25,4 mm). Se debe administrar en el centro del músculo deltoides. Las inyecciones deltoideas se deben alternar entre los dos músculos deltoides. *Administración en el glúteo.* Para la administración de TREVICTA en el músculo glúteo, se utilizará la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm), sin tener en cuenta el peso corporal. La administración se debe hacer en el cuadrante superior externo del músculo glúteo. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. *Administración incompleta.* Para evitar la administración incompleta de TREVICTA, se debe agitar enérgicamente la jeringa precargada durante al menos 15 segundos en los 5 minutos que preceden a la administración para asegurar una suspensión homogénea (ver *Información reservada para médicos o profesionales sanitarios*). Sin embargo, si la dosis inyectada ha sido incompleta, la dosis restante de la jeringa no se debe reinyectar y no se debe administrar otra dosis dado la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará clínicamente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en estados psicóticos graves o de agitación aguda. No se debe utilizar TREVICTA para controlar estados psicóticos graves o de agitación aguda en los que es necesaria un control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se usa a la vez que otros medicamentos que se espera que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autónoma, alteración de la consciencia y elevación de la creatinafosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SMN, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, que se caracteriza por movimientos rítmicos involuntarios, predominantemente de la lengua y/o de la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la posibilidad de suspender la administración de todos los antipsicóticos, incluido la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Leucopenia, neutropenia y agranulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y agranulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo únicamente relevante a de leucopenia/neutropenia inducida por medicamentos se deben someter a vigilancia estrecha durante los primeros meses de tratamiento y se considerará la suspensión de TREVICTA ante el primer signo de leucopenia clínicamente relevante sin que intervengan otros factores causantes. A los pacientes con neutropenia clínicamente relevante se les monitorizará estrechamente a fin de detectar la aparición de fiebre u otros síntomas o signos de infección y, si se presentan estos síntomas, se administrará un tratamiento rápido. A los pacientes con neutropenia grave (recuento total de neutrófilos <1 x 10^9/L) se les retirará la administración de TREVICTA y se les hará un seguimiento de los niveles de glóbulos blancos hasta su recuperación. Se tendrá en cuenta la acción prolongada de TREVICTA. Reacciones de hipersensibilidad. Se pueden producir reacciones de hipersensibilidad incluso en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.8). Hiperglucemia y diabetes mellitus. Se han notificado hiperglucemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso coma diabético y cetoacidosis con el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica antipsicótica habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polidipsia, poliuria, polifagia y astenia) y los pacientes con diabetes mellitus deben ser monitorizados regularmente de un empeoramiento del control de la glucosa. Aumento de peso. Se han notificado casos de aumento significativos de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipotensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o isquemia de miocardio, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipotensión (p. ej., deshidratación e hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se ajustará la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos de pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en estos pacientes. Pacientes de edad avanzada con demencia. TREVICTA no se ha estudiado en pacientes de edad avanzada con demencia. No se recomienda la administración de TREVICTA a pacientes de edad avanzada con demencia, debido al riesgo aumentado de mortalidad global y de reacciones adversas cerebrovasculares. La experiencia obtenida con risperidona que se describe a continuación se considera aplicable también a paliperidona. *Mortalidad global.* En un metaanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como risperidona, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con risperidona, la mortalidad fue del 4% en comparación con el 3,1% de los pacientes que recibieron placebo. *Reacciones adversas cerebrovasculares.* En ensayos clínicos aleatorizados y controlados con placebo en los que pacientes con demencia recibieron tratamiento con algunos antipsicóticos atípicos como risperidona, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplica por 3 aproximadamente. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y beneficios de prescribir TREVICTA a pacientes con enfermedad de Parkinson o con demencia con cuerpos de Lewy (DCL), porque ambos grupos tienen un mayor riesgo de Síndrome Neuroléptico Maligno y una mayor sensibilidad a los antipsicóticos. Los manifestaciones de este aumento de la sensibilidad pueden incluir confusión, embotamiento, inestabilidad postural y caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Se indicará al paciente que solicite asistencia médica urgente si el priapismo no se ha resuelto en el trascurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de reducir la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescriba TREVICTA a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej., ejercicio intenso, exposición a calor extremo, tratamiento concomitante con medicamentos de actividad anticolinérgica o deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con el uso de antipsicóticos. Dado que los pacientes tratados con antipsicóticos presentan a menudo factores de riesgo añadido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transcurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto antiemético. En los estudios preclínicos con paliperidona se observó un efecto antiemético. Si se produce este efecto en los seres humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA en un vaso sanguíneo. Síndrome del iris flácido intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como TREVICTA (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir TREVICTA con medicamentos que prolongan el intervalo QT, como antiarrítmicos de la clase IA (por ejemplo, quinidina o disopiramida) y antiarrítmicos de la clase III (por ejemplo, amiodarona o sotalol), algunos antihistamínicos, antibióticos (por ejemplo, fluoroquinolonas), algunos antipsicóticos y algunos antipalúdicos (por ejemplo, mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que TREVICTA afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos metabolizados por las isoenzimas del citocromo P-450. Dado que paliperidona actúa principalmente sobre el sistema nervioso central (SNC) (ver sección 4.8), se debe usar con precaución la combinación de TREVICTA con otros medicamentos que actúan sobre el sistema nervioso central, como los ansiolíticos, la mayoría de los antipsicóticos, los hipnóticos, los opiáceos etc. o el alcohol. La paliperidona puede antagonizar el efecto de la levodopa y de otros agonistas de la dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se prescribirá la dosis mínima eficaz de cada tratamiento. Debido a su capacidad de inducir hipotensión ortostática (ver sección 4.4), es posible observar un efecto aditivo cuando se administra TREVICTA con otros medicamentos que tienen esta capacidad, como otros antipsicóticos o los antidepresivos tricíclicos. Se recomienda precaución al combinar la paliperidona con otros medicamentos que disminuyen el umbral convulsivo (por ejemplo, fenotiacinas o butirofenonas, antidepresivos tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de los comprimidos de liberación prolongada de paliperidona en el estado estacionario (12 mg una vez al día) con comprimidos de liberación prolongada de valproato sódico (de 500 mg a 2.000 mg una vez al día) no afectó a la farmacocinética en el estado estacionario del valproato. No se han llevado a cabo estudios de interacción entre TREVICTA y el litio, sin embargo, no es probable que se produzcan una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a TREVICTA. Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vitro* ni *in vivo* de que esas isoenzimas desempeñen un papel importante en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración conjunta de paliperidona oral de liberación prolongada una vez al día con carbamazepina 200 mg dos veces al día produjo una reducción de aproximadamente un 37% de los valores medios de C_{max} y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellas síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición materna a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo induso si la administración de TREVICTA es muy anterior a la lactancia. TREVICTA no se debe utilizar durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la visión, como sedación, somnolencia, síncope o visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a TREVICTA. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas al medicamento observadas con mayor frecuencia notificadas en ≥5% de los pacientes en dos ensayos clínicos controlados a doble ciego de TREVICTA, fueron aumento de peso, infección de las vías respiratorias altas, ansiedad, cefalea, insomnio y reacción en el lugar de inyección. Tabla de reacciones adversas. A continuación se recogen todas las RAM notificadas con paliperidona en función de la frecuencia estimada en los ensayos clínicos realizados con TREVICTA y con palmitato de paliperidona inyectable mensual. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1.000 a <1/100), *raras* (≥1/10.000 a <1/1.000), *muy raras* (<1/10.000) y *frecuencia no conocida* (no se puede estimar a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	Frecuencia no conocidas
Infecciones e infestaciones		infección de vías respiratorias altas, infección urinaria, gripe	neumonía, bronquitis, infección de vías respiratorias, sinusitis, cistitis, otitis, amigdalitis, anticomicosis, celulitis	infección oftálmica, acarodermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, aumento del recuento de eosinófilos	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos			hiperprolactinemia[a]	secreción inadecuada de hormona antidiurética, glucosuria	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, pérdida de peso	diabetes mellitus, hiperinsulinemia, aumento del apetito, anorexia, disminución del apetito, triglicéridos en sangre elevados, colesterol en sangre elevado	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio[a]	agitación, depresión, ansiedad	trastornos del sueño, disminución de la libido, nerviosismo, pesadillas	manía, estado de confusión, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo[a], acatisia[a], sedación/somnolencia, distonía[a], mareo, discinesias[a], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotriz, mareo postural, trastornos de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, falta de respuesta a los estímulos, pérdida del conocimiento, reducción del nivel de conciencia, convulsiones[a], trastornos del equilibrio	coma diabético, coordinación anómala, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido
Trastornos del oído y del laberinto			vértigo, acufenos, dolor de oídos		
Trastornos cardiacos		bradicardia, taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	

Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolia pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, dolor faringolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, congestión respiratoria, sibilancias	hiperventilación, neumonía por aspiración, estertores, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, odontalgia	molestias abdominales, gastroenteritis, sequedad de boca, flatulencia	pancreatitis, edema lingual, incontinencia fecal, fecaloma, disfagia, queilitis	obstrucción intestinal, íleo
Trastornos hepatobiliares		niveles elevados de transaminasas	niveles elevados de gamma-glutamiltransferasa y de enzimas hepáticas		ictericia
Trastornos de la piel y del tejido subcutáneo		erupción de la piel	urticaria, prurito, alopecia, eccema, sequedad de la piel, eritema, acné	erupción farmacológica, hiperqueratosis, caspa	angioedema, trastornos de la pigmentación, dermatitis seborreica
Trastornos osteomusculares y del tejido conjuntivo		dolor osteomuscular, dolor lumbodorsal, artralgia	valores elevados de creatinfosfoquinasa en sangre, espasmos musculares, rigidez articular, debilidad muscular, dolor cervical	hinchazón de las articulaciones	rabdomiólisis, alteraciones posturales
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales					síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea	disfunción eréctil, trastornos de la eyaculación, retrasos de la menstruación, trastornos menstruales[f], ginecomastia, galactorrea, disfunción sexual, dolor mamario	hinchazón o malestar mamario, aumento del tamaño de las mamas, flujo vaginal	priapismo
Trastornos generales y alteraciones en el lugar de administración		fiebre, astenia, fatiga, reacciones en el lugar de inyección	edema facial, edema[g], alteraciones de la marcha, dolor torácico, molestias en el pecho, malestar general, induración	hipotermia, escalofríos, aumento de la temperatura corporal, polidipsia, síndrome de abstinencia de fármacos/drogas, abscesos en el lugar de inyección, celulitis en el lugar de inyección, quistes en el lugar de inyección, hematomas en el lugar de inyección	descenso de la temperatura corporal, necrosis en el lugar de inyección, úlceras en el lugar de inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

[a]No es posible determinar la frecuencia de las reacciones adversas notificadas después de la comercialización, ya que dependen de notificaciones espontáneas. Por tanto, la frecuencia de estas reacciones adversas se define como 'no conocida'. [f]Ver el apartado 'Hiperprolactinemia' a continuación. [g]Ver el apartado 'Síntomas extrapiramidales' a continuación. **[f]Insomnio comprende:** El insomnio inicial y el insomnio medio; **Convulsiones incluye:** Convulsiones, y convulsiones del gran mal; **trastornos menstruales incluye:** Trastornos menstruales, retrasos de la menstruación, menstruación irregular, oligomenorrea; **[g]Edema incluye:** Edema generalizado, edema, edema periférico, edema puntiforme.

