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Stigma in the Addicted Person

El estigma en la persona adicta

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Sign, mark, brand, blemish, blame, stain, scar, shame, affront or disgrace are some of the synonyms used in English to approach the understanding of the word 'stigma', a word which is further defined by the Oxford English Dictionary "as a mark of disgrace or infamy; a sign of severe censure or condemnation, regarded as impressed on a person or thing; a 'brand'".

Throughout history there have been many diseases, health problems or disorders that have been typecast in this way. The only thing this has achieved has been to remove the person from their social environment and to prevent them from receiving the necessary support and enjoying their human rights. Such people have ended up being despised, marginalised, someone to be avoided. In short, we are dealing with a deeply discrediting label.

We have seen it applied to diseases such as leprosy, plague, schizophrenia and even epilepsy. What's going on here? Aren't these individuals people who deserve to be treated the same as others?

Erving Goffman defined "stigma" as the expectation of a stereotypical and discrediting judgment of oneself by others in a particular context (Goffman, 1968).

In recent decades, in addition to the stigmatization of the mentally ill, we have seen how the same phenomenon has occurred in HIV/AIDS, both in relation to the syndrome itself, and even the personal characteristics of the sufferer. And although not a new phenomenon, people who have a substance use disorder, with all that this entails, are also victims of the same disregard, and this reflects badly on our society.

There was also a time when substance abuse was strongly linked to HIV, which made this prejudice even worse. Society tends to pigeonhole certain people and the media facilitates such representations and beliefs (Rengel, 2005). There is also a tendency to label those who have an addictive disorder negatively, highlighting the negative aspects and identifying their condition as an important part of the story, even when this is not the case.

According to sociologist Javier Rubio, the process of constructing this stigma is *always* arbitrary and cultural, and arises from the need to censor people who deviate from what is or is not recognised as socially and culturally acceptable. It operates as an all-encompassing definition with the capacity to discredit the individual/consumer of toxic substances in social exchanges. The stigmatization process turns the drug addict into a dispossessed person, with his/her social identity being established by comparison with non-consumers, and this comparison serves to fix his/her social position as someone who is different and inferior. What is more, the drug use/addiction itself generates a deterioration in the social environment (with relatives, peers, neighbours, etc.) and in the workplace; by living his/her life through the substance, a psychosocial lifestyle is created in accordance with the new situation and the new role, that of a substance-dependent individual (Rubio, 2001).

The consumption of alcohol and other drugs triggers behaviours that are inappropriate to the social construct; addicts may suffer physical and/or psychological disease that distances them from the context of normality, and may sometimes be involved in criminal acts while also being considered accident prone and associated with intimate partner violence or crime. But it is wrong to label them as junkies, idlers or delinquents, without taking into account that their condition as people who have lost control over

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their actions or the inescapable urge to use the drug has been brought about by the addiction itself. Although in principle the stigma is smaller for users of legal substances, when certain thresholds are crossed and the consequences of consumption become apparent this perception fades, as can be seen with alcohol consumption among the homeless and the risk of social exclusion that these people are subject to (Panadero, Vázquez & Martín 2017).

The determination of certain groups to de-stigmatise issues of gender, mental illness or HIV could serve as an example and guide to try to break the stigma of the addict.

We know that the use of psychoactive substances is surrounded by a dark cloud of symbolism. Psychoactive substances may be prestige products, but there will always be aspects of their use which seem to attract almost universal stigma and marginalization, even going as far as to link substance use to crime (Esbec & Echeburúa, 2016).

Processes of stigmatization include the intimate process of social control between family and friends, social and health-related decisions and government policy decisions. Negative moralising normally sees substance abuse associated with health issues, accidents or social problems, intoxication, addiction or dependency, as well as loss of control. Now we call this Substance Use Disorder, and marginalisation and stigma are commonly added to the mix. Those being treated for alcohol or drug problems are frequently and disproportionately marginalised, resulting in adverse outcomes in the therapeutic process (Room, 2005).

We should try to combat the lack of understanding towards people with addictive disorders since the great majority of people with addiction problems suffer social rejection and are isolated and stigmatised.

It seems paradoxical that we can see the use of certain substances being encouraged, publicised and applauded while the consequences are repudiated.

We see three aspects to this problem:

a. Self-stigma, or concealment of the problem on the part of the sufferer (isolation, non-recognition, etc.), frequently conditioned by shame, which affects health behaviours and generates invisibility, thus negatively affecting socio-political decision making (Dolezal & Lyons, 2017)

   Self-stigma occurs, for example, when people with mental illnesses internalise negative stereotypes and prejudices about their condition, which can reduce help-seeking behaviour and treatment adherence. The problem is that while attempts have been made to combat self-stigma, the effectiveness of interventions is has so far been uncertain, according to a meta-analysis carried out in 2013 (Büchter & Messe, 2017).

   Ultimately, the conception of oneself or self-perception is that of "I am inferior. Therefore, people will dislike me and I cannot be secure with them" (Perry, Gawel & Gibbon, 1956).

b. Social stigma through rejection by the part of the population that does not understand what a person with an addiction is and continues to catalogue addiction to any substance as a vice. Attempts have been made to evaluate different interventions with the mentally ill, and the results highlight the importance of focusing on the behavioural outcomes of the stigmatization process (discrimination and social inequality), which is consistent with models of social justice or rights emphasising social and economic equity for people with disabilities (such as equal access to services, education, work, etc.). However, they also call into question the broad approaches of public education in favour of more specific interventions based on contact (Stuart, 2016); the program proposed by Socidrogalcohol along these lines has been supported from the outset by the affected groups and family members.

c. Finally, the stigma in the public healthcare sector where people like this are seen as a nuisance, and where there is a tendency to label them before even listening to them. It is most likely a lack of sensitivity or even proper training that triggers a certain rejection among these professionals.

   And without needing to go any further, let us not forget that stigma and its consequences are exacerbated when women are involved or when the addict has some physical and especially mental illness, that is to say, when he/she suffers a comorbidity or the coexistence of different sicknesses, diseases or disorders (Foundation Transform Drug Policy, 2010).

This problem was mitigated to a certain extent by the fact that addicts are considered to be sick, according to the WHO's definition of illness as "Alteration or deviation from the physiological state in one or more parts of the body, because of generally known reasons, manifested by characteristic signs and symptoms, and whose evolution is more or less predictable", since for the WHO, health is *a state of complete physical, mental and social well-being, and not only the absence of disease or infirmity* (WHO, 1946) even when considering dependency disorder. As a result such people have the same right to care as any other type of patient. This has made it possible for more people to be provided with care, although this has not yet occurred across the board.

But what is important is perhaps that it is based on the concept of health as the state of complete physical, mental and social well-being, and not just the absence of disease. Therefore, not only does it depend on good physical or physiological condition, but also on the influence of the psychological aspects of one's environment (socioeconomic, family, work, emotional, environmental factors), which in the final analysis is what should be considered when dealing with anybody with a dependency disorder, applying the bio-psycho-social model which governs their care.

We have to take into account that the healthcare resources for attending to these people also frequently reinforce this stigma and that governments in general forget the importance of investing in their recovery; they appear unaware of the fact that the saving that could be achieved when investing in prevention is much greater than the cost, and that all dimensions - social, welfare, prevention, administrative resources, absolutely all of them - are permeated by stigma.

Stigmatization of families supporting an adult with substance abuse disorder is widespread and undermines their ability to support the individual and maintain their own well-being. In a recent study, "keeping it secret and minimising contact with others" and "lack of knowledge and empathy" are shown to exacerbate the problem. It also speaks of the useful role of nursing and, in general, professionals working with addictions, who could help reduce stigma through a special approach, thereby challenging the attitudes of some clinicians, and improving ways of communicating with families (McCann & Lubman, 2017).

At the scientific society Socidrogalcohol, we are aware of these issues and propose an awareness raising scheme with the goal of reducing the stigmatization of people with addictive disorders through a programme which aims to:

- Promote an approach which is integrated, public and free, involving coordination with non-governmental organisations, patient organisations and the private sector, in which physical, psychological and social aspects are equally important in achieving the total recovery of the person.
- Demand care structures appropriate to the needs of patients and their families: outpatient treatments, hospital resources for detoxification, day centres, therapeutic communities, specific programs for dual disorders, sheltered housing, reinsertion programs and support and coordination with mutual support groups.
- Standardise services and care resources: standardisation of integrated resources within public health networks.
- Provide each centre with a small team of professionals, in accordance with their characteristics, working in a multidisciplinary way with a bio-psycho-social approach.
- Demand that the rights of these patients to receive treatment and care under the same conditions as anyone suffering other pathologies are upheld and consolidated.
- Demand governmental support for patient and family organisations.
- Increase social awareness of the fact that addiction is a disease.
- Raise social awareness of the need to reintegrate addiction sufferers, and that stigma does not contribute to this but complicates it.

To this end, a program of action has been developed which takes into account the three agents involved in the problem, i.e. the person him/herself (by involving addict groups and their relatives), society in general, and public healthcare professionals, with the contents and materials being created accordingly. On the one hand, we have drawn up a document containing the points of equity, homogeneity and entitlement to healthcare set out above. Furthermore, endorsements have been requested in order to raise awareness, but above all to give the whole programme maximum publicity and to let others feel that they are also part of the process. We also have the support of patient associations, professional groups, foundations, etc., both in Spain and in different parts of Europe.

At the same time, we have produced written material, such as diptychs and leaflets, which has been complemented by a series of specific posters which show the addict as equal to anybody else requiring public healthcare, all accompanied by gifs, testimonial videos for social networks, TV and radio spots. The aim is to get the message across to the greatest possible audience. And finally, materials are being developed to raise awareness also among all professionals, counting on the help of nursing staff, professional colleges, doctors, psychologists and social workers. We are using the media and also organising debates in the autonomous communities and at the national level to generate the maximum possible resonance.

In addition, the social networks could not be ignored. The campaign uses the hashtag #RompeElEstigma both on Facebook and Twitter to spread and highlight the message, and on many occasions we use a second hashtag #CombateLaAdiccion. The choice of name for the campaign and the hashtag, which is the same, was made for a simple reason: stigma, as outlined at the beginning of this article, is something that accompanies a multitude of diseases, and by using the same message we can join forces with other groups also fighting for the same cause. Sometimes, however, we are interested in focusing on the message that stigma is present in addiction, and for this reason the word 'addiction' is always present.

The materials that have been produced transmit two main messages. 1. That addiction is a disease. 2. That anyone can suffer it and that its appearance, age, sex, condition, etc. cannot be used to label the person. To this end, the materials are produced as an interrelated series of items, that is, the radio ads, the TV spot, the posters and the diptychs use the same characters, the same messages and the same scenarios.

To make the campaign identifiable, we have come up with a mascot in the form of a bird which, caged in its stigma, manages to liberate itself and gain its freedom. A friendly and fun image that reaches out to its target and provides a focal point of unity and understanding for all involved in this obstacle to the proper care of addiction.

The bird itself develops as the campaign progresses, facing up to its own 'self-stigma'; its logo initially features a capital 'E' for 'Estigma' but this ends up being torn off as the bird finds freedom and replaced by the 'L' of 'Libertad'.

In addition to the actions described above, in order to disseminate the campaign the structure and organisation of Socidrogalcohol's delegations in the autonomous communities was used. After the material was printed, it was delivered to each community, with each local delegation being in charge of distributing to the different resources. In addition, they were encouraged to use the endorsements of the primary document, and to be actively involved in the distribution, for example, with the option of adding a tagline at the end of the advertisements, such as "With the collaboration of ...", adding the name of the association or entity. The intention is to reach out as far as possible; we understand that the task of destigmatising involves each and every one of the social agents concerned, and without this it will be difficult to reach society in general.

The campaign is not closed. On the contrary, it is alive and programmed for continuous change that adapts itself to society and moments in time, as well as to the observations of those who can put it into practice. New materials in multiple forms, videos, publications, etc. will be published. At the very least we should be able to plant the word 'stigma' firmly within the field of addictive disorders so that at least reflection and debate are encouraged, because without this we cannot contribute to or encourage change, nor develop an approach of how best to deal with it.

The importance of the implementing this program against stigma can be found in the words of UN Secretary-General Ban Ki-moon in 2008 (Ki-moon, 2008).

"*No one should be stigmatised or discriminated against because of their dependence on drugs. I urge Asian governments to amend antiquated penal legislation laws that criminalises the most vulnerable sectors of society, and to take all necessary measures to ensure that these people can live in dignity.*"

Conflict of interests

The authors state that there is no conflict of interest.

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Working on a Standard Joint Unit: A Pilot Test

Estableciendo la unidad de porro estándar: estudio piloto

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Abstract

Introduction. Assessing cannabis consumption remains complex due to no reliable registration systems. We tested the likelihood of establishing a Standard Joint Unit (SJU) which considers the main cannabinoids with implication on health through a naturalistic approach.

Methodology. Pilot study with current cannabis users of four areas of Barcelona: universities, nightclubs, out-patient mental health service, and cannabis associations. We designed and administered a questionnaire on cannabis use-patterns and determined the willingness to donate a joint for analysis. Descriptive statistics were used to analyze the data.

Results. Forty volunteers answered the questionnaire (response rate 95%); most of them were men (72.5%) and young adults (median age 24.5 years; IQR 8.75 years) who consume daily or nearly daily (70%). Most participants consume marihuana (85%) and roll their joints with a median of 0.25 gr of marihuana. Two out of three (67.5%) stated they were willing to donate a joint.

Conclusion. Obtaining an SJU with the planned methodology has proved to be feasible. Pre-testing resulted in an improvement of the questionnaire and retribution to incentivize donations. Establishing an SJU is essential to improve our knowledge on cannabis-related outcomes.

Keywords: Cannabis; 9-Tetrahydrocannabinol; standard unit; pilot study.

Resumen

Introducción. Explorar el consumo de cánnabis sigue siendo complejo debido a la falta de sistemas de registro. Se evaluó la factibilidad de obtener una Unidad de Porro Estándar (UPE) que considere los principales cannabinoides con implicación clínica mediante un estudio naturalístico.

Metodología. Estudio piloto con consumidores actuales de cánnabis de cuatro áreas (universidades, ocio nocturno, servicio ambulatorio de salud mental y asociaciones cannábicas) en Barcelona. Se diseñó y administró un cuestionario sobre patrones de consumo y se determinó la predisposición a donar un porro para análisis. Se utilizaron estadísticos descriptivos para analizar los datos.

Resultados. Cuarenta consumidores de cannabis respondieron a la encuesta (tasa de respuesta 95%), siendo la mayoría hombres (72,5%) y jóvenes adultos (mediana de edad 24,5 años; RIQ 8,75 años) que consumen a diario o casi diariamente (70%). La marihuana es el derivado más consumido (85%), habiendo de mediana 0,25 gr de marihuana por porro. Un 67,5% de los participantes se mostraron predispuestos a donar un porro para análisis.

Conclusión. La obtención de la UPE con la metodología prevista es factible. Tras el piloto el cuestionario ha sido adaptado y se ha introducido un incentivo para estimular la donación de muestras. Establecer la UPE permitirá avanzar en el conocimiento de las consecuencias del consumo de cannabis.

Palabras clave: Cannabis; 9-Tetrahidrocannabinol; unidad estándar; estudio piloto.

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Cannabis is the most abused illicit drug worldwide (United Nations Office on Drugs and Crime, 2015). In 2013 , 30% of the Spanish population between 15-64 years declared to have consumed cannabis once in their lives (Delegación del Gobierno para Plan Nacional sobre Drogas, 2015). Little is known on which consumption patterns increase the possibility of suffering cannabis-related consequences. Evaluating cannabis health outcomes faces several difficulties, as for example dealing with its variable composition or different quantities consumed. As a result, although doses have shown to be essential to evaluate drug-related outcomes, cannabis use is often only described by the frequency of use (Mariani, Brooks, Haney, & Levin, 2011; Norberg, Mackenzie, & Copeland, 2012; van der Pol et al., 2013; Walden & Earleywine, 2008). One example are characterizations of risky cannabis use, as for example daily use (Coffey, Lynskey, Wolfe, & Patton, 2000). However, specific information on the type of cannabis and its potency (concentration of 9-Tetrahydrocannabinol) is often missing, ignoring its importance when evaluating related health outcomes (Di Forti et al., 2009).

With alcohol, which is also characterized by a huge variability between types of beverages, similar difficulties were tackled establishing a standard unit (Miller, Heather, & Hall, 1991; Rodríguez-Martos Dauer, Gual Solé, & Llopis Llácer, 1999; Stockwell, Blaze-Temple, & Walker, 1991). Nowadays the "standard drink" is widely used in alcohol assessment and has contributed to the characterization of risky users, enabling public health recommendations.

Working on a homogenization of cannabis assessment could lead to equivalent benefits. A standard unit for cannabis would allow describing cannabis use patterns not only using frequency but also quantity. Few attempts to develop cannabis units have been published (Norberg et al., 2012; Zeisser et al., 2012). However, they show several weaknesses. For example, units base on grams of cannabis and do not consider that cannabis can have a high variability in its composition (EMCDDA, 2008). Meanwhile, quantity of cannabis' main psychoactive cannabinoid - 9-Tetrahydrocannabinol (9-THC) (Mechoulam & Gaoni, 1964) - present in the proposed units remains unknown. As well as the "standard drink" accounts for grams of alcohol, a standardized unit for cannabis should consider the quantity of its main psychoactive constituent with implication on health (Hall & Degenhardt, 2009; Hall, 2015). In addition, standard units should be based on the most used administration form. For cannabis, smoking a rolled cigarette in form of a joint, is the most common administration form (U.S. Department of Health and Human Services, 2014).

The Spanish Ministry of Health, through its National Plan on Drugs, recently approved a project to establish a "Standard Joint Unit" (SJU). This unit will consider the quantity of 9-THC in donated joints. In order to check the likelihood of obtaining a SJU through a naturalistic study, a pilot test was conducted. The present paper reports its main results and analyzes preliminary data.

Material and methods

Sample

During September to December 2014 forty cannabis users were recruited by convenience in four different settings of Barcelona (Spain): universities, cannabis associations, one out-patient mental health service and nightclubs (N=10 in every setting). For the pilot study, the sample size was adjusted to 10% of the expected final study sample. Participant's eligibility criteria were (1) having consumed cannabis at least once in the last 60 days, (2) being able to decide to participate and 3) being adult.

Procedure

Participants were informed about the study objective, anonymity and confidentiality of their data. Once accepted, they were administered a questionnaire. For the out-patient mental health service recruitment proceeded indirectly via informed psychiatrist who invited their patients to participate.

Instruments

Questionnaires previously used in similar contexts were reviewed for suitable questions (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2015; Ministerio de Sanidad, Servicios Sociales e Igualdad, 2013; Villalbí, Suelves, Saltó, & Cabezas, 2011). Finally the pilot questionnaire included 15 questions, which can be divided into four groups: 1) Socio-demographical variables (sex, age, marital status, highest educational level achieved and current employment status); 2) Patterns of cannabis use (type of cannabis derivate used, tobacco proportion used in joints, preparation of joints, frequency of cannabis consumption in the last 30 days, mean joints smoked on one typical occasion in the previous 30 days, joint sharing); 3) Preliminary data on the SJU (specified below) and predisposition to donate a joint for analysis; 4) Main reason for cannabis use and the Cannabis Abuse Screening Test (CAST) (Cuenca-Royo et al., 2012; Legleye, Karila, Beck, & Reynaud, 2007).

CAST screens for risk of problematic cannabis use, and consists of six questions, which can be answered with the options "never", "rarely", "from time to time", "fairly often" and "very often". Using the binary CAST option, final scores can be matched to either non problematic use (0-1), low risk of having cannabis-related problems (2-3) or high risk of having cannabis related problems (4-6). (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2009).

The construction of the SJU is based on the following data: type of derivate consumed, weekly expenditure on cannabis, weekly amount of grams consumed, weekly number of joints consumed and frequency of acquisition. During the pilot-test, no joints were collected for analysis.

For the final study joints will be analyzed using HPLC-UV, according to the recommended methods for the identification and analysis of cannabis and cannabis products by the United Nations Office on Drugs and Crime using HPLC-UV (United Nations Office on Drug and Crime, 2009).

Data Analysis

Descriptive statistical analyses were made using SPSS version 19. Percentages were used for categorical data and median, range and interquartile range for quantitative data.

Ethics statement

The study protocol was approved by the Committee on Ethics of the Hospital Clínic (HCB/2014/0770). No informed consent was necessary due to anonymous participation. Study procedures were planned according to the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2013).

Results

Procedure and questionnaire

Recruitment proceeded without incidents and with a response rate of 95%. The designed questionnaire needed minimal changes like some additional response options. Only the question on the frequency of cannabis consumption in the last 12 months had to be reviewed due to incorrect formulation.

Sample description and preliminary data

a) Socio-demographical data

Participants (N=40) were mostly men (72.5%), young adults (median 24.5 years, range 18-47) and single (72.5%). At the moment of the survey, 40% had finished their secondary studies and 42.5% were working (Table 1).

b) Consumption patterns

Our sample consumed marihuana (85%), hashish (10%) and hashish oil (5%). Home-grown marihuana was the first supply in 34% of the marihuana users, who occasionally also acquired cannabis if their plants were not productive. The majority (70%) affirmed to smoke on more than 20 days in the last month, 55% declared to smoke 2 to 4 joints per smoking occasion and 68.5% usually do not share their joints. 85% stated to roll their joints similarly every time and 90% smoked cannabis with tobacco (Table 2).

c) Preliminary data on SJU and predisposition to donate a joint

Participants declared to roll 4 joints (median value) with 1 gram of cannabis (0.25 gr of cannabis/ joint). This

Table 1. *Socio-demographical characteristics of the sample recruited for the pilot study (N=40).*

Socio-demographical data	Values N (%)
Gender	
Men	29 (72.5)
Women	11 (27.5)
Age	
Median (IQR)	24 (8.75 years)
Range (years)	18 – 47 years
Marital status	
Single	29 (72.5)
Married	4 (10.0)
Separated/ Divorced	2 (2.0)
Widow/er	0 (0.0)
Others	5 (12.5)
Highest educational level achieved	
Primary school (6 years of school completed)	1 (2.5)
4 years of secondary school completed	9 (22.5)
5 or more years of secondary school competed	14 (35.0)
University degree	16 (40.0)
Working situation	
Working	17 (42.5)
Unemployed	13 (32.5)
Currently absent from work	5 (12.5)
Receiving a disability pension	3 (7.5%)
Other situations without earning money	2 (5.0%)

Table 2. *Description of consumption patterns and CAST scores of the recruited sample (N=40).*

Item asked	N (%)
Type of derivate consumed	
Marihuana obtained in a cannabis association	18 (45.0%)
Home-gown marihuana	12 (30.0%)
Marihuana obtained in the illicit market	2 (5.0%)
Hashish	4 (10.5%)
Hashish oil	2 (5.0%)
Missing (several types of cannabis)	2 (5.0%)
Tobacco use to roll the joint	36 (90.0%)
Prepares the joints similarly	34 (85.0%)
Frequency of consumption in the last 30 days	
More than 20 days	28 (70.0%)
Between 10 and 19 days	4 (10.0%)
Up to 9 days	8 (20.0%)
Number of joints consumed in one typical occasion	
1 joint	8 (20.0%)
2-4 joints	22 (55.0%)
6-8 joints	5 (12.5%)
More than 9 joints	2 (5.0%)
Missing (consumed less than one joint per occasion)	3 (7.5%)
Shares the joint in most of the cases	13 (32.5%)
a CAST scores	
0-1 (non-problematic use)	2 (5.0%)
2-3 (low risk use)	15 (37.5%)
4 or more (high risk use)	23 (57.5%)

Note. [a] CAST: Cannabis Abuse Screening Test

proportion was similar for marihuana and hashish (Marihuana IQR=1.92; Hashish IQR=2.25). Preliminary data suggests that one joint costs on average less than 2 € (data not shown in tables). Two out of three participants stated that they would donate a joint without receiving any retribution (67.5%). Thirteen individuals denied (6 at nightclubs, 4 at universities, 2 in out-mental health service and 1 in the cannabis association). Main reasons were not receiving retribution and wanting to smoke their joints.

d) Main reasons for consumption and CAST scores

Main reasons for cannabis consumption were seeking for positive feelings as for example pleasure (70%), avoid negative feelings as for example anxiety (20%) and neutral reasons as for example habit (10%). CAST scores were in 57.5% higher than 4 points (high-risk use).

Discussion

Planned methodology to establish a SJU was tested. Participant's predisposition to donate a joint indicates that working on a SJU obtained through a naturalistic study approach is feasible. Additional data related to cannabis use could be retrieved with a questionnaire which needed minimal changes.

Study procedure and questionnaire

One out of three participants affirmed not to be predisposed to donate a joint, often due to no retribution. In order to incentivize joints donations, non-economical retribution options were studied. Finally for the donation the participant will receive a USB with preventive information on cannabis. Minimal changes were done to adapt the questionnaire. One example is the question on the type of derivate consumed, which was adapted to retrieve more than one option of consumption. This change was especially necessary for home-grown marihuana users, which occasionally also acquire cannabis. For the final study, these users will be asked to estimate the value (price) of their own cultivated cannabis.

Preliminary data on the Standard Joint Unit

To optimize our study resources, for the SJU only joints of the most prevalent types (marihuana and hashish) will be considered. Few donations of other joints are expected and might be discouraged due to higher prices.

The numbers of joints rolled with one gram of cannabis were comparable within marihuana and hashish (approximately 4 joints with 1gr of cannabis). This data is consistent with previous studies (van der Pol et al., 2013; van der Pol et al., 2014). Other comparable studies like the published by Norberg et al (2012) stated that a *Standard Cannabis Unit* accounted for 0.25gr of cannabis (Norberg et al., 2012), which is similar to our results. In our larger study, these data will be analyzed considering amounts of tobacco (%) and concentrations of the main cannabinoids (9-THC and CBD). The analytical procedure to quantify the cannabinoids was validated and will proceed following the recommendations of the UNODC (United Nations Office on Drug and Crime, 2009).

Most of our sample declared to roll their joints similarly every time (85%) and not sharing it (68.5%). Considering that most of our participants are nearly daily smokers of 2 to 4 joints per day, consuming up to 1gr of cannabis daily or nearly daily may not be uncommon among these cannabis users of Barcelona.

Information retrieved is believed to be consistent due to the high proportion of frequent users, who mostly roll their joints similarly every time and do not share them. These data include prices, grams acquired per occasion and number joints resulting from a specific cannabis amount. In consequence, proceeding to analyze the joints donated by the participants in the real study was decided.

Associations between quantity consumed and CAST results will be analyzed in the larger study. Preliminary data obtained through the pre-test indicate a significant prevalence of users having a high risk of suffering cannabis related problems. According to the definition of the European Monitoring Centre for Drugs and Drug Addiction, users consuming at least 20 days in the last month are high-risk users (EMCDDA, 2004). In our sample 70% declared to use cannabis on more than 20 days in the last month. With the CAST, 58% were categorized as high-risk users (CAST>4). The last edition of the Spanish National Survey on Drugs found that beyond cannabis users in the last year, prevalence of problematic cannabis use was 25% (Delegación del Gobierno para Plan Nacional sobre Drogas, 2015). Associations with reasons for consumption will be explored and may reveal important data on personal risks as suggested in previous studies (Aleixandre, Río, & Pol, 2004; González, Sáiz, Quirós, & López, 2000).

Strengths and limitations

Reporting all phases of the study will contribute to the understanding of the SJU. Working on a SJU which considers quantity of 9-THC is innovative and to our knowledge no other feasibility reports have been published. With the pilot test we have been able to explore crucial aspects of the study, as for example the donation of joints. The pilot test has helped to improve our methodology and to avoid unnecessary costs.

