

Adicciones

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Considerations on the use of Odds Ratio versus Prevalence or Proportion Ratio

Reflexiones sobre el uso de la Odds Ratio o la Razón de Prevalencias o Proporciones

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In 2017, we published an article explaining how to estimate prevalence ratios using different regression models (Espelt, Mari-Dell'Olmo, Penelo & Bosque-Prous, 2017). In health science research, we often work with cross-sectional or longitudinal studies. The variables of interest in these studies may be dichotomous variables (i.e. yes vs no) related to a disease or health condition, and we usually represent them as proportions, such as prevalence or cumulative incidence (e.g. percentage of at-risk drinkers or percentage of new cases of hazardous drinking in a given period, respectively) (Hernandez-Avila, Garrido-Latorre & Lopez-Moreno, 2000; Moreno-Altamirano, López-Moreno & Corcho-Berdugo, 2000). In this sense, when we work with dichotomous dependent variables and proportions, the first estimate we show is the prevalence or cumulative incidence of the disease or unhealthy behavior. Once the prevalence or cumulative incidence has been estimated, what will interest us is to ascertain whether this prevalence or cumulative incidence changes depending on the different independent or explanatory variables. For this reason, after a first table describing the sample, a second table is usually presented showing the proportions according to the different independent or explanatory variables (with their respective statistical tests). Up to this

point, we would all agree. However, we are often interested in showing the measures of association between these dichotomous dependent variables and the independent or explanatory variables in both a crude and an adjusted way. It is at this point that some questions arise which we already tried to answer in the article published in 2017 with data from a European study on alcohol (Espelt et al., 2017). Which measure of association is better: the odds ratio (OR) or the prevalence or proportions ratio (PR)? Which should we select? If we simply want to see whether there is an association between variables, the answer would be that both measures perform equally well. However, if we wish to interpret the magnitude of this association, we must be aware that OR and PR are not interpreted in the same way. The problem is that the OR is difficult to understand and is often interpreted as if it were a PR. This misinterpretation is worse in the cases when the prevalence, proportion or cumulative incidence of disease or health behavior is high (Szklo & Nieto, 2012) because in these cases, the OR is not similar to the PR, and by using an OR instead of a PR we would be overestimating the association. For example, an OR of 2.65 can perfectly well be a PR of 2.08 (Espelt et al., 2017), and here the problems begin. It is not the same to say that there is 265% more disease in one category rather

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than 208%. If we review the scientific literature, we will find that most cross-sectional or longitudinal studies published with dichotomous dependent variables show associations with OR while few present associations with PR (Espelt et al., 2017). From our point of view, in order to give coherence to the design so that the descriptive tables of proportions are totally comparable with the crude data of associations, thus ensuring that there are no possible errors in the interpretation of the data of these associations, the most reasonable solution would be to use PR as a measure of association whenever possible for designs with proportions (cross-sectional or longitudinal). This is especially important when ORs are shown in tables because non-specialists are highly likely to misinterpret OR as PR and understand OR as higher probability, higher risk or higher prevalence when they should really think of it as a comparison of probabilities: the odds of an outcome happening compared to the odds of the non-occurrence of that outcome, i.e. the *relative* odds. Nevertheless, epidemiologists or researchers also fall into these errors sometimes, and we find articles with inadequate vocabulary to explain associations (Barlés Arizón, Escario & Galbe Sánchez-Ventura, 2014; Díaz Geada, Busto Miramontes & Caamaño Isorna, 2018; Mori-Gammarra et al., 2018).

To this end, our previous article provided the steps to calculate prevalence ratios with two statistical packages, STATA and R. On this occasion, we would also like to facilitate the procedure with the statistical package SPSS, which is widely employed in our environment, using the menus. Table 1 shows how to obtain the PRs from the binomial regression model using SPSS. It is very important that the dependent variable is coded as 0 and 1, with 1 being the health outcome or disease of interest.

Table 1. *Explanation of the steps to estimate PR using log-binomial regression models with SPSS*

Tool Bar (step by step)
Menu tools → Analyze → Generalized Linear Models → Generalized Linear Models → Type of Model [Custom; Distribution: Binomial; Link function: Log] → Response [Dependent variable: auditc; Type of Dependent Variable: Binary; Reference Category: First (lower value)] → Predictors [Factors: educ, sex; Covariates: age] → Model [Model: educ, sex, age] → Estimation [maximum iterations: 100000] → Statistics [report exponentiated coefficients]

In many articles, when we analyze the association between a dependent variable and one or more independent or explanatory variables, we try to control for possible variables that could be confounding factors (Babiyak, 2009). One of the statistical techniques used to control for other variables is to fit regression models. In the different studies using regression models, we found crude associations as well as associations adjusted for some of these confounding variables. For example, living in an urban environment is protective against alcohol consumption compared

to living in a rural environment [PR=0.86 (95%CI = 0.78-0.95)]. However, this protective effect disappears [PR=0.91 (95%CI = 0.80-1.05)] when different individual variables and factors such as sports centers, unemployment rate, number of pubs, and other accessibility variables are accounted for (Obradors-Rial, Ariza, Continente & Muntaner, 2019).

In the cited article, it is easy to note from the prevalence table that the prevalence of high-risk drinking in urban areas (51.1%) is lower than in rural areas (59.3%) (Obradors-Rial et al., 2019). A simple division of the prevalence of high-risk drinking in the urban environment by the prevalence of high-risk drinking in the rural environment reveals the association given by the regression model (RP = 0.86). However, we stated that the adjusted association between high-risk drinking and urban/rural environment is 0.91. Can we determine the adjusted prevalence of alcohol consumption in the urban and rural environment which gives us this association? With the statistical program STATA, we can estimate the adjusted prevalence for each of the categories of the independent variable of interest (Muller & MacLehose, 2014). If we return to the article published in 2017 (Espelt et al., 2017), we can observe in Table 2 that the prevalence of risk drinkers in Estonian men was 16.75% while in women it was 4.24%, which implies a PR of 3.95. Estonia's age- and education level adjusted prevalence ratio was 3.87. However, by applying the regression model and estimating its marginals (Table 2), we find that the prevalence of high-risk drinkers in men adjusted for age and level of education was 16.48% and that of women was 4.26%. If we divide the prevalence of high-risk drinking in men versus women, we obtain the same adjusted PR as in the model.

Table 2. *Syntax to obtain crude and adjusted PR with STATA and R*

Adjusted Model Syntax
STATA <pre>glm auditc i.sex i.educ age, family(binomial 1) link(log) eform margins i.sex i.educ</pre>
R <pre>install.packages(pkgs = c("Epi", "foreign")) library(Epi) library(foreign) model<-glm(auditc ~ sex + educ + age, data=data, family=binomial(link=log)) summary(model) round(ci.lin(model, Exp=T),2) library(prediction) pred <- prediction(model, at = list(sex=c("Women","Men")), type = "response")</pre>

In conclusion, from our point of view, in studies in which the independent variable or variable of interest is a proportion, it is more useful to use the prevalence or proportion

ratios as a measure of association since this implies greater coherence and avoids errors of interpretation.

Conflict of interests

The authors of this article declare no conflict of interest. Albert Espelt is associate editor of the journal *Adicciones*, but this did not play any role in the process of publication.

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The influence of gender roles in alcohol consumption: a qualitative study of adolescents and young adults in Asturias

La influencia de los roles de género en el consumo de alcohol: estudio cualitativo en adolescentes y jóvenes en Asturias

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Abstract

Despite the implementation of prevention policies aimed at addressing alcohol consumption among both adolescents and young adults, there has been a considerable increase in those who abuse alcohol in Spain over the last decade. Official surveys on this phenomenon show that both the prevalence and risky consumption of men and women are reaching similar levels, with even higher figures for these behaviours in the case of girls at the end of adolescence.

The aim of this article is to understand the influence of gender roles in the consumption of alcohol among adolescents and young adults. To this end, focus groups have been employed to identify similarities and differences both in drinking patterns and alcohol abuse among young males and females, as well as in the social meaning that both groups attribute to these practices.

The results obtained show that the variables gender and age act in a combined way on the learning of alcohol consumption, as well as on the motivations and expectations that adolescents and young adults have regarding these practices. In addition, in this study three differentiated stages are identified: in the first, gender roles are clearly defined; in the second, there is a certain transgression of these roles mainly by young women, and in the third, there is a return to traditional gender roles.

Keywords: Gender; Alcohol; Adolescence; Young adult; Qualitative research.

Resumen

A pesar del desarrollo de políticas de prevención dirigidas a abordar el consumo de alcohol en adolescentes y jóvenes, durante la última década se ha producido un aumento considerable de quienes realizan un consumo abusivo de esta sustancia en España. Las encuestas oficiales sobre este fenómeno muestran un acercamiento entre varones y mujeres en las prevalencias de consumo y en los consumos de riesgo, e incluso una mayor incidencia de estas conductas en el caso de las mujeres al final de la etapa adolescente.

El objetivo de este artículo es conocer la influencia que ejercen los roles de género en estas pautas de consumo en adolescentes y jóvenes. Para ello, se han realizado grupos focales que han permitido identificar las similitudes y diferencias que se producen tanto en las prácticas de consumo y abuso del alcohol que desarrollan estos colectivos, como en el significado social que unos y otras atribuyen a las citadas prácticas.

Los resultados obtenidos muestran que las variables género y edad actúan de forma combinada en el aprendizaje del consumo de bebidas alcohólicas, así como en las motivaciones y expectativas que los y las adolescentes y jóvenes tienen sobre dichas prácticas. Además, en este estudio se identifican tres etapas diferenciadas, en la primera de ellas los roles de género se encuentran claramente definidos, en la segunda se observa cierta transgresión de los mismos fundamentalmente por parte de las mujeres y en la última se advierte una vuelta a los tradicionales roles de género.

Palabras clave: Género; Alcohol; Adolescencia; Juventud; Investigación cualitativa.

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According to the World Health Organisation's 2014 Global Status Report on Alcohol and Health, the harmful use¹ of alcohol causes 3.3 million deaths annually, which represents 5.9% of deaths in 2012. This report also indicates significant differences in relation to sex, with 7.6% of male deaths attributed to alcohol, while for women this percentage drops to 4% (World Health Organisation, 2014). A considerable proportion of these deaths is made up of young people, with 25% of deaths among people aged 20 to 39 attributed to the use of alcohol. Furthermore, this type of abusive consumption increases the risk of contracting certain physical (cardiovascular disorders, cirrhosis, etc.) and mental diseases (anxiety, depression, etc.), in addition to increasing the likelihood of suffering some type of accident or getting involved in violent acts. It is therefore hardly surprising to see that abusive alcohol consumption ranks third among the main health risks in the world, constituting a major public health problem and generating substantial social and health costs for the users, for those around them and for society in general.

In Spain, the most recent national Survey on the Use of Drugs among Secondary School Students (ESTUDES), conducted by the Spanish Observatory on Drugs and Drug Addiction (OEDT) in 2014, indicates that alcohol is by far the most widely used substance among the school population of 14 to 18 years of age. Indeed, 78.9% of the adolescent population admits to having drunk alcohol at some time in their lives, with a slightly higher figure for women, regardless of the time period under consideration.

The aforementioned survey puts the onset for alcohol consumption at the early age of 13.8 years, with very similar data for male and female adolescents at 13.8 and 13.9 years respectively.

Regarding the abuse of this substance, one in four people aged 14 reported having suffered from alcohol poisoning at some time in their lives, rising to 56.5% at age 16 and reaching 74.1% at age 18. For at least a decade, the proportion of adolescents admitting to getting drunk sometime in their lives has been higher among females than males (51.4% of girls versus 48.7% of boys).

After reaching the age of 18, changes appear in the prevalence and patterns of alcohol use conditioned by age and sex. On the one hand, drinking ceases to be centred on the weekend, its use extending to weekdays with increasing age, particularly among men. On the other hand, the latest national Survey on Alcohol and Drugs in Spain (EDADES 2015-2016) shows that daily alcohol use is 3.5 times higher among men compared to women, with a correspondingly

greater prevalence among men of alcohol abuse (alcohol poisoning and binge drinking), despite a decrease in the prevalence of this type of practice with increasing age. Comparing the male-female figures for binge drinking, for example, there is a difference of approximately 5 percentage points among the 15 to 19 age group, increasing to approximately 10 points in the case of 20 to 24-year-olds, with the percentage of men binge drinking doubling that of women beyond this age.

Incorporating the gender perspective into the study of alcohol consumption among adolescents and young people is a relatively recent development, particularly in Spain. Quantitative research has focused on identifying gender differences in alcohol use among these age groups (Galán, González & Valencia-Martín, 2014; Colell, Sánchez-Niubò & Domingo-Salvany, 2013; Roberts, 2012; Emslie, Lewars, Batty & Hunt, 2009; Delgado, Bautista, Inglés, Espada & Torregrosa, 2005), with studies addressing motivations and consequences on health associated with abuse figuring among the most important (Bousoño Serrano et al., 2017; Díaz-Mesa et al., 2016; Secades Villa, López Núñez, Fernández Artamendi, Weidberg & Fernández Hermida, 2013; Measham & Østergaard, 2009; De la Villa Moral Jiménez, Rodríguez Díaz & Sirvent Ruiz, 2005).

Research of a qualitative nature, on the other hand, has tried to understand the meaning of alcohol abuse among adolescents and young adults, showing that the beginning of this behaviour is connected to the idea of it as something characteristic and normative of this stage (Davies, Martin & Foxcroft, 2013), closely linked to the acquisition of maturity (Romo Avilés, Marcos Marcos, Gil García, Marquina Márquez & Tarragona Camacho, 2015; Ortiz García & Clavero Díaz, 2014). The incorporation of women into this practice during the last decade is therefore not surprising since they increasingly identify alcohol as a constituent part of their social life, one which facilitates incorporation into leisure spaces and practices traditionally considered male (Gómez Moya, Arnal Gómez, Martínez Vilanova & Muñoz Rodríguez, 2010).

This convergence between young men and women regarding alcohol use has been considered by women as a way to break traditional gender codes (Romo Avilés et al., 2015). From some feminist positions, drinking alcohol in public has been interpreted as a reflection of male dominance in public and leisure spaces. A greater female presence in this type of space and the adoption by women of the same behaviour traditionally associated with males would therefore mean the end of such dominance. However, in this transgression of gender roles, one should not ignore the potential danger to which women are exposed when carrying out these risky behaviours (Rolfe, Orford & Dalton, 2009).

Literature shows us that alcohol consumption is a gender influenced activity, but gender roles are not static.

1 Term introduced by the Global Strategy to Reduce the Harmful Use of Alcohol, referred only to the effects of alcohol consumption on public health, without prejudice to religious beliefs and cultural norms (WHO, 2010).

The redefinition of these and the influence of alcohol has been analyzed in some studies which have concluded that changes in the normative patterns of consumption reveal significant breaks in gender roles during adolescence (Romo Avilés et al., 2015; Romo Avilés, Meneses Falcón & Gil García, 2014; Gómez Moya et al., 2010). However, such investigations do not usually differentiate how such gender role changes occur at different stages of adolescence and youth, a time when alcohol use begins, according to the information provided by the principal surveys, and when the riskiest behaviours (alcohol poisoning and/or binge drinking) occur.

Using qualitative methodology, the present article seeks to examine this question in more depth by analysing the experiences, perceptions and meanings that adolescents and young adults attribute to the use and abuse of alcohol in three different age cohorts: 13-15, 16-18 and 19-24 years of age. The goal is to find out how gender roles influence alcohol consumption among these population groups, identifying similarities and differences in terms of gender in their practices and the reasons they use when defending said practices. This should help increase current knowledge of how the process of initiation into alcohol by young males and females occurs, and how the drinking patterns and their connection with adult life are established during their youth.

Method

To carry out the research used for this article, a qualitative methodology was employed, consisting of the administration and analysis of six focus groups for adolescents and young people. This information collection technique proved successful, given that it favours the interactions between members of each group, which in turn enables us to gain a deeper knowledge of the life experiences of adolescents and young adults in relation to alcohol and, moreover, allows an analysis of the influence of social and cultural context on the meanings attributed to their behaviour.

The selection of focus group participants was based on the following variables: sex, age, socioeconomic diversity and educational level, following the criteria set forth by Sánchez Gómez (2004): I) purposive and reasoned sampling; II) selection of informants who can best explain the phenomenon studied; III) cumulative and sequential sampling to saturation point; IV) comprehensive information, rich in nuances, deep and complete. The selection process has sought to guarantee both homogeneity and heterogeneity. The former is necessary in order to show the collective discourse beyond the individual one. While the latter would allow the existing diverse social discourses to appear.

The fieldwork was carried out from March to May 2013 in Oviedo, capital of the Principality of Asturias, an auto-

nous community in northern Spain. Following the selection criteria outlined above, six focus groups were set up, composed of adolescents and young people, half of them female, the other half male. This distribution was considered appropriate to ensure that conversation flowed freely without being conditioned by the presence of members of the other sex in the group. Especially, as we thought in advance and indeed did occur, because issues related to sexuality, violence, stereotypes and gender roles could arise in the groups. This might happen alongside other issues which may be experienced differently by boys and girls and also by opposing discourses that would have hindered the group dynamic. In addition, and according to age, three cohorts differentiated by developmental criteria were established around the cognitive and emotional maturity of each age group: 13-15, 16-18 and 19-24 years of age.

With regard to socio-economic diversity, habitual criteria such as educational level, parental income and profession were considered, but given that this information was difficult to gather during the selection phase for potential group members, we opted as an alternative for combining place of residence together with school type (state, private or private financed by state allowances) of those studying for the compulsory secondary education certificate or the Baccalaureate (high school certificate). Thus, the selection of participants was spread across four areas: centre, periphery, rural, and URBAN². Oviedo can be described as a city that has developed territorially in a concentric way. The centre of the city is populated by people with high socioeconomic level, largely the regional bourgeoisie, whose purchasing power is reflected especially in those families whose children go to private schools and, to a lesser extent, private schools financed by state allowances. In the peripheral neighbourhoods we find mainly working-class families of medium to low social profile, while the URBAN area is mainly inhabited by disadvantage population, with high rates of unemployment, lower educational level, weak rates of economic activity and high level of poverty and exclusion compared to the rest of the city (Ayuntamiento de Oviedo, 2008). Our focus groups also included people who live in the rural areas covered by the council, although despite the particular characteristics of this geographical environment, we did not find that discourses of adolescents and youngsters involved differed greatly depending on their urban or rural origin. In order to guarantee diversity in terms of educational and/or cultural level, in those age groups where several options were available, subjects were selected from each of the possible educational and training paths: Baccalaureate, vocational training and uni-

2 This zone includes neighbourhoods or spaces in which, at the time of the research, economic, environmental and social regeneration actions were being carried out through an URBAN project co-financed by the European Regional Development Fund (FEDER).

versity degrees. Apart from those at school or studying, the discussion groups also contained working and unemployed people wherever possible.

Finally, the main criterion for inclusion in the sample was that alcohol was drunk during leisure time, or that the subject belonged to a peer group in which drinking was associated with leisure.

As can be seen in Table 1, the sample consists of 44 adolescents and young adults, 23 female and 21 male, aged 13 to 24. These subjects were recruited by professionals who habitually work with this population: teachers and managers at schools and occupational training centers for unemployed people under 25, staff in social intervention units and different municipal services and programs. In addition, and in order to ensure the participation of people with certain profiles, the snowball technique was used, although being a sample of a qualitative nature, it was not intended to be representative of the population in any way.

The focus groups were moderated by a sociologist and two trained psychologists. Sessions generally followed this pattern: presentation of the research, initial stimulus aimed at generating conversation, secondary stimuli directed at guiding it when it did not occur naturally and/or needed to be redirected, and a final stimulus. Each focus

group session lasted between 60 and 90 minutes approximately.

The focus groups were recorded and transcribed, for later codification and analysis using the ATLAS.ti computer program, version 7. For greater reliability in this process, each of the researchers carried out a separate coding of the focus group discussion, which were pooled in successive meetings with the rest of the team, leading to a common list of codes (Table 2). Based on these codes, each one of the coded fragments was analyzed in the same way, i.e. first by each researcher individually and subsequently together in the team, until a consensual interpretation was arrived at. In this way a triangulation of the results was obtained through independent and contrasted analyses of the three authors of this article.

This investigation was carried out according to the professional deontological principles required in dealing with people, such as guarantees of confidentiality and anonymity. In addition, the ethical guidelines that regulate work with adolescents were followed, with parents of the participating adolescents being informed about the characteristics of the research, the objectives addressed, and the method used, and being required to provide written consent.