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica.* Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección.* En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la dosificación realizada por los investigadores, síntomas como induración, rubefacción e hinchazón no se presentaron o fueron leves en ≥95% de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP).* En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y mioclonía), distonía (incluye distonía, espasmo cervical, emprostótonos, crisis oculógiras, distonía bucomandibular, risa sardónica, tetanía, hipertonía, torticolis, contracciones musculares involuntarias, contractura muscular, blefaroespasmo, oculogiración, parálisis lingual, espasmo facial, faringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurototonos, espasmo lingual y trismus) y temblor. *Aumento de peso.* En el estudio a largo plazo de retirada aleatorizada, se notificaron aumentos anormales de ≥7% de peso corporal desde el momento inicial hasta el momento final del estudio, analizados a doble ciego, en el 10% de los pacientes del grupo de TREVICTA y el 1% de los pacientes del grupo de placebo. A la inversa, se notificaron reducciones anormales del peso corporal (≥7%) desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, en el 1% de los pacientes del grupo de TREVICTA y el 8% de los pacientes del grupo de placebo. Las variaciones medias del peso corporal desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, fueron de +0,94 kg y -1,28 kg en los grupos de TREVICTA y placebo, respectivamente. *Hiperprolactinemia.* Durante la fase de doble ciego del estudio a largo plazo de retirada aleatorizada, se observaron niveles de prolactina por encima del intervalo de referencia (>13,13 ng/ml en los varones y >26,72 ng/ml en las mujeres) en un porcentaje más elevado de varones y mujeres del grupo de TREVICTA que del grupo placebo (9% frente a 3% y 5% frente a 1%, respectivamente). En el grupo de TREVICTA, la variación media entre el momento inicial y el final en un estudio doble ciego controlado con placebo fue de +2,90 ng/ml para los varones (frente a -10,26 ng/ml en el grupo placebo) y de +7,48 ng/ml para las mujeres (frente a -32,93 ng/ml en el grupo placebo). Una mujer (2,4%) del grupo de TREVICTA tuvo una reacción adversa de amenorrea, mientras que no se observaron reacciones adversas potencialmente relacionadas con la prolactina en ninguna mujer del grupo placebo. No hubo reacciones adversas potencialmente relacionadas con la prolactina en ninguno de los grupos de varones. Efecto de clase. Con el uso de antipsicóticos pueden aparecer prolongación del intervalo QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicada, paro cardiaco y Torsades de pointes. Se han notificado casos de TEV, entre ellos de embolia pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos. Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del QT y síntomas extrapiramidales. Se han descrito Torsades de pointes y fibrilación ventricular en un paciente expuesto a sobredosis de paliperidona oral. En caso de sobredosis aguda se debe tener en cuenta la posibilidad de que estén implicados varios fármacos. Tratamiento. Al evaluar las medidas terapéuticas y de recuperación, se tendrán en cuenta la naturaleza de liberación prolongada del medicamento, así como la prolongada vida media de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio se deben tratar con las medidas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales graves, se debe administrar medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos y continuos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros fármacos antipsicóticos, código ATC: N05AX13. TREVICTA contiene una mezcla racémica de paliperidona (+) y (–). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une estrechamente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D-2. Asimismo, paliperidona bloquea los receptores alfa 1adrenérgicos y, en menor medida, los receptores histaminérgicos H-1 y los receptores alfa 2 adrenérgicos. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque se trata de un potente antagonista de D2, motivo por el que se cree que alivia los síntomas de la esquizofrenia, produce menos catalepsia y menos reducción de las funciones motoras que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. La eficacia de TREVICTA para el tratamiento de mantenimiento de la esquizofrenia en pacientes que han sido tratados adecuadamente durante al menos 4 meses con la formulación inyectable mensual de palmitato de paliperidona y las últimas dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retirada aleatorizada, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizada, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual administradas en el músculo deltoides o glúteo (50-150 mg) durante 17 semanas (los ajustes de dosis fueron en las semanas 5 y 9). Un total de 379 pacientes recibieron una dosis única de TREVICTA en el músculo deltoides o glúteo durante la fase de estabilización abierta (la dosis era 3,5 veces la última dosis de palmitato de paliperidona mensual). Los pacientes que se consideraban clínicamente estabilizados al final de la fase de estabilización de 12 semanas se aleatorizaron en proporción 1:1 para recibir TREVICTA o un placebo en una fase doble ciego de duración variable (la dosis de TREVICTA fue la misma que la última dosis recibida durante la fase de estabilización; esta dosis se mantuvo fija durante toda la fase de doble ciego). En este periodo, 305 pacientes sintomáticamente estables fueron aleatorizados para continuar el tratamiento con TREVICTA (n=160) o placebo (n=145) hasta que se produjese la recaída, la retirada prematura o el final del estudio. La variable principal de eficacia fue el tiempo hasta la primera recaída. Se pusa fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 283 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICTA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,81 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICTA en comparación con placebo. En la figura 1 se representa la gráfica de Kaplan Meier del tiempo hasta la recaída para cada grupo de tratamiento. Se observó una diferencia significativa (p<0,0001) entre los dos grupos de tratamiento en el tiempo hasta la recaída a favor de TREVICTA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICTA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

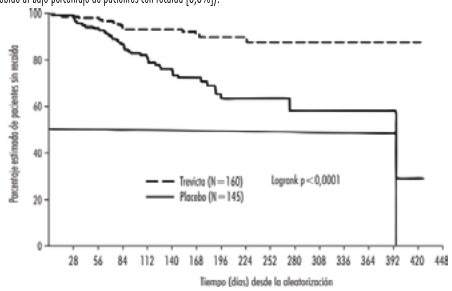


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída – Análisis final

En el estudio de no inferioridad, 1.429 pacientes con enfermedad aguda (puntuación PANSS total media en el momento inicial: 85,7) que cumplían los criterios DSM-IV de esquizofrenia se incorporaron a la fase abierta y recibieron tratamiento con palmitato de paliperidona inyectable mensual durante 17 semanas. Se permitía ajustar la dosis (esto es, 50 mg, 75 mg, 100 mg o 150 mg) después de 5 semanas y 9 inyecciones y el lugar de inyección podía ser el deltoides o el glúteo. De los pacientes que cumplían los criterios de aleatorización en las semanas 14 y 17, 1.016 fueron aleatorizados en proporción 1:1 para seguir recibiendo una vez al mes la inyección de palmitato de paliperidona mensual o bien cambiar a TREVICTA, multiplicando por 3,5 la dosis de las semanas 9 y 13 de palmitato de paliperidona inyectable mensual, durante un periodo de 48 semanas. Los pacientes recibieron TREVICTA una vez cada 3 meses y una medicación inyectable placebo durante los meses restantes para mantener el ciego. En este estudio, el criterio de valoración de la eficacia principal era el porcentaje de pacientes sin recaída al final de la fase doble ciego de 48 semanas, basado en la estimación de Kaplan-Meier de las 48 semanas (TREVICTA: 91,2% palmitato de paliperidona inyectable mensual: 90,0%). No fue posible calcular la mediana de tiempo hasta la recaída en ninguno de los grupos, dado el escaso porcentaje de pacientes con recaídas. La diferencia (IC 95%) entre los grupos de tratamiento fue del 1,2% (-2,7%; 5,1%), lo que satisface el criterio de no inferioridad basado en un margen de -10%. Por tanto, el grupo de tratamiento con TREVICTA fue no inferior al grupo tratado con palmitato de paliperidona inyectable mensual. Las mejorías funcionales, determinadas según la Escala de Funcionamiento Personal y Social (PSP), que se observaron durante la fase de estabilización abierta se mantuvieron durante la fase de doble ciego en ambos de tratamiento.