The hetero-administered questionnaire may potentially have induced an information bias. Bivariate statistical analyses were not performed as variable categories were in some cases too infrequent. Nevertheless, pilot studies are meant to explore feasibility and adequacy of the study procedure.

Conclusions

The pilot test contributed to optimize our methodology, enhancing the likelihood of establishing a SJU. Standardized

cannabis assessment which considers quantity is essential to explore which patterns of cannabis use increase the risk of suffering negative consequences. Due to cannabis high prevalence of use and its implications for public health, improving evidence-based knowledge on cannabis risks is highly needed.

Contributions

Cristina Casajuana Kögel, Hugo López-Pelayo, María Mercedes Balcells and Antoni Gual designed the study. Cristina Casajuana wrote the first draft of the manuscript. All other authors contributed to the editing and final review of the manuscript. All authors approved the final paper.

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Conflict of interest

Hugo López-Pelayo has received honoraria and travel grants from Lundbeck, Lilly, Janssen, Pfizer, Rovi, Esteve. Laia Miquel and María Mercedes Balcells have received honoraria from Lundbeck. Lídia Teixidó has received honoraria from Pfizer. Antoni Gual has received honoraria, research grants, and travel grants from Lundbeck, Janssen, Pfizer, Lilly, Abbvie D&A Pharma and Servier. All other authors declare no potential conflict of interest. Previous stated honoraria had no influence on this article.

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Anxiety, Depression and Tobacco Abstinence

Ansiedad, depresión y deshabituación tabáquica

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Abstract

There is evidence of the relationship between mental illness and smoking and increased risk of depressive episodes after quitting smoking, even with specific treatments for abstinence. Objective: To assess the influence of a cessation program on the emotional state of patients by measuring levels of anxiety / depression and differences depending on the presence of psychiatric history. Method: A prospective observational study of patients taking part in a combined program (pharmacological and cognitive-behavioral) for giving up smoking. Anxiety (A) and depression (D) were measured using the HADS questionnaire at baseline, first and third month of abstinence. Results: Anxiety and depression showed significant and progressive improvement during treatment (A: baseline 9.2 ± 4.5, 5.9 ± 3.6 1 month, 3 months 4.5 ± 3.1, p <0 05 / D: baseline 5.5 ± 4.1; 1 month 3 ± 3; 3 months 2.3 ± 2.1, p <0.05), in psychiatry population (A: baseline 11.3 ± 4 , 5; 1 month 7.1 ± 3.7, 5.3 ± 3.5 3 months, p <0.05 / D: baseline 7.4 ± 4.8, 4.2 ± 3.6 one month; 3 months 3 ± 2.9, p <0.05), regardless of treatment. Abstinence rate: 58.5%, unaffected by baseline levels of anxiety and depression. No significant neuropsychiatric side effects were detected. Conclusions: Anxiety and depression levels evolved favourably during the program, achieving good results regardless of the presence of psychiatric pathology.

Keywords: Anxiety; depression; tobacco; psychiatric patients; tobacco abstinence.

Resumen

Existe evidencia de la relación entre patología mental y tabaquismo y del mayor riesgo de sufrir un episodio depresivo al dejar de fumar, incluso con tratamientos específicos para la abstinencia. Objetivo: valorar la influencia de un programa de abandono del tabaco en el estado emocional de los pacientes mediante la medición de los niveles de ansiedad/depresión y las posibles diferencias en función de la presencia de antecedentes psiquiátricos. Método: estudio de cohortes observacional y prospectivo de pacientes que acudieron a dejar de fumar mediante programa combinado (farmacológico y cognitivo-conductual). Se midió ansiedad (A) y depresión (D) utilizando el cuestionario HADS al inicio, primer y tercer mes de abstinencia. Resultados: la ansiedad y la depresión presentaron mejoría significativa y progresiva a lo largo del tratamiento (A: basal 9,2±4,6; 1 mes 5,9±3,6; 3 meses 4,5±3,1; p<0,05 / D: basal 5,5±4,1; 1 mes 3±3; 3 meses 2,3±2,1; p<0,05), en la población psiquiátrica (A: basal 11,3±4,5; 1 mes 7,1±3,7; 3 meses 5,3±3,5; p<0,05 / D: basal 7,4±4,8; 1 mes 4,2±3,6; 3 meses 3±2,9; p<0,05), e independientemente del tratamiento. Tasa de abstinencia: 58,5%, no se vio afectada por los niveles basales de ansiedad y depresión. No se detectaron efectos secundarios neuropsiquiátricos relevantes. Conclusiones: los niveles de ansiedad y depresión evolucionan favorablemente durante el programa, alcanzándose buenos resultados, independientemente de la presencia de patología psiquiátrica.

Palabras clave: Ansiedad; depresión; tabaco; pacientes psiquiátricos; abstinencia tabáquica.

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Evidence of the link between mental illness and tobacco dependence has been provided (Lawrence, Hafekost, Hull, Mitrou, & Zubrick, 2013), and the fact that those with psychiatric pathology have higher levels of anxiety and depression when compared to non-smokers has also been documented. Furthermore, quitting smoking carries a greater short-term risk of major depressive episodes, which can even be triggered by a sudden reduction in nicotine intake (Lagrue, Dupont, & Fakhfakh, 2002; Mykletun, Overland, Aaro, Liabo, & Stewart, 2008). Nevertheless, a review of studies using specific questionnaires with disparate results to assess the variation in levels of anxiety and depression after several weeks of not smoking shows that it is not yet completely clear how anxio-depressive symptomatology responds after a certain period of abstinence (Bolam, West, & Gunnell, 2011; Dawkins, Powell, Pickering, Powell, & West, 2009; Marqueta, Jimenez-Muro, Beamonte, Gargallo, & Nerin, 2010; McDermott, Marteau, Hollands, Hankins, & Aveyard, 2013; Sampablo et al., 2002; West & Hajek, 1997).

Not only do smokers have worse levels of anxiety and depression, or a greater susceptibility to mental pathology, but there is also a well-documented link between smoking and psychiatric pathology (Sobradiel & García-Vicent, 2007), with a prevalence of more than double among smokers compared to the general population. In addition, these patients carry a greater risk of relapse, higher drop-out rates, more severe withdrawal symptoms — all of which pose a serious challenge to a smoking cessation clinic.

There is sufficient evidence of the efficacy of first-line drugs for quitting smoking (nicotine replacement therapy (NPT), Bupropion and Varenicline) in healthy patients. The evidence with patients suffering mental illness is greater with NPT and Bupropion, and more limited with Varenicline given that patients with this profile did not take part in the marketing studies. Furthermore, following the approval of both drugs, cases began to appear in which the safety of the drug was questioned and the alarm was raised regarding the greater risk of serious neuropsychological effects in both patients with and without a history of psychiatric problems. As a result, the Food and Drug Administration (FDA) in the USA decided to include a "black alert" warning on the drug packaging which is still in place today (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm169988.htm). This in turn provided the motivation for a series of studies (Ahmed et al., 2013; Anthenelli et al., 2013; Cinciripini et al., 2013; Foulds et al., 2013; Garza, Murphy, Tseng, Riordan, & Chatterjee, 2011; Gunnel, Irvine, Wise, Davies, & Martin, 2009; McClure et al., 2009; Kasliwal, Wilton, & Shakir, 2009; McClure et al., 2010; Stapleton et al., 2008; Tonstad, Davies, Flammer, Russ, & Hughes, 2010), some of which were even sponsored by the FDA, with a large range of methodologies and populations with the aim of analysing the possible neuropsychological effects of the drugs in general as well as their efficacy with mentally ill patients, although greater media attention fell on those involving Varenicline. Studies measuring levels of anxiety and depression in a standardised manner are fewer in number (Anthenelli et al., 2013; Cinciripini et al., 2013; Garza et al., 2011; McClure et al., 2009; McClure et al., 2010) and occasionally used complex questionnaires or were based on a measurement of withdrawal symptoms (Cinciripini et al., 2013), and at times limited to a small number of patients (Garza et al., 2011) with controversial results.

Research into the safety of these drugs is still ongoing today and although there are no contraindications to their use with psychiatric patients, careful monitoring of such patients is strongly advised.

Given the above, we attempt to evaluate the influence of a smoking cessation programme on the emotional state of patients by measuring their anxiety/depression levels throughout the treatment and whether a history of mental illness leads to possible differences. The programme was carried out in a secondary hospital unit for quitting smoking.

Material and Methodology

A prospective longitudinal observational cohort study was carried out with consecutive inclusion of patients attending the smoking cessation clinic at Seville's Hospital Universitario Virgen Macarena in order to quit smoking from March 2011 to October 2012. The STROBE declaration guidelines for the publication of observational studies were followed.

Participants

The study included smokers over the age of 18 with an accumulated smoking history of > 10 pack-years who agree to participate in a combined smoking cessation programme (pharmacological treatment plus cognitive behavioural therapy). Exclusion criteria were being an ex-smoker, being pregnant or attempting conception, lactation, inability to understand the questions in the anxiety/depression questionnaire, patients treated with nicotine patches, and refusal to take part in the study. The presence or a history of psychiatric pathology were not grounds for exclusion.

Smoking cessation treatment programme

A combined programme of pharmacological and individualised cognitive-behavioural psychological treatment was carried out with five control points: baseline, 15 days, first, second and third month. On the first visit, the pneumologist, who was the same in each case, established the clinical history, including psychiatric history, and decided on the pharmacological treatment based on the

characteristics of each patient (comorbidity, concomitant medication, cost of treatment and preferences agreed with the patient): Bupropion (150 or 300 mg) or Varenicline (0.5 mg/day for 3 days; 0.5 mg/12 hours from the 4th to 7th day and 1 mg/12 hours from the 8th day on), with a duration of two months in both cases. Rescue nicotine gum was allowed at a decreasing rate over the first few days after complete cessation. The psychologist used a COoximeter of the type Micro-smokerlyzer (Model Micro Co, from Micro Medical Limited, Kent, UK) to measure exhaled CO, the HADS questionnaire (Hospital Anxiety and Depression Scale) (Zigmond & Snaith, 1983), the Fagerström test and the Richmond test. In other follow-up visits possible problems connected with the medication were assessed and abstinence was monitored.

Patients who did not complete the scheduled visits were telephoned to check for possible adverse effects, especially those of a neuropsychiatric nature. Patients who stopped smoking were asked to take a COoximeter test, and those whose abstinence could not be proved (impossible to contact patient and measure CO) were considered to have failed.

Variables:

- Principal variable:
  - Changes in the scores obtained for anxiety and depression symptoms after one month and at three months on the HADS questionnaire, which consists of 14 items divided into two subscales (anxiety and depression). The scores were reported as absolute scores for each subscale and scoring interval. Scores of 11 or above on either scale were considered to represent a high probability of suffering anxiety or depression disorder, scores between 8 and 10 were borderline and scores of 7 or below represented a low probability of this type of disorder.
- Secondary variables
  - Abstinence rate: established by measuring exhaled CO.
  - Adverse effects related to the medication for tobacco cessation: the most frequent adverse effects of the drugs employed, as well as those less frequent (anxiety, suicide ideation, suicide attempts, onset/worsening of psychiatric illness), were registered systematically. Any side effect or symptom that appeared and did not correspond to those mentioned was also recorded. Patients who did not attend follow-up visits were questioned by telephone. The moment symptoms appeared was recorded: early (first few days), first week, second week, third week, first month, second or third month. The intensity of symptoms was measured using a Likert scale from 0 to 3 (0: none, 1: light, 2: moderate, 3: strong).
- Other variables: epidemiological data and personal history, smoking history, motivation levels for quitting smoking (Richmond test) and nicotine dependence (Fagerström test) and assessment of withdrawal symptoms with a specific questionnaire of 12 questions connected to the most frequent symptoms and scored on a 4-point Likert scale from 0 to 3 (0: no withdrawal symptoms, 1: light withdrawal symptoms, 2: moderate, 3: severe).

Statistical analysis

To calculate the sample size, a preliminary analysis of the changes in anxiety/depression levels of a group of patients in the smoking cessation clinic was carried out. The mean baseline and first month anxiety score (which can be extrapolated to depression) was used. Using the program nQuery Advisor to calculate the difference (2.5 ± 2) it was found that 678 patients were needed to obtain a 95% confidence interval with statistical significance at 0.05. To counteract the expected dropout rate of 25% and 20% in the first and third month respectively, typical of a smoking cessation clinic like ours, we arrived at a total sample of 1140 patients.

SPSS version 22.0 (2014) was used for statistical analysis. The descriptive results were analysed for all patients included from the beginning. The abstinence rate was calculated through an intention-to-treat (ITT) analysis in which patients who dropped out during the follow-up were considered to be smokers. Comparisons between groups were made using the chi-square test for variable categories and the t-Student test for continuous variables. The comparison of anxiety and depression scores over time was carried out using a repeated measures analysis. The lowest significance level was considered to be $p < 0.05$. The point estimate was complemented by an estimation of 95% confidence intervals.

Ethical considerations: This study was presented and approved by the Clinical Ethics and Research Committee of the Hospital Universitario Virgen Macarena in Seville, Spain.

Results

Participants

The study included 1144 patients from March 2011 to October 2012. The dropout rate during patient follow-up was high at 25.6% in the first month and an additional 20.3% in the third (Figure 1) and due to programme abandonment in all cases. However, the likelihood of this was taken into account at the study design stage. An analysis of the population characteristics over the follow-up was made, and despite the losses, the population remained homogeneous. The characteristics of the study's final population of 678

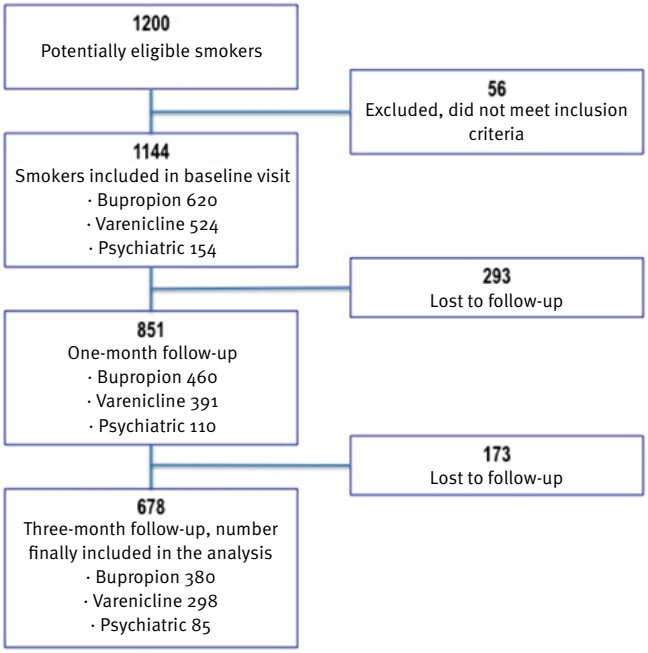


Figure 1. Data samples

patients can be seen in Table 1. The patients who completed the follow-up were middle-aged (49.9 ± 11 years of age), with slightly more men than women and a relatively high accumulated tobacco consumption (37.4 ± 22.2 pack-years). Almost half showed cardiovascular risk factors (46.6%) and around 15% were diagnosed with COPD or sleep apnea syndrome. We found that 12.6% of the patients had at some point in their lives been diagnosed with psychiatric illness, the majority of which (63.5%) were cases of depression. The majority were highly motivated to quit smoking and almost half were heavily nicotine dependent.

Psychiatric patients

The prevalence of psychiatric symptoms at the clinic was 13.4%. Of these, 85 patients completed the programme. The general characteristics of this subgroup are detailed in Table 1. Depression was the most frequent of the psychiatric diagnoses (54 cases), followed by anxiety disorder (27 cases). Four patients were diagnosed with other problems: schizophrenia (1), phobias (2), bipolar (1). Twenty-four of the patients had been hospitalised for decompensation of their psychiatric symptoms at some point in their lives and seven had attempted suicide. Mean age was similar to that of other patients, although there was a clear predominance of women and less motivation to quit (7.7 ± 1.3 among those with psychiatric symptoms vs 8.1 ± 1.2 without; $p < 0.05$).

Drugs against psychiatric illnesses were taken by 72% (benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, IMAOs, antipsychotics …).

Changes in anxiety and depression

The mean baseline score for anxiety was 9.2 ± 4.6 points, which is in the "borderline" category for screening. However, the mean baseline score for depression fell within the "low probability" range: 5.5 ± 4.1 (Table 2), and we can highlight

Table 1. *General characteristics of the population finally included in the study.*

Characteristics	Final population n=678	Non-psychiatric n=593	Psychiatric n=85	p
Age (years)	49.9 ± 11	49.7± 11	51.1± 11.8	0.593
Males (%)	57.5	61.7	28.2 **	**0.000**
Smoking onset age (years)	15.8 ± 5.2	15.6± 4.2	17.5± 9.3	0.578
Accumulated smoking (pack years)	37.4 ± 22.2	37.9± 22.5	34.2± 19.6	0.538
Comorbidity (%)				
COPD	15.2	15.3	14.1	0.718
CVRF†	46.6	45.7	52.9	0.834
OSAHS	15.6	16	12.9	0.640
Psychiatric#	12.6	---	---	---
Richmond Test Total+	8 ± 1.2	8.1± 1.2	7.7± 1.3 *	**0.033**
Low (%)	5.9	5.6	8.2	
Moderate (%)	5	4.9	5.9	
High (%)	89.1	89.5	85.9	
Fagerström Test Total+	6 ± 2.4	6± 2.4	6.2± 2.3 *	**0.012**
Light (%)	21.2	22.3	14.1	
Moderate (%)	32.7	32.9	31.8	
High (%)	46	44.9	54.1	
Treatment (%)				
Bupropion	56	59.7	30 **	**0.000**
Varenicline	44	40.3	70 **	**0.000**

Note. Data are expressed in means ± standard deviation and absolute frequency (%).
*p<0.05, **p<0.01; comparisons between smokers without and with psychiatric history.
† Cardiovascular risk factors (PAH, DM, DLP, ischemic cardiopathy)
#Includes anxiety, depression and others (schizophrenia, bipolar disorder, phobias, ...)
+Richmond and Fagerström tests: total tests and by interval (≤4 points: low/light; 5-6 points: moderate and ≥ 7 points: high)

the fact that up to 70.3% of these patients also scored low for anxiety.

An analysis of what happened to anxiety and depression levels once the patients stopped smoking revealed a significant fall in the total HADS score as well as in both of its subscales (anxiety and depression) over the three months of the programme (Table 2, Figures 2 and 3). The significance was maintained when comparing the reductions of the beginning of the month with the first month, the first month with the third month, and the beginning with the third month in all of the cases. The decrease between the second and third month remained progressive and significant despite patients being free of medication at that point.

Psychiatric patients

The baseline HADS scores for this subgroup of patients were significantly higher in both subscales than those obtained by the non-psychiatric patients, falling within the high probability range in the case of anxiety. Despite this, scores for both anxiety and depression declined significantly over the course of treatment in both groups, with no differences being found at one month or at three months (Table 2, Figures 4 and 5).

Treatment subgroup

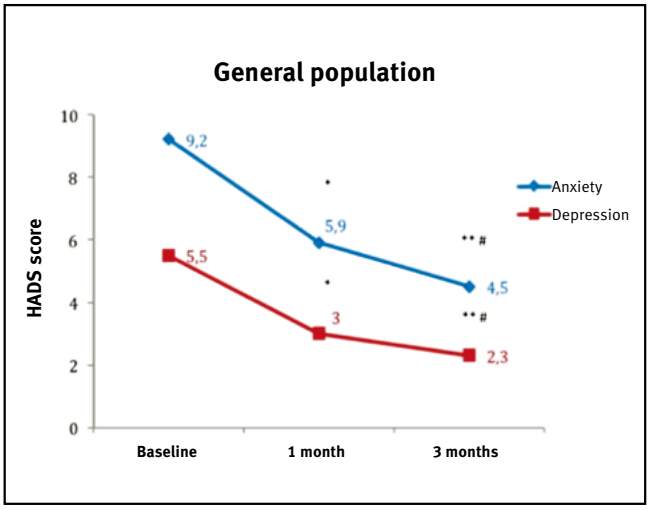
Although the study was not designed to carry out a comparison between the different drugs involved, we did compare treatment groups and found that both groups were homogeneous in all the characteristics assessed.

At baseline, the scores for anxiety were higher in both treatment groups than those for depression. Independently of this, both scores decreased significantly during the follow-up period (Table 2, Figures 4 and 5).

Table 2. *Changes in the global levels of anxiety and depression over the duration of the programme and by population group.*

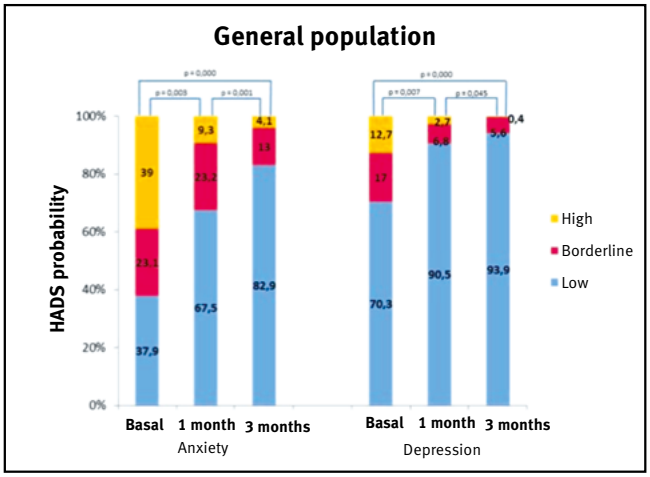
	Anxiety			Depression		
	Baseline	**1 month**	**3 months**	**Baseline**	**1 month**	**3 months**
Total population (n=678)	9,2±4,6	5,9±3,6 *	4,5±3,1 ** #	5,5±4,1	3±3 *	2,3±2,1 ** #
Non-psychiatric (n=593)	8,9±4,5	5,7±3,6 *	4,4±3** #	5,3±4	2,8±2,6 *	2,2±2,1 **#
Psychiatric (n=85)	11,3±4,5	7,1±3,7 *	5,3±3,5 ** #	7,4±4,8	4,2±3,6 *	3±2,9 ** #
Bupropion (n=380) Varenicline (n=298)	8,9±4,6 9,6±4,7	5,9±3,7* 6±3,5 *	4,4±3 ** # 4,6±3,2** #	5,4±4 5,8±4,3	2,9±2,5 * 3±2,7 *	2,2±2** # 2,4±2,1** #

Note. Data is expressed in mean total scores obtained in the HADS questionnaire for each of the anxiety and depression subscales ± standard deviation. * p<0.001 Comparisons made between baseline and 1 month; ** p<0.001 Comparisons between baseline – 3 months; # p<0.001. Comparisons between 1 month – 3 months.



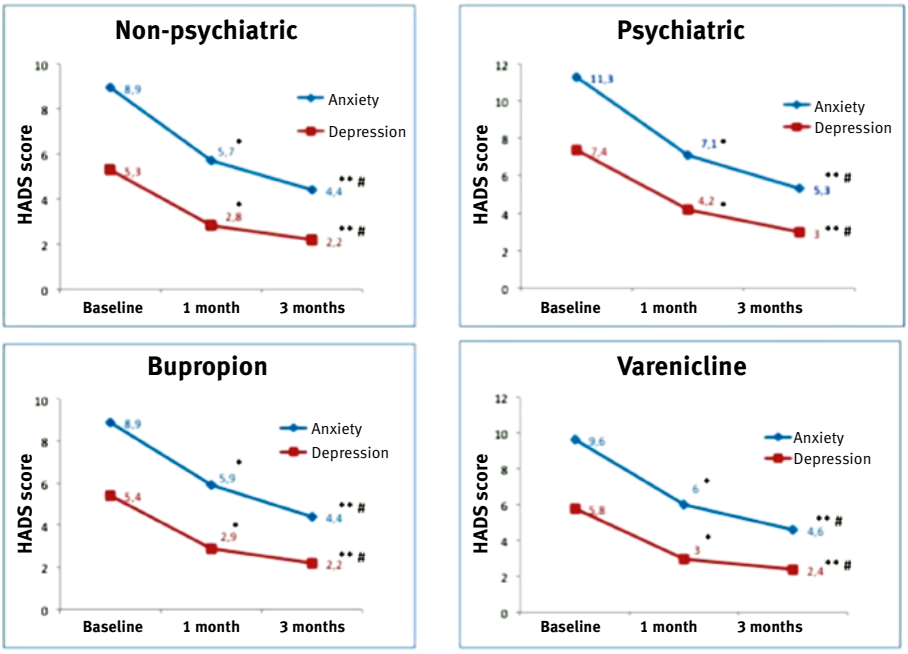
Note. The data is expressed as the mean of total points obtained in the HADS questionnaire for each of the anxiety and depression subscales.
* p<0.001 Comparisons between baseline – 1 month; ** p<0.001 Comparisons between baseline – 3 months; # p<0.001 Comparisons between 1 month – 3 months.

Figure 2. Change in global anxiety and depression levels based on HADS in the general population.



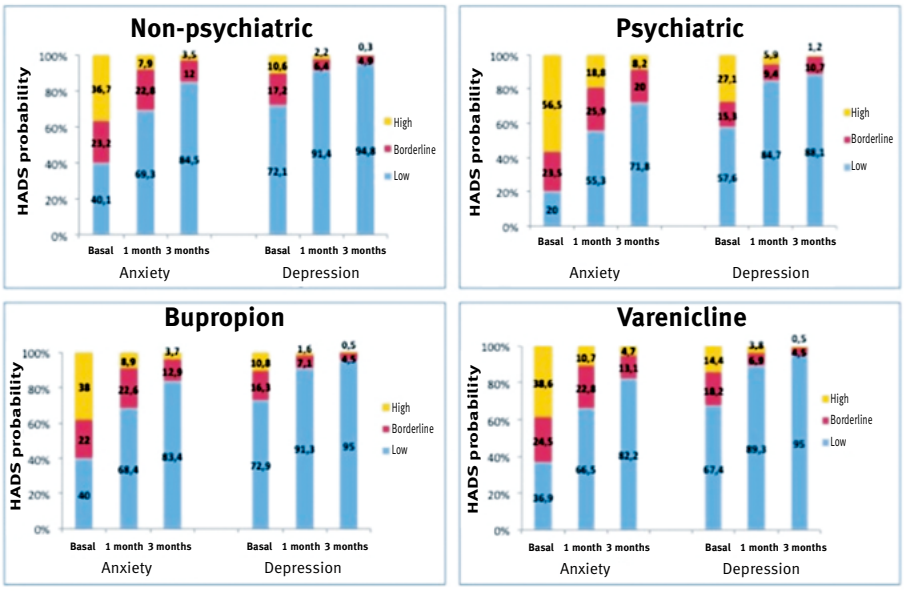
Note. Data are expressed as absolute frequency (%) of patients in each probability group for diagnosis of anxiety or depressive syndrome based on the HADS questionnaire scores for anxiety subscale (0-7 points: low probability, 8-10 points: borderline, › or equal to 11: high probability). Significant comparisons in all cases at p<0.05.

Figure 3. Changes in the levels of anxiety and depression by the probability of suffering anxiety or depression disorder during the programme in the general population.



Note. The data are expressed as mean total points scored on the HADS questionnaire for each of the anxiety and depression subscales. * p<0.001 Comparisons between baseline – 1 month; ** p<0.001 Comparisons between baseline – 3 months; # p<0.001 Comparisons between 1 month – 3 months.

Figure 4. Changes in global anxiety and depression levels based on the HADS questionnaire by population subgroup.



Note. The data are expressed as absolute frequency (%) of patients in each probability group for diagnosis of anxiety or depressive syndrome based on the HADS questionnaire scores for anxiety subscale (0-7 points: low probability, 8-10 points: borderline, › or equal to 11: high probability). Significant comparisons in all cases at p<0.05.