Table 1. *Profile of the focus groups and sociodemographic variables of selected participants*

Group code	Nº Participants	Sex	Age	Resident in		Studies and type of educational centre	
GF01	8	Female	13-15 years	Centre	2	Compulsory Education State School	4
				Suburb	3	Compulsory Education Private School with public funding	4
				URBAN	1		
				Rural	2		
GF02	8	Male	13-15 years	Centre	2	Compulsory Education State School	6
				Suburb	5	Compulsory Education Private School with public funding	2
				URBAN	1		
				Rural	-		
GF03	10	Female	16-18 years	Centre	2	State High School	7
				Suburb	4	Private High School with public funding	3
				URBAN	3		
				Rural	1		
GF04	5	Male	16-18 years	Centre	1	State High School	3
				Suburb	2	Private High School with public funding	3
				URBAN	1		
				Rural	1		
GF05	5	Female	19-24 years	Centre	2	Occupational Training Program for unemployed	1
				Suburb	1	At university	3
				URBAN	1	Degree/Diploma	1
				Rural	1		
GF06	8	Male	19-24 years	Centre	1	High School	1
				Suburb	3	Occupational Training Program for unemployed	3
				URBAN	4	Voc. Training	1
				Rural	-	At university	2
						Degree/Diploma	1

Table 2. *List of codes*

Codes	Subcodes
Weekend routine associated with drinking	Day(s) going out Frequency Area Time How to reach going out area and how to get home
Strategies to convince parents to be allowed to go out	
Type of group with which to go out and drink	Number / sex Age Sociodemographic characteristics
Type of alcohol consumption	Drinking place Drinking strategies Choice of bar <i>Botellón</i> * Reasons for drinking Self-image, attributed reputation
Negative experience associated with drinking	Risk taking associated with this pattern
Risk reduction strategies	
Perception of public safety	Police intervention Fights
Use of social networks when and/or after drinking	
Intra-family communication on the subject of drinking	
Training/information programmes	Effectiveness Proposals
Gender	Gender identity Gender roles Gender stereotypes Gender differences/similarities

Note. * Meeting of young people in public areas to chat, listen to music and drink alcohol bought in stores.

Results

Stage 1: The influence of gender relations on the beginning of alcohol consumption

The process leading up to the first alcoholic drink is narrated in detail in the focus groups with 13 to 15-year-olds. Discourses of both sexes coincide by pointing to older men as the key figure in this initiation rite who sometimes also facilitate access to alcoholic beverages, especially in the case of girls.

In the following fragment, adolescents between the ages of 13 and 15 relate how other men, whether they are friends or family members, introduce them to alcohol. And as some of them indicate, they even have their first alcoholic drink in the company of their male parents:

Moderator: Who were you with when you had your first alcoholic drink?

Boy 1: With friends.³

Boy 2: With my brother.

Boy 1: With friends, a fine example they set, eh?

Boy 3: Yes, with friends, always.

Boy 4: With friends, and there are times when even my parents or relatives get you to try it.

Boy 5: I always drink with friends, I never drink alone. With friends on Saturdays and that.

Boy 6: Me, the first time with my father, the second time with my father, the third time, not yet. (GF02, boys, 13-15 years old)

Apart from the ironic comment of participant 1, the group is completely in agreement about this role of initiator, as befits a socially accepted behaviour. These boys perform a double function. On the one hand, they initiate the others in the consumption of alcohol. On the other, they facilitate the learning of a series of strategies aimed at managing alcohol consumption in order to avoid risks and to confront them might they occur.

Boy 3: Well, whatever your friends tell you.

Boy 1: That's it, whatever they tell you. I learn these tricks from them, I had no idea.

Boy 4: I sometimes ask my parents, especially my father; they advise me what I can do and so on. (GF02, boys, 13-15 years old)

³ In Spanish the word "friend" has different ending for men and women. In this fragment and in the next one, the male form is referred to.

Adolescent girls aged 13 to 15, meanwhile, similarly report that they go through this process with boys who are slightly older than them and who already drink occasionally and are therefore more experienced:

Girl 1: Us girls, there are people who might be older than you and who have already gone out more often and who teach you tricks for not getting drunk so much: don't mix, no... There are always little tricks that they teach you... and which bars are more suitable than others that are not so good. So, maybe they tell you not to go to this or that area because they sell illegal stuff or... stay in well-lit areas, and... that is, never get too drunk because you know what happens... don't leave the glass standing about. Always cover the glass... (GF01, girls, 13-15 years old)

As can be seen, these tips are full of socially assigned gender roles. Girls are warned about the kind of environments which are most suitable for them, as well as about the possible aggressions they may suffer in these contexts, along with the recommendation not to drink too much and to beware at all times of what could happen.

These males, who are usually boyfriends of one of the girls in the group, or older brothers, not only teach how to drink and manage the risks associated with drinking, but accompany and protect the girls during this learning process:

Girl 2:... the boyfriend of a friend of ours is two years older than us so he's been out more and when we go out he comes with us and, yes, he tells us to be careful. (GF01, girls, 13-15 years old)

(...)

Girl 3: Ah, well, yes, there are people who use the older ones, that is, those of legal age for that, to buy you whatever or to look out for me if I want to go I don't know where, or that you pretend to be my brother, things like that. So, we have a friend whose boyfriend's buddy is over eighteen, and then of course, thanks to him, she gets, I mean, the boyfriend can go to bars that aren't meant for minors... that is, as if they are together with others and get more than they could get alone. (GF01, girls 13-15 years old)

As we can see in these two stories, boys play a clear role in the beginning of alcohol consumption for adolescent girls. It is they who facilitate the girls' approach to the places where alcohol is drunk and access to the substance itself. But they also play an important role in the learning of the rituals around drinking and the protection of young women against the risks and dangers they may be subject to in bars and other similar leisure spaces.

In addition, younger adolescents also refer in their conversations to a third person who takes responsibility for

keeping an eye on those who are under the influence of excessive drinking. This role can be exercised by either a male or a female member of the group, but there are important gender differences with respect to the value and meaning given to this figure.

In adolescent groups, when this protective role is exercised by a male, a control function is attributed, usually by a boy over his girlfriend, as can be seen in the following story:

Girl 2: Yes, we and our friend's boyfriend are the ones who control the rest of the group. He does it because he wants to control his girlfriend and helps us control ourselves. (GF01, girls, 13-15 years old)

Conversely, when a girl takes this role, it is seen as linked to the idea of caring and immediately establishes an association between caring and motherhood, which is then also devalued by the group, criticising the girls who do this as being spoilsports:

Girl 2: Yes, those of us who normally almost don't drink at all get called spoilsports because we're like: "Stop drinking".

Girl 3: "Stop drinking", you know because then you're falling over, you don't remember, then the hangover and... they don't listen to us. Then they say the typical thing: "Yes, mummy". (GF01, girls, 13-15 years old)

Curiously, when a male behaves in the same way in the group of younger boys, unlike what happens in the group of girls, this caring does not appear to be devalued by the other members, but is desired by them and also valued positively by both the group and by those exhibiting this behavior:

Boy 4: It was me and it's still me. They even tell me to do it: "because you don't drink much, please help me if I overdo it". Or if they don't ask, I do it quietly anyway and feel good about it. You're taking care of them, in inverted commas, and helping them not to make mistakes. (GF02, boys, 13-15 years old)

Stage 2: The generalization of risky alcohol consumption in adolescence and the adherence to/break with assigned gender roles

The stories of adolescents aged 16 to 18 show that abusive drinking is a common and normalised practice, linked to weekend leisure. Although there are no gender differences linked to prevalence and patterns of use in their conversations, this is not the case when describing the way one behaves after excessive drinking and the meaning that young women and men attribute to their actions. In this stage, a certain transgression of gender roles is observed, especially in the case of females.

Young males and females both identify the exaggerated expression of emotions after abusive alcohol consumption as typically female behaviour. But while the conversations of the girls strongly approve of affective behaviour, boys in theirs talk pejoratively about crying girls, as can be seen in these two fragments:

Girl 2: Yes, but you know, the boys, huh? There are boys who drink and when they drink, in general, with some it seems they haven't drunk at all and others, yes they have. But, well, the girls, whenever they drink, they show it and it's much more noticeable.

Girl 3: We are more affectionate, us girls. Me, at least I am more... huggy.

Girl 2: They can be very drunk and so on and you wouldn't notice. Some people, anyway. Others yes, of course you notice. But the girls, I think you always notice them.

Girl 3: Yes.

Girl 2: Because they're, like, much more expressive.

Girl 3: Much more. (GF03, girls, 16-18 years old).

Boy 3: The girls, half of them end up crying. Over nothing.

Boy 1: I see a row of girls crying, one starts crying and the other one cries because she cries.

Boy 2: Yes.

Boy 3: All crying.

Boy 1: Yes. (GF04, boys, 16-18)

It is striking how stereotyped both conversations are; they clearly link the externalisation of emotions with women, as opposed to men, who can either cope with abusive amounts of alcoholic without it affecting their behaviour or, as shown below, they express themselves aggressively. But as mentioned above, while the girls emphasise that they express positive emotions, such as affection, boys perceive that women cry when they drink excessively, ridiculing their behaviour, which they see as group driven and unjustified. On the one hand, the irrational and unfounded side of female behaviour is highlighted, as for example participant 3 says with "over nothing". And, on the other, they interpret it as if it were an almost contagious reaction, that is, inevitable, occurring because of group pressure which nullifies the individual capacity of each one of the girls, who let themselves get carried away by their emotional side.

The behaviour of male adolescents appears to be more varied. Girls point out that when boys drink more than they should, it is either not noticeable, as female participant 2 states, or their behaviour turns aggressive.

For their part, the way male adolescents see their behaviour is very similar to that expressed by their female counterparts, stating that the typical male behaviour in the

contexts of leisure and drinking involves violence, which is reported by some of the participants in the focus group as being motivated by excessive drinking and/or fighting connected with affective relationships:

Girl 6: And they become more aggressive than usual.

Girl 5: Yes, that's right.

Girl 3: They get jealous

Girl 6: Yes, that too. And they mess with everyone. There are more rows, more accidental pushing and shoving, I do not know what else.

Girl 3: Well, they get a bit too cocky (GF03, girls, 16-18 years old).

Moderator: And what do you think might be the reason that there are quite a lot of fights in the bar areas of town?

Boy 1: Alcohol.

Boy 2: Because of alcohol or a girl.

Boy 1: Alcohol makes you furious, when you drink you don't think and before you know it you've already been in a fight and everything. (GF04, boys, 16-18 years old)

These discourses highlight a relationship between aggression and masculinity which again refers to traditional gender roles. Women perceive that men fight to demonstrate their superiority over others, their masculinity. Although this masculine aggressiveness is not valued positively by women, who in fact use the term "cocky" contemptuously to refer to this masculine behaviour. On the other hand, males consider violence as a typically masculine conduct, which is normalized and accepted.

However, there are two striking issues that need to be analysed. On the one hand, the discourse of both male and female participants refer to the male intrinsic violence, which is exacerbated by excessive drinking: "they become more aggressive than normal", "alcohol makes you furious". This indicates that, despite the social advances against gender violence, the male one continues to be a type of socially normalised behavior and perceived as such by both sexes. But, additionally, when this violence coincides with abusive alcohol consumption, it seems that intentionality and male responsibility are diluted, they do it "unintentionally", as claimed by both male participant 1 and female participant 6.

On the other hand, in the discourse of both male and female adolescents there are references to what either constitutes gender violence or at least violence in affective relationships which however, is not identified as such, but only labelled as a matter of 'jealousy', as pointed out by female adolescent 6, or implied when male adolescent 2 says "by a girl". This would re-legitimise violent masculine behaviour and refer to an interpretation of violence linked to

the emotional relationships as typical of past eras in which jealousy and passionate character justified it.

In contrast to the expression of emotions, which, as we have seen, is considered a fundamentally feminine capacity, aggressive behaviours are no longer exclusive to men. Examples of female aggressiveness linked to excessive drinking appear in the discourses. But again, the meaning that both sexes assign to such behaviours differ. In this stage of the end of adolescence, women identify masculine aggression as part of the construction of traditional masculinity, not with female identity. Thus, when women are violent they are perceived as going against the norm, breaking with traditional gender roles:

Girl 7: I see more men than women, but I see men doing it because they want to show how manly they are, but with women, sometimes we care much less about all this, but there are also some women who have their character and pride and say: "Well, here I am, I'm the most".

Girl 8: There are some girls that are worse than men.

Girl 7: In fact, once I saw one knocking a guy out.

Girl 8: Oh, wild! If I'd been there, I'd have cheered her on.

Girl 7: I don't know, that also depends, but usually it's more the men, to prove... (GF03, girls, 16-18 years old)

In these discourses we can observe how female aggressiveness is perceived as a challenge to traditional femininity. The participants in the focus group assign a positive value to the behaviour of those few who dare to use violence, which they interpret as a kind of instrument of personal self-affirmation, of overcoming the traditional passivity and devaluation imposed on women: "There are some with character, with pride," even feeling all powerful: "Look at me, I'm the most". Nevertheless, the expression of surprise and even admiration in relating the fight between a woman and a man observed on one occasion, with the former coming off best, shows that such behaviour is not socially normalised.

This same narrative appears among male adolescents, who also talk about an example of female violence after drinking too much:

Boy 3: It might seem more normal for boys to fight, but just last year, I think you were there too.

Boy 4: Yes.

Boy 3: At the door of [mentions a well-known late night bar], I do not know if you know it, there was a girl who threw a glass into the face of another girl and left her bleeding and everything. (GF04, boys, 16-18 years old)

Paradoxically, male and female adolescents hardly speak about the habitual aggressive behaviours of men, but they

do comment on how and when they saw a woman hit a man or throw a glass in the face of another woman. Although infrequent, such actions acquire great visibility precisely because they go beyond the traditional gender norms, as some authors have shown when analysing processes of gender role transformation (Dema Moreno, 2008).

Finally, another gender difference that appears in the focus groups has to do with forms of physical and virtual interaction among adolescents. In the girls' narratives, their need to interact and establish social relationships outside their own peer group is revealed, while the boys prefer interaction within it:

Girl 3: For example, we, I often end up sitting, or my friends too, because your feet hurt. The boys don't have that problem, they're lucky, and well... But yes, they're always like more, at least in my group, they're, the boys, okay? they're with us, but they're like over there doing their thing, and we're just the ones who, well, go over and say hello, or let's go somewhere, let's go for a walk. They're more like, more static, you know. But they also drink three times as much. (GF03, girls, 16-18 years old)

The boys also indicate that they interact mostly with the group they're out with, giving two types of reasons in their discourse: mainly, on the one hand, highlighting how they value the group that welcomes them, offering them a space of well-being and autonomy and, secondly, the drinking, which makes them feel good, so they feel no need to establish social relationships or interact with other people outside the group:

Boy 1: Well, you also drink and you're with friends and because you feel in a warm atmosphere with your friends you feel comfortable and when you are already a little... when you've had a couple, you feel good, even if you've drunk... I know what I mean but I don't know how to explain it. It happens with him and another friend, when we're together and we've had a bit to drink...

Boy 3: We're on our little cloud.

Boy 1: It feels good that there's no one else around us.

Boy 3: That's right.

Boy 1: But, and that, okay? We like that, too.

Boy 3: That's right, even without being drunk.

Boy 1: Yes, without being drunk.

Boy 3: We're always doing our thing. (GF04, boys, 16-18 years old)

It is rather striking to observe these differentiated behaviours of young men and women, which highlight a break in traditional gender roles. In contrast to traditional forms of masculine sociability, in which males occupy a space

and connect with other groups, in these fragments it can be observed that female adolescents are the ones who establish links beyond the peer group itself, occupying different spaces in leisure venues. Conversely, male adolescents report that they remain in the same place, in a static manner, relating only to members of their peer group, a practice that alludes to the roles that women traditionally played in public spaces.

As far as the virtual space is concerned, there are comparable patterns. Both sexes coincide in pointing out differences in the use of social networks and the role they play in their weekend leisure related to alcohol consumption. As can be seen in the following fragments, both emphasise that the use of information and communication technology by girls is related to taking photos that they subsequently upload to social networks:

Girl 1: I think I've never seen a guy with a camera.

Girl 3: Me neither. The photos uploaded are always like a big bunch of girls and just four boys.

Girl 1: Yes.

Girl 3: And they're always about football. (GF03, girls, 16-18 years old)

Boy 4: I never left the house with a camera to go out on a Saturday. If there are any photos of me it'll be because someone else takes them, not because I go taking pictures of others.

Boy 1: Me neither. You meet a girl that you know and she's like: "Oh, photo, photo, photo."

(...)

Boy 4: Me too, if they get uploaded it's by other people... Anyway, you can see: "male 3 photos, male 3 photos and female 35 photos, male 3 photos". (GF04, boys, 16-18 years old)

The narratives of both groups come together in this regard, with girls responsible for taking pictures with which they tell the stories of their night-time outings, while boys are not involved in this to the same extent. Their conversations reflect that they clearly see this feminine practice as excessive ("You meet a girl that you know and she's like: Oh, photo, photo, photo"). Girls, meanwhile, refer to the traditional male roles in the content of their photos ("They're always about football").

Boys on the other hand do not use social networks to the same extent, so they voice a stereotyped criticism from a gender perspective of the way girls use ICTs:

Boy 4: I don't know, I think that, I don't know if they do it to make out, but sometimes it seems that there are groups of girls who, more than going out to socialise, go out to take photos to put on Tuenti. That's the feeling I get.

Boy 1: Yes, yes.

Boy 4: Yes, I don't know, they go and say: "Well, I'm going to show off here a bit in front of these people and then I'll go home and upload the photos I took this evening". And sometimes that's what they do, just that and nothing else.

Boy 3: Photo, Tuenti. (GF04, boys, 16-18 years old)

This conversation shows how male adolescents interpret female use of ICTs as abusive and responding to a need for social approval. They consider that girls dedicate their time to showing an image of themselves, and even see this practice as constituting an end in itself ("Sometimes that's what they do, just that and nothing else"), as if they did not go out to have fun but only to take photos, with the aim of making out, as indicated, albeit tentatively, by participant 4.

Stage 3: Towards an adult mode of alcohol consumption mediated by gender identity

In this final stage, women aged 19 to 24 continue to associate weekend leisure with going out to bars and having alcoholic drinks, but they state that at this age they exercise greater control over their bodies and their behaviour and, thus drink moderately without seeking intoxication, as was the case when they were younger:

Girl 1: It's what my friends and I call "heat stroke", which is when you're not out to look... I know there are people of my age, I'm 24, they're out every weekend, especially guys, that want to get drunk one way or another. (GF05, girls, 19-24 years old)

Conversely, they do not perceive men as having gone through this change with age, but instead continue to drink large quantities with the aim of getting drunk and losing control:

Girl 1: And when you're on an Erasmus year and you're in a mixed group it's true that the guys have an attitude towards alcohol that is totally different, they're like: "We can hold our drink better, so we drink more and it's only natural we end up drunk as skunks and smashing up public property" and, well, poor guys, it's not all of them, but I think that in general the attitude towards alcohol is really different. (GF05, girls, 19-24 years old)

As can be seen, young women understand that this behaviour is connected to the male need to reaffirm their masculinity, which they in turn link to a greater physical tolerance to alcohol. As we saw in the 16-18 stage, this in a way works to legitimise greater male aggressiveness. The violence in this case is no longer restricted to just involvement in fights, but also leads to acts of vandalism, such as destruction of public property.

In male conversations, the association between leisure and alcohol also appears, although this consumption is not constrained to the weekend, but also to weekdays:

Boy 5: Depends on... (all laughs) Thing is, it doesn't have to be the weekend to go out partying, or... to have a good time out there, right? I mean, going out, I don't know... sometimes, say a Monday, you might want to do something with some friends, let's have a drink, and in the end you've had four. I don't know, it's just spontaneous... spontaneous moments... (GF06, boys, 19-24 years old)

In their conversations, as young women do in theirs, young men also refer to moderate drinking, but in this case it is usually associated with weekdays, while at weekends they continue drinking excessively:

Boy 4: On Wednesdays and Fridays for sure. Maybe... depends on the week, and in addition to Wednesday and Friday, Thursday and Saturday as well. But Thursdays and Saturdays can vary (laughs). But... let's see... it's not about going out all night and getting all those times. On Wednesdays, you go out for a couple of beers in a certain bar that... well, has different beers that aren't Mahou and Carlsberg... (GF06, boys, 19-24 years old)

Regarding their abusive consumption of alcohol, the main reason they give is strong peer group pressure, as well as the difficulties they have in managing it:

Boy 3: And me too... above all avoid... show off your courage, like "Why don't we have two Jägermeisters in a row or an absinthe? I don't know..."