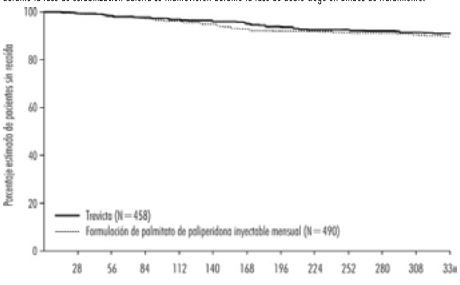


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{ss}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos *in vivo* de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. Estudios *in vitro* han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos *in vivo* y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona. TREVICTA está diseñado para liberar paliperidona durante un periodo de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (ClCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (ClCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (ClCl=10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{∞}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con personas sanas. Población de edad avanzada. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con la edad. Índice de masa corporal (IMC)/peso corporal. En los pacientes obesos y con sobrepeso se observaron valores de C_{max} más bajos. En el estado estacionario aparente de TREVICTA, las concentraciones valle eran similares en los pacientes normales, con sobrepeso y obesos. Raza. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el origen racial. Sexo. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el sexo. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no tiene un efecto en la farmacocinética de paliperidona. El efecto del consumo de tabaco sobre la farmacocinética de paliperidona no se ha estudiado en el caso de TREVICTA. Un análisis de farmacocinética poblacional basado en los datos obtenidos con comprimidos de liberación prolongada de paliperidona demostró una exposición a paliperidona ligeramente más baja en los fumadores que en los no fumadores. No es probable que esta diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) en inyección intramuscular y de paliperidona en administración oral a ratas y perros mostraron efectos fundamentalmente farmacológicos, como sedación y efectos mediados por la prolactina en glándulas mamarias y genitales. En animales tratados con palmitato de paliperidona se observó una reacción inflamatoria en el lugar de inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas con risperidona oral, que se convierte en gran medida en paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y en la supervivencia de las crías. No se han observado embriotoxicidad ni malformaciones después de la administración intramuscular de palmitato de paliperidona a ratas gestantes a dosis máximas (160 mg/kg/día), equivalentes a 2,2 veces el nivel de exposición de los humanos a la dosis máxima recomendada de 525 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la motricidad y del aprendizaje en las crías cuando se administraron a animales gestantes. Ni el palmitato de paliperidona ni la paliperidona han demostrado ser genotóxicos. En estudios sobre el potencial carcinogénico de la risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y de los adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico del palmitato de paliperidona administrado en inyección intramuscular a ratas. Se observó un incremento estadísticamente significativo de adenocarcinomas de las glándulas mamarias en ratas hembra a las que se administraron dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho experimentaron un incremento estadísticamente significativo de adenomas y carcinomas de las glándulas mamarias cuando se expusieron a dosis de 30 y 60 mg/kg/mes, que representan 0,6 y 1,2 veces el nivel de exposición humana a la dosis máxima recomendada de 525 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la relevancia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina cíclica) con émbolo, tope trasero y capuchón protector (goma bromobutílica), equipada con una aguja de seguridad de pared fina de 22 G 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 pulgadas (0,72 mm x 25,4 mm). Tamaño del envase: Envases con 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 515,00 €; PVP: 570,91 €; PVP (IVA): 593,75 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 670,00 €; PVP: 725,91 €; PVP (IVA): 754,95 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 824,00 €; PVP: 879,91 €; PVP (IVA): 915,11 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.236,00 €; PVP: 1.291,91 €; PVP (IVA): 1.343,59 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver *Información reservada para médicos o profesionales sanitarios*). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007. EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 5 de diciembre de 2014. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2016. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

1. NOMBRE DEL MEDICAMENTO. Xeplion 25 mg suspensión inyectable de liberación prolongada. Xeplion 50 mg suspensión inyectable de liberación prolongada. Xeplion 75 mg suspensión inyectable de liberación prolongada. Xeplion 100 mg suspensión inyectable de liberación prolongada. Xeplion 150 mg suspensión inyectable de liberación prolongada. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** 25 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 39 mg de palmitato de paliperidona equivalentes a 25 mg de paliperidona. 50 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 78 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. 75 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 117 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. 100 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 156 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. 150 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 234 mg de palmitato de paliperidona equivalentes a 150 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). **4. DATOS CLÍNICOS. 4.1. Indicaciones terapéuticas.** Xeplion está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos estabilizados con paliperidona o risperidona. En determinadas pacientes adultos con esquizofrenia y respuesta previa a paliperidona o risperidona oral, Xeplion puede ser utilizado sin necesidad de estabilización previa con tratamiento oral si los síntomas psicóticos son leves o moderados y es necesario un tratamiento con un inyectable de acción prolongada. **4.2. Posología y forma de administración.** Posología. Se recomienda iniciar Xeplion con una dosis de 150 mg en el día 1 de tratamiento y 100 mg una semana después (día 8), ambos administrados en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). La tercera dosis se debe administrar un mes después de la segunda dosis de inicio. La dosis de mantenimiento mensual recomendada es de 75 mg; algunos pacientes pueden beneficiarse de dosis inferiores o superiores dentro del rango recomendado de 25 a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. Los pacientes con sobrepeso u obesos pueden requerir dosis situadas en la parte superior del intervalo (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. El ajuste de la dosis de mantenimiento se puede hacer mensualmente. Al realizar ajustes de la dosis, se deben tener en cuenta las características de liberación prolongada de Xeplion (ver sección 5.2), dado que el pleno efecto de las dosis de mantenimiento puede no resultar evidente durante varios meses. *Cambio desde pacientes con tratamiento previo con risperidona oral a Xeplion.* El tratamiento recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con Xeplion. Algunos pacientes se pueden beneficiar de una retirada gradual. Xeplion debe iniciarse según se describe al principio de la sección 4.2 anterior. *Cambio desde inyectables mensuales de acción prolongada a Xeplion.* Al realizar el cambio de tratamiento de los pacientes desde risperidona inyectable de acción prolongada, inicie el tratamiento con Xeplion en lugar de la siguiente inyección programada. A partir de entonces, Xeplion se debe continuar en intervalos mensuales. No es necesario seguir el régimen de dosificación inicial de una semana incluyendo las inyecciones intramusculares (día 1 y 8, respectivamente) según se describe en la sección 4.2 anterior. Los pacientes previamente estabilizados con diferentes dosis de risperidona inyectable de acción prolongada pueden alcanzar una exposición similar a paliperidona en estado estacionario durante el tratamiento de mantenimiento con dosis mensuales de Xeplion según se describe a continuación:

Dosis de risperidona inyectable de acción prolongada y Xeplion necesaria para alcanzar una exposición a paliperidona similar en estado estacionario

Dosis previa de risperidona inyectable de acción prolongada	Inyección de Xeplion
25 mg cada 2 semanas	50 mg mensualmente
37,5 mg cada 2 semanas	75 mg mensualmente
50 mg cada 2 semanas	100 mg mensualmente