Figure 5. Changes in anxiety and depression levels depending on the probability of suffering anxiety or depression disorder during the programme by population subgroup.

Results of the programme

The abstinence rate at three months on our programme was 58.5%, with 60.8% and 55% quit rates for those taking Bupropion and Varenicline respectively. Among psychiatric patients, abstinence was achieved by a slightly lower percentage (53.2%) than in the total. We found no differences in the baseline levels of anxiety and depression between the patients who managed to give up smoking and those who did not, either in the general population or the psychiatric patient subgroup (Table 3).

Analysis of adverse effects by treatment

An analysis was carried out of the impact of adverse effects reported during the course of treatment, with patients who dropped out being contacted by telephone. Those we did not manage to contact were labelled as lost to follow-up. This left a final total population of 1052 (92% of the sample). The most frequent adverse effects reported globally were nervousness (36.2%), nausea (22%), insomnia (18.9%) and dryness of the mouth (12.1%). Other adverse effects were present only on a very small scale. The majority were slight (98%) and appeared early. Serious side effects

Table 3. *Abstinence rates at 3 months and baseline anxiety and depression values by smoker status.*

	Smoker	CO#	Anxiety	Depression	Non smoker	CO#	Anxiety	Depression
Total population (n=1144)	41,5	31,6±12,9	9,5±4,8	5,8±4	58,5	1,9±0,5	9,2±4,7	5,5±4,1
Psychiatric (n=154)	46,8	33,2±16,1	11,1±4,6	7±4,2	53,2	2±0,7	11,7±4,4	7,5±4,8

Note. Data is expressed as %age of patients who smoke and do not smoke, results of CO-oximetry in parts per billion (ppb) and total points obtained in the HADS questionnaire for each of the anxiety and depression subscales.
#CO: measurement of carbon monoxide in expired air by CO-oximetry.
*Significance at p<0.05, comparisons between smokers and non-smokers.

Table 4. *Global incidence of adverse effects connected with the treatment of withdrawal symptoms in the general and psychiatric populations.*

	General population (n: 1052)				Psychiatric population (n: 145)			
Adverse effect	**Incidence**	**Slight**	**Moderate**	**Severe**	**Incidence**	**Slight**	**Moderate**	**Severe**
Nausea	22	62,1	37,9	0	23,4	79,4	20,6	0
Vomiting	4,4	100	0	0	1,4	100	0	0
Constipation	1,4	80	20	0	3,4	80	25	0
Abdominal pain	2,7	55,5	44,5	0	2,7	100	0	0
Headaches	5,3	78,6	19,4	0	10,3	100	0	0
Dryness of the mouth	12,1	49,6	49,6	0,8	15,1	59	31,8	9,2
Pseudo flu	2,9	80,6	19,4	0	2,7	100	0	0
Insomnia	18,9	50	46,7	3,3	18,6	51,8	44,5	3,7
Nightmares	6,9	65,7	27,3	7	10,3	73,3	20	6,7
Nervousness	36,2	39,1	59,9	1	37,2	35,2	57,4	7,4
Mood disorders	3,2	52,9	44,1	3	4,8	100	0	0
Severe mental events*	0	0	0	0	0	0	0	0

Note. Results expressed as %ages. *Suicide ideation, hospitalization for exacerbated mental pathology.

were exceptional and only reported as nightmares (7%), insomnia (3.3%), mood disorders (3%), nervousness (1%) and dryness of the mouth (0.8%). In no case was it necessary to withdraw the drug (Table 4). The side effects reported by the psychiatric patients were similar to those described by the general population, as can be seen in Table 4, while Table 5 shows adverse effects by drug used.

Discussion

The results of our study display a notable and progressive reduction in levels of anxiety and depression over the duration of the smoking cessation programme, independently of baseline levels and whether or not patients suffered psychiatric symptoms prior to the start of treatment and even in the month after the end of treatment. Abstinence rates at three months were good, both for Bupropion and Varenicline, and initial levels of anxiety and depression did not appear to influence results.

With regard to initial anxiety and depression levels, the levels we found in smokers attended in our unit were not as high as the literature had led us to expect (Bolam et al., 2011; Lagrue et al., 2002; Marqueta et al., 2010; Mykletun et al., 2008; Waal-Manning & de Hamel, 1978), and although their levels of anxiety were higher than those of depression, in no case were they of high probability for either diagnosis, according to the HADS. Nevertheless, our initial scores are in line with those found in studies such as Sampablo (2002) or Dawkins (2009) which used the same questionnaire in specific populations of smokers. Both studies, albeit with very small sample sizes, yielded higher scores for anxiety than depression, but in neither case did they fall in the pathological range.

The most relevant findings in our research were obtained when analysing the results of monitoring anxiety and depression levels at one and three months after quitting with a simple tool such as the HADS. Independently of baseline levels we found, for example, that there was a significant improvement in both throughout the follow-up, with a 4.7 point fall in anxiety at the end of the of the follow-up, and a 3.2 point drop in depression, reaching levels considered to be non-pathological. These results again match those reported by other authors (Anthenelli et al., 2013; Dawkins et al., 2009; Foulds et al., 2013; Marqueta et

Table 5. *Incidence of adverse effects connected with the treatment of withdrawal symptoms by drug used.*

	BUPROPION (n=554)				VARENICLINE (n=498)			
Adverse effect	**Incidence Nº / %**	**Slight**	**Moderate**	**Severe**	**Incidence Nº / %**	**Slight**	**Moderate**	**Severe**
Nausea	26 / 4,7	100	0	0	206 / 41,3	57,3	42,7	0
Vomiting	0 / 0	0	0	0	46 / 9,2	100	0	0
Constipation	1 / 0,2	100	0	0	14 / 2,8	78,6	21,4	0
Abdominal pain	5 / 0,9	100	0	0	13 / 2,6	38,5	61,5	0
Headaches	45 / 8,1	75,5	24,5	0	11 / 2,2	100	0	0
Dryness of the mouth	108 / 19,5	40,7	58,4	0,9	19 / 3,8	100	0	0
Pseudo flu	15 / 2,3	86,6	13,4	0	16 / 3,2	75	25	0
Insomnia	148 / 26,7	54	46	0	51 / 10,2	39,2	49	11,8
Nightmares	13 / 2,3	84,6	15,4	0	60 / 12	61,7	30	8,3
Nervousness	156 / 28,1	30,1	69,3	0,6	225 / 45,2	45,4	53,3	1,3
Mood disorders	9 / 1,6	45,5	55,5	0	25 / 5	56	40	4
Severe mental events*	0 / 0	0	0	0	0 / 0	0	0	0

Note. Results expressed as %ages. *Suicide ideation, hospitalization for exacerbated mental pathology. #Cases: number of cases with side effects compared to number of cases assessed.

al., 2010; McClure et al., 2009; McDermott et al., 2013; West et al., 1997), although different measurement approaches to ours were used (Anthenelli et al., 2013; Marqueta et al., 2010; McClure et al., 2009; McDermott et al., 2013) and/or a follow-up of just one month (West et al., 1997). The study by Marqueta (Marqueta et al., 2010) with more than 500 patients is notable, and although it only measured anxiety with the State-Trait Anxiety Inventory (STAI) it showed how this improved significantly until the third month of follow-up, albeit with an anxiety peak in the days leading up to and after quitting smoking. In line with our own research, the majority of these studies have revealed an improvement from the first month onward, a time when withdrawal symptoms are strongest (20 days without smoking), and some authors have attributed an anxiogenic effect to nicotine (West et al., 1997). In some cases, however, it appears that the improvement flattens out after the first month both for anxiety (Marqueta et al., 2010; Dawkins et al., 2009; McDermott et al., 2013) and for depression (Dawkins et al., 2009; McClure et al., 2009), although in our case it was persistent and significant.

The research of Sampablo (2002) provides a striking contrast to our results. He found that after 6 months of monitoring, those smokers who managed to give up appeared to have progressively higher anxiety levels than those who failed to stop, although the scores for depression were worse among those who continued to smoke. It should be noted, however, that the sample size was rather small (50 patients) and the treatment to quit smoking used Bupropion exclusively, without behavioural support. Similarly, Garza (2011), in a study with healthy patients treated with Varenicline versus placebo, did not show any improvement in anxiety and depression scores either, with initial values practically normal in both groups and deterioration peaking in the third week (the height of withdrawal symptoms). It is worth mentioning that in our study, the smoking cessation programme combined pharmacological with behavioural treatment, and that psychological support was maintained throughout follow-up, which could be a determining factor behind the improvement.

Psychiatric patients

Psychiatric symptoms were found in 13.4% of cases, a level below that reported in other research (Gutiérrez, Otero, del Amo, & Ayesta, 2013; Marqueta et al., 2010; McDermott et al., 2013; Purvis, Mambourg, BalvanzMagallon, & Pham, 2009; Sobradiel et al., 2007; Stapleton et al., 2008), which estimated a prevalence of between 18.7% (McDermott et al., 2013) and 48% (in more selected populations) (Purvis et al., 2009) among smokers, and around 45% among those who request help to stop smoking (Sobradiel et al., 2007).

These patients had worse scores in anxiety and depression compared to healthy participants, although there was clear improvement over time even though more than half had previously been diagnosed with depressive syndrome. Our results are borne out by the findings of McClure (2009), in which higher initial depression scores were found on comparing smokers with and without depression, but with progressive improvement in both patient groups in the first month, which remained stable in the third. However, a recent study carried out exclusively with a group of more than 500 smokers diagnosed with depressive syndrome (Anthenelli et al., 2013) reports a mean score for their patients which could be considered normal for anxiety and

depression, although they did not include other psychiatric diagnoses.

Treatment subgroups

Although we have already stated that the aim of the present study was not to compare Bupropion and Varenicline, we did independently assess the development of anxiety and depression levels with each of the drugs involved. Both treatment groups showed clear improvements in these levels from the first month which were progressive and comparable until the third month for both Bupropion and Varenicline, even when taking into account that the latter was used over a shorter period than that recommended in order to improve treatment compliance. Because the decrease in anxiety and depression in the first two months could be conditioned by the pharmacological treatment applied, it is important to highlight the fact that once both drugs were stopped the differences between the second and third month remained significant and the symptoms continued to decrease.

Abstinence rate

The abstinence rate was high (58.5%) even when including the psychiatric group, which stopped smoking in more than half the cases (53%), possibly influenced by the characteristics of the study and the close patient follow-up. The results of the psychiatric population in particular stand out, despite what is described in the literature, where higher dropout ratios and greater difficulty in giving up smoking is reported in the psychiatric patient group (Killen et al., 2008). These results may be explained, however, by the fact that a broad range of patients were included under the concept of psychiatric pathology, from those who were diagnosed with a condition at the beginning of the study to those who had at some point in their lives suffered symptoms. There is a study, for example, which measured abstinence rates at 12 months with different treatment approaches and reported results in line with ours when comparing the same type of treatment (psychological plus pharmacological) at three months, and which did not find a link between abstinence results and psychiatric history either (Raich et al., 2015). Although most researchers assessing abstinence rates with different drugs exclude the psychiatric population from their methodology, there are some studies, such as that of McClure (McClure et al., 2009), which do not report differences in terms of abstinence between patients with and without depression treated with Varenicline and present similar rates to ours (48%), and even higher in the case of Stapleton (Stapleton et al., 2008). Conversely, data have been reported elsewhere which suggest abstinence rates up to 30% worse among psychiatric patients, as in the research carried out by Purvis (2009), albeit it with a very small and selected sample of patients. Recently, Cinciripini (2013) has reported abstinence rates of 38% and 37% for Bupropion and Varenicline respectively at three months, although in a population with no psychiatric history. These results were similar to those of Anthinelli (2013) using Varenicline with depressive patients (36%), and although these rates are considerably lower than ours, the approach on which they are based did not include cognitive-behavioural treatment. Finally, it is worth pointing out that no baseline differences in anxiety and depression were found between those who managed to quit smoking and those who did not.

Side effects

An analysis of adverse events was even carried out one month after treatment ended and included possible long term effects. Varenicline produced a considerable number of side effects, with almost half the patients reporting nervousness (42.5%) and a large number suffering nausea (41.3%). It should be noted that, in terms of nausea, while these results are higher than those found in clinical trials carried out prior to the commercialization of the drug (Gonzalez et al., 2006; Jorenby et al., 2006) at around 29% or in more recent research (Cinciripini et al., 2013), they are more in line with other later series which included psychiatric patients (McClure et al., 2009; McClure et al., 2010; Stapleton et al., 2008; Kasliwal et al., 2009), which found a range of incidence rates between 38% and 63% in some cases. Nevertheless, the drug was well tolerated and in no case was it necessary to suspend treatment, although it is true that treatment was of shorter duration than normal. Bupropion had a lower incidence of adverse events, with nervousness and insomnia being the most frequent (28.1% and 26.7% respectively), in line with percentages described in the literature (Cinciripini et al., 2013; Gonzalez et al., 2006; Jorenby et al., 2006). Although our study is not powerful enough to detect unusual adverse events, it can be highlighted that no serious neuropsychiatric effects were registered with any of the drugs used. This is supported by the most recently published results in the literature (Meszaros et al., 2013; Thomas et al., 2013) and other classic studies (Tonstad et al., 2010), which in some cases include a psychiatric population, as we have done (Stapleton et al., 2008). In contrast to our findings, there are some controversial results in the literature, with some studies reporting a high risk of serious neuropsychiatric effects, in particular hospitalization and suicide ideation, in some cases with greater propensity if patients had a psychiatric history (Ahmed et al., 2013; Moore, Furberg, Glenmullen, Maltsberger, & Singh, 2011; Kasliwal et al., 2009).

Potential limitations

The above notwithstanding, our study is subject to a number of limitations. One of the most important is the losses to follow-up. These may produce a bias in the evaluation of results given that we cannot know the levels of anxiety and depression in the patients who abandoned the programme. In principle, this can be offset by the fact that

a comparison of the population's general characteristics was made at the beginning and finally included in the study which showed that they were very similar, including baseline scores for anxiety and depression. Therefore, at least the initial levels of anxiety and depression did not condition the losses to follow-up. Nevertheless, it would have been interesting to assess the levels of anxiety and depression at the point of dropout and to determine whether they gave rise to relapses.

A further limitation to take into account is the short duration of follow-up (three months) since it has been noted that depressive episodes can arise in the long term after quitting smoking. However, the aim of our research is to determine the connection of this type of symptomatology with the use of specific treatment for smoking cessation. Thus the three month follow-up period (which includes one month after the end of pharmacological treatment) guarantees the monitoring of any anxio-depressive symptomatology which could be linked to the actual taking of the medicine.

Conclusions

the smokers on our programme presented moderately high baseline levels of anxiety. Psychiatric patients, which made up 13.4% of the sample had even higher baseline anxiety levels. These levels, however, descended significantly over the three month duration of the smoking cessation programme. The improvement was more marked during the first month, when withdrawal symptoms are at their strongest. The psychiatric patients followed a similar pattern, although they started from a worse baseline situation. Furthermore, the programme achieved a high success rate at three months (58.5%), with similar results independently of the presence of psychiatric pathology. The improvement in anxiety and depression levels was brought about with the different drugs used, which were relatively safe given that although adverse effects were rather frequent, they were in general light and did not lead to an interruption of treatment. We should therefore provide multicomponent smoking cessation treatment even for patients with psychiatric illnesses, incorporating the monitoring of possible neuropsychiatric effects alongside anxiety and depression levels with simple tools integrated into the routine of smoking cessation consultation.

Acknowledgements

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Conflict of interests

The authors declare no conflict of interest.

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Mobile Abuse in University Students and Profiles of Victimization and Aggression

Abuso del móvil en estudiantes universitarios y perfiles de victimización y agresión

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Abstract

The vast majority of young people have mobile phones. This has become a must-have item in their lives, with traditional socialization spaces displaced by virtual ones. They use their mobile phones for many hours a day, to the detriment of their psychological and social functioning, showing greater vulnerability to abusive or excessive use, and more likely to become problematic or addicted users. This paper aims to study the impact of mobile phone abuse in a sample of college students, assessing the social, personal, and communicational realms and deepening understanding of the different cyberbullying profiles, analyzing who has more personal and social problems using mobiles: victims or aggressors. Whether the number of hours of mobile phone use has an effect on these problems will also be explored. The sample (1,200 students) was selected by multistage cluster sampling among the faculties of the University of Extremadura. Data were obtained through Victimization (CYB-VIC) and Aggression (CYB-AGRES) through the mobile phone scales, and the Questionnaire of Experiences related to Mobile (CERM). The results show that mobile phone abuse generates conflicts in young people of both sexes, although girls have more communication and emotional problems than boys. In addition, age, field of knowledge, victim/aggressor profile, and hours of mobile phone use are crucial variables in the communication and emotional conflicts arising from the misuse of mobile.

Keywords: Abuse mobile; Profiles *ciberacoso*; Aggressor; Victim and university students.

Resumen

La gran mayoría de jóvenes disponen de teléfono móvil, convirtiéndose en un objeto imprescindible en su vida, que ha desplazado los espacios de socialización tradicionales por espacios virtuales. Es utilizado por ellos, durante muchas horas, en detrimento de su funcionamiento psicológico y social, mostrando mayor vulnerabilidad a su uso abusivo o excesivo, y mayor propensión a convertirse en un uso problemático o adictivo. En este trabajo se pretende estudiar las repercusiones sociales, personales y comunicacionales del abuso del móvil de los estudiantes universitarios, y profundizar en los diferentes perfiles del ciberacoso, analizando quién presenta más problemas personales y sociales con el uso del móvil: ¿víctimas o agresores? También si el número de horas de uso del móvil tiene un efecto sobre dichos problemas. La muestra (1200 estudiantes) fue seleccionada mediante muestreo polietápico por conglomerados de entre las distintas Facultades de la Universidad de Extremadura. Los datos fueron obtenidos a través de las Escalas de Victimización (CYB-VIC) y Agresión (CYB-AGRES) a través del Teléfono Móvil y el Cuestionario de Experiencias relacionadas con el Móvil (CERM). Los resultados muestran que el uso abusivo del móvil genera conflictos en los jóvenes de ambos sexos; aunque las chicas manifiestan más problemas comunicacionales y emocionales que los chicos. Además, la edad, el campo de conocimiento, el perfil víctima/agresor y las horas de uso del móvil son variables determinantes sobre los conflictos comunicacionales y emocionales derivados del uso abusivo del móvil.

Palabras clave: Abuso del móvil; Perfiles de ciberacoso; Agresor; víctima; Estudiantes universitarios

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The use of Information Technology and Communications (ICT) is an essential aspect of modern societies. Access to such tools is increasingly easy and their use is not problem-free. Among ICTs, the mobile phone (smartphone) is the most popular. The intensive use of smartphones has been a cause of concern to researchers and institutions alike (Gómez, Rial, Braña, Varela & Barreiro, 2014). While their use does not in itself pose a problem, the problematic relationship established with them does (Chóliz, 2010; Echeburúa, Labrador & Becoña, 2009) because their use over a large number of hours a day or in an uncontrolled manner can condition social relationships (Bianchi & Phillips, 2005; Kamibeppu & Sugiura, 2005).

There is no agreement on what constitutes a borderline between overuse and problematic or pathological use, since the term ICT "addiction" has not yet been officially recognized by international organizations such as the American Psychiatric Association (APA) or the World Health Organization (Labrador, Villadangos, Crespo & Becoña, 2013; López-Fernández, Honrubia-Serrano & Freixa-Blanxart, 2012). However, there is evidence of the onset of behavioral, emotional and social problems related to mobile phone use, especially among adolescents and young people (Pedrero, Rodriguez & Ruiz, 2012).

College students and the adolescent population are the age groups considered to be at highest risk (Weare, 2004); the mobile phone is of much greater importance for them than for other age groups (Kubey, Lavin & Barrow, 2001; Morahan-Martin & Schumacher, 2000; Treuer, Fabián & Friredi, 2001). The vast majority of young people have one and it is turning into a must-have item in their lives and leisure time. The mobile is fundamentally a relational tool (Aguado & Martínez, 2006) that provides the user with the necessary processes of communication and socialization (Ellwood-Clayton, 2003; INE, 2014; Taylor & Harper, 2003) to the extent that it has displaced traditional socialization spaces, giving rise to virtual spaces with an important social function (Díaz-Gandasegui, 2011). Being permanently connected seems to satisfy a great need for constant contact with peers (Kuss & Griffiths, 2011). Once young people have a mobile they appear unable to do without it, using it for many hours to the detriment of their psychological and social functioning (Pedrero, Rodríguez & Ruiz, 2012), showing greater vulnerability to overuse (Ruiz-Olivares, Lucena, Pino & Herruzo, 2010) and a higher likelihood of becoming problematic or addictive users (Walsh, White & Young, 2008). Boys are more prone to the intensive use of mobiles for games and technology functions for leisure or entertainment (Chóliz & Villanueva, 2011; Chóliz, Villanueva & Chóliz, 2009; Pedrero, Rodriguez & Ruiz, 2012). For them the mobile is an element that helps them advance their social position within the group (Ling, 2002). For girls, on the other hand, mobile phone use has aspects that are more emotional (Beranuy, Chamarro, Graner & Carbonell, 2009; Chóliz, Villanueva & Chóliz, 2009; Ling, 2002; Mante & Piris, 2002), relational and social, showing a preference for written messages (Pedrero, Rodriguez & Ruiz, 2012) and spending more hours talking on the phone (Ruiz-Olivares et al., 2010) in order to maintain interpersonal relationships, promote bonding and boost intimacy in communications (Colás, González & de Pablos, 2013; Costa, 2011; De Haro, 2010).

The mobile phone is ubiquitous on university campuses and often used in environments where learning takes place (Lepp, Barkley & Karpinski, 2015; Tindell & Bohlander 2012). In addition to recreational purposes (Barkley & Lepp, 2013), university students use mobile phones to find information about their studies, communicate, organize and collaborate with peers (Organista-Sandoval, McAnally-Salas & Lavigne, 2013). In these areas, certain differences in the frequency or type of use in terms of gender, age and field knowledge of university students have been noted (Ruiz-Olivares et al., 2010). As a result, studying the differences in the emotional and communicational impact of mobile phone abuse in terms of these variables is important.

Currently, the exponential rise in the use of ICTs, as well as the mastery and familiarity of young people (the interactive generation) with these technologies has meant that traditional forms of bullying have changed over time, with the appearance of more specific phenomena in which ICTs are used to harass the victim (Smith, Mahdavi, Carvalho & Tippett, 2006). This new form of abuse, called cyberbullying, consists of intentional and repeated aggression by a group or an individual continuously using digital forms of social contact (mainly Internet, mobile phones and online video games) on a victim who cannot defend him/herself (León, Felipe, Fajardo & Gómez, 2012).

Cyberbullying is a variation on conventional types of abuse (physical, verbal and social-relational), but also has certain characteristics that set it apart (Heirman & Walrave, 2009; Li, 2008; Ortega, Calmaestra & Mora-Merchan, 2008; Slonge & Smith, 2008; Ybarra & Mitchell, 2004): in cyberbullying there are no safe places to be, which creates greater insecurity in the victim; the fact that bullying can even take place inside your own home causes feelings of helplessness and vulnerability. Harassment is made public and can be observed indefinitely and by a large number of people. Physical strength or size do not play a role because digital stalkers do not need to be stronger than their victims. Finally, the aggressors can hide behind a cloak of anonymity, which creates a sense of helplessness among the victims.

The increasing use of mobile telephones and the overexposure to social networks catch our attention and cause social alarm, particularly since it was discovered that young people and adolescents are exposed to cyberbullying (Gá-

mez-Guadix, Orue, Smith & Calvete, 2013), either as aggressors or victims. The mobile phone is the device most commonly used to harass, torment and intimidate others deliberately and repeatedly (Del Río, Bringué, Sádaba & González, 2009). Sádaba and Bringué (2010) have defined it as "the screen that never goes out". Having a mobile phone at hand at all times means being able to participate in bullying others at any time and anywhere, and also to be continuously exposed to bullying for most of the day. A study by Giménez, Maquilón and Arnaiz (2015) affirms that internet access via smartphone is significantly associated with participation in episodes of cyberbullying. They show that 94.2% of cyber attackers have their own mobile phones, and 80.2% access the internet through it, compared with 94.7% of cyber victims. Among the mobile technology applications principally used by both sides are "WhatsApp", voice calls (Giménez, Maquilón & Arnaiz, 2014) and social networks.

Going to university is a transition period which in many cases involves becoming independent of the family, experiencing stress in the new situation or looking for new friends, circumstances that can lead to a change in internet use (Fernandez-Villa et al., 2015). All of this, alongside young people's exposure to cyberbullying, means that university students are a population of special interest for the study of behaviors related to cyberbullying.

This paper aims to study the social, personal and communicational repercussions of mobile phone abuse in terms of gender, age, field of knowledge and number of hours of mobile use of college students, and to deepen our knowledge of the different profiles of cyberbullying, analyzing who has greater personal and social problems using mobile phones: victims or aggressors. Furthermore, we will investigate whether the number of hours of mobile phone use affects these problems, given the negative effects that technological harassment has on victims and aggressors at emotional, academic and psychosocial levels.

Method

Participants

The inclusion criterion for participants was being enrolled in the University of Extremadura for the 2014-2015 academic year. The participant sample consisted of 1,200 students. Average age was 20.95 years (SD = 3.430; range 18-32); 58.4% (n = 700) were women and 41.6% (n = 500) men. Students were enrolled in the first (50.9%), second (25%), third (17.5%) and fourth (5.8%) years of different degree courses in the University of Extremadura. The number of participants was determined by the number of students enrolled in the 2014-2015 academic year, given a sampling error of 3% and a confidence level of 95.5%. Student selection was carried out using multistage cluster sampling and random selection of degree and year of students in the University of Extremadura faculties. Not all students reported their age and field of scientific knowledge, with the result that 120 and 88 cases respectively were lost in the analyses of age and field of knowledge,.

Measurement Tools

Sociodemographic questionnaire, specifically developed for research, containing questions about students' age, gender, field of scientific knowledge and their subjective perception of hours of daily mobile use.

Victimization through mobile phone scale, CYB-VIC (Buelga, Cava & Musitu, 2010). This scale aims to determine the number of victimizations sustained during the past year through the mobile phone and occurring in a particular context. The victimization scale consists of 10 items assessing behaviors which involve aggression: 1) Harassment "They have insulted or ridiculed me with messages or calls"; 2) persecution "They have threatened me, with the intention of scaring me"; 3) vilification "They have told false rumors or lies about me"; 4) violation of privacy "They have shared my secrets with others"; 5) social exclusion "They have called me/told me to be online/but did not speak or meet me"; 6) identity theft "They have pretended to be me in order to say or do bad things online". Responses were made on a four-point Likert scale, with the following options: 1 = never, 2 = rarely, 3 = often 4 = always. The validation of the Buelga, Cava and Musitu scale (2012), yielded a Cronbach alpha reliability coefficient (α) of 0.85. With our participants the following indices were obtained: α = 0.75, composite reliability (CR) = 0.79, with an average variance extracted (AVE) of 0.50. These indices indicate an adequate overall level of reliability.

Aggression through mobile phone scale, CYB-AGRES (Buelga & Pons, 2012). This scale attempts to establish the number of cyber aggressions committed during the past year using the mobile phone. The scale consists of 10 items assessing behaviors which involve aggression: 1) harassment "I have insulted or ridiculed people with messages or calls"; 2) persecution "I have threatened people in order to frighten them "; 3) vilification "I have told lies or false rumors about someone"; 4) violation of privacy "I have told other people's secrets in order to annoy them"; 5) social exclusion "I made calls and did not speak, or I told people to be online and did not meet them there"; 6) identity theft "I have pretended to be someone else in order to say or do bad things by mobile phone or internet." Responses were made on a four-point Likert scale (never, rarely, often and always). The α reliability coefficient of the scale obtained in the Buelga and Pons study (2012) was 0.88. With our participants, the scale yielded an α of 0.82, FC = 0.85, and AVE = 0.52.