Boy 5: Exactly... (laughs).

Boy 3: Well, you know, me... you have to keep a bit of a cool head to avoid falling for those provocations that... (laughs)... there are many throughout the evening...

(all laugh)

Boy 4: Don't lie, don't lie, you fall for it...

Boy 2: Every time... (all laugh). (GF06, boys, 19-24 years old)

On the whole, it seems that a change towards lower-risk alcohol use sets in among young women in this age group, but not so much in the case of men. With their new patterns of alcohol use, women aged 19 to 24 make strong and stereotyped criticisms from a gender perspective of drinking by underage persons, especially cutting in the case of female adolescents:

Girl 2: Let's see, we always talk about it, we live in the centre and when we go out on a Saturday it's... it's rea-

lly shocking to see the girls, wearing those heels they don't know how to walk in, ok, just like we did too, but you see them and then they get really drunk and cry. I remember one day going up [mentions a well-known street of bars] and I really didn't see anyone having a good time, but some boys fighting, some girls crying and everything... And I said, mother of God, what is this?... And, yes, they seem to be very young, but I think it's because we are getting older and then you see the difference more, but if you'd recorded me back then maybe I'd have been just like them. (GF05, girls, 19-24 years old)

Through these narratives, the existence of greater social sanction can clearly be observed for female adolescents whose behaviour deviates from the female role, as well as the internalised gender stereotypes that are used to describe these behaviours. It even seems that it is through the behaviour of younger girls that the older ones become aware of the transgression which, from a gender perspective, they were themselves guilty of during their own adolescence: "OK, like we did too, but you see them and then they get really drunk and cry". Thus, there is a need to establish a clear difference between their actions and those of younger generations.

Young men, meanwhile, also criticise the drinking of girls, which, like their female peers, they describe as abusive, but they seem to attribute the phenomenon to social change. From their perspective, girls and young women today drink more than in previous generations, exceeding the quantities of male drinkers, which they also consider inappropriate from the point of view of gender roles:

Boy 6: People's attitudes have been changing a lot, I think, in recent years, I think that a few years ago everything changed loads. Girls even drink more than boys and then act in a very different way than I did, for example, when I was 16. My sister herself, just a kid, has changed completely from how I was at her age. I don't know, they get drunk, when they get home they can't stand up, when, you know, once, okay, but when it happens several times... And then, I don't know, you walk down the street and they're lying there on the ground... and, I don't know, I don't know what the change is due to or what... (GF06, boys, 19-24 years old)

Through these discourses we can again observe the extreme visibility, already explained above, of behaviours that transgress gender roles. As in the case of women evidencing violent behaviour, it is still surprising that female adolescents will drink until they reach the point of alcohol poisoning and that they do so in public spaces. According to these narratives it seems that it is only the girls who get drunk and are "lying there on the ground", when the diffe-

rences in the prevalence of drunkenness between the sexes barely reaches three points according to the ESTUDES Survey conducted in 2014.

In short, we can see in the conversations provided by young adults how they approximate to assigned gender roles, which leads to a differentiated prevalence and patterns of alcohol use according to sex, as well as the need to confirm these gender roles through criticism of and distancing from transgressive behaviours that occur in adolescence and early adulthood.

Discussion

The results of this study reveal first of all the clear influence of gender roles on patterns of alcohol use during adolescence and the first stage of adulthood. Secondly, having taken into account the different age cohorts established for the configuration of the focus groups, it has been possible to see how this influence manifests itself in three different stages: the process of initiation and learning about alcohol use, the development and the generalisation of risky drinking in the final stage of adolescence and, finally, the consolidation of alcohol consumption in the first stage of youth, which is likely to mark the drinking patterns of these people in adulthood. These results also reflect drinking at an early age, the routines and social relationships established around such use, the different values these have depending on gender, the development of motivations when consuming alcohol and the reduced perception of risk that accompanies drinking throughout the process.

The few Spanish studies that have incorporated a gender perspective indicate that changes in the patterns of male and female alcohol use reveal a series of breaks with the traditional gender system (Romo Avilés et al., 2015; Gómez Moya et al., 2010). However, as they did not take into account the existence of the three stages analysed in this article, they were not able to identify the gender differences that occur during adolescence and early adulthood, something that only becomes apparent with an intersectional analysis such as the one carried out in this study and which may also have special relevance in social interventions with this type of population, as will be explained below.

This study indicates that during the first phase of adolescence, gender roles are still clearly defined, and coincides with other research to identify that alcohol use and leisure contexts are male practices and spaces which both boys and girls access through older figures, usually males with whom there is some family bond and/or affective friendship (Romo Avilés et al., 2015; Gómez Moya et al., 2010; Lyons & Willott, 2008). In this initial phase, it is striking to note the existence of a practice related to the care and protection of both male and female adolescents in leisure spaces after abusive alcohol intake. Some authors have identified that the peer group works as a protective community that

favours the safety of its members when risky drinking occurs (Romo Avilés et al., 2015). However, our study shows that the caring role does not correspond to the group as a whole, but fundamentally to those members who drink less.

From a gender perspective, our analysis highlights how the social value attributed to this practice differs when performed by a young man or woman. In the case of women, it is associated with the traditional value of care, which results in a devaluation of the behaviour and of the person who performs it, while, conversely, when it is the men who carry out said tasks of care and control, such action is recognised and valued by the peer group.

The discourses analysed in this article concur with data provided by the ESTUDES Survey, which indicate that at the end of adolescence a normalisation and generalisation of abusive drinking takes place in both sexes, associated with weekend leisure, especially in the case of young women. But more important than the prevalence of alcohol use is the role that alcohol plays in the construction of the identity of both boys and girls, as evidenced by the literature (Romo Avilés et al., 2015; Romo-Avilés et al., 2014; Lindsay, 2012; Rolfe et al., 2009; Peralta, 2007). The results obtained in the analysis of the focus groups show that male adolescents build their masculinity on abusive drinking and that peer group pressure is central to this process, particularly in the incitement to drink. The narratives of both sexes also connect excessive drinking and male violence as a normalised and accepted expression of masculinity, in accordance with the traditional masculine role.

In the case of female adolescents, however, there is a subversion of traditional female gender roles. Not only because of the higher prevalence of alcohol consumption at this vital moment, as reported in the ESTUDES Survey, but also because of the way in which they occupy physical and virtual spaces that they talk about in the focal groups. Contrary to the traditional division of public-private space, where the former is associated with men and the latter with women (Murillo, 1996), the conversations analysed refer to women occupying physical and virtual spaces to a greater extent than men. This practice is related to questions of gender identity, such as the feminine need to feel part of a larger community than the group itself, which provides young women with greater security in their night-time outings (Alcedo Rodríguez, Dema Moreno, Fontanil Gómez & Solís García, 2014). Furthermore, female adolescents use ICTs to capture their nights out in images and disseminate them on social networks. Such posts allow them to display their carefully prepared image publicly, thus representing a key element in the construction of the female identity, in such a way that by using social networks they show they can participate in traditionally masculine practices and spaces, while at the same time seeking as far as possible not to compromise their femininity (Hutton, Griffin, Lyons, Niland & McCreanor, 2016).

Although male violence, both in the public and private space, has been a traditional object of study in research with a gender perspective, violence by females has only recently begun to be analysed, with the work of Day, Gough and McFadden (2004) standing out in the field of night-time leisure. In the focus groups, both sexes report some violent episodes by women that are interpreted as a break with traditional gender roles, but also, above all, by women as a type of subversion and even as a form of female empowerment. Despite the fact that these events are infrequent, they become quite visible in the narratives, which could be interpreted as the beginning of a process of change in gender roles that has not yet been normalised. Some authors have shown that it is precisely when processes of change in gender roles are under way that extreme visibility of those behaviours going beyond the norm is observed (Dema Moreno, 2008).

Finally, during the first stage of adulthood the transgressive characteristics of the previous stage disappear and the young women move closer to assigned gender roles. At this crucial time, and coinciding with the perception of our focus groups participants, the EDADES Survey shows that women begin to reduce risky alcohol use, while men maintain and consolidate it. It is also at this time that both men and women start voicing strong criticism when discussing behaviours of the adolescents in the previous stage that go beyond gender norms. Although young women may have behaved transgressively themselves during their own adolescence, gender roles are so deeply rooted that there is a manifest need to break with past behaviour and direct it towards the socially accepted model. Thus the patterns of alcohol consumption that characterise adult women and men begin to emerge at this stage, with a higher prevalence in men in terms of greater alcohol intake and the various problems associated with the harmful consumption of alcohol (Observatorio Español de la Droga y la Toxicomanía, 2015).

It should be noted once again that the sample used to carry out this research is not statistically representative of Spanish adolescent and youth, given that purposive sampling was used with the aim of establishing the influence of gender roles in the process of initiation and development of alcohol use. With this goal in mind, some issues that appear in the conversations of adolescents and young adults have been mentioned, without in-depth analysis, such as the meaning of gender violence in leisure contexts and particularly when linked to alcohol, and this could well be featured in future lines of research.

As we have tried to show throughout this article, gender and age are interrelated and act in a combined way. By incorporating an intersectional approach, it has been possible to gain a comprehensive understanding of the meanings that adolescents and young adults attribute to alcohol use, as well as the behaviours they develop in relation to this substance. This approach is not only useful from a

theoretical point of view, but could be considered when intervening socially in this field, as other female authors have also indicated (Jiménez Rodrigo & Guzmán Ordaz, 2011). In short, for actions, particularly preventive ones, to be more effective, not only gender roles have to be taken into account, but also different moments of developmental stages that people go through during adolescence and early adulthood have to be considered.

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Conflict of interests

The authors of this article declare that there is no potential conflict of interests related to its preparation and publication.

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Evolution of alcohol and tobacco consumption in young people in Spain, after the law 42/2010 against smoking: 2011-2014

Evolución del consumo de alcohol y tabaco en jóvenes en España, posterior a la ley 42/2010 frente al tabaquismo: 2011-2014

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Abstract

The objective of the study was to evaluate alcohol and tobacco consumption in young people in Spain, after Law 42/2010, during the interval of 2011-2014. The sample consisted of 3270 young people aged between 15 and 24 years who completed the National Survey of Health in Spain (ENSE) of 2011 and the European Survey of Health in Spain (ESES) of 2014. Variables: consumption, type of tobacco, attempts to quit smoking, consumption and type of alcoholic beverage, binge drinking, and sociodemographic variables. Logistic regression analysis was performed with the sociodemographic variables. The results indicated a decrease in tobacco and alcohol consumption from 2011 to 2014, and increased attempts to quit smoking. Beer is the most popular drink, most consumption is carried out between 1 and 2 days per week, and half of the young people who drink alcohol have taken part in binge drinking in the last 12 months. There are significant differences in tobacco and alcohol consumption. Between 2011 and 2014, the number of occasional and daily smokers, and alcohol consumption decreased, coinciding with the entry into force of Law 42/2010. Binge drinking is the most common pattern among young people. The factors that relate to greater consumption of tobacco are: being male, being married, and not having university studies. On another hand, the variables related to alcohol consumption are: being male, having Spanish nationality and university studies.

Key Words: Alcohol consumption; Tobacco consumption; Law 42/2010; Binge drinking; Health surveys.

Resumen

El objetivo del estudio fue evaluar el consumo de alcohol y tabaco en jóvenes en España, posterior a la ley 42/2010, periodo 2011-2014. La muestra estaba formada por 3270 jóvenes entre 15 y 24 años de la Encuesta Nacional de Salud en España (ENSE) de 2011 y la Encuesta Europea de Salud en España (ESES) de 2014. Variables: consumo, tipo de tabaco, intentos de dejar de fumar, consumo y tipo de bebida alcohólica, consumo intensivo de alcohol en una misma ocasión y variables sociodemográficas. Se realizó análisis de regresión logística con las variables sociodemográficas. Los resultados indicaron una disminución del consumo de tabaco y alcohol desde 2011 a 2014, aumentado los intentos de dejar de fumar. El tipo de bebida que más está aumentando es la cerveza, el consumo mayoritario es entre 1 y 2 días/semana y la mitad de jóvenes que consumen alcohol han tenido un consumo intensivo en una misma ocasión en los últimos 12 meses. Existen diferencias significativas en el consumo de tabaco y alcohol. Entre 2011 y 2014 ha descendido el número de fumadores ocasionales, a diario y consumo de alcohol, coincidiendo con la entrada en vigor de la ley 42/2010. El consumo intensivo de alcohol, binge drinking, es el patrón que más se está dando entre jóvenes. Los factores que se relacionan con mayor consumo de tabaco son: ser hombre, estar casado y no tener estudios universitarios. Por otro lado, las variables relacionadas con consumo de alcohol son: sexo masculino, nacionalidad española y estudios universitarios.

Palabras clave: Consumo de alcohol; Consumo de tabaco; Ley 42/2010; Consumo intensivo; Encuestas epidemiológicas.

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Drugs are psychoactive substances that affect perception, mood, consciousness, and behavior (Patiño, 2008). In 2015, the most frequently consumed drugs in Spain in the past 12 months were alcohol (77.6%) and tobacco (40.2%) (Spanish Observatory for Drugs and Drug Addiction, 2016). Alcohol consumption is increasing in the population, but the age of onset of consumption is decreasing (Medina-Mora, 2015).

The age group between 15 and 34 years has the highest prevalence of alcohol and tobacco consumption, whereas the population between 15-24 years shows a higher risk consumption, especially of alcohol, estimated at 11.8%. Risk consumption is regular consumption of 20 to 40 grams of alcohol per day for women and of 40 to 60 grams for men. It is a pattern of alcohol consumption that increases the risk of harmful health consequences (Anderson, Gual & Colon, 2011). The most popular type of consumption in the group of 15-24-year-old in Spain is called “botellón” [“big bottle”], carried out by 52.2% of youth within this age range. The “botellón” is an “outdoor meeting of youth, noisy and usually nocturnal, in which alcoholic beverages are consumed in abundance” (Real Academia Española, 2001). The “botellón” is usually carried out in public spaces (squares or parks) where young people chat and listen to music (Gómez-Fraguela, Pérez & Triñanes, 2008). The occasional consumption of alcohol in large quantities and for a short period of time, the so-called “*binge drinking*,” occurs in the age group between 15 and 29 years (National Plan on Drugs, 2015).

The consumption of alcohol and other drugs are the most worrisome behaviors in young people worldwide (López, Santín, Torrico & Rodríguez, 2014; Luengo, Otero-López, Romero & Gómez, 1996). Youth is the stage of highest risk for the onset of consumption of these substances, with the average age in Spain being between 13 and 16 years. During the youth stage, polydrug use is relevant, especially that of alcohol and tobacco, and their consumption is the most common at this stage, especially between ages of 15 and 24, in individuals who have participated in the “botellón” in the past year. In Spain, out of every 10 people between ages 15-24 who participated last year in a “botellón,” 6 were polydrug users. Polydrug use is related to the consumption of alcohol, as in 90% of the cases, alcohol is present (EMCDDA, 2016; Royo-Isach, Vidal & Zapata, 2015). Polydrug use of low-proof alcohol and tobacco are the main risk factors for high-proof alcohol consumption (Hernández-Serrano, Font-Mayola & Gras, 2015). In relation to polydrug use of alcohol and tobacco, there is an interaction between the two drugs. Smoking is a risk factor for alcoholism, and alcohol consumption acts as a risk factor for becoming a smoker (Lajtha & Sershen, 2010; Higgins et al., 2014) because the consumption of alcohol increases the speed at which the body breaks down

nicotine, which therefore remains in the body for less time. This can lead to increasing the number of cigarettes consumed. This means that when someone wants to quit smoking, the consumption of alcohol will make it more difficult (Gubner et al., 2016).

Young people’s consumption is influenced by various youth characteristics, such as personal identity, desire to experience new sensations, and the importance of feeling that one belongs to the group (López et al., 2014; Luengo et al., 1996). It is also determined by factors like not being liked by others, feeling more secure and self-confident, and being more sociable. Young people’s decision to consume is conditioned by their previous experiences when taking risks that may have arisen during their lifetime (González-Iglesias, Gómez-Fraguela, Gras & Planes, 2014).

Young people have a pattern of recreational use that can influence the perception of risk (Royo-Isach et al., 2015). Young people’s alcohol consumption may cause changes in their behavior, memory, and learning ability (Sánchez, Redondo, García & Velázquez, 2012). Also, adolescent alcohol use is associated with suicidal ideas (Bousoño Serrano et al., 2017). Smoking alters the sense of taste and smell, reduces the feeling of hunger and, like alcoholic beverages, it is associated with various diseases (Ruiz-Risueño, Ruiz-Juan & Zamarripa, 2012).

Based on the above, alcohol and tobacco are the drugs consumed most frequently by youth, and this age group has the highest prevalence and risk consumption, because they mostly use these drugs recreationally, and this can be influenced by the characteristic behaviors of this age. Polydrug use of these two drugs is highlighted as a habitual pattern, and the most popular type of alcohol consumption in recent years, which also presents the most problems, is the intensive consumption of alcohol, the so called binge drinking.

Hence, given the relationship between the consumption of both drugs (alcohol and tobacco), on the one hand, and the new Spanish Law 42/2010 of health measures against smoking and regulating the sale, supply, consumption and advertising of tobacco products (Official State Bulletin, 2010), and international studies that confirm the relationship between policies against smoking and the reduction in the consumption of alcohol (Kasza, Mckee, Rivard & Hyland, 2012; Lee, 2007; Lee, Chen, Hwang & Yeh, 2010; Young-Wolff et al., 2013) on the other, a study was proposed to evaluate the consumption of alcohol and tobacco in Spanish youth, subsequent to above law governing tobacco consumption in the 2011-2014 interval.

Method

Design and participants

The study is descriptive and cross-sectional. The object of study were the records of the individuals aged between

15 and 24 years, who participated in the National Health Survey of Spain (ENSE) of 2011 (Ministry of Health, Social Services, and Equality, 2013) and in the European Health Survey in Spain (ESEE) of 2014 (Ministry of Health, Social Services, and Equality, 2015). We used the latest published institutional records of both surveys, totaling 3,270 records; 1,656 from 2011 and 1,614 from 2014.

The study instruments

As indicated above, we used representative data records of Spanish youth aged between 15 and 24 years from the 2011 ENSE (Ministry of Health, Social Services, and Equality, 2013) and the 2014 ESEE (Ministry of Health, Social Services, and Equality, 2015). Sections V and W of these surveys were used as the instrument. Section V corresponds to the “consumption of tobacco” and contained 3 questions (Can you tell me whether you smoke?; What kind of tobacco do you smoke more frequently?; and During the past 12 months, how many serious attempts to quit did you carry out in which you went at least 24 hours without smoking?). Section W corresponds to the “consumption of alcohol” and consists of 2 questions [During the past 12 months, how often have you taken alcoholic beverages of any kind (i.e., beer, wine, liquor, distilled drinks and cocktails, or other alcoholic beverages)? and During the past 12 months, how often have you consumed 5 or more standard drinks on the same occasion? [“Occasion”, according to the ENSE and the ESEE, is considered consuming the drinks in an interval of about 4 to 6 hours]].

The ENSE and the ESEE are cross-sectional surveys conducted by the National Institute of Statistics (INE), in collaboration with the Ministry of Health, Social Services, and Equality (MSSSI) of Spain. They are performed representatively (each participant is assigned a weighting coefficient to ensure representativity) with the non-institutionalized population of Spain. The type of sampling is stratified, three-stage, by census sections, family homes, and people. The records are available for any researcher on the INE website of anonymized microdata, in a free access file.

Variables

The sociodemographic variables were: age, sex, level of education, marital status, nationality.

The dependent variables were: current tobacco use, type of tobacco most frequently smoked, attempts to quit smoking in the past 12 months, frequency of consumption of alcohol in the past 12 months, type of beer consumed, frequency of consumption of 5 or more alcoholic beverages on the same occasion during the last 12 months.

Statistical analysis

The statistical analysis of the data was performed with the IBM SPSS Statistics program version 22 (IBM Corp, Armonk, NY, USA), licensed from the University of Castilla

la Mancha (UCLM). Statistical analysis consisted of a descriptive analysis through the calculation of counts (n) and proportions (%) for the qualitative variables and the calculation of the mean (M) and standard deviation (SD) for the quantitative variables. The proportions of the categorical variables were also compared, using chi-square tests for the contingency tables. In addition, a logistic regression (LR) was performed to identify the variables associated with the consumption of alcohol and tobacco. All the hypotheses were contrasted bilaterally, and in all statistical tests, values with a 95% confidence level ($p < .05$) were considered significant.