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). Dosis omitidas. *Dosis para cualquier intervalo de ajuste.* Se recomienda que la segunda dosis de iniciación de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y las siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8 ± 4 días), el momento de reinicio recomendado depende del tiempo que haya transcurrido desde la primera inyección del paciente. *Omisión de la segunda dosis de inicio (>4 semanas desde la primera inyección).* Si han transcurrido menos de 4 semanas desde la primera inyección, se le debe administrar al paciente la segunda inyección de 100 mg en el músculo deltoides tan pronto como sea posible. Se debe administrar una tercera inyección de Xeplion de 75 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de inicio (> 4 y ≤ 7 semanas desde la primera inyección).* Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xeplion, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de inicio (> 7 semanas desde la primera inyección).* Si han transcurrido más de 7 semanas desde la primera inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. *Omisión de la dosis de mantenimiento mensual (1 mes o 4 semanas).* Tras la iniciación, el ciclo de inyección recomendado de Xeplion es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. *Omisión de la dosis de mantenimiento mensual (>6 semanas o 6 meses).* Si han transcurrido más de 6 semanas desde la última inyección de Xeplion, la recomendación es la siguiente: *Para pacientes estabilizados con dosis de 25 o 100 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para pacientes estabilizados con dosis de 150 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (>6 meses).* Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. *Pacientes de edad avanzada.* No se ha establecido la eficacia y la seguridad en la población de edad avanzada >65 años. En general, la dosis recomendada de Xeplion en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (ver *Insuficiencia renal* más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). *Insuficiencia renal.* No se ha estudiado Xeplion sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se recomienda iniciar Xeplion con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver sección 4.4). *Insuficiencia hepática.* Basándose en la experiencia con paliperidona oral, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y la eficacia de Xeplion en niños y adolescentes <18 años de edad. No hay datos disponibles. Forma de administración. Xeplion se utiliza únicamente para uso intramuscular. No se debe administrar por ninguna otra vía. Se debe inyectar lentamente, profundamente en el músculo deltoides o en el glúteo. Cada inyección debe ser administrada por un profesional sanitario. La administración debe realizarse en una sola inyección. La dosis no se debe administrar en inyecciones divididas. Las dosis de iniciación del día 1 y del día 8 se deben administrar ambas en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. Se debe cambiar del glúteo al deltoides (y viceversa) en caso de dolor en el lugar de inyección si no se tolera bien el malestar en el lugar de inyección (ver sección 4.8). También se recomienda alternar entre los lados izquierdo y derecho (ver más adelante). Para consultar las instrucciones de uso y manipulación de Xeplion, ver prospecto (información destinada únicamente a médicos o profesionales del sector sanitario). *Administración en el músculo deltoides.* El tamaño de la aguja recomendado para la administración inicial y de mantenimiento de Xeplion en el músculo deltoides viene determinado por el peso del paciente. En los pacientes ≥90 kg, se recomienda la aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). En los pacientes <90 kg, se recomienda la aguja de calibre 23 de 1 pulgada (25,4 mm x 0,64 mm). Las inyecciones en el deltoides se deben alternar entre los dos músculos deltoides. *Administración en el músculo glúteo.* El tamaño de la aguja recomendado para la administración de mantenimiento de Xeplion en el músculo glúteo es el de una aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). La administración se debe realizar en el cuadrante superior externo de la zona glútea. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en pacientes que se encuentran en un estado sumamente agitado o psicótico grave. Xeplion no se debe utilizar para el tratamiento de estados agitados agudos o psicóticos graves cuando esté justificado el control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al recetar paliperidona a pacientes con enfermedad cardiovascular conocida o antecedentes familiares de prolongación del intervalo QT, y en caso de uso concomitante con otros medicamentos que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos del Síndrome Neuroléptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la consciencia y elevación de los niveles séricos de creatina fosfocinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiólisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de paliperidona. Discinesia tardía. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos $<1x10^9$/L) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia poscomercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona o oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente que incluye coma diabético y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con Xeplion se les deben monitorizar los síntomas de la hiperglucemia (tales como polidipsia, poliuria, polifagia y debilidad) y a los pacientes con diabetes mellitus se les debe monitorizar regularmente el empeoramiento del control de glucosa. Aumento de peso. Se ha notificado un aumento de peso significativo con el uso de Xeplion. El peso debe controlarse regularmente. Uso en pacientes con tumores dependientes de prolactina. Los estudios de cultivo de tejidos sugieren que la prolactina puede estimular el crecimiento de células en los tumores de mama humanos. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona se debe utilizar con precaución en pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes sobre la base de su actividad alfa-bloqueante. Según los datos agrupados de los tres ensayos controlados con placebo, de dosis fijas y 6 semanas de duración con comprimidos orales de paliperidona de liberación prolongada (3, 6, 9 y 12 mg), el 2,5% de los pacientes tratados con paliperidona oral comunicaron hipotensión ortostática, en comparación con el 0,8% de los sujetos tratados con placebo. Xeplion debe utilizarse con precaución en pacientes con enfermedad cardiovascular conocida (p. ej., insuficiencia cardiaca, infarto de miocardio o isquemia, trastornos de la conducción), enfermedad cerebrovascular o afecciones que predispongan al paciente a la hipotensión (p. ej. deshidratación e hipovolemia). Convulsiones. Xeplion debe utilizarse con precaución en pacientes con antecedentes de convulsiones u otros trastornos que potencialmente puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona aumentan en pacientes con insuficiencia renal y por tanto, se recomienda un ajuste de la dosis en pacientes con insuficiencia renal leve. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos en pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en dichos pacientes. Pacientes de edad avanzada con demencia. No se ha estudiado Xeplion en pacientes de edad avanzada con demencia. Xeplion se debe utilizar con precaución en pacientes de edad avanzada con demencia y con factores de riesgo de padecer ictus. La experiencia con risperidona citada más adelante se considera válida también para paliperidona. *Mortalidad global.* En un metanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, tales como risperidona, aripiprazol, olanzapina y quetiapina, tenían un mayor riesgo de mortalidad en comparación con placebo. Entre los pacientes tratados con risperidona, la mortalidad fue del 4% frente al 3,1% con placebo. *Reacciones adversas cerebrovasculares.* Se ha observado un aumento de aproximadamente 3 veces del riesgo de reacciones adversas cerebrovasculares en los ensayos clínicos aleatorizados controlados con placebo en la población con demencia al utilizar algunos antipsicóticos atípicos, tales como risperidona, aripiprazol y olanzapina. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y los beneficios de prescribir Xeplion a los pacientes con enfermedad de Parkinson o Demencia con Cuerpos de Lewy (DCL), ya que ambos grupos pueden tener mayor riesgo de padecer Síndrome Neuroléptico Maligno, así como tener una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, obnubilación, inestabilidad postural con caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (incluida risperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Durante la vigilancia post-comercialización, también se han notificado casos de priapismo con paliperidona oral, que es el metabolito activo de risperidona. Se ha de informar a los pacientes de la necesidad de acudir al médico urgentemente en caso de que el priapismo no haya sido resuelto en el transcurso de 4 horas. Regulación de la temperatura del organismo. Se ha atribuido a los medicamentos antipsicóticos la interrupción de la capacidad del organismo para reducir la temperatura corporal central. Se aconseja proceder con especial cautela cuando se prescriba Xeplion a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej. ejercicio físico intenso, exposición a calor extremo, que reciban medicamentos concomitantes con actividad anticolinérgica o que estén sujetos a deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con medicamentos antipsicóticos. Dado que los pacientes tratados con antipsicóticos suelen presentar factores de riesgo adquiridos de TEV, se han de identificar todos los posibles factores de riesgo de TEV antes y durante el tratamiento con Xeplion y adoptar medidas preventivas. Efecto antiemético. Se observó un efecto antiemético en los estudios precínicos con paliperidona. Este efecto, si se produce en humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de enfermedades como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de Xeplion en un vaso sanguíneo. Síndrome del Iris Flácido Intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como Xeplion (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir Xeplion con medicamentos que prolonguen el intervalo QT, p. ej. antiarrítmicos de clase IA (p. ej., quinidina, disopiramida) y antiarrítmicos de clase III (p. ej. amiodarona, sotalol), algunos antihistamínicos, algunos otros antipsicóticos y algunos antipalúdicos (p. ej. mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que Xeplion afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos que sean metabolizados por las isoenzimas del citocromo P-450. Dado que los efectos principales de paliperidona se ejercen sobre el sistema nervioso central (SNC) (ver sección 4.8), Xeplion debe utilizarse con precaución en combinación con otros medicamentos de acción central, p. ej., ansiolíticos, la mayoría de los antipsicóticos, hipnóticos, opiáceos, etc. o con el alcohol. Paliperidona puede antagonizar el efecto de levodopa y otros agonistas de dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se debe recetar la dosis mínima eficaz de cada tratamiento. Debido a la posibilidad de que induzca hipotensión ortostática (ver sección 4.4), se puede observar un efecto aditivo si se administra Xeplion con otros tratamientos que también tengan esta posibilidad, p.ej., otros antipsicóticos, tricíclicos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenotiazinas o butirofenonas, tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de comprimidos orales de paliperidona de liberación prolongada en estado estacionario (12 mg una vez al día) con comprimidos de divalproex sódico de liberación prolongada (de 500 mg a 2000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xeplion y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a Xeplion. Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vivo* ni *in vitro* de que esas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{max} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad del principio activo inalterado excretado en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP o en la biodisponibilidad de paliperidona. Con dosis más altas de carbamazepina, podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al inicio del tratamiento con carbamazepina, se debe reevaluar y aumentar la dosis de Xeplion, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xeplion, si es necesario. La administración concomitante de una sola dosis de un comprimido de paliperidona oral de liberación prolongada de 12 mg con comprimidos de divalproex sódico de liberación prolongada (dos comprimidos de 500 mg una vez al día) tuvo como resultado un aumento de aproximadamente el 50% en la C_{max} y el AUC de paliperidona, probablemente como resultado de un aumento de la absorción oral. Dado que no se observó ningún efecto sobre el aclaramiento sistémico, no se espera que se produzca una interacción clínicamente significativa entre los comprimidos de divalproex sódico de liberación prolongada y la inyección intramuscular de Xeplion. Esta interacción no se ha estudiado con Xeplion. Uso concomitante de Xeplion y risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando Xeplion sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a paliperidona durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xeplion no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estas, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10); *frecuentes* (≥1/100 a <1/10); *poco frecuentes* (≥1/1.000 a <1/100); *raras* (≥1/10.000 a <1/1.000); *muy raras* (<1/10.000); y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	No conocidas[a]
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, cistitis, infección de oídos, amigdalitis, onicomicosis, celulitis	infección de ojos, acarodermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, recuento de eosinófilos aumentad	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia[b]		secreción inapropiada de la hormona antidiurética, presencia de glucosa en orina	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, disminución de peso, apetito disminuido	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, aumento de los triglicéridos en sangre, aumento del colesterol en sangre	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnia[a]	agitación, depresión, ansiedad	trastorno del sueño, manía, disminución de la líbido, nerviosismo, pesadillas	estado confusional, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo[c], acatisia[c], sedación/somnolencia, distonia[c], mareos, discinesia[c], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotora, mareo postural, alteración de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, sin respuesta a estímulos, pérdida de la consciencia, disminución del nivel de consciencia, convulsión[c], trastorno del equilibrio, coordinación anormal	coma diabético, temblor cefálico en reposo
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma, trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		
Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastorno de conducción, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringeolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, disfagia, sequedad de boca, flatulencia	pancreatitis, hinchazón de la lengua, incontinencia fecal, fecaloma, queilitis	obstrucción del intestino, íleo
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas		ictericia