Questionnaire of Experiences related to Mobile, CERM (Beranuy et al., 2009). This questionnaire is designed to examine the degree of "addiction" to the mobile phone among the participants of the study. This questionnaire also has 10 four-point Likert items, ranging from 1 to 4 in increasing order of intensity (1 = not at all, 2 = a little, 3 = somewhat and 4 = rather). It consists of two factors: conflicts and communication/emotional use. The "*conflicts*" factor refers to the personal and social impact of mobile phone abuse (Beard & Wolf, 2001; Young, 2007): "Have you been at risk of losing a significant relationship, job or educational opportunity because of mobile phone use? ". The "*communication and emotional use*" factor assesses the communicational and emotional repercussions resulting from mobile phone abuse: "Do you think life without a mobile is boring, empty and sad?".

The scale has good reliability, with an α of 0.80 (Beranuy et al., 2009). With our participants, scores of 0.80 α, FC = 0.80, AVE = 0.50 were obtained. Furthermore, the dimensions or factors of the questionnaire yielded acceptable reliability and AVE ≥ 0.50 [conflicts (α = 0.67, FC = 0.78, VME = 0.50); communication and emotional use (α = 0.72, FC = 0.80, VME = 0.50)].

Procedure

The different tools were applied to students during the 2014/2015 academic year. The American Psychological Association's ethical guidelines (APA, 2009) concerning the informed consent of participants were followed, despite this being an investigation that causes no harm, given that it researches methods of classroom management in an educational context. The confidentiality of data obtained and their use exclusively for research purposes was guaranteed. Questionnaires were completed within the context of the classroom and under the presence of the researcher, who was trained to clear up any doubts arising with regard to the questions. Participation was entirely voluntary, no compensation was offered. The questionnaires were completed in 20 to 25 minutes.

Data analysis

The data analysis techniques used were of a quantitative type, using SPPS (version 21) to apply statistical techniques such as Student t test, ANOVA and MANOVA. The data were subjected to the Kolmogorov-Smirnov, Rachas and Levene tests. Given that $p > 0.05$ in all tests, the assumptions of normality, randomization and homoscedasticity were verified, which in turn justified the use of parametric tests.

Results

Mobile phone abuse and differences by students' gender, age and field of scientific knowledge.

Table 1 shows the results of the Student t test. We found significant differences in the "*communication and emotional use*" factor associated with the gender variable. Girls appear to have more communication and emotional problems through mobile phone use than boys ($t = 6.160$, $p < 0.001$, $r = 0.18$).

The ANOVA test (Table 2) yielded significant differences among the mean scores of age groups in the two factors. The goodness of fit test for Bonferroni multiple comparisons shows that the differences found in the first factor, "*conflicts*", are only significant among the 18 to 20 group, compared with the over 25 group ($p = 0.008$). Regarding the second factor, " *communication and emotional use*", the differences are significant among the youngest group (18 to 20), compared with the other groups ($p = 0.001$), with the 21 to 24 group ($p < 0.001$) and over 25 group.

Table 3 displays the data from the ANOVA test, which shows that there were significant differences concerning students' scientific field in the scores for the "*communication and emotional use*" factor. Students from the scientific and technical knowledge areas obtained lower scores than the other students.

The goodness of fit test for Bonferroni multiple comparisons of shows that there are no significant differences between scientific fields: health sciences, judicial and social sciences and humanities. However, significant differences were found between the technical sciences area and the other scientific fields: $p < 0.001$ with the field of health sciences; $p < 0.001$ with the judicial and social sciences field; $p = 0.017$ with the humanities.

Mobile phone abuse and victim and aggressor profiles.

In order to select those students who had experienced the roles of victim and aggressor on a greater number of occasions and with greater intensity, the 75th percentile value was calculated for the scores on the *victimization through mobile phone scale* (CYB-VIC) and the *aggression through mobile phone scale* (CYB-AGRES). These scales record student responses regarding their participation by the number of victimizations sustained or cyber aggressions committed over the past year using mobile phones.

The descriptive and percentiles scores for each of the profiles were: victims (M = 12.69, SD = 2.75, 75th percentile: 14), aggressors (M = 11.67, SD = 2.99 75th percentile: 12). Subgroups were selected from the final sample and it was found that there were students who could be included in several possible combinations within these roles, so that finally the following profile subgroups were established: victims (n = 110), offenders (n = 184), victim/aggressor (n = 217) and without profile (n = 605).

In the next step, we investigated the possible influence of the student's profile when being harassed by mobile phone, as well as the hours of mobile use, on the scores for factors in the *questionnaire of experiences related to mobile*, CERM. A multivariate analysis of variance (MANOVA) was carried out with the hours of mobile phone use (up to two hours a

Table 1. *Gender differences in mobile phone experiences.*

CERM Factors	Male (n=500)		Female (n=700)		Student *t* test		
	M	*SD*	*M*	*SD*	*t*	*p*	*r*
Conflicts	6.79	2.36	6.66	1.94	-.946	0.344	0.03
Communication and emotional use	9.42	2.94	10.50	2.84	6.16	0.000	0.18

Table 2. *Age group differences in mobile phone experiences.*

	Intervalos de edad							
CERM factors	18 - 20 (n=623)		21 - 24 (n=354)		25 - 32 (n=103)		ANOVA	
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Conflicts	6.85	2.14	6.63	2.12	6.17	1.77	4.95	0.007
Communication and emotional use	10.44	2.93	9.72	2.84	8.95	2.79	15.51	0.000

Table 3. *Differences among fields of knowledge in mobile phone experiences.*

	Fields of knowledge									
	HS (n=246)		JSS (n=550)		TC (n=232)		H (n=84)		ANOVA	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Conflicts	6.84	2.05	6.80	2.12	6.48	2.20	10.28	2.81	1.953	0.119
Communication and emotional use	10.28	2.81	10.48	2.93	8.86	2.64	9.95	3.23	17.94	0.000

Note. HS=Health Sciences; JSS=Judicial and Social Sciences; TS=Technical Sciences; H=Humanities.

Table 4. *Means and standard deviations for the "Conflictos" and "Communicative y Emotional Use" factors according to hours of mobile use and cyberbullying abuse profile.*

		Cyberbullying profile							
CERM Factors	Daily hours of mobile use	Victim		Aggressor		Victim / aggressor		No profile	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Conflicts	up to 2 hours	5.94	1.21	6.10	1.63	7.34	3.70	5.65	1.21
	3-5 hours	6.78	2.36	7.00	2.39	8.16	2.42	6.21	1.59
	6-10 hours	6.91	1.75	7.23	1.64	7.98	2.31	6.46	2.02
	11 or more hours	9.06	2.33	7.25	1.68	8.07	2.92	6.74	1.69
Communication and emotional use	up to 2 hours	7.89	2.05	8.95	2.36	10.50	3.63	7.70	2.12
	3-5 hours	10.25	3.26	10.4	2.66	11.50	2.44	9.82	2.75
	6-10 hours	11.20	2.74	10.85	2.63	11.70	2.10	10.20	2.50
	11 or more hours	12.47	3.30	12.77	2.63	12.70	2.34	10.90	2.63

day, three to five hours, six to ten hours and more than eleven hours) and the four defined profiles (victim, aggressor, victim/aggressor and no profile) were used as fixed factors, and the two factors of "*conflicts*" and "*communication and emotional use*" from the *questionnaire of experiences related to mobile*, CERM, were employed as dependent variables. The Wilks Lambda (λ) value was used to test for the existence of significant differences, and the partial eta-squared (h^2) value was used as an index of effect size. Table 4 shows the means and standard deviations of the "*conflicts*" and "*communication and emotional use*" factors for hours of mobile phone use and profiles of harassment by mobile.

The results obtained highlight significant differences depending on the participant profiles (Wilks $\lambda = 0.894$, $p < 0.001$, $\eta^2 = 0.055$), the hours of mobile phone use (Wilks $\lambda = 0.891$, $p < 0.001$, $\eta^2 = 0.056$), and the interaction between the profiles and hours of use mobile (Wilks $\lambda = 0.967$, $p = 0.013$, $\eta^2 = 0.017$).

In terms of the participant profiles, statistically significant differences were found in the two factors "*conflicts*" ($F(3, 1200) = 29.60$, $p < 0.001$, $\eta^2 = 0.081$) and "*communication and emotional use*" ($F(3, 1200) = 25.57$, $p < 0.001$, $\eta^2 = 0.071$), with a higher score on average for students with the victim/aggressor and aggressor profiles (see Table 4).

With regard to the "*conflicts*" factor, Bonferroni multiple comparisons show that the largest significant differences are found among victim/aggressor subgroups, followed by the victim profile, compared to participants with no profile or not involved in the mobile phone harassment. The greatest significant differences related to the factor "*communication and emotional use*" were found in the victim/aggressor subgroups, followed by the aggressor profile, compared to participants with no profile. There are differences in both factors among all pairs of different profiles comparisons, except between the victim and aggressor profiles.

Regarding the number of hours of mobile phone use, the results also show statistically significant differences in the factors "*conflicts*" ($F (3, 1200) = 12.21$, $p < 0.001$, $\eta^2 = 0.035$) and "*communication and emotional use*" ($F (3, 1200) = 40.16$, $p < 0.001$, $\eta^2 = 0.107$). Bonferroni multiple comparisons show that for the "*conflict*" factor the greatest significant differences appear among students who use the mobile more than eleven hours a day, and those who use it for two hours. There are no differences between the subgroups using mobiles for over eleven hours and six to ten hours. For the "*communication and emotional use*" factor, the biggest significant differences exist between the over-eleven-hours subgroup compared with the two-hours subgroup. Significant differences are found among all subgroups, and mean scores are higher in students with more hours of daily mobile use.

Finally, in terms of the interaction between the participant profiles and hours of mobile phone use, statistically significant differences were found only in the "*conflicts*" factor ($F (9, 1200) = 2.083$, $p < 0.028$, $\eta^2 = 0.018$). These were found between students who use the mobile more than eleven hours a day and those who use them for up to two hours in the victim and aggressor profiles and those with no profile, while no significant interaction exists in the victim/aggressor profile.

Discussion

The mobile phone has become the most popular technology among young people, and an indispensable tool in their daily lives, but one which at times gives rise to problematic or addictive use (Chóliz, 2012), and which is also the device most used to harass and intimidate others (Del Rio, et al., 2009). The purpose of this study was thus to analyze the social, personal and communicational impact of mobile phone abuse among college students, and deepen our knowledge of different profiles of cyberbullying.

Mobile phone abuse and differences by student gender, age and field of scientific knowledge

Regarding gender, the misuse of mobile phones generates conflicts in young people of both sexes equally, with girls reporting more communicational and emotional problems than boys. These results are consistent with other studies that show that women are more likely than men to suffer negative consequences of maladaptive of mobile use (Beranuy, Oberst, Carbonell & Chamarro, 2009; Takao, Takahashi & Kitamura, 2009). The mobile allows an emotional connection with others (Aguado & Martínez, 2006), resulting in increased use especially among girls (Sánchez-Martinez & Otero, 2009), who use it to maintain this emotional closeness, and to deal with unpleasant emotional states (Chóliz, Villanueva & Chóliz, 2009).

In terms of age, results confirm that the younger participants (18 to 20) had greater communicational and emotional conflicts arising from the use of mobile phones than the older age groups (21 to 24 and over 25). This matches the results of a study by De la Villa and Súarez (2016), who concluded that the problems related to emotional and communication use of mobile phones, as well as conflicts generated by such use, increased during middle adolescence with respect to preadolescence. Thus, the youngest in our study, those who are coming out of adolescence (18 to 20) view the mobile as something natural, while "older" young people (the 21 to 24 and over 25 groups) use mobile phones more professionally and less for leisure, and thus with fewer negative consequences (Beranuy, Chamarro, Graner & Carbonell, 2009). This is also confirmed by certain other studies (Derbyshire et al., 2013), and probably due to the fact that they are increasingly aware of the problem of excessive time spent using mobiles and the possible negative consequences (Labrador & Villadangos, 2010).

Age is therefore an important factor influencing the way people behave and socialize when using the mobile phone. First access to such technology takes place at increasingly early ages, and the availability of mobile phones is significantly higher above age 10, reaching 100% over the age of 17 years (INE, 2015). The younger the users, the greater the percentage of people with high rates of problematic mobile use. The prevalence among Spanish adolescents (12 to 18) is between 15 and 20% (Flores, Jenaro, González, Martín & Poy, 2013; Jenaro, Flores, Gómez-Vela, González-Gil & Caballo, 2007; Labrador & Villadangos, 2010; López-Fernández, Honrubia-Serrano & Freixa-Blanxart, 2012; Sánchez-Martínez & Otero, 2009) and 7.99% in the university population (Jenaro et al, 2007). Rather than being linked to the use of mobiles, these age-related results are more closely connected to the developmental stage of adolescence, characterized by low levels of life experience, difficulty in recognizing subtle addictions and a sense of normality when engaging in risky behaviors (Castellana, Sánchez- Carbonell, Graner & Beranuy, 2007) as well as deficits in delayed gratification, planning and considering future consequences (Corona & Peralta, 2011). It is a stage in which adolescents are more easily influenced and have lower impulse control (Muñoz-Rivas & Agustín, 2005).

With regard to "*communication and emotional use*" students from technical science fields of knowledge score

lower than other students (health sciences, judicial and social sciences and humanities). Two possible hypotheses can help interpret these results: the difficulty of technical degrees on the one hand, and gender bias on the other. With regard to the first of these, among the scientific and technical degrees during the 2014-15 academic year the average number of credits gained, the level of academic performance (measure by credits gained ratio compared to credits enrolled) and the average grades of academic records are the lowest compared to other scientific fields (Ministry of Education, Culture and Sport, 2015). The students perceive technical degrees as being more difficult, and social sciences degrees as easier. The greater demands of technical degrees undoubtedly condition the use of mobile phones by students enrolled on them. They tend to use them more for academic tasks such as accessing the schedule of activities of the different courses on the virtual campus, accessing digital library services, university webmail platform, etc., rather than intensively for recreational, communication and social purposes.

In terms of gender bias, during the 2014-15 academic year the percentage of men enrolled in technical scientific degrees was 74.1%, as against 25.9% women. In other fields, the percentage of women is higher than men. In our sample from the technical science field, 72% were male vs. 28% female. As we noted earlier when analyzing the gender variable, our results show that girls have more communicational and emotional problems than boys. The differences found in the "*communication and emotional use*" factor between students from the scientific and technical knowledge field and those from other fields, could be due to the imbalance between the number of men and women.

Mobile abuse and victim and aggressor profiles

According to the results, the victim/aggressor profile is the subgroup with more *conflicts* with mobile use, followed by the victim profile. A characteristic behavior exhibited by both profiles is the constant checking of messages received via mobile phone, which can carry threatening and harassing remarks made about them by others (Li, 2008; Mason, 2008; Slonje & Smith 2008). This could lead to an increase in personal and interpersonal conflicts. With regard to this, some studies conclude that cyberbullying generates feelings of anxiety, depression, low self-esteem, irritability and sleep disorders in victim and victim/aggressor (Garaigordobil, 2011), which in turn lead to excessive of mobile phone use and increased problematic Internet use (Ehrenberg, Juckes, White & Walsh, 2008; Gámez-Guadix et al, 2013.). Thus, both victims and victim-aggressors change their social and work/academic habits, tend to isolate themselves, and see their mobile as a refuge to help them look for more supportive virtual relationships, and as social substitute for face-to-face relationships with friends (García del Castillo et al, 2008; Giménez et al, 2015; Kuss & Griffiths, 2011).

With regarding to *communication and emotional use,* it is the victim/aggressor subgroup, followed by the aggressor profile, which has the greatest communicational (increased aggressive behaviors, lower impulse control) and emotional effects (restlessness, anxiety, anger and irritation) as a consequence of mobile phone misuse in comparison to participants with no profile. These results are consistent with other studies (Garaigordobil, 2011;. Giménez et al, 2015) which confirm the existence of aggressive behaviors, change of interests and high levels of anxiety among these participants in cyberbullying.

Hours of mobile use

As for the hours of use of mobile, results highlight that students who use mobile phones more than eleven hours a day have more conflicts with its use, and this "use" has a more communicative and emotional angle than for those who use it for two hours. According to Echeburúa and de Corral (2010), people can talk on the phone for profit or pleasure, while an addicted person seeks to relieve the emotional distress (boredom, loneliness, anger, nervousness, etc.). In this regard, some studies have concluded that it is the aggressors who have higher daily mobile consumption than the victims or those not involved (Giménez et al., 2015), to the extent that they risk becoming addicted, especially if we consider that students often underestimate their daily mobile use, claiming to spend between one and four hours, when in reality it has been confirmed that this is considerably higher (Aslanidou & Menexes, 2008; Garmendia, Garitaonandia, Martínez & Casado, 2012; Hunley et al ., 2005).

Finally, regarding the interaction between the participant profiles and hours of mobile use (victim, aggressor and no profile), is was found that those who use mobile phones more than eleven hours a day have greater conflicts compared to those who use it up to two hours. This, however, is not the case with the victim/aggressor profile, where the number of hours does not determine conflicts. Here, one can understand that when responding aggressively, the victims display intrapersonal and interpersonal problems more strongly which arise from mobile phone use. Various studies show that subjects who assume the complex role of victim/aggressor report greater symptoms and higher rates of distress compared to the other bullying profiles (Felipe, León & Fajardo, 2013, Haynie et al. 2001; Kaltiala-Heino, Rimpelä, Rantanen & Rimpelä, 2000; Kim, Leventhal, Koh, Hubbard & Boyce, 2006; Stein, Dukes & Warren, 2007).

Limitations

The present study has several limitations, such as the use of self-reports as the only method of data gathering for the

evaluation of both cyberbullying situations and mobile phone abuse. In addition, differences in the number of cases in each of the roles described means that the results should be considered with caution until they can be expanded in number: victims (n = 110), aggressors (n = 184), victim/aggressor (n = 217) and without profile (n = 605). Furthermore, it should be remembered that the sample is only representative of the university population, so the results cannot be generalized to the non-university population.

Conclusions

On the one hand, it is necessary to highlight the teaching of values for children, young people and adults in order to achieve a positive, harmless and responsible use of communication technologies. These are increasingly available at any time and in any place, and in many cases - mostly among minors - without adequate control or supervision, which exposes children and young people to a considerable number of risk situations. Schools have the obligation and the opportunity to create social spaces and to change attitudes towards the use of these important technologies, provide teachers with resources to prevent undesirable attitudes and tackle the different forms of harassment.

On the other hand and in line with the above, there is a need for implementing prevention programs beyond school, given the importance of eradicating situations where harassment and/or cyberbullying can take place. The aim of such measures is that young people identify with the values of respect, empathy and non-violence, which should prevail at university level. The importance of research is highlighted in order to identify all forms of harassment, with special emphasis on those produced by new technologies, deepening our knowledge of the positive uses and the consequences of abuse by promoting responsible use and healthy enjoyment as strategies which can prevent digital violence.

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Conflict of interests

The authors declare that they have no conflict of interests.

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Binge Drinking among Adolescents: Prevalence, Risk Practices and Related Variables

Consumo intensivo de alcohol en adolescentes: prevalencia, conductas de riesgo y variables asociadas

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Abstract

According to the last Survey on Drug Use among Secondary School Students (ESTUDES 2014-2015), consumption levels of alcohol and other substances have decreased in the last years in Spain. However, available data on binge drinking remain worrying, given the negative consequences related with this pattern. The aim of this paper is to analyse binge drinking among adolescents, providing updated data on prevalence in addition to information about the consequences and some predictive factors of binge drinking. A correlational method was used for this purpose, comprised of administering a survey to Compulsory Secondary School, High School and Vocational Training students. Based on a sample of 3,419 Galician adolescents aged between 12 and 18 years (M = 14.57; SD = 1.76), the results show that binge drinking is a common and global practice, with few socio-demographic differences but related with a wide range of risk practices. Furthermore, variables such as consumption expectancies, consumption by family and friends, as well as curfew time and allowance money have been identified as interesting predictive factors that should be taken into account at the preventive level.

Keywords: Adolescents; Alcohol; Underage drinking; Binge drinking; AUDIT.

Resumen

Según la última Encuesta sobre uso de drogas en Enseñanzas Secundarias (ESTUDES 2014-2015), los niveles de consumo tanto de alcohol como de otras sustancias han disminuido en España en los últimos años. No obstante, siguen siendo preocupantes los datos referidos al consumo intensivo de alcohol (CIA), sobre todo habida cuenta las graves repercusiones asociadas a este patrón. El objetivo del presente trabajo ha sido analizar el consumo intensivo de alcohol entre los adolescentes, ofreciendo datos actualizados no sólo de su prevalencia, sino también de sus consecuencias y posibles factores de pronóstico. Para ello se utilizó una metodología correlacional, consistente en la realización de una encuesta a estudiantes de ESO, Bachillerato y FP de grado medio. La muestra final estuvo compuesta por 3.419 adolescentes gallegos de entre 12 y 18 años (M = 14,57; SD = 1,76). Los resultados obtenidos revelan que el CIA es una práctica frecuente y globalizada, con escasas diferencias a nivel sociodemográfico, pero asociada a un amplio abanico de conductas de riesgo. Por otra parte, variables como las expectativas de consumo, el consumo entre los pares y en el entorno familiar, así como la hora de llegada a casa o el dinero disponible han sido identificadas como interesantes factores de pronóstico que debieran ser tenidos en cuenta en el plano preventivo.

Palabras clave: Adolescentes; Alcohol; Consumo intensivo; AUDIT.

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Abusive consumption of alcohol among adolescents is one of the main public health problems in Spain, as reflected in the 2009-2016 National Strategy on Drugs (National Drug Plan, 2009a). The same occurs on a European level, with the strategy implemented by the European Council in its 2013-2020 EU Action Plan on Drugs (European Council, 2013). Despite the decrease in consumption levels of both alcohol and other drugs in recent years, prevalence figures continue to be high, especially with regards to alcohol, which ranks as the most-consumed psychoactive substance. According to data of the *European School Project on Alcohol and Other Drugs (ESPAD 2011)* (Hibell et al., 2012), 79% of students between the ages of 15 and 16 had consumed alcohol in the last 12 months, and 57% had consumed alcohol in the last month. In Spain, the results of the most recent *National Survey on Drug Use among Secondary School Students* (*ESTUDES 2014-2015)* (National Drug Plan, 2016) highlight that 76.8% of adolescents between the ages of 14-18 had consumed alcohol in the last year, and 68.2% had consumed alcohol in the last month.

Within this context, one of the greatest concerns of professionals and researchers is the establishment of a usage pattern characterized by the ingestion of large amounts of alcohol over short time periods, mainly during the weekend, and usually resulting in drunkenness (Anderson, 2007; Calafat, 2007; Cortés, Espejo & Giménez, 2007). Literature in English usually refers to this consumption pattern as binge drinking (BD), in Spain referred to as intensive alcohol consumption *(consumo intensivo de alcohol* in Spanish [CIA]) (Rodríguez-Martos & Rosón, 2008). According to the World Health Organization (WHO, 2004), BD is defined as the consumption, by an adult, of at least 60 grams of alcohol (6 Standard Drink Units -SDU- in Spain) in a single drinking episode. However, many difficulties arise in making BD operational based on this definition. First, the lack of consensus as to what is considered a Standard Drink Unit (SDU) results in inter-country variability of criteria on the amount of alcohol consumption per episode (Mongan & Long, 2015; Parada et al., 2011). Likewise, the vagueness of the time period considered a "single episode" has led several authors to propose the need for taking into account blood alcohol concentration levels, which entails including duration in the definition of BD (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2004). Given these considerations, authors such as Parada et al. (2011) propose defining BD as the consumption of 6 or more alcoholic drinks for men (5 or more for women) during a single drinking episode (a period of 2 hours) at least once in the last 30 days. Nevertheless, when referring to adolescents, it has been deemed pertinent to reduce to 3 the number of alcoholic drinks ingested on a single consumption episode because the BAC levels reached by adolescents are much higher than those of adults when consuming the same number of drinks (Donovan, 2009).

This lack of consensus in operationalising BD and the use of highly heterogeneous samples has resulted in greatly disparate prevalence rates across different epidemiological studies. For example, recent data from the *National Survey on Drug Use and Health* (Hedden et al., 2015) points out that 6.1% of adolescents between the ages of 12-17 have indulged in BD in the last month in the United States. In addition, results of *ESPAD 2011* indicate that 39% of European students between the ages of 15-16 have indulged in BD in the last month, while in Spain 32.2% of students between the ages of 14-18 indulged in BD in the last 30 days, and 22.2% got drunk (National Drug Plan, 2016).

Obviously, in any case, BD is a serious public health problem with clear, negative consequences. Some studies, for example, have confirmed a close relationship between BD and long-term organic damage, like cirrhosis, hypertension and coronary diseases (Anderson, Cremona, Paton, Turner, & Wallace, 1993; Marmot, 2001; Pincock, 2003). Of no less importance are the alterations that arise on the cerebral level, from structural and functional perspectives (Cadaveira, 2009; López-Caneda et al., 2014; Tapert, 2007), with a great number of studies documenting possible neurocognitive and neurobehavioral repercussions associated with this consumption pattern (Cadaveira, 2010; Guerri, 2010; Guerri & Pascual, 2010; Tapert & Brown, 1999; Ziegler et al., 2005). Literature also points out that adolescents who indulge in BD are also more likely to become involved in various risk behaviours, like fighting (Swahn, Simon, Hamming, & Guerrero, 2004; Wechsler, Davenport, Dowdall, Moeykens & Castillo, 1994), driving under the influence of alcohol (Adams, Evans, Shreffler, & Beam, 2006; Windle, 2003), having problems with the police, being victims of robbery or theft, participating in risky sexual practices (DeCamp, Gealt, Martin, O´Connell, & Visher, 2015; Huang, Jacobs, & Deverensky, 2010) or having a lower academic performance (Miller, Naimi, Brewer & Jones, 2007). Likewise, studies like those by Jones, Oeltmann, Wilson, Brener, & Hill (2001) or Miller et al. (2007) have found a close relationship between BD and the use of other substances, and have even suggested that BD during adolescence is a risk factor for the later development of alcohol abuse/dependency in adulthood (Chambers, Taylor & Potenza, 2003; García-Moreno, Expósito, Sanhueza & Angulo, 2008; Petit, Maurage, Kornreich, Verbanck & Campanella, 2014). One variable that influences the likelihood of appearance of many of these consequences and of their seriousness is the age of onset of the adolescents' alcohol consumption (Motos, Cortés, Giménez & Cadaveira, 2015). Such is the case that delaying the age of onset is contemplated as one of the goals of the *2013-16 National Drug Plan* (National Drug Plan, 2009b) (general objective 4), as well as in different regional plans, like the *2011-2016 Addiction Disorders Plan of Galicia* (Xunta de Galicia [Regional Government of Galicia], 2010) (objective 1.3). Never-

theless, the main, nationwide information system available with regards to BD, ESTUDES, uses a limited sample that includes adolescents between the ages of 14-18. Therefore, the availability of empirical data on the prevalence of BD among younger ages (12-13 years) would be interesting, especially given that the age of onset of alcohol consumption was already 13.9 years in 2014 (National Drug Plan, 2014).