Results

The sample was made up of 3,270 records of youth aged between 15 and 24 years in Spain. Of them, 49.6% were males and 50.4% were females. Mean age was 19.67 years ($SD = 2.902$). In relation to marital status, 96.4% were single (Table 1).

Table 1. Sociodemographic characteristics of the population of youths in Spain (15-24 years) analyzed by years (2011-2014) ($n = 3270$).

	2011 n (%)	2014 n (%)	p
Sex			
Male	842 (50.8%)	780 (48.3%)	0.150
Female	814 (49.2%)	834 (51.7%)	
Country of birth			
Spain	1489 (89.9%)	1465 (90.8%)	0.6409
Foreign	167 (10.1%)	149 (9.2%)	
<i>Marital status</i>			
Single	1601 (96.7%)	1550 (96%)	0.535
Married	51 (3.1%)	55 (3.4%)	
Widowed	0 (0%)	2 (0.1%)	
Legally separated	2 (0.1%)	2 (0.1%)	
Divorced	2 (0.1%)	4 (0.2%)	
Doesn't know	0 (0%)	1 (0.1%)	

Note. N: count; p: significance of chi-square test.

Tobacco use

Concerning smoking, 25.4% of the youth in the study smoked, and 21.5% smoked daily. In relation to gender, 27.8% of the males and 23.2% of the females were smokers (Table 1). Cigarettes, including rolling tobacco (type of tobacco smoked most frequently), were the most frequently consumed (99.1%). Of the daily smokers, 30.1% had attempted to quit smoking, and of them, 20.2% had attempted to quit once and 7.2% had carried out two attempts (Table 2).

Table 2. Tobacco use in the youth population in Spain (15-24 years) analyzed by years (2011-2014) (n = 3270).

	2011 n (%)	2014 n (%)	p
Do you currently smoke?			
Yes, daily	393 (23.7%)	311 (19.3%)	<0.001
Yes, but not on a daily basis	76 (4.6%)	53 (3.3%)	
Doesn't smoke now, but has smoked before	66 (4%)	106 (6.6%)	
Non-smoker or has never smoked on a regular basis	1.119 (67.6%)	1.144 (70.9%)	
Most frequent type of tobacco smoked			
Cigarettes (including tobacco rolling)	392 (99.7%)	358 (98.4%)	0.059
Cigars	0 (0%)	1 (0.3%)	
Other	0 (0%)	5 (1.4%)	
No reply	1 (0.3%)	0 (0%)	
Daily smokers: attempts to quit smoking in the last 12 months			
0 attempts	266 (67.7%)	205 (65.9%)	0.666
1 attempts	80 (20.4%)	62 (19.9%)	
2 attempts	24 (6.1%)	27 (8.7%)	
3 attempts	7 (1.8%)	6 (1.9%)	
4 attempts	2 (0.5%)	2 (0.6%)	
5 attempts or more	8 (2%)	8 (2.6%)	
Does not know/Does not respond	6 (1.6%)	1 (0.3%)	

Note. N: count; p: significance of chi-square test

Temporal trend of tobacco use between 2011 and 2014

In 2011, 28.2% of the youth smoked, and in 2014, this percentage decreased to 22.6% ($p < .001$) (Figure 1). The same result was observed in daily smokers, who decreased from 23.7% in 2011 to 19.3% in 2014 ($p < .001$). In 2011, 32.3% of the youths had tried to quit smoking: 20.4% made one attempt, and 6.1% tried to quit twice. In 2014, the percentage of attempts to quit increased to 34.1% compared with 2011, with 19.9% making one attempt to quit, and 8.7% two attempts ($p = .666$). These results can be observed in Figure 2.

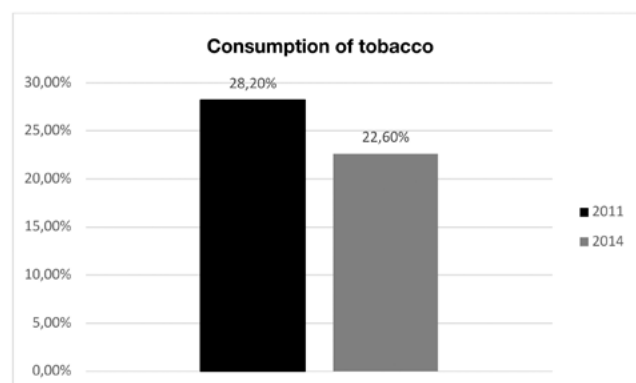


Figure 1. Consumption of tobacco and its evolution over time.

Alcohol consumption

In the past 12 months, 78.6% of the total of the youths of the study drank alcohol, as shown by year of study in Table 3. Regarding gender, 66.49% of the males and 63.1% of the females consumed alcohol. Concerning frequency, 26.9% drank between 1-2 days per week, 22.1% drank once a month, and 18.1% drank between 2 and 3 days a month.

Regarding the beverage, 68.4% of the youths drank beer with alcohol; 15.1% drank wine or sparkling white wine ("cava"); 0.9% consumed Vermouth, "fino" or Sherry; 4.7% drank liqueurs, anise, and "pacharán" (a type of brandy); 66.9% drank cocktails, and 3.4% consumed local drinks, cider, or coffee with brandy.

Table 3. Alcohol consumption of young people in Spain (15-24 years) analyzed by years (2011-2014) (n=3270).

	2011 n (%)	2014 n (%)	P
Frequency of alcohol consumption in the past 12 months			
Daily or almost daily	14 (1.3%)	8 (0.5%)	<0.001
5-6 days per week	37 (3.3%)	6 (0.4%)	
3-4 days per week	0 (0%)	30 (1.9%)	
1-2 days per week	425 (38.1%)	310 (19.2%)	
2-3 days per month	225 (20.2%)	269 (16.7%)	
Once a month	415 (37.2%)	187 (11.6%)	
Less than once a month	0 (0%)	219 (13.6%)	
No, has not drunk alcohol	0 (0%)	80 (5%)	
Never or only a few sips in his/ her lifetime	0 (0%)	505 (31.3%)	
Beer consumption			
Yes	444 (63.3%)	278 (78.5%)	<0.001
No	232 (33.1%)	76 (21.5%)	
Does not know/Does not respond	25 (3.6%)	0 (0%)	
Consumption of wine, cava			
Yes	102 (14.6%)	57 (16.1%)	0.007
No	573 (81.7%)	269 (83.6%)	
Does not know/Does not respond	26 (3.7%)	1 (0.3%)	
Consumption of distilled beverages, cocktails			
Si	488 (69.6%)	218 (61.6%)	<0.001
No	191 (27.2%)	136 (38.4%)	
Does not know/Does not respond	22 (3.1%)	0 (0%)	
Frequency of consumption of 5 or more standard drinks on the same occasion in the past 12 months			
3 to 4 days per week	0 (0%)	1 (0.1%)	<0,001
1 to 2 days per week	70 (44%)	62 (6%)	
2 to 3 days in a month	0 (0%)	64 (6.2%)	
Once a month	0 (0%)	116 (11.3%)	
Less than once a month	0 (0%)	282 (27.4%)	
Not in the last 12 months	0 (0%)	210 (20.4%)	
Never in my lifetime	86 (54.1%)	289 (28.1%)	
Does not know/Does not respond	3 (1.9%)	5 (0.5%)	

Note. N: count; p: significance of chi-square test

Regarding the use of 5 or more standard drinks on the same occasion during the past 12 months (Table 3), 31.6% claimed they had never done this, 17.7% had not done so in the past 12 months, 23.7% had done so less than once a month, 9.8% once a month, 5.4% had done so 2-3 days in one month, and 11.1% had done so 1-2 days per week.

Prevalence of alcohol consumption between 2011 and 2014

To compare the consumption of alcohol by years, we recoded the variables of alcohol consumption as dichotomous (no/yes). With regard to the prevalence of alcohol consumption over time (Figure 2), the percentage decreased from 67.4% to 63.75% from 2011 to 2014 ($p < .001$). The percentage of daily intake also decreased, going from 5 to 6 days per week, between 1-2 days per week, to once a month. The consumption of beer with alcohol increased from 63.3% to 78.5% in 2014 ($p < .001$). The consumption of "cava" or wine also increased. With regard to drinking cocktails, in 2011, the percentage was 69.6% and in 2014, it was 61.6% ($p < .001$). In 2011, the consumption of local drinks, cider, or coffee with brandy was 3%, and in 2014, it was 4.2%. The prevalence of the beverages can be seen in Table 3.

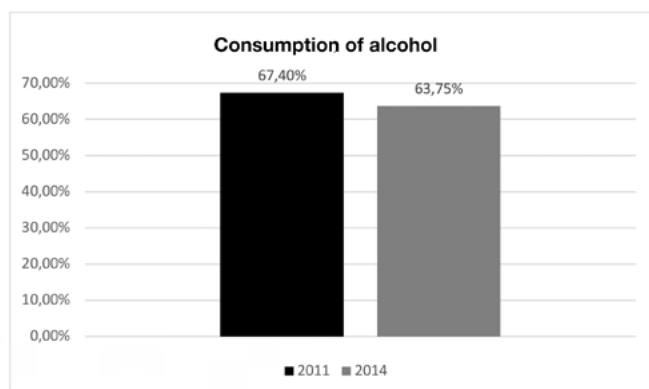


Figure 2. Consumption of alcohol and its evolution over time.

Factors associated with the consumption of tobacco and alcohol

Considering the variables that influence tobacco use, in the logistic regression (Table 4), we observed that males are more likely to consume tobacco than females (OR=1.426, 95% CI [1.125, 1.808]). In relation to marital status, married people are more likely to quit smoking than single people (OR=1.965, 95% CI [1.103, 3.500]). Regarding the level of studies, youths without studies (OR=3.750, 95% CI [1.156, 12.167]), with primary studies (OR=3.488, 95% CI [1.660, 7.331]), secondary school (OR=2.910, 95% CI [1.428, 5.928]), and high school or vocational training (FP) (OR=3.291, 95% CI [1.612, 6.715]) are more likely to quit smoking than university students.

Regarding the variables that influence alcohol consumption in the past 12 months (Table 5), we observed

Table 4. Factors associated with smoking in the youth population in Spain (15-24 years) ($n = 3270$).

	OR (IC del 95%)	P
Sex		
Female	Reference	
Male	1.426 (1.125-1.808)	0.003
Marital status		
Single	Reference	
Married	1.965 (1.103-3.500)	0.022
Widowed, separated or divorced	0.476 (0.058-3.910)	0.490
Educational level		
University studies	Reference	
High school or FP	3.291 (1.612-6.715)	0.001
Secondary	2.910 (1.428-5.928)	0.003
Primary	3.488 (1.660-7.331)	0.001
No studies	3.750 (1.156-12.167)	0.028

Note. 95% CI: 95% confidence interval; p: significance of the model; OR: odds ratio; FP: vocational training.

Table 5. Factors associated with alcohol consumption in the youth population in Spain (15-24 years) ($n = 3270$).

	OR (IC del 95%)	P
Sex		
Female	Reference	
Male	1.377 (1.109-1.710)	0.004
Spanish nationality		
No	Reference	
Yes	1.748 (1.224-2.498)	0.002
Studies		
No studies	Reference	
Primary	2.005 (0.751-5.350)	0.165
Secondary	3.446 (1.316-9.022)	0.012
High school or FP	10.472 (3.961-27.682)	0.000
University studies	14.281 (4.827-42.252)	0.000

Note. 95% CI: 95% confidence interval; p: significance of the model; OR: odds ratio; FP: vocational training.

that males are more likely to consume alcohol than females ([OR=1.377, 95% CI [1.109, 1.710]]), and that young Spaniards are more likely to drink alcohol than youths of other nationalities (OR=1.748, 95% CI [1.224, 2.498]). In relation to the level of studies, youths with studies are more likely to consume alcohol than those who have no studies: university students are more likely to consume alcohol than youths with no studies (OR=14.281, 95% CI [4.827, 42.252]), followed by youths with high school studies or vocational training (FP) (OR=10.472, 95% CI [3.961, 27.682]).

Discussion

In this study, it can be seen that, in recent years, the percentage of occasional smokers and daily smokers has decreased among Spanish youth, as noted in other studies (Hair et al., 2017; Islami, Stoklosa, Drope & Jemal, 2015; Lidon-Moyano et al., 2017; Peiper, Ridenour, Hochwalt & Coyne-Beasley, 2016; National Plan on Drugs, 2016). The proportion of young people who tried to quit smoking also increased. The decrease in the number of smokers may be largely due to Law 42/2010 (Official State Bulletin, 2010) of health measures against smoking and to regulate of the sale, supply, consumption and advertising of tobacco products, which entered into force on January 2, 2011 in Spain, the year that coincides with the first sample collected in the present study. This law extends the ban on smoking in any kind of collective space to areas open to the public that are not in the open air, and to outdoor spaces of schools, health centers, and areas of children's parks and playgrounds. The intention of this law was to combat smoking and to promote citizens' protection, both of smokers and passive smokers, especially the younger ones (Official State Bulletin, 2010; Rana, Pérez-Ríos, Santiago-Pérez & Crujeiras, 2016). As in other countries where tobacco control policies are implemented, the consumption of tobacco has decreased (Callinan, Clarke, Doherty & Kelleher, 2010; Hair et al., 2017; Islami et al., 2015), and, as noted in a study in the United States (Krauss, Cavazos-Rehg, Plunk, Bierut & Grucza, 2014) and also in this study, the anti-smoking laws also seem to affect the consumption of alcohol and also its intensive use, decreasing it. In relation to gender, as the other studies state, males smoke more than females (Higgins et al., 2015; Lakew & Haile, 2015; Martínez, Méndez, Sánchez & Martínez-Sánchez, 2016; Molina et al., 2012; World Health Organization, 2008; Wicki, Kuntsche & Gmel, 2010). However, according to other studies, with the passage of time, the difference in consumption between the two sexes is decreasing (Medina-Mora, 2015; World Health Organization, 2008).

Males, married people, and youth without university studies are more likely to smoke. These results coincide with those obtained in other studies (Lakew & Haile, 2015), with a very similar probability to the present study for married people (OR = 1.71). In relation to the university students, the data obtained in this study indicate that they are less likely to smoke than their counterparts without university studies, in contrast to other studies showing that entering the university increases tobacco consumption (Chen et al., 2004; Intra, 2011; Morrell, Cohen, Bacchi & West, 2005; Pastor et al., 2009). The data of the present study may be due to the rise of the use of electronic cigarettes, as can be seen in several studies of university students (Copeland, Peltier & Waldo, 2017; Rakotozandry et al., 2016) and young people in general (Carroll & Wu, 2014; Peiper et al., 2016), in which it is stated that the use of this device has in-

creased in youth and which praise the use of the electronic cigarette as a measure to quit smoking tobacco, especially in young people. In contrast, other investigations (Brose, Hitchman, Brown, West & McNeill, 2015; Córdoba, 2014; Ofei-Dodoo, Kellerman, Nilsen, Nutting & Lewis, 2017; Shi et al., 2016; Sutfin, McCoy, Morrell, Hoepfner & Wolfson, 2013) do not consider the use of electronic cigarettes as a measure to quit smoking, but to reduce consumption.

As in the case of tobacco use, alcohol consumption has also decreased, as the two consumptions are related according to various studies (Lajtha & Serhsen, 2010; Redner, White, Harder & Higgins, 2014). Over the past few years, the consumption of alcohol in young people has also decreased (National Plan on Drugs, 2016). The most frequently consumed beverage is cocktails, followed by beer. However, the consumption of beer has increased, as is the case in other studies conducted in Spain (Galan, Gonzalez & Valencia-Martín, 2014; Ivano, García-Altes & Nebot, 2011) and other countries (La Vecchia et al., 2014; Mutalip, Kamarudin, Manickam, Abd Hamid & Saari, 2014). This increase may be due to the ease of buying beer individually in small quantities and its low cost (Albarracín & Muñoz, 2008; Wagenaar, Salois & Komro, 2009). On another hand, this increase in beer consumption may cause higher risk consumption, compulsive consumption, and consumption of illegal drugs (Dey, Gmel, Studer, Dermota & Mohler-Khuo, 2014; Naimi, Brewer, Miller, Okoro & Mehrotra, 2007).

The type of majority consumption is 1 or 2 times a week. This coincides with students' consumption pattern, which tends to be Thursday and Saturday, as found in other studies (García-Moreno, Expósito, Sanhueza & Angulo, 2008; Pastor et al., 2009; Rodríguez, Agulló & Agulló, 2003).

With regard to the consumption of large amounts of alcohol on the same occasion in a short period of time, called binge drinking, as in other studies, the proportion is high (Golpe, Isorna, Barreiro, Braña & Rial, 2017; Romo-Avilés, Marcos-Marcos, Marquina-Márquez & Gil-García, 2016; Soler-Vila, Galán, Valencia-Martín, León-Muñoz, Gual-lar-Castillón & Rodríguez-Artalejo, 2014; Valencia-Martín, Galan & Rodriguez, 2007). Half of the young people who consume alcohol have presented this pattern in the last 12 months. This fact may be due to the current consumption pattern, which is characterized by consumption in the form of binge drinking, in groups, and lasting a few hours and performed on the weekends (Calafat, 2007; Cortés, Espejo & Giménez, 2007; Golpe et al., 2017; OEDT, 2016; Parada et al., 2011). Binge drinking occurs more frequently in the last period of adolescence and at the beginning of adulthood (Kuntsche, Rehm & Gmel, 2004; Soler-Vila et al., 2014). This form of consumption is increasing, especially in youth and university students (Parada et al., 2012). This threatens their health, as several studies have shown that this pattern of consumption has more health risks (Guerri & Pascual, 2010; Stephens & Duka, 2008).

In relation to gender, males are more likely to consume alcohol and they drink more alcohol than females, coinciding with several studies (Anderson & Baumberg, 2006; Fuller-Thomson, Sheridan, Sorichetti & Mehta, 2013; Galán et al., 2014; Molina et al., 2012).

In the present study, young Spaniards are more likely to drink alcohol, which coincides with other studies such as that of Galán et al. (2014), in which the probability was even higher (OR: 3.45). With regard to educational level, youth with studies are more likely to consume alcohol, especially university students (Mutalip et al., 2014). This higher probability may be due to the fact that they tend to have no family obligations, they live alone, or with roommates, and they relate to students, which encourages consumption of alcohol in large quantities (Wicki et al., 2010), and the high relationship between binge drinking and the university stage (Parada et al., 2012).

Among the limitations of the present study, whose sources were the ENSE and the EESE, records which are cross-sectional studies, it is not possible to determine causal directions between the consumption of alcohol and tobacco and the related variables. In addition, as we have used these sources, we could not use other variables that would have been interesting, such as consumption in the last month, which would have provided more information about the changes in youths' consumption. Also, as these were surveys, the analyzed data correspond to self-reported information. Another limitation was that the psychometric properties of the questionnaires are not known. However, the study possesses great strength, as the data were obtained from national representative surveys with a high number of participants and represent an interesting and useful vision of the evolution of the consumption of alcohol and tobacco among youth, after the implementation of the anti-tobacco law in Spain. Nevertheless, the data of this study must be considered with precaution, as, due to the study design, the variation in smoking consumption cannot be attributed with certainty to the tobacco law, due to the lack of a comparison group.

In conclusion, the consumption of tobacco and alcohol in young Spaniards has dropped from 2011 to 2014, and the number of young people who are trying to quit smoking has increased. This may be due to the anti-smoking policies of 2011 in Spain (Law 42/2010). Cocktails are the most consumed alcoholic beverages, but their consumption is decreasing, and the consumption of beer is increasing. The majority of young people drink 1 or 2 times a week, and one half of the young people who drink alcohol had consumed large amounts on the same occasion in the past 12 months. This is the so-called binge drinking, which is on the increase, and is characterized by the consumption of large amounts of alcohol in a short period of time, typical of young people and students. The variables that are related to increased consumption of tobacco are:

being male, being married, and not having university studies. On another hand, the variables that are related to the consumption of alcohol are: being male, having Spanish nationality, and having studies. In particular, university students are more likely to consume alcohol.

Conflict of interests

The authors of the present study declare that there is no conflict of interest.

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A comparison between phase-III trials and a phase-IV study of nalmefene in alcohol use disorder patients. Is there a difference?

Una comparación entre los estudios de fase 3 y un estudio de fase 4 de nalmefeno en el trastorno por uso de alcohol. ¿Existen diferencias?