Trastornos de la piel y del tejido subcutáneo			urticaria, prurito, erupción cutánea, alopecia, eccema, sequedad de la piel, eritema, acné	erupción debida al medicamento, hiperqueratosis, caspa		angioedema, decoloración de la piel, dermatitis seborreica
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda, artralgia	aumento de la creatina fosfoquinasa en sangre, espasmos musculares, rigidez en las articulaciones, debilidad muscular, dolor de cuello	rabdomiólisis, inflamación de las articulaciones		anomalía postural
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria		
Embarazo, puerperio y enfermedades perinatales						síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea, galactorrea	disfunción eréctil, trastorno de la eyaculación, trastornos menstruales[c], ginecomastia, disfunción sexual, dolor de mamas	malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción vaginal		priapismo
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[a], aumento de la temperatura corporal, alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, escalofríos, sed, síndrome de abstinencia a medicamentos, absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección, hematoma en el lugar de la inyección		disminución de la temperatura corporal, necrosis en el lugar de la inyección, úlcera en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas			

[a]La frecuencia de estas reacciones adversas se clasifica como "no conocidas" porque no fueron observadas en los ensayos clínicos con palmitato de paliperidona. Proceden de notificaciones espontáneas poscomercialización y la frecuencia no se puede determinar, a proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral. [b]Referido a "Hiperprolactinemia" a continuación. [c]Referido a "Síntomas extrapiramidales" a continuación. [d]En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con Xeplion comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,65% en todos los pacientes tratados con palmitato de paliperidona. **[e]Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** retraso en la menstruación, menstruación irregular, oligomenorrea.