The significant implications that BD can entail on clinical and psychosocial levels also justifies that researchers, professionals and institutions focus a major part of their efforts on developing preventive measures to decrease alcohol consumption levels and, especially, of this new way of drinking by binging. For this purpose, the capacity for identifying potential, associated variables is key. As regards the possible role of sociodemographic variables, different studies coincide in pointing out that adolescent boys tend to drink alcohol more intensely than adolescent girls (Fuller-Thomson, Sheridan, Sorichetti & Mehta, 2013; Peralta, Steele, Nofziger & Rickles, 2010) and that the prevalence of BD increases with age, reaching its highest levels in early adulthood (around the age of 20) (Mota et al., 2010; Windle, Mun & Windle, 2005). Beyond gender or age, BD has also been associated with personal variables, such as avoidant coping style (Doumas, Turrisi, & Wright, 2006; Pirkle & Richter, 2006), low perception of risk (Parada et al., 2011) or positive expectancies about the effects of alcohol consumption (Durkin, Wolfe & Clark, 2005; McBride, Barret, Moore & Schonfeld, 2014). Many studies also relate BD with alcohol consumption by peers (Coleman & Cater, 2005; Stickley et al., 2013) and with family-related variables, such as parental attitudes favouring alcohol consumption (Jander, Mercken, Crutzen & De Vries, 2013), being a member of a destructured household (Fuller-Thomson et al., 2013) or high parental consumption levels (Espada, Pereira & García-Fernández, 2008; Pons & Berjano, 1999). Likewise, other variables, such as allowance money, socioeconomic status or curfew time, though with lesser empirical evidence in the context of BD, have also been associated with adolescent alcohol consumption (Humensky, 2010; National Drug Plan, 2014; Varela, Marsillas, Isorna & Rial, 2013).

Given the interest that this issue continues to spark on different levels, the purpose of this study is to objectively analyse BD among the adolescent population of Galicia, defined on the basis of three criteria: a) consumption of 6 or more alcoholic drinks during a single consumption episode, within 2 hours (reflecting the criteria supported by Parada et al., 2011); b) consumption of 3 or more alcoholic drinks during a single consumption episode (within 2 hours), reflecting the viewpoint of those who stress the pertinence of decreasing the amount of drinks when referring to adolescents; and c) getting drunk, therefore intending to evaluate the more subjective component of consumption. In summary, first we intend to obtain new data on the prevalence of this practice among adolescents, by broadening the sample from ages 12-18, while also analysing said prevalence by population segments according to gender, age, ownership of the school, residential area or parents' level of education. Second, we intend to contribute new evidence on the consequences or risks of BD that will be useful for consolidating the importance of this phenomenon. Finally, we intend to identify possible predictive factors for the purpose of guiding preventive efforts.

Method

Participants

A correlational method was used in pursuit of our goals. Specifically, a survey was completed by the student population of Compulsory Secondary School (ESO), High School and Vocational Training in the autonomous region of Galicia (approximately 140,000 students). Bi-level sampling was used to select the sample: by *conglomerates*, for selecting the first-level units (school centres) and by *quotas*, according to gender and level, for selecting the second-level units (individuals). A total of 37 public and private/state-funded centres from the four provinces of Galicia were randomly selected, respecting the existing population quotas. The final sample was comprised of 3,419 adolescents (50.6% boys; 49.4% girls) between the ages of 12-18 (M = 14.57; SD = 1.76). Of these, 2,236 attended public schools and 1,183 attended private/state-funded schools. Of these, 73.3% were enrolled in ESO (38.2% in the first year and 35.1% in the second year), 20.4% were high school students and 6.2% were undergoing basic professional training (Initial Professional Qualification Programmes) or a mid-level Training Programme.

Instruments

Data was collected using a survey designed expressly for this purpose, comprised of questions grouped in five blocks: (1) a first block extracted from the *National Survey on Drug Use among Secondary School Students (ESTUDES 2010)* (National Drug Plan, 2011) referring to the consumption habits of alcohol and other substances (in the last year and in the last month); (2) a second block including questions related to BD. The existent controversy as to the operationalisation of this construct led us to opt for using three different indicators: two quantitative indicators, (a) having consumed 3 or more alcoholic drinks during a single drinking episode (2 hours) and (b) and having consumed 6 or more alcoholic drinks during a single drinking episode (2 hours), and another more subjective indicator (c) having got drunk; (3) a third block including the *Alcohol Use Disorder Identification Test* (AUDIT) in the self-administered version (Rial et al., 2015) to estimate hazardous alcohol consumption, with a satisfactory internal consistency in this study (α = .77); (4) a fourth block extracted from the *European School Survey Pro-*

ject on Alcohol and Other Drugs (*ESPAD 2011)* (Hibell et al., 2012) referring to possible problems associated with alcohol consumption; (5) a fifth block of questions of our own design (based upon the ESTUDES and ESPAD surveys), referring to variables associated with BD highlighted in literature, such as curfew, allowance money, beliefs and expectancies, consumption by family members or peers; and, finally, information referring to sociodemographic variables, such as gender, age, ownership of the school, residential area or parents' level of education.

Procedure

Data was collected in the classroom, in small groups (between 15-20 individuals), using a survey to be completed individually. Data was collected by a team of psychologists experienced in these types of tasks. Each subject was informed of the purpose of the study, confidentiality and anonymity of the responses. Consent and collaboration was granted by both the directors of the educational centres, as well as of the respective students' parent associations. Participation was completely voluntary and completion of the questionnaire required approximately 20 minutes. The study was also approved by the Bioethics Committee of the University of Santiago de Compostela.

Data analysis

A total of 3,714 questionnaires were collected. Filtering of the initial database resulted in the elimination of 295 cases, either for an excessive amount of blank values (15), an incoherent response pattern (22) or due to an age outside of the established range (12-18 years) (258). The differences between binge drinkers and non-binge drinkers underwent bivariate analysis, applying suitable comparisons, depending on the nature of the variables: Student's *t* tests for comparing means and eta squared (η^2) coefficients to calculate the effect size of quantitative variables, as well as χ^2 comparisons to compare percentages and phi (ϕ) coefficients and contingency coefficients (CC) to calculate the effect size of qualitative variables. The IBM SPSS Statistics 20 package was used for data analysis.

Results

An initial interesting fact reflected in Table 1 is that 6 out of every 10 adolescents between 12-18 years of age have consumed alcohol in the last year (58.7%). With regards to BD, it is worth highlighting that 24.5% have consumed 6 or more alcoholic drinks during a single drinking episode in the last year, a figure that drops to 12.8% if referring to the last month. Nevertheless, when evaluating BD as the consumption of 3 or more alcoholic drinks during a single drinking episode, the percentage of drinkers in the last year and in the last month doubles (41.8% and 25%, respectively). Likewise, 34.4% of adolescents claim to have gotten drunk in the last year and 16.5% claim this in the last 30 days. To facilitate comparison of the data obtained by this study with that of ESTUDES 2014-2015 (which interviewed students between the ages of 14-18 years only), Table 1 presents the data specifically for that age group. As shown, the percentages are considerably greater than in the case of the global sample (which also included the age range of 12-13 years), but similar to those of ESTUDES, where 22.2% of the subjects had gotten drunk in the last 30 days.

The results also show (Table 2) the existence of significant differences in the percentage of boys and girls that indulged in BD in the last year and in the last month, with higher percentages for boys, especially in the case of consumption of 6 or more alcoholic beverages. Similarly, results show that BD increases significantly with age, with percentages of up to 20 and 30 times greater in the age range of 16-18 years, compared with the age range of 12-13 years. For purposes of knowing which group comparisons resulted in significant differences, the groups were compared two at a time; the table marks (with the corresponding superscripts) those cases in which differences were significant. Results obtained revealed the existence of significant differences between the three age groups, and noticeably greater between the groups on the ends (12-13 vs. 16-18) (Table 2).

Likewise, the data also revealed statistically significant differences depending on the ownership of the school, with higher rates in public schools. With regards to the residential setting, adolescents residing in urban settings show higher rates of BD. Finally, prevalence rates are proven to increase significantly as the parents' level of education decreases, with the greatest differences appearing in the consumption of 3 or more alcoholic drinks over the last year. Last of all, as performed with ages, comparisons were also done between two groups at a time, for purposes of knowing which group comparisons resulted in significant differences. Table 2 shows that significant differences are obtained practically between all groups, except between adolescents with parents having primary and secondary education levels, when analysing the consumption of 3 or more alcoholic drinks and drunkenness.

Table 1. *Prevalence of BD in Galicia.*

	12-18 years		14-18 years	
	Last year	Last month	Last year	Last month
Alcohol	58.7%	37.9%	73.4	49.7
3 or more alcoholic drinks	41.8%	25%	55.1%	33.9%
6 or more alcoholic drinks	24.5%	12.8%	33%	17.2%
Getting drunk	34.4%	16.5%	46%	22.4%

Associated risks

As per the results of Table 3, adolescents that have indulged in BD in the last year are significantly more involved in all of the risky behaviour types considered, especially in the case of fights, accidents or injuries and unprotected sex. When considering the phi coefficients, it is worth mentioning that those adolescents who consume 6 or more alcoholic drinks present the highest risk of suffering all of these types of consequences. Likewise, the existence of statistically significant differences between binge drinkers vs. non-binge drinkers have been corroborated with regards to the consumption of other substances, particularly tobacco and cannabis (Table 4).

No less interesting is the verification that the percentage of adolescents that could be involved in hazardous alcohol consumption, specifically evaluated by AUDIT, increases significantly among binge drinkers. Again, the highest percentages are obtained among those who had consumed 6 or more alcoholic drinks in the last year (81.3%), followed by those who had gotten drunk (66%) and by those who had consumed 3 or more alcoholic drinks (58.5%), with a 25.7% (χ^2 = 1560.73; $p < .001$) rate of positives in AUDIT for the global sample.

Possible predictive factors

As reflected in Table 5, statistically significant differences have been found in practically all of the beliefs studied, demonstrating that those who indulged in BD in the last year in any of its forms overrated the positive effects of alcohol (especially, "have a lot of fun", "feel happy" and "feel outgoing and extroverted"), while they also underra-

Table 2. *Differences in BD according to sociodemographic variables.*

	Last year					Last month				
Gender	Boys (%)	Girls (%)		χ^2	ϕ	Boys (%)	Girls (%)		χ^2	ϕ
3 or more alcoholic drinks	42.8	40.6		1.34	.02	26.8	22.8		6*	.05
6 or more alcoholic drinks	29.2	19.2		38.65**	.12	16	9.2		29.47**	.10
Getting drunk	36	32.5		3.89*	.04	18.2	14.6		6.63*	.05
Age Group	12-13 years[1] (%)	14-15 years[2] (%)	16-18 years[3] (%)	χ^2	CC	12-13 years[1] (%)	14-15 years[2] (%)	16-18 years[3] (%)	χ^2	CC
3 or more alcoholic drinks	5.1[2.3]	32.5[1.3]	72.1[1.2]	926.62**	.49	1.3[2.3]	14.4[1.3]	48.7[1.2]	642.43**	.43
6 or more alcoholic drinks	1.3[2.3]	15.5[1.3]	46.2[1.2]	577.95**	.41	0.8[2.3]	6.3[1.3]	25.4[1.2]	307.90**	.31
Getting drunk	2.9[2.3]	25.4[1.3]	61.6[1.2]	775.26**	.46	0.5[2.3]	9.2[1.3]	32.4[1.2]	398.63**	.35
Ownership	Public (%)	Private (%)		χ^2	ϕ	Public (%)	Private (%)		χ^2	ϕ
3 or more alcoholic drinks	45.4	33.7		34.75**	.11	27.9	18.7		27.64**	.10
6 or more alcoholic drinks	27.3	18.4		26.26**	.10	14.9	8.1		25.27**	.09
Getting drunk	37.4	28		23.90**	.09	17.7	13.7		6.97*	.05
Setting	Rural (%)	Urban (%)		χ^2	ϕ	Rural (%)	Urban (%)		χ^2	ϕ
3 or more alcoholic drinks	38	44.5		12.02**	.07	22.9	26.6		4.79*	.04
6 or more alcoholic drinks	21.9	26.5		7.97*	.05	11	14.2		6.04*	.05
Getting drunk	30.7	37.2		13.30**	.07	13.9	18.4		9.75*	.06
Parents' Education	Primary[1] (%)[a]	Secondary[2] (%)[b]	Higher[3] (%)[c]	χ^2	*CC*	Primary[1] (%)	Secondary[2] (%)	Higher[3] (%)	χ^2	*CC*
3 or more alcoholic drinks	48.9[3]	46.2[3]	33.5[1.2]	52.01**	.14	30.5[3]	28.5[3]	18.5[1.2]	40.40**	.12
6 or more alcoholic drinks	30.6[2.3]	26.1[1.3]	19.5[1.2]	29.13**	.10	18.1[2.3]	14[1.3]	8.6[1.2]	34.75**	.11
Getting drunk	40.3[3]	38[3]	27.8[1.2]	37.27**	.11	20.1[3]	19.6[3]	11.6[1.2]	30.80**	.11

Note. 1,2,3 Groups with which significant differences have been found ($p < .05$). a: Both have primary education or have not completed primary studies; b: At least one has secondary level education; c: At least one has completed university studies. *$p < .05$

ted the negative effects (especially "have problems with the police", "being unable to stop drinking" or "detrimental to health"). As regards curfew, the analyses completed reveal that the later the time an adolescent comes home after going out, the higher the BD rate (Table 6). Likewise, BD percentages increase as allowance money increases.

Concerning consumption by family members, the results shown in Table 7 reveal that when parents drink alcohol regularly, adolescents also obtain higher BD rates. However, the greatest differences are observed when siblings drink alcohol. Last of all, as detailed in Table 8, a significantly higher percentage of adolescents indulge in BD when their peers also drink alcohol, get drunk, smoke tobacco or use other drugs.

Discussion

Despite the fact that the results of the most recent *National Survey on Drug Use among Secondary School Students* (*ESTUDES 2014-2015)* (National Drug Plan, 2016) reveal a considerable decrease in the consumption of alcohol among students, prevalence rates continue to be high, especially with regards to BD. Given that the age at onset of consumption of alcohol and other substances is increasingly younger, this study opted for expanding the sample to include the ages of 12-18 years, motivated by the extensive literature warning of the serious consequences of this consumption pattern at very young ages (Ellickson, Tucker & Klein, 2003; Motos et al., 2015; Stueve & O´Donnell, 2005). The results obtained reveal that BD is a common, genera-

Table 3. *Risk practices (last 12 months).*

	3 or more alcoholic drinks		χ^2	ϕ	6 or more alcoholic drinks		χ^2	ϕ	Getting drunk		χ^2	ϕ
	Yes (%)	No (%)			Yes (%)	No (%)			Yes (%)	No (%)		
Fights	26	2.7	355.20**	.35	35.8	4.9	468.75**	.40	30.4	3	455.12**	.40
Accidents or injuries	16.7	1.6	221.87**	.28	22.8	3	291.40**	.32	19.5	1.8	281.41**	.31
Problems with parents	10.9	1.1	140.43**	.22	13.7	2.4	138.78**	.22	12.2	1.5	151.95**	.23
Lower academic performance	9	0.8	115.75**	.20	11.9	1.7	135.96**	.22	10.5	0.9	147.71**	.23
Victim of theft/ robbery	3.9	0.3	50.99**	.13	5	0.8	52.91**	.14	4.4	0.4	57.04**	.14
Problems with police	8.1	0.8	103.61**	.19	11.6	1.4	147.15**	.23	9.8	0.7	145.09**	.22
Seeking emergency room treatment/ hospitalisation	5.6	0.8	57.56**	.14	8.3	1.1	96.31**	.18	6.9	0.8	85.99**	.17
Unprotected sex	14.5	0.8	217.39**	.27	21	1.9	319.85**	.33	17.2	0.9	286.57**	.31
Sex you later regretted	13.1	0.6	198.52**	.26	19.6	1.4	318.87**	.33	15.3	0.9	243.67**	.29
Riding with a driver under the effects of alcohol	43.4	18.9	206.87**	.27	51.9	21.7	237.65**	.29	46.8	19.7	233.90**	.28
Driving under the effects of alcohol	7.5	0.4	107.87**	.19	11.3	0.9	173.28**	.25	9.1	0.3	157.10	.24

Note. *p < .05. **p <.001.

Table 4. *Use of other substances (last 12 months).*

	3 or more alcoholic drinks		χ^2	ϕ	6 or more alcoholic drinks		χ^2	ϕ	Getting drunk		χ^2	ϕ
	Yes (%)	No (%)			Yes (%)	No (%)			Yes (%)	No (%)		
Tobacco	62.5	7.5	1017.20**	.59	72.2	16.5	792.97**	.52	68.6	10.1	1065.02**	.61
Marihuana or hash	41.3	2.9	681.91**	.48	53.7	7.7	739.71**	.50	47.8	3.6	838.36**	.54
Cocaine	3.9	0.1	59.65**	.15	6.2	0.3	104.43**	.19	4.7	0.1	81.27**	.17
Ecstasy, amphetamines or hallucinogens	5.7	0.1	91.44**	.18	8.8	0.4	159.76**	.24	6.5	0.2	113.14**	.20

Note. *p < .05. **p <.001.

lised practice (between 24.5% and 41.8% of adolescents in Galicia). Even though the percentages found in the younger age group are low (1.3% for the consumption of 6 or more alcoholic drinks in the last year, 2.9% for getting drunk and 5.1% for the consumption of 3 or more alcoholic drinks), extrapolating these figures to the population means that between 500 and 2,000 children between the ages of 12-13 years in the community of Galicia admit having indulged in BD in the last year.

In addition to estimating the prevalence of BD, this empirical study has also sought to obtain new evidence of the seriousness of this practice on different levels. In alignment with many studies found in literature that relate BD with many negative consequences and risk practices (Miller et al., 2007; Wechsler et al., 1994), it is also observed that adolescents with this consumption pattern are significantly more involved in all of the risky behaviour types considered. In addition, confirmation is also obtained of the trend observed by other authors (Chassin, Pitts & Prost, 2002; Jones et al., 2001) in which adolescents that indulge in BD show a higher probability of initiating the consumption of other substances, as well as of developing risky consumption practices (as revealed by AUDIT) or even of a possible disorder or dependence in adulthood (Norström & Pape, 2012; Viner & Taylor, 2007). From a comparative perspective, of the three patterns analysed, those with the most intense consumption (6 or more alcoholic drinks) show the highest probability of becoming involved in the different

Table 5. *Beliefs and expectancies.*

	3 or more alcoholic drinks		*t*	η^2	6 or more alcoholic drinks		*t*	η^2	Getting drunk		*t*	η^2
	Yes (M)	No (M)			Yes (M)	No (M)			Yes (M)	No (M)		
Feel relaxed	2.13	1.48	-14.33**	.26	2.18	1.61	-11.08**	.20	2.14	1.55	-12.49**	.23
Problems with police	1.33	2.22	17.30**	.30	1.30	2.02	12.65**	.22	1.31	2.13	15.49**	.27
Harm my health	2.52	3.07	11.14**	.20	2.50	2.95	7.93**	.15	2.53	3	9.17**	.17
Feel happy	2.64	1.64	-22.47**	.38	2.75	1.83	-18.77**	.30	2.72	1.72	-22.31**	.37
Forget about my problems	2.51	1.95	-11.21**	.21	2.63	2.03	-10.92**	.19	2.59	1.97	-12.20**	.22
Cannot stop drinking	1.31	2.12	16.31**	.28	1.41	1.90	8.78**	.15	1.32	2.03	13.80**	.24
Have a hangover	2.62	2.80	3.61**	.07	2.69	2.73	0.73	.01	2.69	2.74	1.02	.02
Feel sociable and extroverted	2.74	1.90	-18.01**	.31	2.81	2.07	-14.26**	.24	2.80	1.96	-17.70**	.30
Do something I'll later regret	2.25	2.73	9.59**	.18	2.35	2.59	4.33**	.08	2.33	2.64	6.25**	.11
Have a lot of fun	2.93	1.83	-25.79**	.42	3.08	2.02	-23.34**	.36	3.03	1.90	-26.63**	.42
Feel ill	2.18	2.86	13.90**	.25	2.10	2.73	11.67**	.20	2.16	2.79	12.81**	.22

Note. *p < .05. **p <.001.

Table 6. *Curfew and allowance money.*

		3 or more alcoholic drinks		χ^2	*CC*	6 or more alcoholic drinks		χ^2	*CC*	Getting drunk		χ^2	*CC*
		Yes (%)	No (%)			Yes (%)	No (%)			Yes (%)	No (%)		
Curfew	Before midnight	5.4	94.6	865.30**	.52	2.1	97.9	672.94**	.47	3.8	96.2	775.42**	.50
	Between midnight-2 a.m.	26.2	73.8			8.9	91.1			17	83		
	Between 2-4 a.m.	58.3	41.7			26.8	73.2			45.1	54.9		
	Between 4-6 a.m.	84	16			57.7	42.3			73.5	26.5		
	Later than 6 a.m.	92.1	7.9			77	23			88.1	11.9		
Allowance money	0€	22.4	77.6	294.99**	.33	11.8	88.2	268.82**	.32	19.7	80.3	195.22**	.28
	Up to €10	31.1	68.9			14.6	85.4			26.1	73.9		
	Between €11-20	52	48			27.8	72.2			42.9	57.1		
	Between €21-30	70	30			46.4	53.6			54	46		
	Over €30	82.3	17.7			62.1	37.9			70	30		

Note. *p < .05. **p <.001.

Table 7. *Consumption of alcohol by family members.*

Alcohol use		3 or more alcoholic drinks		χ^2	ϕ	6 or more alcoholic drinks		χ^2	Φ	Getting drunk		χ^2	ϕ
		Yes (%)	No (%)			Yes (%)	No (%)			Yes (%)	No (%)		
Mother	Almost never	40.5	59.5	4.58*	.04	23.2	76.8	5.03*	.04	33.2	66.8	3.70	.04
	Regularly	44.8	55.2			27.2	72.8			37	63		
Father	Almost never	36	64	28.86**	.10	20.2	79.8	20.80**	.09	30.1	69.9	16.67**	.08
	Regularly	46.1	53.9			27.6	72.4			37.4	62.6		
Siblings	Almost never	32.6	67.4	168.48**	.26	18	82	112.90**	.21	26.4	73.6	137.91**	.24
	Regularly	59.3	40.7			37.2	62.8			49.8	50.2		

Note. **p* ‹ .05. ***p* ‹.001.

Table 8. *Use of alcohol and other substances among peers.*

		3 or more alcoholic drinks		χ^2	*CC*	6 or more alcoholic drinks		χ^2	*CC*	Getting drunk		χ^2	*CC*
		Yes (%)	No (%)			Yes (%)	No (%)			Yes (%)	No (%)		
They drink alcohol	None	1.4	98.6	1231.17**	.54	0.3	99.7	776,57**	,46	0.5	99.5	1033.93**	.51
	A few	11.1	88.9			5	95			9.5	90.5		
	Some of them	35.9	64.1			14.7	85.3			23.7	76.3		
	The majority	71.6	28.4			43.1	56.9			61.1	38.9		
	All of them	90.4	9.6			66.9	33.1			79.8	20.2		
They get drunk	None	3.9	96.1	1009.38**	.51	1	99	719.15**	.44	1	99	1042.63**	.51
	A few	31.7	68.3			13.1	86.9			20.7	79.3		
	Some of them	60.2	39.8			32.1	67.9			46.8	53.2		
	The majority	74.1	25.9			51.8	48.2			71	29		
	All of them	94.2	5.8			75	25			92.5	7.5		
They use tobacco	None	7.4	92.6	749,53**	,45	2.2	97.8	545.69**	.40	4.5	95.5	715.76**	.44
	A few	37.6	62.4			16.6	83.4			27	73		
	Some of them	59.8	40.2			36.9	63.1			50.1	49.9		
	The majority	72.5	27.5			50.4	49.6			66.6	33.4		
	All of them	86.4	13.6			67.2	32.8			84.4	15.6		
They use other drugs	None	22.8	77.2	581.05**	.41	10.4	89.6	489.20**	.38	15.4	84.6	670.06**	.43
	A few	58.1	41.9			33	67			48.6	51.4		
	Some of them	71.2	28.8			49.9	50.1			64.7	35.3		
	The majority	81	19			58.2	41.8			81.1	18.9		
	All of them	89.5	10.5			82.1	17.9			91.9	8.1		

Note. **p* ‹ .05. ***p* ‹.001.

risky behaviours considered. Nevertheless, those who get drunk show similar levels of polydrug use.

In terms of prevention, the development of an efficient response requires the identification of some of the variables associated with BD. In this regard, results confirm that BD adolescents have clearly positive beliefs and expectancies about the effects of alcohol, much more so (comparatively) than those with a more moderate consumption, in line with the hypotheses of Cortés et al. (2007) and McBride et al. (2014). Furthermore, the consumption of alcohol and of other substances by peers has proven to be a variable that is closely related to BD. According to Kandel and Andrews (1987), imitating the behaviour of peers is the predominant form of social influence, favouring the choice of friends that reinforce these types of behaviours. The same is true with regards to the influence of consumption

by family members, coherent with social learning theory, which underlines the importance of the subject's identification with the model (Espada et al., 2008). Another two variables that count with lesser empirical evidence in literature are curfew and allowance money. Though previous studies have also related both to the consumption of alcohol (Humensky, 2010; National Drug Plan, 2014; Varela et al., 2013), this study has found that they are also related to BD.

In sociodemographic terms, despite the fact that this pattern could be considered, today, a generalised phenomenon, it is possible to identify a profile with a higher prevalence of BD. Specifically, the percentages found are significantly greater among boys between the ages of 16-18, in urban settings, attending public schools, and among those whose parents have a low level of education.

If we attempt to integrate all of the information referring to those variables that are considered as possible "precedents", in addition to the aforementioned sociodemographic profile, the existence of a pattern associated with BD is worth mentioning, basically defined by beliefs and expectancies (adolescents who tend to overly attribute positive effects to BD), high consumption by peers (not only of alcohol, but also of tobacco and other substances), later curfew (especially after 4 a.m.), greater monetary allowance when going out (especially over €30), and high consumption by family members, especially on behalf of siblings. The available information does not allow for rigorously establishing significant differences among the three BD groups considered, though the variables analysed altogether seem to have a greater capacity for explaining or predicting a more "moderate" consumption pattern (3 or more alcoholic drinks), than for explaining a more "severe" pattern (6 or more alcoholic drinks).

Last of all, as to the possible limitations of this study worth mentioning are, first, the lack of consensus when operationalising BD as the variable object of the study. The absence of a definition of a Standard Drink Unit (SDU) or the lack of specificity of the time period considered "a single drinking episode" makes obtaining a precise measure of BD, comparable with other countries, a truly difficult task. To attempt to attenuate these types of difficulties, this study has opted for using 3 complementary indicators, two quantitative (" having consumed 3 or more alcoholic drinks during a single drinking episode" and " having consumed 6 or more alcoholic drinks during a single drinking episode") and another more qualitative or subjective indicator ("got drunk"). This has also provided some clues as to how the individual's subjective perception is related to the objective amount of consumption. A repetitive result in each of the questions explored by this study is that the figures associated with the behaviour of drunkenness are always positioned midway between the consumption of 3 or more alcohol drinks and the consumption of 6 or more alcohol drinks. It would be worth asking, therefore, if it would be more suitable to operationalise BD as the consumption of 4 or 5 alcoholic drinks during a single drinking episode, given that this seems to better align with the subjective perception of having got drunk. Another option, perhaps more suitable for rigorously operationalising BD could be to identify a series of indicators that includes both the objective number of amount of alcoholic drinks consumed as well as the individual's own perception, somehow attempting to develop (and empirically validate) a brief BD scale. It is important to point out that the sample of 3,419 adolescents may, to a certain extent, be considered representative of the autonomous region of Galicia, but its extrapolation to other communities is questionable. Last of all, it is also important to advise that this study is exploratory and, therefore, does not allow for establishing causal relationships. Though it is conceptually possible to anticipate which variables might be acting as predictors or consequences of BD, only a longitudinal design could confirm causal relationships.