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Abstract

Concerns regarding the external validity of phase-III trials are common to many medical disciplines, with relevant discrepancies found between experimental and clinical samples in some diseases such as hypertension. The aim of this study was to compare the samples included in the pivotal, phase-III clinical trials of nalmefene with that of a recently conducted phase-IV trial. Baseline characteristics of the studies were compared through univariate analysis. Significant differences were found in the percentage of low-risk drinkers included. Differences were also found in the prescription and intake pattern of nalmefene, as well as in the rate of psychiatric and addictive comorbidities, which were much higher in the phase-IV study. These data suggest that in the field of alcohol use disorders there are also relevant differences between experimental and clinical samples, a fact that reinforces the need for phase-III trials to be balanced with observational, phase-IV trials.

Keywords: Phase-III trial; Phase-IV trial; External validity; Nalmefene; Alcohol use disorders.

Resumen

En muchas disciplinas médicas existen diferencias significativas entre las muestras procedentes de estudios experimentales y las muestras procedentes de ámbitos clínicos, como es por ejemplo el caso de la hipertensión. El objetivo del presente estudio fue comparar las muestras procedentes de los ensayos pivotaes de fase 3 de nalmefeno con la muestra de un estudio de fase 4 realizado recientemente. Las características basales de las muestras se compararon mediante técnicas univariantes. Se encontraron diferencias significativas entre el porcentaje de los participantes consumidores de alcohol de bajo riesgo. También se encontraron diferencias en los patrones de prescripción y en la toma de nalmefeno, así como en el porcentaje de comorbilidades psiquiátricas y adictivas, que fueron muy superiores en el estudio de fase 4. En su conjunto, estos datos sugieren que en el campo del trastorno por uso de alcohol (TUA) existen también diferencias relevantes entre muestras procedentes de estudios experimentales y muestras procedentes de estudios clínico-observacionales. Este hecho refuerza la necesidad de que los estudios de fase 3 sean complementados con estudios observacionales de fase 4.

Palabras clave: Fase 3; Fase 4; Validez externa; Nalmefeno; Trastorno por uso de alcohol.

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Alcohol imposes a heavy burden on societies around the world, most of which is inflicted by those who drink heavily, that is, those affected by an alcohol use disorder (Whiteford et al., 2013). The treatment of AUDs is therefore of high importance. A combination of psychosocial and pharmacological strategies is usually recommended. Regarding pharmacological treatment, last decades have witnessed the appearance of different compounds with proven efficacy on several outcomes. Such is the case of nalmefene, an opioid antagonist recently approved for the treatment of alcohol patients who aim for a reduction objective. The approval was based on three pivotal phase-III trials (Gual et al., 2013; Mann, Bladström, Torup, Gual & van den Brink, 2013; van den Brink et al., 2013).

Phase-III trials are a basic and very important step in the process leading to drug approval by regulatory agencies. They are usually largely sized, randomized trials with a homogenous study sample. All these characteristics lead to high statistical power and high internal validity.

While experimental designs such as those of phase-III studies are essential for internal validity assessment and are the cornerstone of drug efficacy assessment, it has been extensively noted in many areas that, usually, external validity remains disproportionately neglected (Dekkers, von Elm, Algra, Romijn & Vandenbroucke, 2010; Pearson & Coomber, 2010; Rothwell, 2005). This fact might yield relevant consequences, such as the fact that patients from experimental settings might differ significantly from patients in real world settings (Hoertel et al., 2014; Uijen, Bakx, Mokkink & van Weel, 2007), ultimately jeopardizing the feasibility, applicability and even the relevance of experimental findings (Persaud & Mamdani, 2006).

In this context, previous studies in several diseases such as hypertension, social anxiety rheumatoid arthritis and others (Farahani, Levine, Gaebel & Thabane, 2005), have found that phase-III and phase-IV patients are not always similar, a fact that could have relevant implications. Therefore, we believe it is also necessary to evaluate, in the field of alcohol use disorders, whether patients in “real-life” are comparable to patients of previous experimental studies, and what differences might exist. This is in fact, one of the reasons leading to the need of phase-IV studies (Linden, 1984).

In the present paper we aim at comparing the baseline characteristics of patients recently enrolled in a phase-IV trial of nalmefene with those of patients who participated in the phase-III trials.

Method

The present study compared patients from two different types of studies. The first group of patients belongs to an observational, multisite, single arm, phase 4 study

conducted among alcohol dependent outpatients taking nalmefene for the first time as a treatment for alcohol use disorder. To be enrolled in this phase-IV trial, patients had to be adults (≥ 18 years) diagnosed with alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) or the International Classification of Diseases (ICD-10) criteria who according to routine clinical criteria, had been started on nalmefene for the first time. The study consisted of 4 visits: baseline, 1 month, 6 months and 12 months. Patients continued to receive their usual treatment independent of study visits and procedures.

The second group consisted of patients who participated in the three phase-III trials of nalmefene. Data from these patients was gathered from existing publications in the literature. Phase-III trials were kept independent of each other for study comparisons. Therefore, a total of 4 groups were formed. Each phase-III trial was compared to the phase-IV study. All available variables for the 4 studies at baseline were included. Statistical comparisons were conducted with univariate tests (T-test or chi-square depending on variable type).

Results

A total of 110 patients were included from 4 sites in the Spanish region of Catalonia, between 2015 and 2016. A full description of the phase-IV study results is available elsewhere (Barrio, Ortega, Guardia, Roncero, Yuguero & Gual, 2018). Table 1 illustrates the differences between this study and the phase III trials of nalmefene regarding the main study variables at baseline.

Important differences were found regarding the percentage of low drinking risk level, with the present study showing a much higher rate (45%) as compared to the ESENSE trials (1-5%). Consequently, in the high/very high categories, numbers were reversed, with 38% of patients in this study allocated to this category, as compared to 76-78% in the phase III trials. Another illustration of these relevant differences is the fact that in this study, mean alcohol consumption (60.4 g/day) was significantly lower (85-92 g/day in ESENSE trials).

Also relevant, we found a significantly lower prevalence of family history of alcohol problems in our sample. Finally, when comparing the percentage of days with study medication intake, a higher proportion in the phase-IV trial was observed. Also relevant is the fact that the number of patients taking nalmefene on a daily basis was higher. Given the inclusion criteria of phase-III trials, addictive comorbidities were only present in the phase-IV study. Similarly, only the SENSE trial allowed psychiatric comorbidities among patients, which were nonetheless much less frequent than in the phase-IV trial.

Discussion

This study found significant differences between phase-IV and phase-III patients taking nalmefene. When compared to phase-III trials, patients in real settings showed a higher rate of both addictive and psychiatric comorbidities, a fact that is in sharp contrast with the samples of randomized, controlled studies, which are usually more restrictive in their inclusion criteria. In fact, the high rate of psychiatric comorbidities in alcohol patients is a well documented phenomenon (Fein, 2015; Flensburg-Madsen et al., 2009). This finding supports the criticisms targeted at the external validity of experimental studies (Persaud & Mamdani, 2006) and at the same time suggests that, studies like the SENSE trial (van den Brink et al., 2014), where patients with psychiatric comorbidities were included, should be the norm rather than the exception.

It should also be noted that a great number of patients in the phase-IV trial were already labeled as low-risk drinkers at baseline. In fact, almost half of the patients were considered low-risk drinkers at study entry, a fact that at first sight could seem contradictory to nalmefene therapeutic indications. It should be noted, however, that risk assessment for phase-IV study purposes was based on the previous 28 days. It is probable that clinicians, when decid-

ing the risk category of patients, take into account a longer timeframe. Also, similar to what has been observed in phase-III trials, it is possible that the mere fact of patients deciding to enter into treatment leads to significant reductions in drinking. Interestingly, the percentage of low risk drinkers in the phase-IV trial is very similar to that of phase-III trials if we add up the baseline low risk drinkers and the low risk drinkers prior to nalmefene initiation.

Age at onset of drinking problems was another variable showing clear differences. While real differences could be expected between real practice and experimental studies, it could also be due to different methods of recollection. While a younger age of onset of drinking problems could suggest a greater disease severity, baseline alcohol parameters were, conversely, milder in the phase-IV study sample, with lesser heavy drinking days and lesser mean alcohol consumption. It also looks like patients in the phase-IV trial had a superior rate of medication intake. In fact, results of the phase-IV (Barrio et al., 2018) suggest that, despite being labeled as an “as-needed” medication, patients and clinicians in real world practice will frequently use it on a scheduled, daily basis.

Several limitations apply to this study. The most relevant is the different design of phase-IV and phase-III trials, a fact

Table 1. Main sociodemographic characteristics of included patients and comparison with phase III trials

Characteristic	Phase IV (n=110)	ESENSE 1 (n=306)	ESENSE 2 (n= 358)	SENSE (n=509)
Age: mean (SD)	44.4 (9.4)	51.0 (10.1)*	45.1 (10.7]	44.3 (11.2]
Sex male (%)	66.4%	66.6%	74.3%	77.2%*
Higher education (%)	27.3%			32.4%
Age at the Onset of Drinking Problems: mean (SD)	23 (12.4)	37.9 (13.1)*	32.6 (10.8)*	33.4 (11.6)*
Drinking Risk Level				
Low (%)	45.5%	3%*	1.4%*	15.5%*
Medium (%)	16.4%	22.2%	19.0%	32.8%*
High (%)	21.8%	37.3%*	36.0%*	29.1%
Very High (%)	16.3%	39.9%*	43.6%*	22.4%
g-Glutamyltransferase (IU/L) : mean (SD)	84 (128.2)	51.7	51.8	40.9
Alanine Aminotransferase (IU/L) : mean (SD)	29.2 (15.5)	29.2	28.7	28.5
Previously Treated for Alcohol Dependence (%)	46.4%	29.7%*	39.7%	33.6%*
Previously Treated for Alcohol Withdrawal (%)	30%	19.6%*	15.9%*	26.9%
Personal history of psychiatric problems (%)	36.4%			3.7%*
Family History of Alcohol Problems (%)	48.2%	62.4%*	60.1%*	51.7%
Addictive comorbidities*** (past or present) (%)	65.5%			
Percentage of days taking study medication (%)	64%	48%*	57%	48.4%*
Monthly heavy drinking days (baseline) : mean (SD)	13.5 (11)	19.5 (7.3)*	19.7 (7.0)*	14.1 (6.2)
Mean alcohol consumption (grams per day; baseline) : mean (SD)	60.4 (74.6)	84.8 (42.1)*	92.2 (46.9)*	68.6 (40.0)

Note. *=significant at $p < 0.05$ when compared to phase IV study values with univariate tests (t-student or chi-square).

** defined as the presence of diabetes, hypertension, high blood cholesterol or any other significant medical condition.

*** defined as any substance use disorder (except nicotine dependence), past or current, as clinically evaluated in the first visit of the study.

that implies caution when interpreting the comparisons undertaken in this study. Also, it is important to mention that the phase-IV trial included patients from 4 different sites, all belonging to the same city. In this sense, phase-III trials had a much wider representation, with patients from different countries being included.

Conclusion

All in all we believe this study suggests that, as previously shown in other diseases, samples from experimental studies might differ in some aspects from patients in routine clinical practice. While efforts targeted at increasing phase-III trials' external validity should be encouraged, this study also confirms that phase-IV studies are indeed a crucial part of the research process.

Contributions

Pablo Barrio and Antoni Gual designed the study. Pablo Barrio 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

Dr. Barrio, Dr. Roncero, Dr. Guardia and Dr. Gual have received honoraria from Lundbeck. Dr. Barrio has also received honoraria from Pfizer. Dr. Roncero has also received honoraria from Janssen-Cilag, Otsuka, Server, GSK, Rovi, Astra, MSD and Sanofi. Dr. Yuguero and Dr. Ortega have no conflict of interest to declare

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Trends in tobacco use among adolescents in Spain (2002-2018)

Tendencias en el consumo de tabaco adolescente en España (2002-2018)

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Abstract

Smoking is the single greatest preventable cause of death in the world today. Adolescence is the developmental period during which smoking is most commonly initiated and addiction is likely to happen. The aim of this study is to examine trends in tobacco use among school-aged adolescents in Spain from 2002 to 2018 by sex and age. The sample is composed of 51,046 adolescents aged 15 to 18. Data is representative of the adolescent school population in Spain in 2002, 2006, 2010, 2014 and 2018. The smoking questionnaire provided by the international team of the study Health Behavior in School-aged Children (HBSC) was used. Odds Ratios and 95% confidence intervals were estimated using logistic regression. Data show a decrease in daily tobacco use between 2002 (26.5%) and 2018 (8.7%), but no change was found between 2006 (17.9%) and 2010 (17.4%). This decreasing pattern is stronger in girls than boys to the extent that no differences by sex were found in 2018. Similarly, the decrease was greater in older adolescents, but in this case, the differences by age remained. Daily smoking prevalence among Spanish adolescents aged 15 to 18 in 2018 is 8.7%. Results confirm the need to maintain tobacco prevention and control policies. Measures are presented in order to fight this public health problem.

Key Words: Tobacco; Adolescence; Trends; Monitoring; Epidemiology.

Resumen

El tabaco es la principal causa de muerte prevenible en todo el mundo. La adolescencia es una etapa clave en la iniciación al hábito tabáquico y en la proclividad a desarrollar adicción a esta sustancia. El objetivo de este trabajo es analizar cómo ha evolucionado el consumo de tabaco de los chicos y chicas adolescentes escolarizados en España desde 2002 a 2018 y si hay diferencias en las tendencias por sexo y por edad. La muestra está conformada por 51.046 participantes de 15 a 18 años, representativos de la población adolescente escolarizada en España en los años 2002, 2006, 2010, 2014 y 2018. Se utilizó el cuestionario de consumo de tabaco consensuado por el equipo internacional del estudio Health Behaviour in School-aged Children (HBSC). Se estimaron las Odds Ratio y los intervalos de confianza del 95% mediante regresiones logísticas. Los resultados muestran una disminución en el consumo diario de tabaco adolescente entre 2002 (26,5%) y 2018 (8,7%) aunque con un periodo de estabilidad entre 2006 (17,9%) y 2010 (17,4%). Esta tendencia de descenso es mayor en las chicas (21,9 puntos) que en los chicos (13,1 puntos) hasta el punto de que en 2018 no hay diferencias en función del sexo. También es mayor en el grupo de 17-18 años (20,2 puntos) que en el de 15-16 años (15,8 puntos), aunque en este caso, permanecen las diferencias en función de la edad. La prevalencia de consumo de tabaco diario en adolescentes de 15 a 18 años es del 8,7% en 2018. Se concluye la conveniencia de no suprimir ni disminuir las políticas de prevención y control del tabaquismo y se proponen nuevas medidas para hacer frente al problema de salud pública que está suponiendo el consumo de tabaco en España.

Palabras clave: Tabaco; Adolescencia; Análisis de tendencias; Monitorización; Epidemiología.

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Each year, tobacco kills around 7 million people worldwide (World Health Organization, 2017), and it is estimated that this mortality rate will rise to 8.3 million by 2030, accounting for 10% of all deaths (Mathers & Loncar, 2006). In Spain, more than a quarter of a million deaths were attributable to smoking between 2010 and 2014, at an estimated average rate of almost 52,000 per year. This figure represents 13% of all deaths of people over 35 in Spain (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2016).

Adolescence is a crucial period for experimentation with drugs and the onset of addictive disorders. Brain development during this time includes changes in functionality and organization which result in greater activity in the areas related to the search for new experiences while the inhibitory control system is still growing. This predisposes boys and girls at these ages to carry out a greater number of impulsive actions and risky behaviors including the use of drugs (Chambers, Taylor & Potenza, 2003).

With respect to smoking, both national (ESTUDES, EDADES) and international (ESPAD, Eurobarometer) surveys place the age of onset in adolescence and early youth (European Commission, 2017; European Monitoring Centre for Drugs and Drug Addiction, 2016; Moreno et al., 2016; Plan Nacional sobre Drogas, 2018a; Plan Nacional sobre Drogas, 2018b). Adolescent girls and boys who start smoking believe that they will be able to stop soon and easily, but the addictive nature of nicotine causes most of them to develop a dependence on this substance and to continue smoking for many years (Gruber, 2001). In addition to the problems of tobacco addiction, smoking in adolescence has immediate consequences on physical health (US Department of Health and Human Services, 2012), is linked with depressive symptoms (Espada, Sussman, Huedo & Alfonso, 2011), suicidal ideation (Bousoño et al., 2017) and with other addictive behaviors such as intensive alcohol consumption (Golpe, Isorna, Barreiro, Braña & Rial, 2017), cannabis use or gambling (Míguez & Becoña, 2015). Faced with this reality, international institutions and national governments have taken measures to fight this problem (European Parliament and Council, 2014; WHO, 2003). The most important of these in Spain was the approval in 2005 of the law on measures against smoking (Law 28, 2005) and its subsequent amendment in 2010 (Law 42, 2010), as well as the implementation of research projects and prevention campaigns (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2017, Plan Nacional sobre Drogas, 2017).

Measures aimed at controlling tobacco use seem to have had an effect on the prevalence of smoking in the global adolescent population (European Monitoring Centre for Drugs and Drug Addiction, 2016; Hublet et al., 2015; Organisation for Economic Cooperation and Development, 2017;) and in Spain (Plan Nacional sobre Drogas, 2018b;

Villalbi et al., 2012), leading to a general decline in use, in line with a similar trend among the general population (European Commission, 2017; Instituto Nacional de Estadística, 2013; Instituto Nacional de Estadística, 2017; Plan Nacional sobre Drogas, 2018a). Nevertheless, this decrease is not continuous; a more in-depth analysis of the data of recent years reveals instability and variation.

Analyzing the ESTUDES survey between the years 2002 and 2016 (Plan Nacional sobre Drogas, 2018b) shows certain fluctuations in all types of smoking (daily, last 30 days, last 12 months and lifetime). For example, in the data for daily use we found periods of slight increases (2002-2004 and 2010-2012), stability (2006-2008 and 2014-2016) and decrease (2004-2006, 2008-2010 and 2012-2014), with 8.8% smoking daily in 2016. Differences between the sexes have almost disappeared (8.6% in boys and 9.0% in girls) compared to 2002, when the difference was 6.5 points (17.7% in boys and 24.2% in girls). Other studies confirm these irregularities in Spanish adolescent smoking trends for the same period (Villalbi et al., 2012).

At the international level, the ESPAD survey (European Monitoring Center for Drugs and Drug Addiction, 2016) also finds this generalized downward trend in all European countries between 2002 and 2010. The percentage of adolescents who smoke daily in 2015 was 10%, with the highest values (20% or more) found in Bulgaria, Croatia, Italy and Romania, while the lowest values (5% or less) were observed in Albania, Iceland, Moldova and Norway. The differences between boys and girls have been decreasing over time to the point in 2015 where they no longer exist or are minimal. Similarly, the international study HBSC (Hublet et al., 2015) indicates a global decrease in smoking between 2002 and 2010, although different trends depending on the region were found. Thus, while a decrease was observed in Southern European and Anglo-Saxon countries, smoking in Northern and Central European countries remained stable, and Eastern European countries and North America saw an increase in adolescent smoking. These fluctuations have also been reflected in the latest Eurobarometer, where an increase in consumption has been detected in the youngest group (15-24 years), rising from 24% in 2014 to 29% in 2017 (European Commission, 2017).

Given these examples of instability observed in reports on smoking, it is essential to perform more comprehensive analyses to determine how adolescent smoking has actually evolved in Spain so far this century and whether this trend is developing simultaneously across both sexes and the different stages of adolescence, or whether, conversely, there are groups with different patterns of use. Only in this way can political decisions be taken which are adjusted to the reality of the data. The objective of this paper is thus to examine the trends in tobacco use in a sample of adolescents representative of the school population in Spain from 2002 to 2018, analyzing them by sex and age.

Methods

Study design and sample

Our research draws on the data of the Health Behavior in School-aged Children (HBSC) study, the aim of which is to obtain a global vision of the lifestyles of the adolescent school population, thereby facilitating evidence-based health promotion.

The sample was selected following multistage random cluster sampling stratified by age, geographical area, habitat and school type. The sample units were classrooms, chosen at random from the census provided by the Ministry of Education. The item response rates for each of the versions accessed by this study were 98.52% in 2002, 98.50% in 2006, 96.57% in 2010, 97.6% in 2014 and 95.73% in 2018.