Reacciones adversas notificadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de risperidona, por lo tanto, los perfiles de las reacciones adversas de estos compuestos (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. Descripción de algunas reacciones adversas. Síntomas extrapiramidales: Durante la experiencia post comercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de Xeplion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). Reacción en el lugar de la inyección. La reacción adversa relacionada con el lugar de la inyección notificada con mayor frecuencia fue el dolor. La mayoría de estas reacciones se notificaron con gravedad de leve a moderada. Las evaluaciones del dolor en el sitio de la inyección en los sujetos, basada en una escala analógica visual, indican que el dolor tiende a disminuir en frecuencia e intensidad con el tiempo en todos los estudios de fase 2 y 3 con Xeplion. Las inyecciones en el músculo deltoides se perciben como un poco más dolorosas que las correspondientes inyecciones en el glúteo. Otras reacciones en el lugar de la inyección fueron en su mayoría de intensidad leve e incluyeron induración (frecuente), prurito (poca frecuente) y nódulos (raro). Síntomas extrapiramidales (SEP): SEP incluye un análisis agrupado de los siguientes términos: parkinsonismo (incluye hipersecreción salival, rigidez musculoesquelética, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tensión muscular, acinesia, rigidez de la nuca, rigidez muscular, modo de andar parkinsoniano y reflejo de la glabella anormal, temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreatetosis, atetosis y mioclonía), distonía (incluye distonía, hipertonía, torticolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo orofaríngeo, pleurotótonos, espasmo lingual y trismo) y temblor. Hay que destacar que se incluye un espectro más amplio de síntomas que no tienen forzosamente su origen en el trastorno extrapiramidal. Aumento de peso: En el estudio de 13 semanas de duración que incluyó un régimen de dosificación inicial de 150 mg, la proporción de sujetos con un aumento anormal de peso ≥7% mostró una tendencia relacionada con la dosis, con una tasa de incidencia del 5% en el grupo placebo, en comparación con tasas del 6%, 8%, y 13% en los grupos tratados con 25 mg, 100 mg y 150 mg de Xeplion, respectivamente. Durante el periodo abierto de transición/mantenimiento de 33 semanas de duración del ensayo de prevención de recidivas a largo plazo, el 12% de los pacientes tratados con Xeplion cumplieron este criterio (aumento de peso de ≥7% desde la fase doble ciego hasta el final del estudio); la media (DE) del cambio de peso desde el nivel basal del periodo abierto fue de +0,7 (4,79) kg. Hiperprolactinemia: En ensayos clínicos, se observaron medianas de aumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un aumento de los niveles de prolactina (p. ej., amenorrea, galactorrea, alteraciones de la menstruación, ginecomastia) se notificaron en <1% de los sujetos. Efectos de clase. Con antipsicóticos puede aparecer prolongación del QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicable, parada cardíaca y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, incluidos casos de embolismo pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del intervalo QT y síntomas extrapiramidales. Se han notificado Torsades de pointes y fibrilación ventricular en un paciente en relación con la sobredosis de paliperidona oral. En caso de sobredosis aguda, se debe tener en cuenta la posibilidad de que estén implicados varios medicamentos. Administración: Al evaluar el tratamiento necesario y la recuperación hay que tener en cuenta la naturaleza de liberación prolongada del medicamento y la prolongada vida media de eliminación de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio deben tratarse con las medidas terapéuticas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales intensos, se administrará medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros antipsicóticos. Código ATC: N05AX13. Xeplion contiene una mezcla racémica de paliperidona (+) y (-). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D2. Paliperidona también bloquea los receptores adrenérgicos alfa1 y bloquea, en menor medida, los receptores histaminérgicos H1 y los adrenérgicos alfa2. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D2 potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos catalepsia y reduce las funciones motrices en menor medida que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. Tratamiento agudo de la esquizofrenia: La eficacia de Xeplion en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Las dosis fijas de Xeplion en estos estudios se administraron en los días 1, 8, y 36 en el estudio de 9 semanas de duración, y, además, el día 64 en los estudios de 13 semanas de duración. No fue necesario administrar suplementos antipsicóticos orales adicionales durante el tratamiento agudo de la esquizofrenia con Xeplion. El criterio principal de eficacia del estudio se definió como una reducción de las puntuaciones totales de la Escala de los Síndromes Positivo y Negativo (PANSS), como se muestra en la siguiente tabla. La PANSS es un inventario multi-elemento validado compuesto por cinco factores destinados a evaluar los síntomas positivos, los síntomas negativos, el pensamiento desorganizado, la hostilidad/excitación incontrolada y la ansiedad/depresión. La función se evaluó mediante la escala de Funcionamiento Personal y Social (PSP). La PSP es una escala homologada que mide la capacidad del paciente para desempeñar sus actividades personales y sociales en cuatro áreas del comportamiento: las actividades socialmente útiles (incluidos el trabajo y el estudio), las relaciones personales y sociales, el cuidado personal y los comportamientos disruptivos y agresivos. En un estudio de 13 semanas de duración (n=636) que comparó tres dosis fijas de Xeplion (inyección inicial en el deltoides de 150 mg seguida por tres dosis en el glúteo o en el deltoides de cualquiera de 25 mg/4 semanas, 100 mg/4 semanas o 150 mg/4 semanas) con placebo, las tres dosis de Xeplion fueron superiores a placebo en términos de la mejoría de la puntuación total de la PANSS. En este estudio, tanto los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntuación de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de Xeplion en el día 8. Los resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de Xeplion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

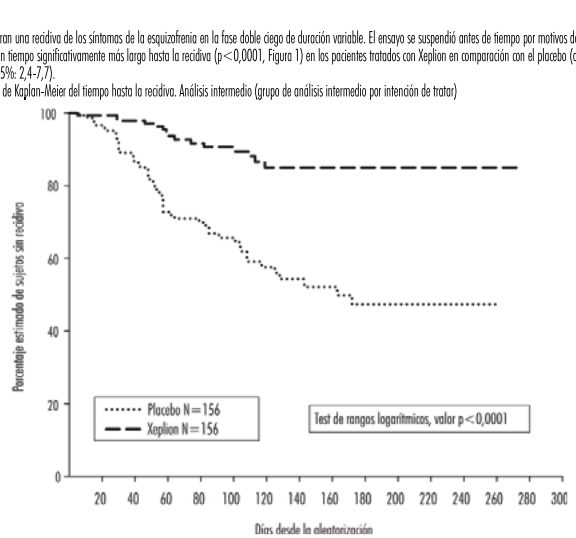
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración de la eficacia