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

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The Relationship between Consumption of Alcohol and Other Drugs and Problematic Internet Use among Adolescents

Relación entre el consumo de alcohol y otras drogas y el uso problemático de Internet en adolescentes

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Abstract

Alcohol and drug use among adolescents has been causing great concern for decades in Spain and in the European Union as a whole. In addition, the technology boom experienced over the last two decades has contributed to the emergence of a new public healthcare issue: problematic Internet use. The increasing importance that both problems have been gaining in recent years has led some authors to analyze the relationship between alcohol and the consumption of other drugs alongside problematic Internet use, and to provide relevant empirical evidence. Based on a sample of 3,882 Spanish adolescents aged between 12 and 18, the results obtained confirm that there is a relationship between the consumption of alcohol (measured by the AUDIT) and other drugs (measured by the CRAFFT and the CAST), and problematic Internet use (measured by the EUPI-a). Problematic Internet users among them not only have more significant levels of substance use, but also a three-times greater chance of developing hazardous drug use (39.4% vs 13.3%). This highlights the need to develop transversal prevention capable of acting on the common variables to both issues, beyond developing programs focused on specific behaviors. In this sense, values-based education and life skills training should be given priority in prevention.

Keywords: Internet; Adolescents; Alcohol; Drug use; Prevention.

Resumen

En España y en el conjunto de la Unión Europea el consumo de alcohol y otras drogas entre los adolescentes viene causando una enorme preocupación social desde hace décadas. Por otra parte, el auge tecnológico experimentado en las dos últimas décadas ha contribuido a la aparición de un nuevo problema sociosanitario: el uso problemático de Internet. El creciente protagonismo que ambos problemas han ido adquiriendo en los últimos años ha llevado a algunos autores a analizar la relación entre el consumo de alcohol y otras drogas y el uso problemático de Internet, aportando evidencias empíricas al respecto. La realización del presente trabajo, a partir de una muestra de 3882 adolescentes españoles de entre 12 y 18 años, ha permitido constatar que efectivamente existe una estrecha relación entre el consumo de alcohol (medido a través del AUDIT) y otras drogas (medido a través del CRAFFT y del CAST) y el uso problemático de Internet (medido a través del EUPI-a). No solo se han encontrado unos niveles de consumo significativamente mayores entre los usuarios problemáticos, sino que la probabilidad de desarrollar un consumo de riesgo de drogas llega a ser incluso 3 veces mayor entre éstos (39,4% vs 13,3%). Ello pone de manifiesto la necesidad de desarrollar una prevención transversal capaz de actuar sobre las variables comunes a ambas problemáticas, más allá de desarrollar programas centrados en conductas específicas. En este sentido, la educación en valores y habilidades de vida debieran ocupar un lugar prioritario en materia de prevención.

Palabras clave: Internet; Adolescentes; Alcohol; Consumo de drogas; Prevención.

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The consumption of alcohol and other substances among young people constitutes one of the main public healthcare problems in Spain. Although the levels of consumption of different substances appear to have declined in recent years, prevalence figures remain high, as the data from the latest National Survey on Drug Use among Secondary School Students in Spain [ESTUDES 2014-2015] (Plan Nacional sobre Drogas, 2016) reveal, with 76.8% of students between 14 and 18 years of age having consumed alcohol in the previous year (68.2% in the previous month), 31.4% having smoked tobacco (25.9% in the previous month) and 25.4% having used cannabis (18.6% in the previous month). Other substances such as cocaine, ecstasy, amphetamines or hallucinogens have much lower prevalence figures at below 3%. Regarding risky alcohol consumption, while ESTUDES does not use any screening tool as such, it does offer data on street drinking ('botellón') (which stands at 57.6% in the previous year), binge drinking (32.2% in the previous month), drunkenness (22.2% in the previous month) and risky drinking at the weekend (31.9%). No less worrying is the prevalence of problematic cannabis use obtained through the Cannabis Abuse Screening Test (CAST) (Legleye, Piontek & Kraus, 2011), which amounts to 2.5% of Spanish adolescents between 14 and 18 years of age.

However, the consumption of alcohol and drugs is not the only issue that society faces. The rapid technological advances witnessed over the past two decades has furthered the expansion and massive use of the Internet and social networks. According to data from the National Institute of Statistics (INE) (2016), 95.2% of children in Spain between the ages of 10 and 15 have used the Internet in the last 3 months. This technological boom has contributed to the emergence of a new social concern about how adolescents use the Internet. Despite the innumerable benefits brought about by technological advances, there are many risks that can arise from their misuse (Livingstone, Haddon, Görzig & Ólafsson, 2011; Muñoz-Miralles et al., 2016; Rial, Golpe, Gómez & Barreiro, 2015; Valkenburg & Peter, 2011). Apart from studies warning of the abusive use of the Internet by young people (Blinka et al., 2015; Gencer & Koc, 2012), with uncontrolled access to pornographic, violent, racist and sexist content, there are also those alerting to the many high-risk practices (Garaigordobil & Aliri, 2013; Strassberg, McKinnon, Sustaíta & Rullo, 2013; Wolak, Finkelhor & Mitchell, 2004) related to Internet use, such as cyberbullying, sexting and grooming. Some authors have even gone so far as to discuss the possibility of developing an addiction (Jorgenson, Hsiao & Yen, 2016; Young, 1996) or, at least, problematic Internet use (Anderson, Steen & Stavropoulos, 2016; Shapira et al., 2003). While Internet addiction or problematic use was initially identified primarily as a result of the overuse of the Internet, this approach has given way among both professionals and researchers to a focus which sees the problematic use of the Internet as a different problem that goes beyond the mere time online (Beard & Wolf, 2001; Hansen, 2002). In any case, it is precisely the lack of agreement regarding the conceptualization and operationalization of this problem which is behind the considerable variation in prevalence figures estimated by the different studies. For example, at the national level, the work of Oliva et al. (2012) claims that 0.76% of adolescents and young people have a serious level of internet addiction and 21.9% are moderately addicted, while Gómez, Rial, Braña, Varela and Barreiro (2014) put the prevalence of problem users among compulsory secondary education students at 19.9%.

Both problems (consumption of alchol and other drugs, and use of the Internet), are tha cause of grave social concern today, so much so that they are the focus of the latest edition of the *European School Survey Project on Alcohol and Other Drugs* (ESPAD) (European Monitoring Center for Drugs and Drug Addiction, 2016). Furthermore, the increasing importance that they have been acquiring has led in recent years to different authors concerning themselves with analyzing the relationship between these two problems, both in terms of consumption habits (Evren, Dalbudak, Evren & Demirci, 2014; Lee, Han, Kim & Renshaw, 2013; Rücker, Akré, Berchtold & Suris, 2015). High comorbidity between both, as well as hazardous consumption, especially in the case of alcohol has been found. For example, Ko et al. (2008) or Wartberg et al. (2016) coincide precisely in pointing out that problematic Internet users are more likely to have risky alcohol consumption.

In Spain there is still a dearth of studies analyzing the relationship between the problematic use of the Internet and substance use, and those that have been carried out tend to explore this relationship in a partial way. Thus, for example, the work of Secades-Villa et al. (2014) establishes a link between the time spent online and the frequency of consumption of alcohol, tobacco, cannabis and other illegal drugs among European adolescents, but does not examine the problematic use of the Internet itself, nor the 'hazardous consumption' of drugs with the appropriate instruments. The work of Fernández-Villa et al. (2015), meanwhile, analyzes the relationship between problematic Internet use and the consumption of different substances among university students without finding any association between the two. Nevertheless, the authors themselves acknowledge that this result could be explained by the fact that a classification criterion was used that does not distinguish between cases of occasional or problematic use. In fact, when the relationship with the consumption of alcohol risk is examined in the study, results reveal that problem users are more likely to obtain a positive result in screening. In another study, Gámez-Guadix, Calvete, Orue and Las Hayas (2015) find a positive relationship between

problematic Internet use and the consumption of alcohol risk in adolescents, but do not address the consumption of other drugs.

In short, we are dealing with an issue that has been attracting increasing interest among institutions and researchers worldwide, without, however, producing much evidence to date. This is particularly the case in our country, where most of the work has focused on analyzing the relationship between both problems, but usually with some limitations: either (1) paying attention exclusively to alcohol without taking the consumption of other drugs into acount, or (2) or not assessing hazardous consumption as such by using suitable instruments such as the *Alcohol Use Disorders Identification Test* [AUDIT] (Vent, Source, Saunders & Grant, 1989), the CRAFFT *Abuse Screening Test* (Knight et al., 1999) or the *Cannabis Abuse Screening Test* [CAST] (Legleye et al., 2011), or (3) using samples from university students rather than adolescents, the latter being a key population with regard to prevention.

Consequently, the present work has a twofold objective: (1) to perform a descriptive analysis of the habits of Internet use, high-risk practices and problematic Internet use, as well as consumption habits for the different substances and the hazardous consumption of alcohol and other drugs, and (2) to analyze the relationship between the problematic Internet use and the hazardous consumption among adolescents through the use of appropriate screening tools with proven psychometric properties.

Method

Participants

A selective methodology was employed, consisting of a survey of compulsory secondary education (ESO) and baccalaureate students in the provinces of A Coruña and Pontevedra. For sample selection, purposive sampling was used in an attempt to access as wide and heterogeneous a sample as possible. A total of 15 educational centers in different municipalities took part, both public and private/state-maintained private ('concertado'), both urban and rural.

The initial number of questionnaires collected was 4063, although 62 were eliminated after an exhaustive review process, either because they had an excessive number of missing values (32) or incoherent response patterns (30). In addition, a further 119 cases were eliminated because they were outside the age range under study (12-18 years). Thus the final sample consisted of 3882 adolescents (49.9% males and 50.1% females) aged between 12 and 18 (M = 14.52 and SD = 1.72). Of these, 2669 attended public schools and 1213 were in private or state-maintained private schools, with 74.8% in compulsory secondary education (38% in the first cycle and 36.8% in the second) and 25.2% baccalaureate students.

Instrument

The data were collected through a questionnaire which was specially drawn up for the present study and included questions grouped in four blocks: (1) the first comprises questions of our own creation to assess the habits of Internet use (frequency of use and time spent online) and possible high-risk practices (sexting, online betting, contact with strangers, etc.) (2) a second block was extracted from the ESTUDES (2010) National Survey on Drug Use among Secondary School Students (Plan Nacional sobre Drogas, 2011) to collect information on the consumption habits for both alcohol and other substances; (3) a third block that includes four screening tools: the Alcohol Use Disorders Identification Test (AUDIT) in its self-administered version (Rial, Gómez, Araujo, et al., 2015) to estimate risky alcohol consumption, the internal consistency of which in the present work was acceptable (α =, 82); the Cannabis Abuse Screening Test (CAST) (Legleye et al., 2011) to estimate the risk of cannabis use, with high internal consistency (α =, 85); the version of the CRAFFT Abuse Screening Test translated into Spanish and validated by Araujo et al. (2015), which presented an α of .62, and the Problematic Internet Use Scale (EUPI-a) (Rial, Gómez, Isorna, Araujo & Varela, 2015). Although the EUPI-a is a tool with less of a tradition than other existing ones, it is an instrument adapted to the Spanish cultural context which has been specifically developed and validated for the adolescent population of our country and which has displayed satisfactory psychometric properties, both in terms of internal consistency (α = .87), sensitivity (81%), specificity (82.6%) and construct validity, with a duly tested cut-off point for screening; and (4) a final section collecting information on sociodemographic variables such as gender and age.

Process

The data were collected in the classrooms of each center, in small groups (between 15 and 20 individuals), through a questionnaire that each student completed individually. A team of psychologists with proven experience in the accomplishment of this type of tasks carried out the information collection. All participants were informed of the purpose of the study, as well as the confidentiality and anonymity of their responses. The consent and collaboration of the each center's management as well as the respective parents' associations was obtained. Participation was totally voluntary and questionnaire completion time was approximately 20 minutes. The work was also approved by the bioethics committee of the University of Santiago de Compostela.

Data analysis

A bivariate tabulation was made with the use of Student's *t* tests for the comparison of means and χ^2 contrasts for the comparison of percentages. Correlation analysis was also performed (with Pearson for metric variables and Spear-

man for ordinal variables). Finally, a univariate and multivariate logistic regression analysis, adjusted for gender and age, was performed to predict the high-risk use of alcohol as well as other substances. The analyses were performed using the IBM SPSS Statistics 20 statistical package.

Results

Problematic Internet use and high-risk practices

As shown in Table 1, the use of the Internet among adolescents is widespread: 83% are online every day or almost every day, with 56.4% connecting for a moderate period of time (three hours or less), while 10.8% spend more than 5 hours a day online and 15.9% say they are online "throughout the day". Girls have a higher connection frequency and spend longer online, with 15 being the age when the greatest increase in the use of the Internet is observed, both in terms of frequency and connection time. Furthermore, 63.8% of adolescents are be registered in three or more social networks, with a significantly higher percentage among women (67.3% vs 60.3%), and particularly above the age of 15 (80.6% %). The most common high-risk practices are: contact with strangers (31.9%) and access to websites with erotic content (30.1%). While women more frequently feel threatened, harassed or humiliated online and have been blackmailed by threats of disseminating photos or videos of them with erotic content, boys admit to a greater extent threatening, harassing or humiliating others, contacting strangers, accessing websites with erotic content and placing bets online. Involvement in most of the high-risk practices analyzed is generally greater with increasing age, and rising especially sharply from the age of

Table 1. *Habits of Internet and social network use, high-risk practices and problematic use.*

	Global (%)	Sex		χ^2	Age (years)			χ^2
Connection frequency		Male (%)	Female (%)		12-14 (%)	15-16 (%)	17-18 (%)	
Never/almost never	1.1	1.2	1	8.60*	2.1	0.1	0.5	343.72**
Occasionally during the month	3.2	3.9	2.4		5.4	1	0.8	
Occasionally during the week	12.7	13	12.4		20.7	4.7	4.7	
Every/almost every day	83	81.9	84.2		71.8	94.2	94	
Time online per day								
Less than 1 hour	14	14.5	13.5	65.37**	22.9	5.3	5.6	589.33**
1-2 hours	24.2	26.5	21.8		31.9	17.1	16	
2-3 hours	18.2	19.9	16.6		18.5	19.6	14.3	
3-5 hours	16.9	17.3	16.7		13.2	20.9	19.9	
Over 5 hours	10.8	10.6	11		7.1	13.2	17.4	
All day	15.9	11.3	20.5		6.5	23.9	26.8	
Social networks								
None	7.8	8.7	6.8	20.15**	12.6	3.1	3	477.20**
1 or 2	28.4	31	26		40.5	16.3	16.4	
3 or more	63.8	60.3	67.3		46.8	80.6	80.6	
High-risk practices								
Victim of threats, harassment or humiliation	5.9	4.5	7.4	14.80**	5.9	6.1	5.8	.08
Initiator of threats, harassment or humiliation	4.6	6	3.1	18.92**	3.5	5.7	5	9.93*
Sexting	5.2	4.5	5.8	3.23	1.9	7.9	9.8	88.57**
Victim of blackmail (publishing/ disseminating photos or videos of yours with erotic content)	3	1.9	4.1	14.85**	2.8	3.2	3.3	.70
Accessing erotic websites	30.1	49.9	10.3	717.23**	17.2	40.5	47	302.19**
Online betting	6.7	11.8	1.5	162.51**	4.3	7.9	11.1	40.30**
Contact with strangers	31.9	34.4	29.5	10.57**	23.8	39.8	39.9	114.32**
Meeting strangers	14	14.7	13.2	1.79	8.9	18	20.8	82.01**
Problematic use (EUPI-a)	18.4	16.6	20.4	8.92*	14	22	24.7	50.65**

Note. *p < .05; **p <.001.

15 onwards. Regarding problematic Internet use as such, 18.4% of adolescents exceeded the cut-off point established on the EUPI-a scale (≥ 16), and can thus be considered problematic users. This percentage was significantly higher among girls and in the older age group (17-18). In addition, in order to analyze the relationship between the problematic Internet use and time online, a Spearman correlation analysis was carried out, obtaining a value $r_{xy} = .45$ ($p < .001$). This shows that time online only accounts for 20% of the variance in problematic Internet use ($r_{xy}^2 = .20$).

Consumption of alcohol and other drugs

As shown in Table 2, the most commonly consumed substance among adolescents is alcohol (52.1% previous year, 32.3% previous month), followed by tobacco and cannabis. The results obtained regarding consumption habits in the previous year by gender show that there are only significant differences in relation to smoking, with a slightly higher percentage among girls. Regarding the previous month, statistically significant differences have also been found in the consumption of alcohol, intensive consumption (3 or more alcoholic drinks per sitting and drunkenness) and tobacco, with higher percentages, once again, in the case of girls. There is also a considerable increase in the levels of consumption of many substances with increasing age. The results of screening for hazardous use also show that 19.8% of adolescents drank alcohol (AUDIT), 3.8% consumed cannabis (CAST) and 18% consumed alcohol and other drugs in general (CRAFFT). There were no differences based on gender, although age differences were found, with a significant increase in the consumption of alcohol and other drugs with increasing age.

Relationship between problematic Internet use and consumption of alcohol and other drugs

The relationship between the problematic Internet use and the consumption of alcohol and other drugs was initially verified through an analysis of correlations between the EUPI-a, CRAFFT, AUDIT and CAST scales, all of which statistically significant (r_{xy} EUPI-CRAFFT = 0.39, $p < .001$) (r_{xy} EUPI-AUDIT = 0.36; $p < .001$) (r_{xy} EUPI-CAST = .11; $p < .001$). However, correlation and effect sizes indicate that this

Table 2. *Substance use habits and hazardous consumption.*

	Global (%)	Sex		χ^2	Age (years)			χ^2
Substance use habits (previous year)		Male (%)	Female (%)		12-14	15-16	17-18	
Drinking alcohol	52.1	50.7	53.4	2.74	32.9	68.2	76.9	569.59**
3 or more alcoholic drinks per day	33.1	31.8	34.2	2.31	14.4	47.1	60.9	631.02**
6 or more alcoholic drinks per day	18.1	18.7	17.2	1.34	6.4	25.9	36.8	373.70**
Getting drunk	26.3	25.4	27	1.18	10.1	38	50.8	542.83**
Tobacco	23.4	21.2	25.4	9.2*	11.9	31.2	41.8	300.55**
Marijuana or hashish	14.8	15.3	14.3	0.65	5.9	20.3	30.3	266.76**
Cocaine	0.9	1.1	0.6	1.97	0.6	1.2	1	3.84
Écstasy, amphetamines or hallucinogens	1.1	1.2	0.9	0.89	0.6	1.4	1.8	9.44*
Substance use habits (previous month)								
Drinking alcohol	32.3	30	34.5	8.69*	16.1	43.7	57.8	489.18**
3 or more alcoholic drinks per day	20	18.2	21.8	7.36*	7.1	28.4	41.7	436.12**
6 or more alcoholic drinks per day	8.6	8.9	8.3	0.33	3.1	11.3	19.5	179.36**
Getting drunk	12.9	11.7	14	4.70*	4.5	17.1	29.6	292.58**
Tobacco	16.1	14.3	17.8	8.54*	8	21.3	30.2	209.42**
Marijuana or hashish	8.5	8.6	8.4	0.04	3.6	11.5	17.6	137.98**
Cocaine	0.4	0.4	0.4	0.00	0.4	0.4	0.2	0.81
Écstasy, amphetamines or hallucinogens	0.4	0.3	0.5	0.26	0.3	0.6	0.2	2.61
Hazardous consumption								
AUDIT	19.8	19	20.6	1.37	5.3	30.1	43.8	538.35**
CAST	3.8	4.2	3.4	1.27	1.8	5.5	6.1	40.38**
CRAFFT	18	17.2	18.9	1.64	5.1	26.8	39.3	454.79**

Note. *$p < .05$; **$p < .001$.

Table 3. *Differences in substance use habits among problematic Internet users.*

Substance use habits (previous year)	EUPI		χ^2
	Positive (%)	Negative (%)	
Drinking alcohol	65.7	48.9	62.62**
3 or more alcoholic drinks per day	47.5	29.8	78.87**
6 or more alcoholic drinks per day	27.9	15.7	56.17**
Getting drunk	39.5	23.3	76.03**
Tobacco	35.8	20.4	74.09**
Marijuana/hashish	23.8	12.7	54.26**
Cocaine	1.4	0.7	3.10
Écstasy/amphetamines/ hallucinogens	2	0.8	6.82*
Substance use habits (previous month)			
Drinking alcohol	42.6	29.8	42.13**
3 or more alcoholic drinks per day	29.2	17.8	44.87**
6 or more alcoholic drinks per day	13.5	7.4	25.82**
Getting drunk	20.6	11	46.16**
Tobacco	24.2	14.1	42.22**
Marijuana/hashish	13.3	7.2	26.30**
Cocaine	0.1	0.4	0.56
Écstasy/amphetamines/ hallucinogens	0.9	0.3	2.72

Note. *p < .05; **p <.001.

relationship is relevant only in the case of drugs and alcohol, where it is moderate (> .30) (Weinberg & Abramowitz, 2002).

To analyze this relationship in greater depth, the sample was divided into two groups (problematic Internet users vs. non-problematic users), and their consumption habits in the previous year and the previous month were compared. The results reported in Table 3 reveal statistically significant differences for almost all substances, with rates almost twice as high among problem users.

The same can be said of hazardous consumption, with significantly higher rates among problem users, three times higher in the case of CRAFFT (39.4% vs. 13.3%) (c^2 = 248.66; p < .001). The analysis of the effect size once again reveals that this is a moderate relationship in both alcohol ($CC_{EUPI\text{-}AUDIT}$ = .21) and drugs in general ($CC_{EUPI\text{-}CRAFFT}$ = .25) and practically non-existent in the case of cannabis ($CC_{EUPI\text{-}CAST}$ = .08). Similarly, the mean scores obtained on the different screening scales are significantly higher for problematic users, with an almost identical pattern for effect sizes ($\eta_{EUPI\text{-}CRAFFT}$ = .26; $\eta_{EUPI\text{-}AUDIT}$ = .22; $\eta_{EUPI\text{-}CAST}$ = .08).

Finally, logistic regression analysis (Table 5) revealed that both age and problematic Internet use are risk factors for the development of alcohol and other drug abuse. Specifically, increasing age, the probability of obtaining a positive result in AUDIT (POR = 1.95 [95% CI: 1.83 – 2.08]) and in the CRAFFT (POR = 1.87 [95% CI: 1.75 – 1.99]). With regard to problematic Internet users, these present almost three and four times greater likelihood of developing hazardous use of alcohol and of drugs in general, respectively.

Discussion

The results obtained serve to reinforce some of the findings in ESTUDES 2014-15 (Plan Nacional sobre Drogas, 2016), according to which alcohol remains the psychoactive substance most consumed by adolescents, followed by tobacco and cannabis. Furthermore, the data confirm the trend already noted by other authors (Vargas & Trujillo, 2012; White et al., 2015) regarding the reduction of the gender gap in the consumption of different substances, which is even inverted in the case of alcohol and tobacco. Although the rates found in the lowest age range are apparently small, when carried over to population figures, would mean that between 2000 and 5000 Galician adolescents between 12 and 14 got drunk, smoked tobacco and consumed cannabis in the previous month. These figures are of particular concern in view of the important implications that the consumption of these substances can have on the developing brain, as can be seen in the works of Cadaveira (2009), Jacobus and Tapert (2015), and Yuan,

Table 4. *Differences in hazardous consumption among problematic Internet users.*

Hazardous consumption	EUPI		Contrast
	Positive	Negative	
AUDIT	38.1% Mean = 4.54	15.8% Mean = 1.83	χ^2= 165.92** t = -16.67**
CAST	7% Mean = 0.70	2.9% Mean = 0.28	χ^2= 24.69** t = -4.95**
CRAFFT	39.4% Mean = 1.51	13.3% Mean = 0.62	χ^2= 248.66** t = -18.01**

Note. *p < .05; **p <.001.

Table 5. *Logistic regression models for predicting hazardous consumption.*

	AUDIT		CRAFFT	
Variable	Univariate POR (95% CI)	Multivariate[1] POR (95% CI)	Univariate POR (95% CI)	Multivariate[1] POR (95% CI)
SEX				
Male	1	1	1	1
Female	1.11 (0.94-1.30)	1.11 (0.92-1.34)	1.12 (0.95-1.32)	1.07 (0.89-1.30)
AGE	1.97 (1.86-2.10)	1.95 (1.83-2.08)	1.88 (1.77-1.99)	1.87 (1.75-1.99)
EUPI-a				
Negative	1	1	1	1
Positive	3.28 (2.73-3.96)	2.92 (2.38-3.69)	4.25 (3.52-5.13)	3.90 (3.17-4.80)

Note. POR = Prevalence of odds ratio; CI= confidence interval; 1Adjusted for the other independent variables included in the column.

Cross, Loughlin and Leslie (2015). In terms of hazardous consumption, it is important to note that the overall prevalence figures obtained 'mask' very unequal percentages depending on age range, with rates of up to eight times higher registered in the group of 17 to 18-year olds in comparison with the youngest age group (12-14).

With regard to the Internet, the data obtained show that its use is nowadays widespread among Spanish adolescents. Although both Internet and social network use are more intensive with increasing age, it is noteworthy that between the ages of 12 and 14, seven out of ten adolescents are online daily, and one in four for more than five hours. It should be pointed out, however, that in spite of a positive and significant correlation between the hours that adolescents spend online and problematic Internet use being found, the magnitude of this relationship turned out to be moderate, which shows that problematic Internet use is a different issue, which goes beyond time spent online and whose defining element is the degree of interference it causes in the life of the adolescent (Beard & Wolf, 2001). Moreover, it is observed that the vast majority are members of a social network and almost half of three or more. It is clear, therefore, that adolescents make relatively intensive use of the Internet, with the consequences, both physical and psychosocial, that this can lead to (Randy et al., 2015).

The most frequent high-risk practices are contact with strangers and access to websites with erotic content, which can be of concern when dealing with individuals whose brain maturity does not yet allow them to develop an adequate cognitive, emotional and behavioral response to certain situations (Owens, Behun, Manning & Reid, 2012). With regard to the prevalence of problematic Internet use, this stood at 18.4%. This result is similar to that obtained in other studies carried out on the same population and with the same screening tool as the one by Gómez et al. (2014) and Gómez, Rial, Braña, Golpe and Varela (2017), or that obtained by López-Fernández, Freixa-Blanxart and Honrubia-Serrano (2012) using the *Problematic Entertainment Use Scale for Adolescents*. However, it is important to point out that for both theoretical and methodological reasons there is still a significant problem of comparability between the results of the different studies, which is one of the main challenges to date in this field of research.

Beyond the analysis of the consumption levels of the different substances and the possible problematic use that adolescents make of the Internet, the results obtained also show the existence of a link between both behaviors. This not only confirms the findings of other studies regarding the relationship between problematic Internet use and consumption of alcohol risk (Fernández-Villa et al., 2015; Gámez-Guadix et al., 2015), but also evidence that problematic Internet use is associated with the hazardous use of other drugs. A logistic regression analysis has also shown a significantly higher rate of hazardous consumption among adolescents who make problematic use of the Internet, up to four times in the case of CRAFFT.