In all the analyses we used sampling weights by age, geographical area and school ownership to adjust for imbalances in the sample, thereby adjusting the data to the population parameters. Given the low level of tobacco use shown by girls and boys under 15 years of age, the analysis of this study focuses on adolescents aged 15 to 18. The total sample amounted to 51,046 adolescents, with an estimated sampling error of approximately 1.1% in each version. The data are representative of schoolchildren in Spain aged between 15 and 18. For more technical information, see the reports of the HBSC study for the different versions of the study (Moreno, Muñoz, Pérez & Sánchez-Queija, 2005; Moreno et al., 2008; Moreno et al., 2012; Moreno et al., 2016; Moreno et al., in press).

Procedure and instrument

Data collection was via questionnaires completed by the pupils during school hours and with total guarantees of anonymity, in accordance with international study protocol guidelines (Roberts et al., 2009). From this questionnaire, approved by the Coordinating Ethics Committee of Biomedical Research of Andalusia, the variables sex (boy / girl), age (15-16 years / 17-18 years), version (2002 / 2006 / 2010 / 2014 / 2018) and smoking frequency were selected. The latter was assessed with the question: How often do you currently smoke tobacco? The response categories were: every day / at least once a week, but not every day / less than once a week / I do not smoke.

Statistical analysis

Results are shown disaggregated by sex and age. For age, they are divided into two groups: 15-16 year olds, who are still in compulsory education, and 17-18 year olds, continuing their education voluntarily. The data were analyzed with logistic regression, a method also used in other studies of national and international trends (Hublet, et al., 2006; Looze, et al., 2013; Sánchez-Queija, García-Moya & Moreno, 2017; Sánchez-Queija, Moreno, Rivera & Ramos, 2015; Schnohr et al., 2015; Zaborskis, Sumskas, Maser & Pudule, 2006). Odds Ratios (OR) and 95% confidence intervals (95% CI) were calculated. First, logistic regression equations were performed to show the differences by sex and age group in each of the versions covered (2002, 2006, 2010, 2014 and 2018). Second, trend analyses were carried out to show global tendencies across the entire period, that is, between 2002 and 2018, as well as at four-year intervals to learn more about the general trend. For this purpose, 2002 will be the reference year for changes between 2002 and 2006, 2006 will be the reference for changes up to 2010, 2010 for changes to 2014, and finally, 2014 is the reference for changes up to 2018. Both trend analyses took sex and age variables into account in order to illustrate whether the development of adolescent smoking patterns is similar or different for boys and girls, and for the 15-16 and 17-18 age groups. SPSS v.21 was used for the statistical analyses.

Results

Table 1 shows the sample data of this study.

Table 2 shows the different types of smoking prevalences by sex and age, except those for daily use, which are presented in more detail in Table 3 and Figure 1. The data reflect a decrease in general terms in schoolchildren smoking weekly and also less than once a week, as well as an increase between 2002 and 2018 in teenagers who do not smoke at all. However, there are some moments when smoking peaked, especially in the 2006 and 2010 versions of the study.

To analyze daily tobacco use in depth, this variable was dichotomized into daily smoking (codified 1) versus other frequencies and non-smoking (coded 0). Table 3 shows the results of the logistic regression between the daily smoking

Table 1. Description of the sample of the five study versions by age and sex.

		2002 n	2006 n	2010 n	2014 n	2018 n	Total n
15-16 years	Boys	1374	2032	1237	2949	3655	11247
	Girls	1531	2231	1350	3082	3619	11813
17-18 years	Boys	1454	2356	1007	3909	4824	13550
	Girls	1643	3115	975	3800	4903	14436
Total		6002	9734	4569	13740	17001	51046

Table 2. Tobacco use prevalence: weekly, less than once a week, and no-smoking in the adolescent school population in Spain in 2002, 2006, 2010, 2014 and 2018.

Smoking frequency	Age (years)	Sex	2002		2006		2010		2014		2018	
			%	CI	%	CI	%	CI	%	CI	%	CI
Weekly	15-16	Boys	7.1	6.4-7.7	4.6	4.1-5.0	3.7	3.1-4.2	4.1	3.7-4.4	3.9	3.6-4.1
		Girls	8.3	7.6-8.9	7.3	6.7-7.8	6.1	5.4-6.7	5.6	5.2-5.9	5.0	4.6-5.3
	17-18	Boys	7.3	6.6-7.9	5.1	4.6-5.5	7.6	6.8-8.3	6.2	5.7-6.6	6.1	5.7-6.4
		Girls	6.9	6.2-7.5	7.1	6.5-7.6	7.7	6.9-8.4	6.5	6.0-6.9	7.2	6.8-7.5
Less than once a week	15-16	Boys	7.7	7.0-8.3	5.1	4.6-5.5	4.9	4.2-5.5	3.8	3.4-4.1	5.2	4.8-5.5
		Girls	5.6	5.0-6.1	7.6	7.0-8.1	6.7	5.9-7.4	4.8	4.4-5.1	6.8	6.4-7.1
	17-18	Boys	6.2	5.5-6.8	5.5	5.0-5.9	5.6	4.9-6.2	6.7	6.2-7.1	5.2	4.8-5.5
		Girls	6.0	5.3-6.6	6.2	5.7-6.6	6.6	5.8-7.3	5.5	5.1-5.8	6.8	6.4-7.1
No smoking	15-16	Boys	66.8	65.6-67.9	79.6	78.7-80.4	79.7	78.5-80.8	85.9	85.3-86.4	85.6	85.0-86.1
		Girls	62.1	60.8-63.3	69.8	68.8-70.7	70.0	68.6-71.3	82.8	82.1-83.4	82.4	81.8-82.9
	17-18	Boys	61.3	60.0-62.5	71.5	70.6-72.3	66.2	64.8-67.5	75.1	74.3-75.8	77.2	76.5-77.8
		Girls	50.5	49.2-51.7	62.5	61.5-63.4	64.3	62.9-65.6	73.5	72.7-74.2	75.2	74.5-75.8

variable and the variables sex, age and sex-age combined in each of the versions analyzed in this study. The percentage of adolescents who smoke daily is shown to have fallen from 26.5% in 2002 to 8.7% in 2018. As to sex, girls in both age groups smoked daily to a greater extent than boys in 2002 and 2006. However, in 2010 and 2014 these differences decreased, remaining significant only in one of the two

age groups (15-16 year olds in 2010 and 17-18 year olds in 2014), while in 2018 no significant differences were found in any of the age groups. Regarding age, the 17-18 group presents greater tobacco use than the 15-16 year olds in all versions of the study and in both sexes. Figure 1 shows how smoking has evolved in each specific group across the 16 years.

Table 3. Percentage of daily smoking, OR and 95% CI in the adolescent school population in Spain in 2002, 2006, 2010, 2014 and 2018.

	2002	2006	2010	2014	2018
% total	26.5	17.9	17.4	10.3	8.7
Sex					
Boys (%)	21.9	14.6	15.7	9.5	8.8
Girls (%)	30.5	20.6	19.0	11.1	8.6
OR (95% CI)	1.560 (1.387-1.754)***	1.511 (1.357-1.683)***	1.260 (1.080-1.469)**	1.190 (1.064-1.331)**	0.973 (0.873-1.085)
Age					
15-16 (%)	21.3	13.2	14.6	6.5	5.5
17-18 (%)	31.3	21.5	21.1	13.3	11.1
OR (95% CI)	1.679 (1.493-1.888)***	1.805 (1.615-2.016)***	1.566 (1.343-1.827)***	2.187 (1.934-2.473)***	2.155 (1.908-2.433)***
By groups					
Boys 15-16 (%)	18.4	10.8	11.7	6.2	5.3
Girls 15-16 (%)	23.9	15.4	17.2	6.8	5.7
OR (95% CI)	1.390 (1.160-1.666)***	1.505 (1.254-1.807)***	1.579 (1.262-1.976)***	1.107 (0.900-1.362)	1.089 (0.886-1.338)
Boys 17-18 (%)	25.2	17.9	20.7	12.0	11.5
Girls 17-18 (%)	36.6	24.2	21.5	14.6	10.8
OR (95% CI)	1.711 (1.464-1.999)***	1.464 (1.280-1.675)***	1.047 (0.843-1.299)	1.256 (1.009-1.435)**	0.927 (0.815-1.055)

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

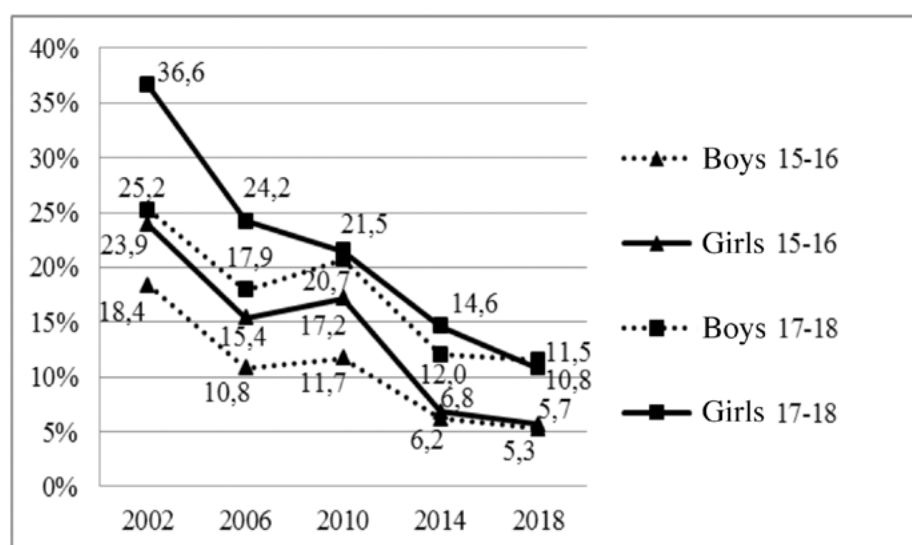


Figure 1. Daily smoking by sex and age

Table 4 shows the trend analysis for both the full period comparison (2002 vs 2018), as well as the four-year comparisons (2002 vs 2006, 2006 vs 2010, 2010 vs 2014 and 2014 vs 2018). In global terms, the decrease in adolescents smoking daily is confirmed, falling from 26.5% at the beginning of the period studied to 8.7% at the end (OR = 0.22; 95% CI = 0.20-0.25). On analyzing the change in each specific group, a strong decrease is detected in both groups of girls, especially the older ones (25.1 points) (OR = 0.21; 95% CI = 0.18-0.24). However, a comparison of each version to the previous yields a period of stability between 2006 and 2010 for both sexes and all ages.

To analyze whether there are statistically significant differences in daily smoking trends among boys and girls,

the interaction between sex and study version was analyzed (Table 4). The data show that there is a statistically significant interaction between version and sex in the entire period from 2002 to 2018 (OR = 1.61; 95% CI = 1.37-1.90), with the decrease among girls (21.9 points) being more pronounced than in boys (13.1 points). Similarly, the interaction between age and study version was analyzed to investigate whether the drop in smoking over the years was greater in one age group than the other. The results show that smoking fell more sharply among 17-18 year group (20.2 points) than the group of 15-16 year olds (15.8 points) (OR = 0.78; 95% CI = 0.66-0.93).

Table 4. Daily smoking among the adolescent school population in Spain: OR (95% CI) of the study version, sex, age, sex-version and age-version interactions, as well as of each specific group for the comparison of the entire period (2002 vs 2018) and the comparisons between versions (2002 vs 2006, 2006 vs 2010, 2010 vs 2014 and 2014 vs 2018).

OR (CI 95%)					
	2002 vs 2018	2002 vs 2006	2006 vs 2010	2010 vs 2014	2014 vs 2018
Version	0.222 (0.196-0.252)***	0.578 (0.512-0.651)***	0.937 (0.806-1.091)	0.557 (0.477-0.651)***	0.736 (0.653-0.830)***
Sex	1.567 (1.393-1.764)***	1.567 (1.393-1.764)***	1.479 (1.327-1.648)***	1.279 (1.095-1.492)**	1.210 (1.082-1.354)**
Age	1.686 (1.499-1.897)***	1.686 (1.499-1.897)***	1.777 (1.591-1.986)***	1.579 (1.354-1.842)***	2.197 (1.942-2.484)***
Sex-version	1.615 (1.375-1.897)**	1.060 (0.903-1.244)	1.156 (0.957-1.397)	1.056 (0.873-1.279)	1.248 (1.067-1.459)**
Age-version	0.782 (0.661-0.927)**	0.949 (0.807-1.116)	1.126 (0.931-1.361)	0.719 (0.590-0.875)**	1.019 (0.857-1.212)
Boys 15-16	0.247 (0.202-0.302)***	0.536 (0.440-0.652)***	1.090 (0.872-1.364)	0.503 (0.399-0.633)***	0.841 (0.680-1.040)
Girls 15-16	0.193 (0.161-0.233)***	0.580 (0.492-0.684)***	1.144 (0.953-1.374)	0.352 (0.289-0.430)***	0.827 (0.677-1.012)
Boys 17-18	0.386 (0.333-0.448)***	0.648 (0.522-0.760)***	1.194 (0.992-1.438)	0.521 (0.435-0.625)***	0.958 (0.839-1.094)
Girls 17-18	0.209 (0.183-0.240)***	0.555 (0.487-0.632)***	0.854 (0.717-1.016)	0.625 (0.523-0.747)***	0.707 (0.621-0.805)***

Note. The reference categories for the study version variable are: 2002 for the 2002 vs 2018 comparison; 2002 for the 2002 vs 2006 comparison; 2006 for the 2006 vs 2010 comparison; 2010 for the 2010 vs 2014 comparison; 2014 for the 2014 vs 2018 comparison. For the sex variable, the reference category is 'boy' and for the age variable '15-16 years'.

*p < .05; **p < .01; ***p < .001

Discussion

This study focuses on the analysis of adolescent smoking trends to date in this century. The results indicate a decrease in absolute terms between 2002 and 2018 in both sexes and in all ages, which coincides with other national (Plan Nacional sobre Drogas, 2018b; Villalbi et al., 2012) and international studies (European Monitoring Centre for Drugs and Drug Addiction, 2016; Hublet et al., 2015; Organization for Economic Cooperation and Development, 2017). However, the data indicate that this trend is not continuous, but alternates with a period in which smoking remained stable (2006-2010). In fact, in three of the four groups analyzed, the percentage of adolescents who smoke daily increased between 2006 and 2010, although such differences do not reach the level of statistical significance. This instability in smoking trends reflects that detected by the ESTUDES survey (Plan Nacional sobre Drogas, 2018b) and by Villalbi et al. (2012).

In terms of smoking patterns by sex and age, the results of this study show that the downward trend in girls is greater than in boys, leading to the disappearance of gender differences in 2018. There has thus been a reversal of the previously observed upward trend in which girls, especially the older ones, smoked much more than boys (Mendoza, López & Sagrera, 2007). Similarly, the fall in daily tobacco use is more pronounced among the older pupils compared to the younger age group, although in this case, the differences remain stable. These data confirm and complement the trends observed in other national and international studies on adolescent smoking (Díaz Geada, Busto Miramontes & Caamaño Isorna, 2018; European Monitoring Centre for Drugs and Drug Addiction, 2016; Hublet et al., 2015; Plan Nacional sobre Drogas, 2018b).

Although daily smoking has decreased significantly in Spain, with values in 2015 (the last year for which we have international comparisons) similar to the European average, it should also be noted that the prevalence of boys and girls smoking every day (8.7%) is still higher than desirable and higher than in other countries (European Monitoring Centre for Drugs and Drug Addiction, 2016). Thus, the data show that in 2018 5.5% of 15-16 year olds smoke daily, rising to 11.1% for 17-18 year olds. In the latter case, it should be noted that these are only adolescents who still remain in the educational system, so this percentage could be even higher when taking into account the population no longer at school at this age.

Since adolescence is a key stage for initiation and maintenance of the smoking habit (Chambers et al., 2003; European Commission, 2017; European Monitoring Centre for Drugs and Drug Addiction, 2016; Gruber, 2001; Moreno et al., 2016; Plan Nacional sobre Drogas, 2018a; Plan Nacional sobre Drogas, 2018b), it is essential and of the utmost priority to develop smoking prevention and control policies that focus on these ages - even more so when

taking into account the latest data from the Survey on Alcohol and Drugs in Spain (EDADES, Encuesta sobre Alcohol y otras Drogas en España) recently presented in Spain, which reports that the percentage of daily tobacco use in the population aged 15-64 years increased between 2015 and 2017 (Plan Nacional sobre Drogas, 2018a). Preventing those who have not yet started smoking from doing so, and getting those who smoke in adolescence to stop would prevent more than 90% of lung cancer mortality attributable to smoking and reduce public spending on tobacco-related diseases, which ranges from 6% to 15% in developing countries (Jha, 2011). However, at the national level, efforts to fight this public health problem do not currently appear to be sufficiently effective: the anti-tobacco law failed to have the expected impact (Grupo de trabajo sobre tabaquismo de la Sociedad Española de Epidemiología, 2017), tobacco research projects funded by the National Plan on Drugs (Plan Nacional sobre Drogas, 2017) have ceased, tobacco-specific national prevention campaigns have been suppressed (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2017; Plan Nacional sobre Drogas, 2017), the Tobacco Observatory was phased out (Law No. 15, 2014) and the transposition of the new European Directive was not completed in the way proposed by the expert groups working on the subject (Comité Nacional de Prevención del Tabaquismo, 2017).

The problem of adolescent smoking continues to be a current one, but awareness of the issue and actions to tackle it have diminished over time. We are at a key moment in Spain, since Law 28/2005 has recently been modified to complete the transposition of European Directive 2014/40/EU, yet the modifications made have been minimal and focused entirely on equating certain restrictions on tobacco products to electronic cigarettes and refill containers. A great opportunity has been missed to resume the fight against an epidemic that causes thousands of deaths per year in our country and to launch a series of measures necessary to improve the health of our teenage boys and girls and the population in general, as several working groups specialized in the subject have been proposing (Grupo de trabajo sobre tabaquismo de la Sociedad Española de Epidemiología, 2017; Comité Nacional de Prevención del Tabaquismo, 2017). The measures proposed by these groups include those related to neutral packaging; control over tobacco advertising, promotion and sponsorship; the expansion of smoke-free spaces; the imposition of taxes on all tobacco products; the implementation of smoking prevention, sensitization, research and training programs; as well as the appropriate help for smokers. Moreover, such measures cannot merely take the form of a declaration of intent. Implementation requires considerable effort on the part of the government, not only in terms of funding and the provision of resources but also in the firmness of application in the face of pressure from the tobacco industry.

This study is not without limitations. Chief among them is the cross-sectional nature of the study, in which the data are collected at a single moment in time and through anonymous self-reports; this involves certain risks such as social desirability or underestimation of problematic behaviors. However, this is the type of methodology most frequently applied in studies of this type (Villalbí, Suelves, Saltó & Cabezas, 2011). The second limitation is that the sample is limited to schoolchildren, thus excluding young people aged 17-18 who have left school, a fact which may bias the data, most likely by underestimating the level of adolescent smoking. However, the study has important strengths. The large number of participants in the sample brings undeniable descriptive power to the study and provides a fairly accurate reflection of smoking at these ages. Likewise, the possibility of carrying out pertinent statistical analysis at five specific moments in time to examine trends in smoking allows the changes over these 16 years to be revealed quite accurately and makes it possible to take political decisions based on scientific evidence. In conclusion, the results of this study constitute a valuable contribution to the literature on adolescent smoking trends in the 21st century in Spain, as well as to smoking prevention and control policies.

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Conflicts of interest

The authors of this study declare that they have no conflicts of interest.

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Factors associated with tobacco consumption in patients with depression

Factores asociados con consumo de tabaco en pacientes con depresión

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Abstract

Smoking and depression are related in a bidirectional way: smoking is the primary avoidable cause of illness and death in patients with depression, and depression is one of the most consistent risk factors for smoking. The main objective of this study is to investigate the relationship between smoking and depression, analyzing sociodemographic and clinical variables such as severity of symptoms, subtype of affective disorder, and its impact on suicidal behavior in the clinical population.

A sample of 201 patients, over 18 years of age [mean age (SD) = 53.76 (10.36) years; women = 132 (65.7%)], with a history of depressive episode (unipolar or bipolar) or dysthymia (ICD 10 criteria) was studied.

Current smoking prevalence was 43.2% and life-time prevalence 61.2%. No statistically significant differences in smoking prevalence between men and women were found ($X^2 = 3.896$, $p = 0.143$). The average age of onset was 17.81 (5.60) years. There was a tendency towards a linear association between number of cigarettes/day consumed and severity of depression according to the Hamilton Depression Scale (HDRS) in current smokers (Pearson's $R = 0.298$, $p = 0.050$). Multinomial logistic regression analysis showed that current tobacco consumption was associated with higher HDRS scores, with each additional point on the HDRS increasing the likelihood of smoking by 0.062 [$p = 0.032$; OR (95% CI) = 1.064 (1.005-1.125)].