	Placebo	25 mg	50 mg	100 mg	150 mg
R092670-PSY-3007*	n=160	n=155		n=161	n=160
Media basal (DE)	86,8 (10,31)	86,9 (11,99)	--	86,2 (10,77)	88,4 (11,70)
Variación media (DE)	-2,9 (19,26)	-8,0 (19,90)		-11,6 (17,63)	-13,2 (18,48)
Valor p (frente a placebo)	--	0,034		<0,001	<0,001
R092670-PSY-3003	n=132		n=93	n=94	n=30
Media basal (DE)	92,4 (12,55)	--	89,9 (10,78)	90,1 (11,66)	92,2 (11,72)
Variación media (DE)	-4,1 (21,01)		-7,9 (18,71)	-11,0 (19,06)	-5,5 (19,78)
Valor p (frente a placebo)	--		0,193	0,019	--
R092670-PSY-3004	n=125	n=129	n=128	n=131	
Media basal (DE)	90,7 (12,22)	90,7 (12,25)	91,2 (12,02)	90,8 (11,70)	--
Variación media (DE)	-7,0 (20,07)	-13,6 (21,45)	-13,2 (20,14)	-16,1 (20,36)	
Valor p (frente a placebo)	--	0,015	0,017	<0,001	
R092670-SCH-201	n=66		n=63	n=68	
Media basal (DE)	87,8 (13,90)	--	88,0 (12,39)	85,2 (11,09)	--
Variación media (DE)	6,2 (18,25)		-5,2 (21,52)	-7,8 (19,40)	
Valor p (frente a placebo)	--		0,001	<0,0001	

*En el estudio R092670-PSY-3007, se administró una dosis de iniciación de 150 mg a todos los sujetos de los grupos de tratamiento con Xeplion el día 1 y, a partir de entonces, la dosis asignada.
Nota: un cambio negativo de la puntuación denota mejoría.

Mantenimiento del control de los síntomas y retraso de la recidiva de la esquizofrenia: La eficacia de Xeplion en el mantenimiento del control de los síntomas y el retraso de la recidiva de la esquizofrenia se determinó en un estudio doble ciego, controlado con placebo, de dosis flexible, con un plazo más largo, en el que participaron 849 sujetos adultos no ancianos que cumplían los criterios para la esquizofrenia del DSM-IV. Este estudio incluyó un tratamiento abierto agudo de 33 semanas de duración y una fase de estabilización, una fase aleatorizada, doble ciego, controlada con placebo para observar la recidiva, y un período de extensión abierto de 52 semanas. En este estudio, las dosis de Xeplion fueron 25, 50, 75 y 100 mg administrados mensualmente; la dosis de 75 mg solamente estaba permitida en la extensión abierta de 52 semanas. Inicialmente, los sujetos recibieron dosis flexibles (25-100 mg) de Xeplion durante un período de transición de 9 semanas de duración, seguido de un período de mantenimiento de 24 semanas, en el que los sujetos debían tener una puntuación PANSS ≤75. Los ajustes de la dosis sólo se permitieron en las primeras 12 semanas del período de mantenimiento. Se realizó la asignación aleatoria de un total de 410 pacientes estabilizados a Xeplion (mediana de la duración de 171 días [intervalo de 1 día a 407 días]) o a placebo (mediana de la duración de 105 días [intervalo de 8 días a 441 días]) hasta que experimentaran una recidiva de los síntomas de la esquizofrenia en la fase doble ciego de duración variable. El ensayo se suspendió antes de tiempo por motivos de eficacia, dado que se observó un tiempo significativamente más largo hasta la recidiva (p<0,0001, Figura 1) en los pacientes tratados con Xeplion en comparación con el placebo (cociente de riesgos=4,32; IC 95%: 2,4-7,7).

Figura 1: Gráfico de Kaplan-Meier del tiempo hasta la recidiva. Análisis intermedio (grupo de análisis intermedio por intención de tratar)



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas in vivo, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios in vitro se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos in vivo que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios in vitro se ha demostrado que paliperidona no es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios in vivo y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un periodo mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (días 8 y 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a los de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (CrCl=10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{∞}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. El análisis de la farmacocinética poblacional demostró que no había evidencia de diferencias en la farmacocinética relacionada con la edad. Índice de masa corporal (IMC)/Peso corporal. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de Xeplion. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios in vitro realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. No se ha estudiado con Xeplion el efecto del consumo de tabaco en la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte masivamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. No desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Poliisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Xeplion 50 mg suspensión inyectable de liberación prolongada PVL: 171,61 €; PVP: 217,52 €; PVP (IVA): 226,22 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 223,08 €; PVP: 273,99 €; PVP (IVA): 284,95 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 274,59 €; PVP: 325,50 €; PVP (IVA): 338,52 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 411,88 €; PVP: 462,79 €; PVP (IVA): 481,30 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** 25 mg: EU/1/11/672/001. 50 mg: EU/1/11/672/002. 75 mg: EU/1/11/672/003. 100 mg: EU/1/11/672/004. 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 11/2016. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

TREVICTA®

palmitato de paliperidona

suspensión inyectable de liberación prolongada

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[¥] N= 506. Estudio aleatorizado, doble ciego, controlado con placebo que evaluó la eficacia y seguridad del retraso del tiempo hasta la recaída de Trevicta® *vs.* placebo. 93% de los pacientes sin recaídas.

[§] N= 1.429. Estudio aleatorizado, doble ciego, de grupos paralelos, multicéntrico, de no inferioridad de Trevicta® *vs.* Xeplion®, de 48 semanas de duración. La tasa de recaídas fue similar en ambos grupos. Los perfiles de seguridad y tolerabilidad de Trevicta® y Xeplion® fueron comparables a lo largo de la fase doble-ciego de 48 semanas y consistentes con lo observado en otros ensayos con palmitato de paliperidona.

* Para más información consultar la sección 4.4 y 4.8 de las Fichas Técnicas.

1. Ficha Técnica Trevicta®. 2. Gopal S *et al.* Practical guidance for dosing and switching from paliperidone palmitate 1 monthly to 3 monthly formulation in schizophrenia. Current Medical Research and Opinion. 2015;31(11):2043-2054. DOI: 10.1185/03007995.2015.1085849. 3. Ravenstijn P *et al.* Pharmacokinetics, safety, and tolerability of paliperidone palmitate 3-month formulation in patients with schizophrenia: A phase-1, single-dose, randomized, open-label study. J Clin Pharmacol. 2016 Mar;56(3):330-9. DOI: 10.1002/jcph.597. Epub 2015 Oct 5. 4. Berwaerts J *et al.* Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: A randomized clinical trial. JAMA Psychiatry. 2015. DOI: 10.1001/jamapsychiatry.2015.0241. 5. Savitz AJ *et al.* Efficay and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. International Journal of Neuropsychopharmacology. 2016;1–14. DOI: 10.1093/ijnp/pyw018.