Numerous studies until today have highlighted the link between problematic Internet use and substance use (Cía, 2013; Holden, 2001; Sun et al., 2012). This suggests, as proposed in the problematic behavior theory (Jessor, 1991), that different types of deviant behavior might respond to the same determinants. According to this approach, there would be a common "psychosocial propensity" to develop the different problem behaviors defined by personality traits as well as the social context, the perceived environment and the individual's own behavior. Thus, for example, the work of Ko et al. (2008) found that certain psychosocial characteristics such as being a man, a dysfunctional family, having low self-esteem and low life satisfaction were associated with both problematic alcohol consumption and Internet addiction. The main implication of the results obtained at the applied level may be the importance of proposing transversal prevention, beyond approaches or programs focused on specific behaviors, and capable of acting on the variables common to both problem behaviors. Thus, interventions aimed at improving education in values and the learning of life skills could provide a platform on which to develop preventive work, insofar as they

start from an individual-environment interaction model that has been shown to be effective in drug prevention (European Monitoring Center for Drugs and Drug Addiction, 2011; Faggiano, Minozzi, Versino & Buscemi, 2014; Moshki, Hassanzade & Taymoori, 2014).

Finally, the present work has some limitations, the first of which would be the sample used. Despite being based on data from 4000 adolescents, the fact that non-probabilistic sampling was used for their selection and that they originate exclusively from the provinces of A Coruña and Pontevedra limits the external validity of the results. Secondly, it is important to refer to the transversal nature of the work, which prevents causal relationships being established among the variables under study. Finally, mention should be made of the fact that all variables have been self-reported, making it impossible to know for certain to what extent adolescents may have underestimated or overestimated both their levels of consumption and the amount of time they spend online. However, as various experts in the field of addictive behavior have previously pointed out, self-report measures have proven to be reliable and even better than other methods in assessing levels of alcohol and other drug use (Babor , Kranzler & Lauerman, 1989; Winters, Stinchfield, Henly & Schwartz, 1990).

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Conflict of interests

The authors of this article declare that they have no conflict of interest.

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Animal models of drug addiction

Modelos animales de adicción a las drogas

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Abstract

The development of animal models of drug reward and addiction is an essential factor for progress in understanding the biological basis of this disorder and for the identification of new therapeutic targets. Depending on the component of reward to be studied, one type of animal model or another may be used. There are models of reinforcement based on the primary hedonic effect produced by the consumption of the addictive substance, such as the self-administration (SA) and intracranial self-stimulation (ICSS) paradigms, and there are models based on the component of reward related to associative learning and cognitive ability to make predictions about obtaining reward in the future, such as the conditioned place preference (CPP) paradigm. In recent years these models have incorporated methodological modifications to study extinction, reinstatement and reconsolidation processes, or to model specific aspects of addictive behavior such as motivation to consume drugs, compulsive consumption or drug seeking under punishment situations. There are also models that link different reinforcement components or model voluntary motivation to consume (two-bottle choice, or drinking in the dark tests). In short, innovations in these models allow progress in scientific knowledge regarding the different aspects that lead individuals to consume a drug and develop compulsive consumption, providing a target for future treatments of addiction.

Keywords: Reward; Addiction; Animal models; Drugs of abuse.

Resumen

El desarrollo de modelos animales de refuerzo y adicción a las drogas es imprescindible para el avance en el conocimiento de las bases biológicas de este trastorno y la identificación de nuevas dianas terapéuticas. En función del componente del refuerzo que deseemos estudiar podemos servirnos de un tipo de modelos animales u otros. Podemos utilizar modelos de refuerzo basados en el efecto hedónico primario que produce el consumo de la sustancia adictiva, como los modelos de autoadministración (AA) y autoestimulación eléctrica intracraneal (AEIC), o modelos basados en el componente relacionado con el aprendizaje asociativo y la capacidad cognitiva de realizar predicciones sobre la obtención del refuerzo en el futuro, como el modelo de condicionamiento de preferencia de lugar (CPL). En los últimos años los modelos han incorporado modificaciones metodológicas para incluir el estudio de los procesos de extinción, reinstauración y reconsolidación o para modelar aspectos concretos de la conducta adictiva como puede ser la motivación para consumir la droga, el consumo compulsivo o la búsqueda de la droga bajo situaciones de castigo. Otros modelos interrelacionan diferentes componentes del refuerzo o modelan la motivación voluntaria por consumir (modelos de "two-bottle choice" o "drinking in the dark"). En definitiva, las innovaciones en estos modelos contribuyen al avance en el conocimiento científico de los diferentes factores que llevan a tomar una droga y a desarrollar un consumo compulsivo, ofreciendo una vía para identificar futuros tratamientos para la adicción.

Palabras clave: Refuerzo; Adicción; Modelos animales; Drogas de abuso.

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1. Introduction

Studying the hedonic or pleasurable effects of a drug is essential for understanding the mechanisms that cause the development of drug addiction. However, it is a complex matter for which we need to use animal models that allow us to investigate the components involved and identify new therapeutic targets (Koob, Arends & Le Moal, 2014). The use of these animal models has the advantage of allowing great control of experimental variables such as the age at which the animals are exposed to the drug, the dose, duration or exposure time, among others.

A drug itself causes reinforcement which can lead to the development of substance abuse, dependence or addiction in vulnerable persons. Addiction to drugs is a neuropsychiatric disorder characterized by loss of control when seeking and consuming a drug, the appearance of negative emotional states and an intense craving for the drug when consumption ceases, alongside a high propensity to relapse, even after long periods of abstinence. According to Koob & Volkow (2016), drug addiction represents a profound disruption of motivational circuits in the brain caused by a combination of several factors. Firstly, there is a reinforcement deficit and increased stress reactivity due to the desensitization of the brain's reward system and over-activation of stress systems. Secondly, there is an exaggerated incentive salience relating to stimuli or contexts associated with the drug, and rigid stimulus-response habits are established which cause the subject to seek and consume the drug when it is present or when there are signs of its availability. These changes have been associated with a transition from the ventral to the dorsal striatum in controlling the behavior of drug use. Thirdly, there is a deterioration of executive functions such as decision-making, inhibitory control and self-regulation (Romero-Martínez & Moya-Albiol, 2015) due to the dysfunction of the prefrontal cortex, resulting in a lack of control and the inability to inhibit drug-taking behavior despite the negative consequences it entails. Therefore, a transition occurs in some vulnerable persons from the initially controlled consumption of a drug for recreational purposes to compulsive consumption. The presence of a stimulus associated with the drug thus triggers the urge to consume it, and this habit that the subject cannot control (more so than the reinforcing effect of the drug itself which is essential in its recreational use) is one of the main causes of persistent consumption and relapse (Everitt, 2014; Everitt & Robbins, 2013).

It is precisely for the study of these processes and their different phases (such as the acquisition, extinction, and reinstatement of a motivated behavior) that we use animal models. However, although many of the components of addictive behavior can be studied in experimental animals (for example, the primary reinforcing effect of drugs, cognitive aspects such as the processing of drug-context associations, phenomena of sensitization or tolerance to the different effects of the substance, etc.), it is necessary to emphasize that the addiction disorder (or disorders of drug use, according to DSM-5 criteria) is impossible to model in animals. Therefore, paradigms which are explained throughout this review only model specific aspects of addiction.

Among the major animal models used to study reinforcement produced by drugs and addictive behaviors we find the self-administration (SA), conditioned place preference (CPP) or intracranial self-stimulation (ICSS) paradigms; there are other models, nevertheless, which also offer relevant information and are therefore widely used, each of which will be discussed in the following sections.

2. Reinforcement and addiction

To understand the neurobiological mechanisms involved in addiction through animal models, we need to study the initial element of the addictive process, i.e. the reinforcing effect induced by the drug. This is the element that causes a loss of control over drug use to develop in some consumers, as only those substances which are capable of producing reinforcement can increase the likelihood of the drug-taking behavior reoccurring in the future, resulting in the progressive onset in vulnerable persons of symptoms that characterize addiction. It should be noted that the loss of control over consumption only occurs in "vulnerable" individuals; when they are exposed to the drug, the addictive disorder is triggered. Clearly not all individuals who consume a drug and experience reinforcement become addicted to it. An obvious example of this is alcohol. Furthermore, studies in humans and experimental animals indicate that impulsivity is a vulnerability trait predictive of abuse and addiction to psychostimulants (Everitt, 2014). The environment or social context, stage of life development and genetic factors also modulate vulnerability to addiction (Volkow, Koob & McLellan, 2016).

In the psychology of learning, reinforcement is defined as the process responsible for strengthening a response, increasing the rate or probability of occurrence. This strengthening is due to this response being contingently followed by a stimulus or event, known as a reinforcer. In the case of positive reinforcement, the reinforcer (food, for example) appears when the subject performs the response, whereas in the case of negative reinforcement the reinforcer (of an aversive nature, for example a painful stimulus) is made to disappear when the subject performs the response. Therefore, reinforcement is the term referring to the situation or experimental procedure in which a reinforcer is presented or removed on a certain response or behavior, while the reinforcer is the appetitive or aversive stimulus that appears or disappears when an operant behavior is performed, and results in an increase in the likelihood of occurrence or learning of such behavior (Skinner, 1938; Thorndike, 1932). Moreover, one can distinguish between

primary reinforcers, those who have a positive or negative motivational value in themselves (for example, stimuli necessary for survival as food and drink or the avoidance of pain or a predator) and conditioned reinforcers, initially of a neutral nature but which acquire a motivational value by association with the primary reinforcer.

Drugs are considered primary reinforcers because they are able to activate the brain reward system. The main anatomical substrate of this system is the mesolimbic pathway that originates in the ventral tegmental area (VTA) and projects into the nucleus accumbens (NA) and different cortical areas including the anterior cingulate cortex (ACC) and orbitofrontal and prefrontal cortex (Berridge & Kringelbach, 2015; Carlezon & Thomas, 2009; Dalley & Everitt, 2009; Wise, 2008). In these areas dopamine, the main neurotransmitter related to strengthening and pleasure is released (Lammel, Lim & Malenka, 2014), as are other neurotransmitters such as serotonin (Müller & Homberg, 2015). As we mentioned above, there are different components to reinforcement, such as the subjective experience of pleasure or a component related to learning or the ability to generate cognitive representations with predictions of reward in the future. Hence each animal model focuses on a different aspect; for example, models such as intravenous SA or ICSS reflect the primary hedonic reinforcing effect of the drug, while CPP emphasizes the aspect of learning such reinforcement (Berridge & Kringelbach, 2008).

The use of animal models not only allows the evaluation of the reinforcing effects of drugs but have in recent years been redesigned to study the extinction, reinstatement and reconsolidation processes and to more accurately reflect the behavioral characteristics of addiction. The extinction-reinstatement paradigm permits the study of the extinction process (through training sessions in which the animal is exposed to the same conditions as in the acquisition phase but where the reinforcing substance is not present) and the modeling of relapse in drug seeking, which is the principal clinical problem in the treatment of addiction (Ghitza, 2015). Similarly, it has been proposed that manipulation of the memories associated with a drug could be an effective method of removing these memories and so prevent relapse. The memory of the effects produced by drugs or the associative learning between its reinforcing properties and environmental cues associated with its consumption sustain drug consumption, triggering the desire to consume and thus the relapse (Yan et al., 2014). It has been widely demonstrated that after being recovered and becoming accessible, memory undergoes an unstable transitional stage and needs to be consolidated again in order to prevail, a process known as reconsolidation (Alberini, 2011; Inda, Muravieva & Alberini, 2011; Lee, 2010; Muravieva & Alberini, 2011). Updating drug-related memories is an important part of subsequent reconsolidation and has been linked to the persistence of drug addiction (Sorg, 2012; Taylor, Olausson, Quinn & Torregrossa, 2009). Therefore, destabilizing the memory of drug-related learning through behavioral or pharmacological procedures can be a means of promoting abstinence and preventing relapse (Everitt, 2014).

Similarly, animal models have led to increased knowledge of the neurobiological processes underlying the development of dependency and addiction (Koob et al., 2014; Volkow et al., 2016.). Thus, there are ever more studies evaluating the effects of different lesions in specific brain regions, or on pharmaceuticals with specific effects on different neurotransmission systems and how these in turn affect the reinforcing properties of drugs observed in these models. As an example, in our laboratory we have demonstrated the essential role of NMDA glutamate receptors in the reinforcing effects conditioned by different drugs such as morphine, cocaine or ecstasy (Do Couto, Aguilar, Rodríguez-Arias & Miñarro, 2005; García-Pardo, Escobar-Valero, Rodríguez-Arias, Miñarro & Aguilar, 2015a; Maldonado, Cauli, Rodríguez-Arias, Aguilar & Miñarro, 2003). Some studies even evaluate the effects of drug administration in specific brain areas on the reinforcement induced by chronic administration of the drug, which could clarify the involvement of a certain system of neurotransmission in a specific brain area in the reinforcing properties of the drug concerned and/or its ability to induce dependency. The description of advances in the neurobiology of drug addiction obtained by using these models is beyond the scope of this review. In this respect the contribution made recently by Koob and Volkow (2016) is recommended.

3. Animal models of reinforcement

3.1. Models of self-administration

In general, all substances with a high addiction potential for humans are self-administered by animals voluntarily, although it has been difficult to demonstrate this with some drugs. Moreover, this relationship is so strong that SA models are considered to have high predictive power, and different classifications of these models exist. Firstly, we have those paradigms where the animal must perform an operant behavior, such as pressing a lever to receive a dose of the substance, usually orally or intravenously. Secondly, there are the paradigms in which the animal has free access to the substance and can readily consume it orally (Teruel, 2008).

3.1.1. Models of operant learning.

This section includes both intravenous and oral SA since the learning model is similar, regardless of the way in which the substance is ingested.

The intravenous SA paradigm is the most important procedure and the most commonly used in animals, mainly

rodents, to assess the primary intrinsic reinforcing effect of drugs (Moser, Wolinsky, Duxon & Porsolt, 2011; Yahyavi-Firouz-Abadi & See, 2009). In this paradigm animals are trained to obtain the drug by performing an operant response, for example pressing a lever or the inserting its snout into a hole. Thus, when the animal responds, its behavior is reinforced with the injection of the drug and it consequently acquires a new operant response by learning that the behavior in question is associated with obtaining the reinforcer (Yahyavi-Firouz-Abadi & See, 2009). Most SA procedures use a fixed response program (FR) in which the animal must perform a fixed number of responses in order to obtain the dose of the drug (Moser et al., 2011), although a variable response program is used by other studies.

There are different factors, both pharmacological and environmental, to consider when using the SA paradigm, such as the dose of the substance administered, the rate of infusion of the drug, the sex of the animal or the stage of its evolutionary development. However, other factors such as the duration of the SA session or the level of challenge involved in the response required for the drug have proved more decisive (Moser et al., 2011).

3.1.1.1. Advantages and disadvantages of SA. SA is so frequently used because the model has excellent predictive validity, given the great similarity between the results obtained with the model in animals and for human addictive behaviors (Koob et al., 2014. Mead, 2014; Schenk, 2009; Soria, Barbano, Maldonado & Valverde, 2008). Compared to other models of addiction, the SA paradigm is closely related to drug abuse in humans in terms of how the substance is administered and the behavioral response that is generated in order to obtain the administration (O'Connor, Chapman, Butler & Mead, 2011). Moreover, since this paradigm measures how animals behave when seeking drugs, the technique can be used to study the neurobiological mechanisms involved in this process (Fuchs, Feltenstein & See, 2006).

Another important advantage of this paradigm is that it makes it possible to analyze the motivation for drug seeking by using a progressive reinforcement schedule in which the animal has to perform a progressively greater number of responses to obtain it (Richardson & Roberts, 1996). As the SA session progresses, procuring the following reinforcer requires a greater effort by the animal. The maximum number of operant responses that the animal is able to perform to obtain a reinforcer is called "breaking point" and measures the limit of an animal's motivation to seek the drug.

Although intravenous SA is the most commonly used paradigm, it also has some drawbacks, the principal of which is the complexity of the technique. In order to measure the reinforcing effect, it is necessary to surgically implant an intravenous catheter (Graf et al., 2011). One solution to this handicap is to use an alternative SA paradigm, such as oral SA, where the animal is freely able to consume the addictive substance orally, following the same procedure described for intravenous SA (Pautassi, Miranda-Morales & Nizhnikov, 2015). Oral SA is not as reinforcing for animals and has other limitations such as the fact that the animal has to be previously familiarized with the addictive substance in order to drink it voluntarily (it is therefore not used with certain drugs that animals do not usually find reinforcing orally, such as cocaine). Another disadvantage of the SA model is that for the proper application of this technique it is necessary to train animals to learn to acquire operant behavior. This drawback is most pronounced with drugs whose initial reinforcing strength is not particularly high, such as 3,4-methylenedioxymethamphetamine (MDMA) (Trigo, Panayi, Soria, Maldonado & Robledo, 2006; Schenk, 2009). In these cases, the animal is previously trained with a more reinforcing substance such as cocaine (Schenk, 2009), or a priming dose is administered previously (Trigo et al., 2006). In some cases, a food restriction pattern is even used before the SA acquisition phase (Soria et al., 2005).

3.1.1.2. Extinction, reinstatement and reconsolidation processes in SA. SA studies allow us to investigate different processes such as acquisition, maintenance, extinction and reinstatement of the operant response. To this end a procedure comprising several stages is used. The acquisition phase is defined as the time period necessary to achieve a stable rate of drug SA (Soria et al., 2005). This is followed by the maintenance phase which may take days or weeks. Extinction refers to a progressive decrease in the operant response associated with the drug when the substance is not present (Epstein, Preston, Stewart & Shaham, 2006; Shaham, Shalev, Lu, de Wit & Stewart, 2003; Stewart, 2000). After extinction, the restoration phase of the behavior takes place in which the ability is measured of certain stimuli called "primers" (pharmacological, physical or environmental) to restore initially learned operant responses (Soria et al., 2008). Currently, the extinction-reinstatement model in SA is very popular for modeling relapse in drug seeking (Bossert, Marchant, Calu & Shaham, 2013; Epstein et al., 2006; Shaham et al., 2003; Sinha et al., 2011; Soria et al., 2008; Steketee & Kalivas, 2011; Yahyavi-Firouz-Abadi & See, 2009; Yan & Nabeshima 2009). This paradigm has been used with different types of drugs, including MDMA or ecstasy and cocaine (Colussi-Mas, Wise, Howard & Schenk, 2010; Schenk, Gittings & Colussi-Mas, 2011; Schenk, Hely, Gittings, Lake & Daniela, 2008; Trigo, Orejarena, Maldonado & Robledo, 2009). However, it should be noted that although the extinction model has produced a large amount of research, it is not the most clinically relevant. Paradigms involving longer periods of abstinence (whether forced, imposed by punishment, or chosen) are more useful in terms of their ecological validity.

Recently, some studies have evaluated the effects of destabilizing the memory of what animals learned during the acquisition of SA through behavioral (extinction) or pharmacological procedures. In these studies, after achieving stable acquisition of SA, memory is reactivated by briefly exposing the animals to the SA chamber, and a short time afterwards (ranging from minutes to a few hours) the animals are given extinction sessions or receive an injection of an amnesiac drug. Both treatments quickly and effectively reduce drug seeking (accelerating the extinction of the SA response) and block reinstatement (Hellemans, Everitt & Lee, 2006; Lee, Milton & Everitt, 2006; Lee, Platt, Rowlett, Adewale & Spealman, 2005; Sánchez, Quinn, Torregrossa & Taylor, 2010; Yan et al., 2014. Yan, Kong, Wu, Newman & Xu, 2013).

3.1.1.3. Variations on the SA model. Over the last decade, different variations of the SA model have been developed to study the main characteristics of addiction by manipulating the type of reinforcer or the waiting time to obtain it, drug seeking in situations involving punishment, or the development of compulsive drug seeking models. In relation to these variations it is worth mentioning the experiments that allow the animal the choice between a drug and a natural reinforcer in order to study alternative reinforcement caused by sugar and sweet food (Ahmed, 2014; Ahmed, Guillem & Vandaele, 2013). Lenoir, Cantin, Vanhille, Serre and Ahmed (2013) showed that, after a period of training in SA of both cocaine and water sweetened with sucrose, most rats chose to leave cocaine and seek out the alternative reward. These experiments demonstrate that sugar and sweet foods can not only replace drugs but also be even more attractive and reinforcing (Ahmed et al., 2013).

A further variation is the extended access model of SA. This is a model of operant conditioning of excessive drug consumption that provides an approach to studying why some animals make a transition from initially low/moderate to abusive or excessive consumption (Edwards & Koob, 2013). While the consumption of animals whose access to the drug is limited in terms of time (for example, one or two hours daily) is stable over time, animals with extended access to the drug (for example, six hours per day) show an escalation in their SA behavior (Koob et al., 2014). This phenomenon has been observed with the use of different drugs, including cocaine (Roberts, Morgan & Liu, 2007) and heroin (Lenoir, Cantin, Vanhille, Serre & Ahmed, 2013). Escalating SA is a more complete model of addiction because animals subjected to prolonged access to substances of abuse have various symptoms related to the criteria for substance dependence in humans, such as the emergence of uncontrollable drug use despite the negative consequences this causes, compulsive behaviors linked to drug seeking, and increased vulnerability to relapse or reinstatement of the behavior after exposure to different stimuli. Similarly, when animals return for testing after a period of abstinence subsequent to chronic administration of the drug, they display a greater response under a progressive schedule, suggesting that the value of the reward or the effectiveness of the drug is enhanced when subjects are dependent (Koob et al., 2014). Moreover, in the SA paradigm the search for cocaine intensifies after the withdrawal of extended access. This effect is related to the phenomenon called incubation of cocaine craving, in which cocaine seeking induced by the re-exposure to the cues associated with the drug increases progressively during the first two months of cocaine abstinence (Lu , Grimm, Dempsey & Shaham, 2004).

Other researchers have used the SA paradigm in order to model the main features of addiction in humans based on the DSM-IV/5 criteria. In these experiments, the daily SA sessions typically consist of periods of access to the drug (indicated to animals by a light above the active lever or hole and during which the operant response is accompanied by the presence of the reinforcer), and drug-free periods (in which the whole SA box is lit and operant responses have no reinforcing outcome for the animal). Three behaviors linked to addiction criteria in humans are evaluated: loss of control or persistence in drug seeking (by active counting lever/hole responses during periods in which the reinforcer is not available), high motivation for the drug (using a progressive reinforcement schedule where the appearance of the reinforcer increasingly requires the performance of a greater number of operant responses by the animal) and maintenance in consumption despite the negative outcomes arising from it (performance of the operant response despite the existing association between reinforcement and an electric shock in the animal's legs) (Deroche-Gamonet & Piazza, 2014). Such studies allow further research into the pathological transition to addiction that takes place in some drug users as a result of the interaction between individual vulnerability (related to behavioral and personality variables), the degree of exposure to the drug and loss control (Belin, Balado, Piazza & Deroche-Gamonet, 2009, Belin & Deroche-Gamonet, 2012; Deroche-Gamonet, Belin & Piazza, 2004; Deroche-Gamonet & Piazza, 2014; Piazza & Deroche-Gamonet, 2013).

Another variant of operant SA models are those known as second-order schedules. This type of program was introduced and developed in an impressive series of experiments carried out by Bergman, Goldberg, Katz and colleagues in the early 1970s (Goldberg & Gardner, 1981; Goldberg & Tang, 1977; Spear & Katz, 1991) which have become a paradigm of reference in current animals studies to assess reinforcement (Everitt & Robbins, 2000; Giuliano et al., 2015; Giuliano, Robbins, Nathan, Bullmore & Everitt, 2012; Giuliano, Robbins, Wille, Bullmore & Everitt, 2013).

This is an operant SA paradigm in which, as its name suggests, animals (usually rats) are trained to perform an operant behavior to get the reinforcer (such as food or any type of drug) using a continuous reinforcement schedule. During this period each self-administered drug infusion is associated with a stimulus (such as a light or sound) which is contingently presented in the training sessions (thus turning into a conditioned stimulus). Once the animals are on a stable SA schedule, the second-order paradigm is introduced with a fixed response rate, so that each time the animal responds, the conditioned stimulus and the drug infusion are produced, and the rate of responses and intervals is increased (Everitt & Robbins, 2000). Therefore, second-order protocols are more complex, as they include two different schedules at the same time: one of fixed interval (FI) and the other fixed rate (FR). For example, in an FI5min-(FR1:S) schedule, the first response after the end of a 5-minute interval obtains the reinforcer, while in an FI5min-(FR5:S) five responses are required before the reinforcer can be obtained.

Essentially, under second-order schedules the reinforcer is presented in accordance with a program in which a sequence of (more or less extended) responses is intermittently reinforced. The completion of each fixed response schedule is accompanied by the response contingent to the presentation of the conditioned stimulus. For example, a typical second-order schedule would consist of a 60-minute fixed interval schedule with a 30:S (FI60min-FR30:S) response pattern, where the conditioned stimulus is presented after each 30 responses, while the animal must perform a further 30 responses after completion of the fixed interval of 60 minutes before the conditioned stimulus is served alongside the reinforcer, for example, an intravenous infusion of heroin or cocaine, or access to food, depending on the aims of the study (Everitt & Robbins, 2000; Giuliano et al., 2012; Giuliano et al., 2015; Giuliano et al., 2013).

Therefore, in a second-order schedule the behavior specified by a contingency program is treated as a single response that is reinforced according to a given program. Thus, the performance of a number of behaviors by the animal involves the presentation of a stimulus previously linked to an infusion of the reinforcing substance. In order to obtain the drug, the animals must perform a number of responses which are also preset to make the conditioned stimulus appear. In this paradigm long sequences of behavior can be observed before any drug is administered. This is seen as a measure of the strength of the conditioned stimuli which triggers drug seeking (Teruel, 2008) or, in other words, a measure of the effort the animal is willing to make in order to receive the drug (motivation). This model is thus predictive of the behavior generated in humans where the appetitive phase of consumption behavior (collection and preparation of the drug) precedes the act of taking the drug.

3.1.2. Voluntary consumption models.

This section, rather than provide a thorough explanation of models of voluntary consumption, will instead discuss two prominent models, the two-bottle choice and drinking in the dark (DID). These models differ from previous ones in that the substance is readily available, which means that the memory/learning component is much smaller. Thus, given that access to the substance requires very little effort by the animal, it is more difficult to assess the motivational component in these models (i.e., the amount of effort or the number of behaviors or responses the animal is willing to make in order to obtain the drug).

A.- Two-bottle choice. Among the animal models of reinforcement used to evaluate the preference that leads a subject to consume, we find the two-bottle choice paradigm of voluntary consumption. There are different modalities or varieties within this procedure but the main objective is to measure the preference of the animal for the substance of abuse (usually alcohol) and oral consumption thereof compared to an alternative non-addictive substance (such as water) (Bahi, 2012, 2013a, 2013b). To measure this preference, animals are exposed to both substances for days and have the possibility of drinking only water, only alcohol or both substances simultaneously.

In the most commonly applied method, animals initially have access to two bottles of water, and then one of them is replaced by an alcohol solution at a certain percentage % v/v, which is increased progressively (every 3-4 days) to achieve the desired concentration (typically 8-10%). The animals are thus permanently exposed to alcohol with no periods of abstinence. In our laboratory we follow the protocol used by the group around Professor Everitt of Cambridge University, where access to alcohol is available on alternate days. In this case, the animals have three sessions per week (typically Monday, Wednesday and Friday) of 24 hours with unrestricted access to both bottles (one with alcohol and the other with water). There is a period of abstinence lasting 24 and 48 hours on the other weekdays and at the weekend respectively, during which time two bottles of water (and no alcohol) are presented. To counteract the possible learning of place, the bottles are moved for each alcohol exposure session (Barak, Carnicella, Yowell & Ron, 2011; Carnicella, Amamoto & Ron, 2009; Giuliano et al., 2015). To quantify the animal's preference for the substance of abuse, the volume of alcohol and water are measured every day. Similarly, to estimate the amount evaporation that may exist in the bottles, a bottle containing water and another with alcohol are placed in an empty cage (Giuliano et al., 2015).