Our results showed that depressed patients present higher prevalence of current smoking than the general population, also suggesting a relationship between severity of consumption and severity of depressive symptoms.

Key Words: depression; comorbidity; tobacco consumption; risk factor.

Resumen

Tabaquismo y depresión se relacionan de forma bidireccional: el tabaquismo es la primera causa evitable de enfermedad y muerte en pacientes con depresión, y la depresión constituye uno de los factores de riesgo de tabaquismo más consistentes. El principal objetivo del presente trabajo es profundizar en la relación entre tabaquismo y depresión, analizando variables socio-demográficas y clínicas como la gravedad de los síntomas, el subtipo de trastorno afectivo, y su impacto en las conductas suicidas en población clínica.

Se estudió una muestra de 201 pacientes, mayores de 18 años [edad media (SD) = 53,76 (10,36) años; mujeres = 132 (65,7%)], con historia de episodio depresivo (unipolar o bipolar) o distimia (criterios CIE 10).

La prevalencia de tabaquismo actual fue 43,2% y la prevalencia vida 61,2%, no existiendo diferencias estadísticamente significativas entre hombres y mujeres ($X^2 = 3,896$; $p = 0,143$). La edad media de inicio fue 17,81 (5,60) años. Se observó tendencia a asociación lineal entre número de cigarrillos/día consumidos y gravedad de la depresión según la Escala de Hamilton para la Depresión (HDRS) en los consumidores actuales de tabaco (R de Pearson = 0,298; $p = 0,050$). El análisis de regresión logística multinomial puso de manifiesto que el consumo actual de tabaco se asocia con puntuaciones más elevadas en la HDRS, de modo que cada incremento de un punto en dicha escala, la posibilidad de fumar aumenta en 0,062 [$p = 0,032$; OR (95% CI) = 1,064 (1,005-1,125)].

Nuestros resultados muestran que los pacientes deprimidos presentan mayor prevalencia de consumo actual de tabaco que la población general, sugiriendo además una relación entre gravedad de consumo y gravedad de los síntomas de depresión.

Palabras clave: depresión; comorbilidad; consumo de tabaco; factor de riesgo.

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Smoking is the main avoidable cause of illness, disability and death among people with mental disorders (Molina-Linde, 2011). It heightens the risk of certain types of cancer (lip, oral cavity, pharynx, larynx, esophageal, tracheal, bronchial, lung, urinary bladder, kidney, and cervical), as well as other pathologies of great morbidity and mortality, such as cardiovascular diseases, aortic aneurysm, and hypertension, besides playing an important role in respiratory diseases such as chronic bronchitis, and pulmonary emphysema (Becoña, 2004). Smoking is estimated to be responsible for around six million deaths per year (Britton, 2017).

A combination of biological, psychological and social factors, including sex and age, or cultural and economic level form the etiological basis for smoking, with the socio-cultural factors being those on which more emphasis has been placed in the design of smoking prevention campaigns (Higgins & Chilcoat, 2009).

The link between the harmful use of psychoactive substances and other serious health problems is a key aspect in national and international drug policies (Torrens, Mestre-Pintó, Montanari, Vicente & Domingo-Salvany, 2017). Despite the overall reduction in the prevalence of smoking in recent years, smoking rates among patients with mental disorder remain high, above those of the general population (Prochaska, Das & Young-Wolff, 2017; Smith et al., 2018). According to data from the United States, the United Kingdom and Australia, smoking is two to three times more prevalent among mental patients than in the general population (Lasser et al., 2000), and diagnoses show that this increase in prevalence is particularly noticeable among patients with schizophrenia, bipolar disorder, post-traumatic stress disorder and alcoholism. (De Leon & Diaz, 2005; Fu et al., 2007; McClave, McKnight-Eily, Davis & Dube, 2010). In the case of major depressive disorder, 40-50% of patients smoke, approximately twice that of the general population (Action on Smoking and Health, 2016). In the USA's National Comorbidity Survey, about 59% of respondents with a history of depression were smokers, or used to be, compared with less than 39% of those who did not have a history of affective disorder. (Lasser et al., 2000; Ziedonis et al., 2008). A reverse relationship between depression and smoking is also visible, given that the prevalence of depression is also twice as high among smokers compared with the general population (Goodwin et al., 2017; Klungsøyr, Nygård, Sørensen & Sandanger, 2006).

It is known that there is a prospective association between smoking and depression, but evidences regarding the direction of this association are inconsistent. (Fluharty, Taylor, Grabsky & Munafò, 2017).

It has been noted that depression is one of the most consistent risk factors for smoking. Longitudinal studies show that both depressive symptoms (McKenzie, Olsson, Jorm, Romaniuk & Patton, 2010) as well as the diagnosis of ma-

yor depression (Breslau, Kilbey & Andreski, 1993; Dierker, Avenevoli, Merikangas, Flaherty & Stolar, 2001) are associated with an increased risk of developing nicotine addiction among adolescents (Fergusson, Linskey & Horwood, 1996) and adults (Breslau, Novak & Kessler, 2004), as well as with a lower probability of successfully quitting smoking (McClave et al., 2009).

Consequently, greater knowledge of the reasons underlying this co-occurrence of smoking and depression could help develop specific preventive strategies for this subgroup of the population. Some studies have revealed that the conditions share risk factors of both a genetic (Edwards & Kendler, 2012; Kendler et al., 1993; Lyons et al., 2008) and an environmental nature (Fergusson, Goodwin & Horwood, 2003). Other studies link the co-occurrence to the theory of self-medication (Naomi Breslau, Peterson, Schultz, Chilcoat & Andreski, 1998; Lerman et al., 1998), whereby certain depressive symptoms (for example, anhedonia) could prompt the need to smoke (Roys, Weed, Carrigan & MacKillop, 2016), or heighten the pleasurable effect of smoking (Leventhal & Zvolensky, 2015). It has been suggested that nicotine may normalize a dysfunction in cortico-striatal communication in patients who have major depressive disorder with anhedonia (Janes et al., 2018).

Conversely, smoking may exacerbate the risk of depression as a result of the toxic effect of nicotine on the brain (Swan & Lessov-Schlaggar, 2007) through oxidative stress (Vargas et al., 2013) or neurophysiological changes (Markou & Kenny, 2002).

The present study explores the relationship between smoking and depression, seeking clinical and sociodemographic variables that contribute to the risk of smoking among patients diagnosed with affective disorder.

Although there has been substantial research into the relationship between depression and smoking, it has mostly been focused on comorbidity in terms of prevalence, with very few studies taking into account psychopathological aspects such as clinical severity, or different types of depression (unipolar, bipolar and dysthymia). The results of these studies suggest that the severity of depressive symptoms is related to the number of cigarettes smoked per day (Almeida & Pfaff, 2005; Benjet, Wagner, Borges & Medina-Mora, 2004; Massak & Graham, 2008), especially among patients with nicotine dependence (Breslau, Kilbey & Andreski, 1991; Brown, Madden, Palenchar & Cooper-Patrick, 2000; Son, Markovitz & Smith, 1997; Jamal, Willem, Cuijpers & Penninx, 2012), and no such study has yet been carried out in the Spanish context.

The main objective of this study, then, is to deepen our understanding of the link between smoking and depression, analyzing sociodemographic variables and clinical variables such as symptom severity, affective disorder subtypes, as well as the possible impact on suicidal behavior in the clinical population.

Method

This is an observational, descriptive and cross-sectional epidemiological study in which a sub-sample of a multi-center project financed by the Ministry of Health, Social Services and Equality through the Carlos III Health Institute is analyzed (Ref. PI14/02029).

Participants

The sample consists of 201 patients of Caucasian ethnicity over 18 years of age [mean age (SD) = 53.76 (10.36) years; women = 132 (65.7%)] from the Mental Health Center II (La Corredoria) catchment area in Oviedo (Health Area IV of Asturias). Participants were recruited voluntarily, not probabilistically, between September 2015 and June 2017.

All patients presented a history of a current or past episode of depressive (unipolar or bipolar) mood disorder, or dysthymia, according to the criteria of the Tenth Revision of the International Classification of Diseases - ICD 10 (World Health Organization, 1992).

We excluded all participants under 18 years of age, as well as those with comorbidity involving substance use disorders other than smoking, with mental impairment or any serious organic disease, those who do not meet the inclusion criteria or who did not sign the corresponding informed consent and, therefore, did not agree to participate in the study. It is worth pointing out that of those patients who were offered participation in the study only two patients rejected it.

Ethical considerations

This study was approved by the Research Ethics Committee of the Principality of Asturias (Ref. 61/14) and complies with current legislation on clinical research established in the Declaration of Helsinki of the World Medical Association (World Medical Association, 1989), with the Council of Europe Convention on human rights and biomedicine, with the UNESCO universal human rights declaration, and with all Spanish legislation on medical research, biomedicine, data protection and bioethics. All participants provided written informed consent prior to participation in the study.

Assessment protocol

Expert interviewers administered the assessment protocol, which lasted approximately 30 minutes and included the following questionnaires: 1) An ad hoc questionnaire to assess sociodemographic and clinical data, including data regarding the presence or otherwise of somatic disease and of substance use. With regard to smoking, the data collected reflects tobacco use at present (if affirmative, the number of cigarettes per day) and in the past, as well as the age of cessation where applicable. In all cases in which present or past tobacco use is observed, the age of

smoking onset is recorded (García Nieto et al., 2012); 2) The Spanish version of the 17-item Hamilton Depression Scale (HDRS) (Bobes et al., 2003). This hetero-applied scale to determine the severity of the depressive symptoms provides a single score, obtained by adding the scores of each item. In the present study, we decided to use the cut points proposed in the clinical practice guidelines on the management of depression in adults: no depression (0-7 points), minor depression (8-13 points), moderate depression (14-18 points), severe depression (19-22 points) and very severe depression (≥ 23 points) (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2014); 3) The Spanish version of the Barratt Impulsivity Scale (BIS-11) (Oquendo et al., 2001). This is a self-applied instrument designed to measure impulsivity which consists of 30 items scored using a four-point Likert scale of frequency (from rarely or never = 1 to always or almost always = 4) and grouped in three impulsiveness subscales: cognitive (BIS-11-Cognitive) with 8 items, motor (BIS-11-Motor) with 10 items and non-planning impulsivity (BIS-11-Non-planning) with 12 items. It provides a total score (sum of the scores in the three subscales) and scores in the three subscales described. No cut-off point is proposed - the higher the score, the higher the level of impulsivity; 4) The Spanish version of the Childhood Trauma Questionnaire - Short Form (CTQ-SF) (Hernández et al., 2013). This is a self-applied questionnaire designed to explore whether the patient has a history of childhood abuse. It consists of 28 items grouped in five different subscales (five possible forms of abuse), which in turn consist of five items each plus a sixth subscale consisting of three items checking validity to avoid false reports. The five subscales related to possible forms of abuse are as follows: emotional abuse (CTQ-Emotional), physical abuse (CTQ-Physical), sexual abuse (CTQ-Sexual), emotional neglect (CTQ-Emotional Neglect) and physical neglect (CTQ-Physical Neglect). Each item is scored using a five-point Likert scale of frequency (from never = 1 to almost always = 5). It provides a total score (sum of the five abuse and neglect subscales) and independent scores on the five subscales. No cut-off point is proposed - the higher the score, the greater the severity of abuse; 5) The Spanish version of Brugh's List of Threatening Events (LTE) (Motrico et al., 2013). This self-applied scale gathers data on the existence of stressful life events (SLEs) occurring in the six months prior to the assessment. It consists of a list of 12 SLE categories, with each item answered Yes (1 point) or No (0 points) and yields a global score consisting of the scores obtained in each of the 12 items. There is no cutoff point, the higher the score, the greater the number of SLEs suffered.

Statistical analysis

The data were analyzed using version 20 of the Software Package for the Social Sciences for Windows (SPSS, Inc.,

Chicago, IL, EE. UU.). Smoking was taken as the dependent variable of the study, with the sample divided into three groups on the following basis: a) those patients who have never smoked ("never smoked"), b) those who smoked in the past but did not do so at the time of the survey ("past smoker") and, c) those who smoke at the time of the survey ("current smoker").

A univariate analysis of sociodemographic, clinical and psychopathological data was performed. The continuous variables were expressed using the descriptive statistics of mean and standard deviation (SD), and the categorical variables in frequencies and percentages. The comparison between groups was carried out using chi-square statistics (χ^2) on the categorical variables and one-way ANOVA with Duncan test for multiple comparisons on the continuous variables. The level of linear association between quantitative variables was determined by the Pearson correlation coefficient. The analysis of factors linked to the smoking habits of patients with depressive disorder was carried out using a multinomial logistic regression model (main effects model), which included as independent variables all those that were significant in the bivariate analysis, with the addition of sex (Plan Nacional sobre Drogas, 2017) and personal history of attempted suicide (Poorolajal & Darvishi, 2016) because they are considered relevant variables in previous studies (Moral Pélaez, 2006). "Current smoking" was the category of reference. Before carrying out the analysis, the possible existence of multicollinearity among the included variables was discarded by checking correlation coefficients between pairs of variables. The confidence level for statistical significance (α) was set at 95% ($p < 0.05$).

Results

The total sample comprised 201 patients with current diagnosis of depression or dysthymia (ICD 10 criteria) [mean age (SD) = 53.76 (10.36) years; women = 132 (65.7%)]. The most common marital status was married/with partner [$n = 131$ (65.2%)], most had children [$n = 159$ (79.1%)] and lived with their own family, either with their partner [$n = 84$ (41.8%)], with their children [$n = 66$ (32.8%)] or both, and most had a primary education level [$n = 95$ (47.3%)] (Table 1).

At the moment of assessment, most of the sample had a concomitant somatic disease [$n = 141$ (70.1%)] and did not drink alcohol [$n = 146$ (72.6%)], with none of those who did meeting diagnostic criteria for alcohol use disorder since this was an exclusion criterion for participating in the study. The majority of the sample had no family history of suicide attempts (SA) [$n = 160$ (79.6%)], nor of completed suicide [$n = 162$ (80.6%)], although 86 patients (42.8%) had attempted suicide themselves. A majority of 105 patients (52.2%), presented a diagnosis of unipolar depression, with an average severity on the HDRS of 18.65

(5.99), signifying severe depression according to the criteria of the Clinical Practice Guide For Adult Depression Management (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2014).

The mean scores on the other scales were as follows: CTQ-Total = 37.95 (13.06), LTE-Brugha = 2.84 (0.93), BIS-11 Total = 64.63 (11.59) (Table 2).

With regard to smoking, 123 (61.20%) patients had a history of tobacco use, with an average onset age of 17.81 (5.60) years. Of these patients, 38 (30.9%) had quit smoking at an average age (SD) of 45.34 (9.37), implying an average duration of the smoking habit of 27.00 (10.99) years. At assessment, 85 patients (69.1%) remained smokers [mean onset age (SD) = 17.73 (5.38) years; women = 54 (63.5%)], smoking on average (SD) of 16.68 (11.48) cigarettes per day. It is worth noting that there was a tendency towards a linear association between number of cigarettes smoked daily by current smokers and the severity of depression according to the HDRS (Pearson's $R = 0.298$, $p = 0.050$); this did not reach the level of statistical significance, however.

A bivariate analysis comparing patients by their smoking habit (current, past or never), showed that patients diagnosed with depression and currently smoking were significantly younger than ex-smokers [51.69 (9.13) vs. 55.82 (7.50) years; $F = 3.070$, $p = 0.049$] and suffered from greater depression severity according to HDRS than those who had never smoked [19.70 (5.29) vs. 17.23 (7.03); $F = 3.788$, $p = 0.024$]. Moreover, compared to those who had never smoked, past smokers registered statistically higher scores on the BIS-11 Cognitive [20.00 (3.97) vs. 17.75 (4.15); $F = 4.169$, $p = 0.017$] (Tables 1 and 2). For the remaining variables in which no statistically significant results were found, the reader is referred to Tables 1 and 2.

In the multinomial regression analysis, the variables that were statistically significant in the bivariate analysis were taken into account (age, severity of depression according to HDRS and BIS-11 Cognitive), with the addition of other variables considered possible risk factors in the literature (sex and personal history of attempted suicide). This analysis shows that there are no differences in any of the parameters included between current and ex-smokers, while current smoking is associated with higher scores on the HDRS to the extent that each one-point increment on the scale increases the likelihood of smoking by 0.059 [$\beta = 0.062$, $p = 0.037$; OR (95% CI) = 1.060 (1.004-1.121)] (Table 3).

Discussion

There are not many studies on smoking in clinical populations with affective disorders in our environment. The most significant findings include a prevalence of current smoking of 42.3% and a life of our study prevalence

Table 1. Sociodemographic characteristics of the sample

	Total n = 201	Current smoker n = 85	Past smoker n = 38	Never smoked n = 78	X ² (gl) / F (gl)*	p
Sex [n (%)]						
Men	69 (34.3%)	31 (44.9%)	17 (24.6%)	21 (30.4%)	3.896 (2)	0.143
Women	132 (65.7%)	54 (40.9%)	21 (15.9%)	57 (43.2%)		
Age [Mean (DE)]	53.76 (10.36)	51.69 (9.13) ¹	55.82 (7.50) ¹	55.01 (12.34)	3.070 (200) *	0.049
Marital status [n (%)]						
Single	18 (9.0%)	7 (38.9%)	3 (16.7%)	8 (44.4%)	9.190 (6)	0.163
Married / with partner	131 (65.2%)	53 (40.5%)	29 (22.1%)	49 (37.4%)		
Separate / Divorced	38 (18.9%)	22 (57.9%)	4 (10.5%)	12 (31.6%)		
Widower/Widowed	14 (7.0%)	3 (21.4%)	2 (14.3%)	9 (64.3%)		
Children [n (%)]						
Yes	159 (79.1%)	64 (40.3%)	31 (19.5%)	64 (40.3%)	1.297 (2)	0.523
No	42 (20.9%)	21 (50.0%)	7 (16.7%)	14 (33.3%)		
Living with [n (%)]						
Parents	19 (9.5%)	8 (42.1%)	0 (0.0%)	11 (57.9%)	7.184 (8)	0.517
Children	66 (32.8%)	27 (40.9%)	13 (19.7%)	26 (39.4%)		
Partner	84 (41.8%)	38 (45.2%)	18 (21.4%)	28 (33.3%)		
Alone	28 (13.9%)	11 (39.3%)	6 (21.4%)	11 (39.3%)		
Other	4 (2.0%)	1 (25.0%)	1 (25.0%)	2 (50.0%)		
Educational level [n (%)]						
Primary school	95 (47.3%)	34 (35.8%)	23 (24.2%)	38 (40.0%)	5.334 (4)	0.255
Secondary/higher secondary	77 (38.3%)	36 (46.8%)	10 (13.0%)	31 (40.3%)		
University	29 (14.4%)	15 (51.7%)	5 (17.2%)	9 (31.0%)		

Note. ¹: Groups with statistically significant differences (Duncan's test for multiple comparisons); SD: Standard deviation

of 61.2%, with no difference in prevalence between men and women. There are hardly any differences between the variables studied and smoking status, so that smokers and ex-smokers only differ in age (51.69 years vs. 55.01 years respectively), while smokers and non-smokers present other differences, for example in depression severity or impulsivity level. The inclusion of the differential variables in the logistic regression analysis shows that there are no differences between smokers and ex-smokers, while the group of active smokers is differentiated from those who have never smoked by depression severity as measured by the HDRS.

Our results agree with those published in the literature regarding the higher prevalence of current smoking among patients with depression compared to the general population. In terms of lifetime prevalence, while the 61.2% rate found in our sample is similar to that observed in the US in the National Comorbidity Survey (Ziedonis et al., 2008), it is lower than that in Spain's general population, where 72.5% has smoked at some time in their lives (Plan Nacional sobre Drogas, 2017). Turning to current active smoking, patients with depression present a prevalence of 42.3%, considerably higher than the 30.8% found in the Spanish population, according to data from the National Plan On Drugs ((Plan Nacional sobre Drogas, 2017). Nevertheless, these data must be read with caution given the age factor, since the Spanish population is on average younger (42.98 years) than our sample (53.76 years).