B.- Drinking in the dark. This paradigm was originally described by Rhodes, Best, Belknap, Finn & Crabbe (2005). The most common variation of this model uses

isolated mice whose water bottle is replaced by a bottle containing ethanol at different percentages depending on the object under investigation. Access to the substance of abuse is made available in this way starting during the animal's dark cycle (hence the name) and usually with a duration of between 2 and 4 hours, thus simulating the binge drinking pattern of alcohol consumption common among teenagers at the weekend. Using this procedure, the animals can normally reach high blood concentrations of ethanol, so it is very interesting for the study of alcohol addiction (Thiele & Navarro, 2014).

The basic idea behind this paradigm is that the substance should be consumed in a cycle of darkness in which intake levels are higher. The animals have to choose between freely consuming or avoiding alcohol without being subjected to any injection, thus minimizing various stress conditions to which animals are subjected in other animal models of binge alcohol consumption. Another advantage of this paradigm is that it requires no prior training for animals nor prior inclusion of other components, such as for example, sweet substances to increase the motivation of the animal to consume ethanol. It follows that the drinking in the dark model is widely used and very productive in the study of the neurobiological and genetic factors involved in alcohol consumption.

3.2. Conditioned place preference (CPP)

CPP is a paradigm that evaluates the conditioned reinforcing effect of substances of abuse, given that the contextual stimuli (such as the color or texture of the floor or the compartment where the drug is received) can acquire appetitive properties when associated with the primary reinforcing stimulus, in this case the substance of abuse (Aguilar, Rodríguez-Arias & Miñarro, 2009; Bardo & Bevins, 2000; Tzschentke, 1998, 2007). To achieve this goal, researchers use a box with two or three compartments which are clearly distinct in terms of the stimuli present in the different models of boxes available. For example, in our laboratory (García-Pardo et al., 2014, 2015a, 2015b; Roger-Sánchez, Rodríguez-Arias, Miñarro & Aguilar, 2013a, 2013b) two compartments are used with different color and texture. One of them has a rough floor which is white, while the other has a smooth black floor, both being separated by a neutral central platform. The animals thus receive the drug in an environment with specific characteristics in order to evaluate later if they have learned to associate the environmental cues of the place where the drug is received and the reinforcing effect it produces. Similarly, using this paradigm can evaluate the reverse process, conditioned place aversion (CPA), which has been observed with high doses or abstinence of certain drugs. For example, opiate dependent animals develop CPA through the compartment associated with the administration of an opioid antagonist such as naloxone or naltrexone (García-Carmona, Baroja-Mazo, Milanés & Laorden, 2015; Maldonado, Cauli, Rodríguez-Arias, Aguilar & Miñarro, 2003).

Unlike other more complex paradigms such those described above, CPP is characterized by its great methodological simplicity, resulting in very frequent use, in conjunction with the fact that under the right conditions, CPP may be sensitive to a wide range of substances (Aguilar et al., 2009; Aguilar, Roger-Sánchez, Rodríguez-Arias & Miñarro, 2015; Tzschentke, 1998, 2007). Thus, in our laboratory we have demonstrated CPP with different types of drugs such as cocaine (Montagud-Romero et al., 2015.), MDMA (Daza-Losada et al., 2007; Daza-Losada, Miñarro, Aguilar, Valverde & Rodríguez-Arias, 2011; Daza-Losada, Rodríguez-Arias, Aguilar & Miñarro, 2009; Do Couto et al., 2011; 2012; García-Pardo et al., 2014, 2015a, 2015b; Roger-Sánchez et al., 2013a, 2013b; Roger-Sánchez, Aguilar, Manzanedo, Miñarro & Rodríguez-Arias, 2013c; Vidal-Infer et al., 2012), opioids (Manzanedo, Aguilar, Rodríguez-Arias & Miñarro, 2001b; Manzanedo, Aguilar, Rodríguez-Arias, Navarro & Miñarro, 2004; Manzanedo, Serrano, Aguilar, Rodríguez-Arias & Miñarro, 2001a), alcohol (Roger-Sánchez, Aguilar, Rodríguez-Arias, Aragón & Miñarro, 2012) and nicotine (Navarrete et al., 2013).

Generally, the CPP paradigm consists of three phases: a first phase known as "pre-conditioning" that serves to confirm that there is no innate preference of the animal to one of the compartments. In the second phase, called acquisition or conditioning in which the association between the reinforcing effect of the drug and environmental cues is established through the administration of the drug in one of the compartments and the administration of a control substance in the other compartment with different environment. This combination is repeated over several sessions separated by a time interval which differs depending on the characteristics of the drug being tested. For example, with the protocols we follow in our laboratory, in the case of cocaine the time interval between the drug injection and the injection of saline is 4 hours, with the process being repeated for 4 days. In the case of MDMA, the animal receives the drug or control substance alternately every 24 hours over 8 days. In the final phase, called "post-conditioning" the existence of conditioning is assessed. If the animal has associated the reinforcing value of the drug and the environmental stimuli, it will spend more time in the compartment where it has received the substance and is therefore considered to have acquired CPP (Aguilar et al., 2009; Parker & McDonald, 2000; Wang, Luo Ge, Fu & Han, 2002; Wang, Luo, Zhang & Han, 2000).

Furthermore, it is worth noting that the CPP procedure can also be used to evaluate other processes such as the extinction of motivated behavior and its reinstatement (Aguilar et al., 2009; García-Pardo et al., 2014, 2015a, 2015b.). For this purpose, after CPP acquisition the animals are subjected to a process of extinction, defined as a decrease

in the frequency or intensity of the learned response after removal of the unconditioned stimulus (in this case the drug) that reinforced learning (Pavlov, 1927). Here, the animal is continuously exposed to the conditioned stimulus (the compartment which is linked to the drug) without the presence of the unconditioned stimulus (the drug) so that the association between the reinforcing value and environmental cues weakens, and the conditioned preference finally disappears. While there are variations of the process of extinction, for example, forced extinction (confinement in the compartment associated with the drug after administration of the control substance) or spontaneous extinction (unrestricted movement through both compartments without any treatment), the underlying objective is always to decrease the CPP originally induced by the drug (Yahyavi-Firouz-Abadi & See, 2009). An important detail is that the period needed for the preference to be extinguished is influenced by different factors such as the motivational properties of the drug (Pulvirenti, 2003), previous exposure to drugs (Daza-Losada et al., 2009; Do Couto et al., 2011), the dose with which acquisition was produced (García-Pardo et al., 2015a) or exposure to aversive events in the acquisition phase or even before, such as acute (García-Pardo et al., 2014) or repeated stress (García-Pardo et al., 2015b).

The CPP paradigm is also useful for studying reinstatement brought about by the re-exposure to drugs or stress. Reinstatement refers to the recovery of a learned or conditioned response and involves renewed learning of the association between the environmental reinforcing effect of the substance and the cues once extinction has taken place (Aguilar et al., 2009; Do Couto et al., 2006; Do Couto, Aguilar, Lluch, Rodríguez-Arias & Miñarro, 2009; García-Pardo et al., 2014, 2015a, 2015b). Reinstatement can be induced by different factors, either pharmacological, physical or social, or in experimental contexts such as dose priming, which involves re-exposure to a low dose of the drug with which conditioning took place (Cruz, Marín & Planeta, 2008; Daza-Losada et al., 2007), exposure to a stressful situation like an electric shock to the legs (Bossert, Marchant, Calu & Shaham, 2013) or defeat in an agonistic encounter (García-Pardo et al., 2014; 2015b; Shaham et al., 2003; Shalev, Grimm & Shaham, 2002; Tzschentke, 2007).

There are different variations of the CPP paradigm based on research objectives. For example, similar to the procedures of extended-access SA, the number of conditioning sessions can be increased in order to assess whether the vulnerability to develop addiction-related symptoms or susceptibility to relapse also rises (Rodríguez-Arias, Castillo, Daza-Losada, Aguilar & Miñarro, 2009). In this study from our laboratory we note that there is an inverted U-shaped relationship between the number of sessions of conditioning and vulnerability to reinstatement. More specifically, mice exposed to 12 sessions of conditioning with 25 mg/kg of cocaine had increased vulnerability to reinstatement induced by a priming dose of cocaine, compared to animals exposed to a greater or smaller number of conditioning sessions. Likewise, in other as yet unpublished studies we have seen that these animals with prolonged conditioning exhibit behaviors similar to those seen in cocaine users, such as continuity in the use of the drug despite adverse consequences, or search for the substance when it is not available (Aguilar et al., in preparation).

Finally, the CPP paradigm may also be used to study the effects of certain pharmacological and behavioral manipulations of the reconsolidation process. As discussed above, the memories of the effects produced by the drugs, and by signals associated with their consumption trigger the desire to consume, as well as relapse. In these studies, animals acquire the CPP in the normal way, after which the memories of the drug are reactivated (by exposing the animals to the compartment associated with the drug during conditioning for a short period of time). After a short interval (10 minutes to 2 hours) they are subjected to CPP extinction sessions or an amnesic treatment. These techniques cause a rapid extinction of the conditioned response and prevent the reinstatement of CPP after exposure to a priming drug (Liu et al., 2015; Lv, Sun, Cui & Han, 2015; Miller & Marshall, 2005; Slaker et al., 2015).

3.3. Intracranial self-stimulation (ICSS)

The ICSS model is linked to the classic experiments designed by Olds and Milner in 1954, which led to the discovery of the brain's reinforcement system.

In this type of paradigm, animals perform an operant response that allows them to self-administer short electric pulses in different brain areas related to the reinforcer (Koob et al., 2014; Negus & Miller, 2014), because the electrodes are generally placed in the medial forebrain bundle at the level of the lateral hypothalamus or in the nucleus accumbens, areas belonging to the brain's reward system. The frequency or amplitude of the stimulation of these structures is manipulated to generate a wide range of response rates (Negus & Miller, 2014). It is known that acute administration of drugs lowers the ICSS threshold so that the animal needs less stimulation to perceive the reinforcing sensation, while withdrawal increases it (Koob et al., 2014; Negus & Miller, 2014). This means that if a drug lowers the ICSS threshold it is because the drug has high reinforcing power, thus animals do not need as much stimulation to feel reinforcement. As a result, the lower the ICSS threshold, the greater the reinforcing power of the drug.

It is a complex procedure since it requires stereotactic surgery and the intensity of stimulation must be manipulated in order to identify the appropriate value for each animal. This paradigm has shown that the release of dopamine is stimulated ahead of serotonin, which influences the expression of the effects obtained. This is what can be

observed, for example, in the case of MDMA, a nonselective substance of abuse for dopamine producing mixed effects: on the one hand it lowers the ICSS threshold but also decreases the maximum response rate, which can be interpreted as a reduction in the ability to induce drug abuse of this drug in comparison to drugs that induce greater releases of dopamine, such as cocaine or methamphetamine (Bauer, Banks, Blough & Negus, 2013).

4. Conclusion

As discussed throughout this review, animal models of drug addiction provide a very useful tool for studying the neurobiological and behavioral processes involved in addiction, contributing to the identification of new therapeutic targets for the treatment of this disease. Within this global aim, each of the animal models employed focuses on a different component of reinforcement (for example, motivation or learning).

Among the main animal models used to evaluate the reinforcing effects of drugs we find CPP, the SA and the ICSS, although we have seen that depending on the objectives pursued, the substances of abuse in question or the parameters of the addiction we are studying other animal models may also be very useful. Thus, for example for research on alcohol the two-bottle choice and the drinking in the dark paradigms are highly relevant. On the other hand, if we wish to study the motivation of an animal to obtain the drug (similar to what happens in humans) progressive or second order SA programs can offer more relevant results. Finally, if we are interested in the role played by drug-conditioned stimuli in the maintenance of addictive behavior, the CPP paradigm may be the most appropriate.

However, as previously mentioned all paradigms that make use of animals have a number of limitations and even though they try to model the different aspects of drug addiction in the best possible way, the results obtained cannot be extrapolated directly to humans. Although there are a great many similarities in behavioral, pharmacological and neurobiological terms, it is clear that the correlation is not always perfect. Nevertheless, the use of such models has led to important research, and great progress has been made in the field of drug addiction. The goal now should be to improve and perfect the different animal models in order to increase their face and predictive validity.

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Conflict of interests

The authors have no conflicts of interest to disclose.

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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

Adicciones está editada por Socidrogalcohol, Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y otras Toxicomanías. Adicciones publica artículos originales sobre el tratamiento, la prevención, estudios básicos y descriptivos en el campo de las adicciones de cualquier tipo, procedentes de distintas disciplinas (medicina, psicología, investigación básica, investigación social, etc.). Todos los artículos son seleccionados después de pasar un proceso de revisión anónimo hecho por expertos en cada tema. Adicciones publica 4 números al año. Adicciones tiene las secciones de editorial, artículos originales, informes breves, artículos de revisión y cartas al director. La revista se publica en español, aunque admite artículos en inglés. Cuando publica un artículo en inglés, puede exigir su traducción también al español, pero no es la norma.

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

Conflictos de intereses. La política de la revista es que en todos los artículos y editoriales conste expresamente la existencia o no de conflicto de intereses en el apartado correspondiente. Todos los conflictos de interés son importantes, pero especial cuidado hay que poner en el caso de haber recibido para el estudio financiación de la industria farmacéutica, alcoholera, tabaquera, etc. La revista Adicciones sigue en este tema las recomendaciones de ISAJE (International Society of Addiction Journals Editors). Tener conflicto de intereses no significa no poder publicar el artículo. En caso de duda sobre esta cuestión se debe contactar con el editor.

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.

Artículos de revisión. Presentarán la actualización de un tema de forma rigurosa y exhaustiva. Deberán regirse normalmente por metodologías sistematizadas. El contenido del artículo podrá llevar los apartados necesarios para la mejor comprensión de los lectores. En su parte final debe aparecer un apartado de discusión o conclusiones. La extensión preferiblemente no debería superar las 5.000 palabras, pero siempre que esté justificado, se admitirían revisiones más largas.

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

PRESENTACIÓN DE LOS TRABAJOS

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.

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

1. En la *primera página* del artículo se indicarán, en el orden que aquí se cita, los siguientes datos:

- Título del artículo, en minúsculas (en castellano e inglés) excepto la letra inicial.
- Nombre de los autores completo (no sólo iniciales), y uno o dos apellidos del/los autor/es (p. ej.: Miguel García o Miguel García Rodríguez o bien Miguel García-Rodríguez, teniendo en cuenta que la forma que hayan utilizado los autores es la que se enviará a las bases de datos) en minúsculas, excepto la letra inicial. Los distintos autores vendrán separados por punto y coma. Detrás del apellido de cada autor, sin espacio intermedio y en superíndice, deberá ir un asterisco de llamada (1 asterisco para el primero, 2 para el segundo, etc.). Estos asteriscos son necesarios para indicar en el siguiente punto la institución donde se ha realizado el trabajo.
- 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

el autor al cual la secretaría se dirigirá durante el proceso de revisión, a menos que se acuerde mutuamente otra solución.

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.

EL PROCESO DE REVISIÓN DEL MANUSCRITO

Los artículos son enviados a la revista a través de la www.adicciones.es. Los autores reciben al enviar el artículo unas claves para poder entrar en la web y revisar la situación de su artículo. No obstante el editor de la revista enviará un mensaje cuando tenga una decisión tomada o quiera preguntar alguna cuestión. Una vez recibido el manuscrito en la Redacción de la Revista Adicciones empezará el proceso de revisión.

El Editor, normalmente consultando con los editores asociados, puede desestimar de entrada un artículo que entienda que claramente no reúne la calidad suficiente o no entra dentro de las prioridades de la revista. El editor puede rechazar de entrada aquellos artículos que no cumplan estrictamente dicha normativa, sin pasarlo a revisión.

Los manuscritos serán enviados por el Editor o los Editores Asociados a dos o más expertos en el tema (revisores), que harán los comentarios pertinentes sobre el mismo y que requerirán aquellos cambios que estimen necesarios; también pueden dar su opinión sobre la aceptación o rechazo del artículo. La última decisión, basada en el informe de los revisores, o del editor asociado que se hubiese responsabilizado de la revisión, será tomada por el Editor de la revista, que podrá consultar además a los Editores asociados. En todo el proceso de revisión se mantendrá el principio de confidencialidad por parte de los revisores hacia el trabajo que revisan, así como la confidencialidad de los nombres de los revisores entre ellos o ante los autores del manuscrito.

El resultado de la revisión del manuscrito será enviado al autor de correspondencia que viene en el artículo indicándole su aceptación, rechazo o la necesidad de someterse a una nueva revisión una vez tenidos en cuenta los comentarios de los revisores o del editor. El autor, si es el caso, deberá hacer los cambios señalados –cuando esté de acuerdo con ellos–, enviando:

- Una copia del manuscrito revisado.
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Una vez aceptado el artículo, se enviará a los autores las pruebas de imprenta para que las corrijan. Los autores son totalmente responsables de la versión final que se publique. Los autores pueden hacer el uso que crean pertinente para la difusión del artículo, siempre que quede clara toda la información necesaria acerca de la revista donde ha sido publicado.

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

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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 preferblemente durante cuatro meses o más. *Cambio desde TREVICTA a otros medicamentos antipsicóticos.* Si se suspende la administración de TREVICTA, se debe 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, cimbiendo la dosis por 3,5 según se indica en la tabla siguiente. No es necesario 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 cimbistrando 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 dirarios 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 las 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 13, incluida	de la semana 19 a la 24, incluida	desde la semana 25 y 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 dirarios se debe adaptar siempre al paciente individual, teniendo en cuenta los posibles cambios en los motivos de 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. Pero 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 menos de 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 preferblemente 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

*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 sólo 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 y 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 transurren 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 1 ½ (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 debido 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 necesario un control inmediato de los síntomas. Intervalo a 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 use 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 creatinfosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SNM, 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, incluida 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 clínicamente relevante o 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 10⁹/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 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 previamente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgico. 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 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) (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 metanálisis 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. Las 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 transurso 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 prescribe TREVICTA a pacientes que vayan a experimentar circunstancias que pueden 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 adquirido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto anticolinérgico. En los estudios preclínicos con paliperidona se observó un efecto anticolinérgico. 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 alfa1-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, fenotiazinas 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 a 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 fracción de 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 periodos 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 teratogenos 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 mediante 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 las lactantes podrían estar en riesgo incluso 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 del medicamento observadas con mayor frecuencia notificadas en 2≥1% 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 conocida
Infecciones e infestaciones		infección de vías respiratorias altas, infección urinaria, gripe	neumonía, bronquitis, infección de vías respiratorias, sinusitis, cistitis, otitis, amigdalitis, micosis cutánea, celulitis	infección ótica, onicomicosis, dermatitis, 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*	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*	agitación, depresión, ansiedad	trastornos del sueño, disminución de la libido, nerviosismo, pesadillas	manía, estado de confusión, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo*, sedación, somnolencia, distonía, mareo, disfunciones, 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 consciencia, convulsiones*, trastornos del equilibrio	coma diabético, coordinación anormal, 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 cardíacos		taquicardia, 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, siqueria
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, dolor faringolaringeo, 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 lumbar/cervical, artralgia	valores elevados de creatinfosfoquinasa en sangre, espasmos musculares, rigidez articular, debilidad muscular, dolor cervical		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*, ginecomastia, galactorrea, disfunción sexual, dolor mamario	hinchazón a 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†, alteraciones de la marcha, dolor torácico, malestar 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		

*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". Ver el apartado "Hiperprolactinemia" a continuación. Ver el apartado "Síntomas extrapiramidales" a continuación. †Insomnio comprende: El insomnio inicial y el insomnio medio. Convulsiones incluye: Convulsiones, y convulsiones del gran mal; trastornos menstruales incluye: Trastornos menstruales, menstruación irregular, oligomenorrea. Edema incluye: Edema generalizado, edema, edema periférico, edema puerperal.

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 clasificación realizada por los investigadores, síntomas como inducración, rubefacción e hinchazón no se presentaron a fuerzas leves en ≥95% de los 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%, 0,5%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (mostrano extrapiramidal), síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, fobias 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, espasmo facial, crisis oculógiras, distonía bucomandibular, risa sardónica, tetania, hipertonía, tortícolis, contracciones musculares involuntarias, contractura muscular, blefarospasmo, oculogiración, parálisis lingual, espasmo facial, faringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurostótonos, 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 11% 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 11% 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 cardíaco 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 trastorno 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 especie isomérica de paliperidona (+)y(−). *Mecanismo de acción.* Paliperidona es un agente bloqueante selectivo de los efectos de los 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 1 adrenérgicos 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 aleatorizado, 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 aleatorizado, 526 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 pasó fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 233 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 3,31 (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%]).

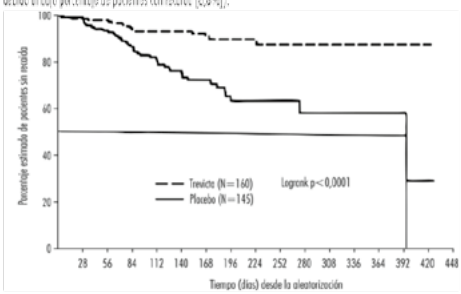


Figura 1. Gráfico de Kaplan-Meier del tiempo hasta la recaída – Análisis final

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 (entre 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 49 semanas. Los pacientes recibían 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 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 los 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 mayorías 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.

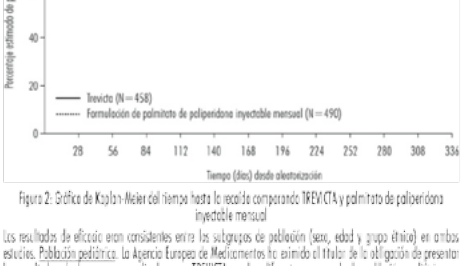


Figura 2: Gráfico de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

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 el 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 con 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_{max}. 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 reclínica 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 intensivamente en el hígado. Se recuperó aproximadamente el 80% de la radioactividad 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 sugirieron que los 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 observa ninguna diferencia conocable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentes 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, CYP2B6/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP2C8. 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 mas 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 (ClCr=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (ClCr=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (ClCr=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_{ss} 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 este 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. Otras antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la methidiol 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 (rata), 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 FARMACEÚTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajustar el 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, tapa-husera 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). Formato 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: 673,00 €; PVP: 725,91 €; PVP (IVA): 754,95 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 924,00 €; 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 de 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 determinados 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 a 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 o 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), dicho que el pleno efecto de las dosis de mantenimiento puede no resultar evidente durante varios meses. ***Cambio desde paliperidona oral de liberación prolongada o 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 Risperidona inyectable 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 necesario 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. ***Medidas para evitar la omisión de dosis.*** Se recomienda que la segunda dosis de inicición 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 se reinicia recomendada dependerá del tiempo que haya transcurrido desde la primera inyección del paciente. ***Omisión de la segunda dosis de iniciación (<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 en 25 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. ***Omisión de la segunda dosis de iniciación (entre 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. Se 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. ***Omisión de la segunda dosis de iniciación (>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 a 6 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 a 6 meses).*** Si han transcurrido más de 6 semanas desde la última inyección de Xeplion, la recomendación es la siguiente: ***Para los pacientes estabilizados con dosis de 25 a 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 los pacientes estabilizados con 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. ***Población 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, ambas administradas 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 a 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 (rabdomiolisis) 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 otras factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados para 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 basal de neutrófilos <1x10⁹/L) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia post-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si aparecen 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 induce coma diabético y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica coherente 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 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-1 bloqueante. Según los datos agrupados de las 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 cardíaca, 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 oral 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, olanzapino 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. Los 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 la 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 reciben 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 preclínicos con paliperidona. Esta 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 de 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 alfa1-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 alfa1-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 combina con fármacos que también tengan esta posibilidad, p. ej., otros antipsicóticos, triciclicos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenotiazinas o butirofenonas, triciclicos 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 vitro ni in vivo* 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_{ss} 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 de principio activo inalterada excretada 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 periodos 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 administrado 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 o 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 estos, 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	Raros	No conocidas*
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, otitis, infección de oídos, amigdalitis, candidiasis, celulitis	infección de ojos, dermatomicosis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, recuento de eosinófilos aumentado	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia†		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‡, 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	insomnio†	agitación, depresión, ansiedad	trastorno del sueño, manía, disminución de la libido, nerviosismo, pesadillas	estado confusional, embotamiento afectivo, orgasmo	
Trastornos del sistema nervioso		parkinsonismo†, acatisia†, sedación/somnolencia, distonía†, mareos, discinesia†, temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotora, marcha 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†, 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, acufenos, dolor de oído		
Trastornos cardíacos		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, hipertensión ortostática	hemtosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringolaríngeo, 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	rabdomiolisis, inflamación de las articulaciones	anomalía postural
Trastornos renales y urinarios			incontinencia urinaria, poliaquiuria, 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*, 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, asenia, fatiga, reacción en el lugar de la inyección	edema facial, edema†, 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, abceso 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, ulceración en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

*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 posmercantilización y la frecuencia no se puede determinar, a proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral. †Referida a "hiperprolactinemia" o continuación. ‡Referido a "Síntomas extrapiramidales" o continuación. §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. **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 estas compuestas (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. Descripción de algunas reacciones adversas. ***Reacción anafiláctica.*** Durante la experiencia post comercializacion, en raros 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). ***Reacciones en el lugar de la inyección.*** La reacción adverse 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. Los 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 involucraron induración (frecuente), prurito (poco 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, marcha de andar parkinsoniano y reflejo de la glabella anormal, temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hiperactividad y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreoatetosis, atetosis y miodistonía), distonía (incluye distonía, hipertonía, tortícolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistotonos, 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 recaídas 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 (4,77) kg. ***Hiperprolactinemia.*** En ensayos clínicos, se observaron medianas de cumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un cumento 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, crítimias 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 crítimias. 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 los monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une fimemente 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 una 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 el 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 (una de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recaída 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 coloandos durante el tratamiento agudo de la esquizofrenia con Xeplion. El criterio principal de eficacia del estudio se definió como una reducción de los 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 todo 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 crojeron resultados estadísticamente significativos a favor de Xeplion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

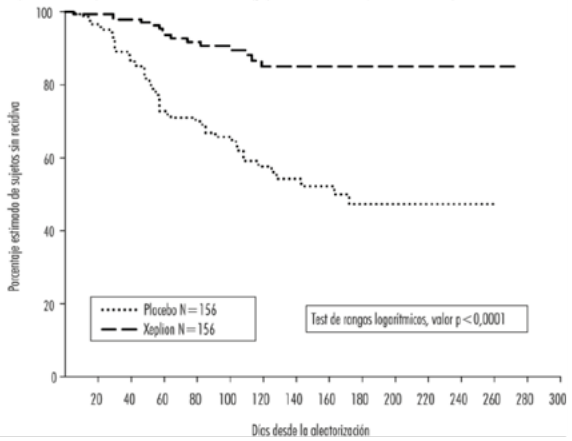
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración 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 (12,35)	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 clínicamente estable, doble ciego, controlada con placebo para observar la recidiva, y un periodo de extensión abierta 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 periodo de transición de 9 semanas de duración, seguido de un periodo 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 periodo 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 experimentaron una recidiva de los síntomas de la esquizofrenia en la fase doble ciego de duración variable. El ensayo se suspendió antes de lo previsto 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 observa 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 rato 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 observa un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona in vitro 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 inalterada por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radioactividad 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 sabe 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 aparente 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 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 medida 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 completamente 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 las 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 la hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve [ClCl = 50 a < 80 ml/min], un 64% en sujetos con insuficiencia renal moderada [ClCl = 30 a < 50 ml/min] y un 71% en sujetos con insuficiencia renal grave [ClCl = 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 depresión 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 rasivamente 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 4,7 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 genotóxicas. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (rata), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (ratón y, en menor medida, rata). Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia 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 monohidrato. Fosfato ácido disódico anhidro. Fosfato dibásico 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 (cídico-olefina-copolímero) con un tapón de látex 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): 284,55 €. 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

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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.