There is some controversy concerning sex differences relation to smoking, both at the epidemiological and the clinical level involving patients in cessation (Marqueta, Nerín, Gargallo & Beamonte, 2017). In our sample of depressive patients, there is no sex difference in current smoking prevalence, which contrasts with the higher prevalence among men found in the general population for all age groups (Plan Nacional sobre Drogas, 2017). These results suggest that patients with depression differ from the general population with regard to smoking, not only because of the increase in the prevalence of current smoking in the clinical population studied, but also given the similarity in smoking rates between men and women, so that the disease could be responsible for these differences in the smoking habit of patients with depression.

Explanations of such an influence of depressive symptoms on smoking have been approached using biological models, looking at common genetic risk factors between smoking and affective disorders (Edwards et al., 2012; Kendler et al., 1993; Lyons et al., 2008), or the theory of self-medication, where tobacco functions to alleviate certain symptoms, especially anhedonia (Roys et al., 2016). Recently, a psychological model to explain comorbidity between smoking and depression based on learning theories has been proposed, highlighting the role of positive affect, negative affect, and cognitive deficit as engines of addiction maintenance (Mathew, Hogarth, Leventhal, Cook & Hitsman, 2017).

Table 2. *Clinical characteristics of the sample*

	Total n = 201	Current smoker n = 85	Past smoker n = 38	Never smoked n = 78	X ² (gl) / F (gl)*	p
Somatic disease [n (%)]						
Yes	141 (70.1%)	54 (38.3%)	29 (20.6%)	58 (41.1%)	3.129 (2)	0.209
No	60 (29.9%)	31 (51.7%)	9 (15.0%)	20 (33.3%)		
Alcohol use [n (%)]						
Yes	55 (27.4%)	27 (49.1%)	10 (18.2%)	18 (32.7%)	1.570 (2)	0.456
No	146 (72.6%)	58 (39.7%)	28 (19.2%)	60 (41.1%)		
FH Attempted suicide [n (%)]						
Yes	41 (20.4%)	21 (51.2%)	8 (19.5%)	12 (29.3%)	2.189 (2)	0.335
No	160 (79.6%)	64 (40.0%)	30 (18.8%)	66 (41.3%)		
FH Completed suicide [n (%)]						
Yes	39 (19.4%)	16 (41.0%)	7 (17.9%)	16 (41.0%)	0.103 (2)	0.950
No	162 (80.6%)	69 (42.6%)	31 (19.1%)	62 (38.3%)		
Current diagnosis (CIE-10) [n (%)]						
Bipolar depression	16 (8.0%)	5 (31.3%)	2 (12.5%)	9 (56.3%)	10.168 (6)	0.118
Unipolar depression	105 (52.2%)	52 (49.5%)	21 (20.0%)	32 (30.5%)		
Recurrent unipolar depression	47 (23.4%)	20 (42.6%)	8 (17.0%)	19 (40.4%)		
Dysthymia	33 (16.4%)	8 (24.2%)	7 (21.2%)	18 (54.5%)		
HDRS [Mean (DE)]	18.65 (5.99)	19.70 (5.29) ¹	19.23 (4.52)	17.23 (7.03) ¹	3.788 (200) *	0.024
HDRS-Cut points						
No depression (0-7)	9 (4.5%)	1 (11.1%)	0 (0%)	8 (88.9%)		
Minor depression (8-13)	24 (11.9%)	8 (33.3%)	4 (16.7%)	12 (50.0%)		
Moderate depression (14-18)	55 (27.4%)	21 (38.2%)	12 (21.8%)	22 (40.0%)	14.217 (2)	0.076
Severe depression (19-22)	61 (30.3%)	31 (50.8%)	12 (19.7%)	18 (50.8%)		
Very severe depression (≥ 23)	52 (25.9%)	24 (46.2%)	10 (19.2%)	18 (34.6%)		
Lifetime attempted suicide [n (%)]						
Yes	86 (42.8%)	43 (50.0%)	12 (14.0%)	31 (36.0%)	4.358 (2)	0.113
No	115 (57.2%)	42 (36.5%)	26 (22.6%)	47 (40.9%)		
CTQ Total [Mean (DE)]	37.95 (13.06)	38.38 (13.27)	39.60 (14.60)	36.67 (12.07)	0.719 (200) *	0.488
CTQ-Emotional	7.78 (3.99)	8.14 (4.41)	7.92 (4.03)	7.33 (3.46)	0.856 (200) *	0.426
CTQ-Physical	6.33 (2.57)	6.10 (2.47)	6.78 (2.63)	6.37 (2.64)	0.936 (200) *	0.394
CTQ-Sexual	5.85 (2.85)	5.80 (2.64)	5.97 (2.81)	5.84 (3.11)	0.048 (200) *	0.953
CTQ-Emotional neglect	10.19 (5.11)	10.47 (5.38)	10.84 (5.62)	9.57 (4.53)	0.996 (200) *	0.371
CTQ-Physical neglect	7.78 (2.90)	7.87 (3.11)	8.07 (3.38)	7.55 (2.40)	0.480 (200) *	0.619
LTE Brugha [Mean (DE)]	2.84 (0.93)	2.97 (0.99)	2.89 (0.89)	2.67 (0.87)	2.123 (200) *	0.122
BIS-11 Total [Mean (DE)]	64.63 (11.59)	65.25 (10.96)	67.78 (12.07) ¹	62.41 (11.73) ¹	3.025 (200) *	0.051
BIS-11-Cognitive	18.67 (4.13)	18.92 (4.03)	20.00 (3.97) ¹	17.75 (4.15) ¹	4.169 (200) *	0.017
BIS-11-Motor	21.92 (5.26)	22.44 (5.27)	22.86 (5.32)	20.89 (5.11)	2.557 (200) *	0.080
BIS-11-Non-planning	24.02 (5.60)	23.88 (5.25)	24.92 (6.28)	23.75 (5.65)	0.601 (200) *	0.549

Note. *: Groups with statistically significant differences (Duncan's test for multiple comparisons); FH: Family Background; BIS-11: Barratt Impulsivity Scale; CTQ: Childhood Trauma Questionnaire; SD: Standard Deviation; HDRS: Hamilton Depression Scale; LTE: List of threatening events.

Table 3. *Variables associated with current smoking compared to past smoking or never smoked*

	B	SE	Wald	df	p	OR	CI 95%
Never smoked							
Intersection	-0.176	1.427	0.015	1	0.902	1.026	0.993 – 1.060
Age	0.026	0.017	2.360	1	0.125	1.647	0.821 – 3.307
Sex (Woman)	0.499	0.356	1.971	1	0.160	1.306	0.677 – 2.522
Lifetime attempted suicide (No)	0.267	0.336	0.634	1	0.426	0.943	0.892 – 0.996
HDRS score	-0.059	0.028	4.362	1	0.037	0.964	0.888 – 1.046
BIS-11 Cognitive	-0.037	0.042	0.767	1	0.381		
Past smoking							
Intersection	-4.519	1.812	6.218	1	0.013	1.039	0.996 – 1.083
Age	0.038	0.021	3.186	1	0.074	0.890	0.396 – 2.000
Sex (Woman)	-0.117	0.413	0.080	1	0.777	1.860	0.803 – 4.309
Lifetime attempted suicide (No)	0.621	0.429	2.096	1	0.148	0.988	0.919 – 1.063
HDRS score	-0.012	0.037	0.100	1	0.752	1.086	0.982 – 1.201
BIS-11 Cognitive	0.082	0.051	2.585	1	0.108		

Note. BIS-11: Barratt Impulsivity Scale; df: Degrees of freedom; HDRS: Hamilton Depression Scale; CI: Confidence interval; OR: Odds ratio; SE = Standard error

Thus, the analyses carried out at a symptomatic level have shown that a combination of high levels of negative affect and low levels of positive affect are independently associated with the severity of nicotine dependence (Leventhal, Kahler, Ray & Zimmerman, 2009; Mickens et al., 2011) or the number of cigarettes smoked (Leventhal, Zvolensky & Schmidt, 2011).

Further, an analysis of the clinical variables reveals that smoking varies significantly depending on the type of depression in question. For example, the current rate of smoking among patients diagnosed with unipolar or recurrent major depression is 47.4%, higher than that observed with depression in bipolar disorder (31.2%) and with dysthymia (24.2%), the latter even being lower than the rate observed in the general population (30.8%), although the corresponding statistical analyses show that the distribution of prevalence among the three smoking conditions is not statistically significant.

Nevertheless, these results would be consistent with those obtained by applying logistic regression since in the model obtained, current smoking is not associated with the diagnosis of depression type, but rather with the severity of the depressive symptoms presented by the patient. Thus, it is expected that patients with dysthymia, a disorder of lower symptomatic intensity than major depressive disorder, will have lower current smoking rates.

In addition, it is important to note that although the possible linear association between severity of depression measured by HDRS and the number of cigarettes consumed by active smokers in the sample is not of statistical significance, the differences in the observed scores between the groups by smoking status (19.70 vs. 17.23) have a significant impact from a clinical point of view. Depression severity among smoking patients falls in the severe depression category (19-22) while non-smoker scores are equivalent to moderate depression (14-18), according to the Clinical Practice Guidelines on the Management of Depression in Adults (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2014).

The relationship between the severity of symptoms and the observed smoking habit coincides with that published in the literature (Almeida et al., 2005; Benjet et al., 2004; Jamal et al., 2012; Massak et al., 2008), although given the cross-sectional nature of the study, it is not possible to establish the direction of the relationship. Thus it cannot clarify whether the severity of the symptoms leads the patient to smoke more, or whether it is smoking which contributes to exacerbated symptoms, although the differences observed in our study depending on the type of depression would point towards the former. Recent studies support this association by demonstrating how depressive symptoms improve when patients managed to quit tobacco in smoking cessation programs (Almadana et al., 2017).

A recent meta-analysis has revealed the link between current and past smoking (ex-smokers) and an increased

risk of suicidal behavior, whether it be suicidal ideation, planning, attempted suicide, or suicide (Berlin, Hakes, Hu & Covey, 2015; Evins, Korhonen, Kinnunen & Kaprio, 2017; López-Castroman et al., 2016; Poorolajal et al., 2016). The three most accepted hypotheses for this relationship connect the increase in suicidality with: the presence of psychopathology associated with a pre-existing suicide risk in smokers; medical illnesses caused by long-term smoking (COPD, cancer) potentially leading to suicide; or the impact of smoking on certain neurotransmission systems, such as the reduction of serotonin and monoamine oxidase levels, linked to an increased risk of suicidality (Berlin et al., 2017; Hughes, 2008).

Our results suggest a higher proportion of patients with a history of suicide attempts in the group of active smokers (50.6%) compared to ex-smokers (31.6%) and non-smokers (39.7%), but the differences are not statistically significant, so that it cannot be said that there is an association between smoking and suicide attempts. It is possible that potential pro-suicidal effects attributable to tobacco are masked by working with a sample of patients with depression, a pathology associated with an increased risk of suicide; a larger sample would be necessary to be able to achieve sufficient statistical power.

This has also been pointed out in a previous study of patients who had completed suicide which investigated the modification of suicide risk attributable to smoking among patients with mental disorders, including affective disorders. The study found a statistically significant difference only in the group of patients with substance use disorders, and therefore recommended using larger clinical population samples (Schneider et al., 2009).

One of the conclusions reached by the present study is that it shows the difficulty involved in investigating the risk factors of bio-psycho-social etiology phenomena such as smoking. The interrelations between some of the variables traditionally associated with smoking can be confounding factors if studied together. This may be seen in our study when applying logistic regression techniques: age or level of impulsivity, which are variables initially showing differences depending on smoking status, finally disappear from the regression model due to a confounding effect.

The present study has certain strengths and limitations. Among the former, we highlight the homogeneity of the sample, as well as the inclusion of patients with different types of affective disorder. The main limitations would be sample size and working exclusively with a clinical population without a healthy control group. Additionally, since it is not a prospective study, a causal relationship cannot be established regarding the observed association. Similarly, a more comprehensive analysis of concomitant somatic diseases might have been useful. Finally, another limitation lies in the fact that specific scales of addiction severity were not used.

In conclusion, this study demonstrates the relationship between smoking and depression, with depressed patients smoking more than the general population, and the possibility that smoking is directly related to the depression severity.

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Conflict of interests

The authors declare no conflicts of interest regarding this study

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Bibliometric and academic network analysis of Spanish theses on drug dependence in the TESEO database

Análisis de redes sociales y bibliométrico de las tesis españolas sobre drogodependencias en la base de datos TESEO

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Abstract

The present study aims to reveal the structure of positions in the field of addiction through the analysis of doctoral theses read in Spain. The source consulted for the selection of the theses was TESEO. Searching for the keywords drug abuse, alcoholism, drug effects and drug addiction treatment during the period 1976-2017 produced 728 theses. The most productive period is 2013-2017, with 208 (28.6%) doctoral theses. The overall rate of publication is increasing, but in the period 2003-2007 output decreased significantly to 5.2% of the total. The university contributing the most theses is the University of Valencia. The academic who has supervised the most theses is Alfonso Velasco Martín, and Emilio Ambrosio Flores is the researcher who has participated most on examining committees. The analysis of the participants in the doctoral thesis process shows a gradual increase of women in authorship, in thesis supervision and as examiners. In terms of subject, the most frequently treated aspects are those related to psychology, pharmacology and medical sciences.

The analysis of doctoral theses on substance abuse provides an overview of the structure and the most influential participants in this area. Increasing public concern and the creation of specific groups and research units are reflected in the growth of scientific output.

Keywords: Academic Dissertations; Gender identity; Substance-Related Disorders; Bibliometrics; Social network analysis; Gender analysis.

Resumen

El presente trabajo tiene por objeto desvelar la estructura de posiciones del campo de las adicciones a partir del análisis de las tesis doctorales defendidas en España. La fuente consultada para la selección de las tesis fue TESEO. La búsqueda se limitó al período 1976-2017 y se utilizaron los descriptores abuso de drogas, alcoholismo, efecto de las drogas y tratamiento de la drogadicción. Se obtuvieron 728 tesis, siendo el quinquenio más productivo el 2013-2017 con 208 (28,6%) tesis doctorales. La evolución de las publicaciones es ascendente, excepto en el quinquenio 2003-2007 en el que la producción baja a un 5,2% del total. La universidad que aporta más tesis es la Universitat de València. El académico que más tesis ha dirigido es Alfonso Velasco Martín y Emilio Ambrosio Flores es el investigador que más ha participado en los tribunales. El análisis de los actores participantes en las tesis doctorales muestra un incremento de presencia de las mujeres como autoras, directoras de tesis y miembros de tribunales. En relación a la temática, los temas más abordados han sido los relacionados con la psicología, la farmacología y las ciencias médicas. El análisis de las tesis doctorales sobre drogodependencias ha dado una visión de su estructura y de las personas más influyentes de la misma. El aumento de la preocupación social en esta área y la creación de grupos y unidades de investigación específicos ha ocasionado un incremento de la producción científica.

Palabras clave: Tesis académicas; Trastornos relacionados con sustancias; Bibliometría; Análisis de redes sociales; Análisis de género.

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The annual reports of the European Monitoring Centre for Drugs and Drug Addiction (2018) show that Spain is one of the European Union countries with the highest rates of cocaine and cannabis use. This fact has stimulated an increase in research into the problem, which has become a priority area for agencies and institutions (González-Alcaide et al., 2008; Melero-Fuentes, 2016; Vidal-Infer, 2010). The consolidation of this research area has led in turn to growing scientific output (Osca-Lluch, 2016) and has promoted the generation of bibliometric studies that characterize this area by subject, substance, sex of the authors or geographical area (Bramness, Henriksen, Person & Mann, 2014; González, Fernandes, Pinto & Agulló, 2015; González-Alcaide et al., 2007; Khalili et al., 2018; Osca-Lluch, 2012, 2016). Nevertheless, these studies have focused only on the analysis of journal articles, while it has been shown that the production of doctoral theses is proportional to scientific articles indexed in international databases, both in their growth over time, as in their distribution across universities (Sánchez, Blázquez, Montesi & Botezan, 2017).

The doctorate the highest degree that can be attained at university level (Curiel-Marín & Fernández-Cano, 2015; Curiel-Marín, Passoni, Olmedo-Moreno & Fernández-Cano, 2018), and the defense of the doctoral thesis is the culminating activity of the doctoral program (MacLennan, Piña & Gibbons, 2018). By developing and writing their theses, doctoral students acquire the methodological knowledge and analytical skills necessary to produce and disseminate the results of their research (Davis, Wladkowski & Mirick, 2017), to establish a career in academia (Piña, MacLennan, Moran & Hafford, 2016) and to become highly qualified workers and competent researchers in different academic fields (Caparrós-Ruiz, 2018).

The number of doctoral theses supervised is an indicator of a successful doctorate (Buela, 2005) and influences the prestige of professors and their academic careers. In fact, the assessment criteria used for the accreditation of teachers in the Academia program, overseen by Spain's National Agency for the Evaluation of Quality and Accreditation (ANECA), both in terms of research and teaching activities, include having been a doctoral thesis supervisor (ANECA, 2017). It should be noted that doctoral theses are one of the indicators of the report "Spanish universities in figures" published by the Conference of Spanish University Rectors (CRUE, 2017), and the titles of doctorates awarded are also used as assessment criteria in various university rankings such as the RUR World University Ranking (Round University Ranking, 2018), THE World University Ranking (Times Higher Education, 2018) or the U-Multirank. Universities Compared. Your way (U-Multirank, 2018).

The analysis of doctoral theses is thus a good indicator of the lines of research and research trends in a given field of science and provides an outline of the social structure of

the discipline since the thesis writing and assessment process involves academic professionals with established roles, such as authors, supervisors, reviewers and members of the examining committee (Arguimbau-Vivó & Fuentes-Pujol, 2009; Delgado, Torres-Salinas, Jiménez-Contreras & Ruiz-Pérez, 2006; Repiso, Torres & Delgado, 2011a).

The present study aims to reveal the structure of academic posts in the field of addiction by combining bibliometrics with an analysis of the academic networks of people involved in supervising and examining doctoral theses defended in Spain, as registered in the TESEO database (<https://www.educacion.gob.es/teseo/irGestionarConsulta.do>). This will provide information complementary to the results obtained in the bibliometric analysis of scientific articles concerning addiction. To this end, the defended theses, their authors, supervisors and examiners, the sex of the participants involved and the subject of the theses are taken for reference.

While a preview of the study (Castelló-Cogollos, Bueno & Aleixandre, 2016) was published as a brief note in the "Current Issues" section of the CendocBogani center for documentation on addiction, this article features a broader and more in-depth analysis of the data obtained for the note in question.

Method

The source consulted for the selection of theses was the TESEO database of the Spanish Ministry of Education, Culture and Sport, which has registered information on theses defended in Spain since 1976, classified according to the codes of the UNESCO thesaurus (<https://en.unesco.org/>).

The search equation for the recovery of doctoral theses on addiction included the keywords: "drug abuse", "alcoholism", "drug effects" and "treatment of drug addiction". Independent searches were conducted with each of the descriptors, and for each academic year from 1976 to 2017. The last academic year included in the search equation was 2017/2018, from which the doctoral theses defended in 2017 were selected. In total, 832 records were downloaded and included for the present study in an "ad hoc" relational database using Microsoft Access which included the title of the thesis, descriptors, author, institution where the thesis was defended, thesis supervisor(s), and members of the examining committee, specifying their role on the committee.

Since records might contain two or more of the keywords used in the search, duplicates were detected when performing individual searches for each of the keywords. The final sample, once duplicates were eliminated, comprised 728 theses. Next, the institutional affiliations, signatures of the authors, supervisors and members of the tribunal and the keywords were homogenized. The sex of each participant in writing and defending the thesis was also noted.

The bibliometric analysis was divided into five major blocks: a) authorship analysis, involving calculations regarding thesis authorship; b) analysis of the supervisors, either as sole supervisor or co-supervisor, including a co-supervision index (number of theses supervised divided by total theses); c) analysis of examining committees, presenting examiner data; d) comparison by sex of the three participant levels (authors, supervisors and examiners), and e) thematic analysis, analyzing the frequency of the keywords found in the theses and the relationships between them.

The Pajek program (<http://mrvar.fdv.uni-lj.si/pajek/>) was used to create and graphically display the networks of keywords, committees and the combination of supervisor and examiner. The size of the vertices is proportional to the number of occurrences. The thickness of the lines connecting two vertices are proportional to the number of times the two terms appear simultaneously in the total number of theses. For inclusion in the graphic representation of keywords, the co-occurrence of three or more keywords in the same doctoral thesis was required, and involvement in three or more doctoral theses was deemed necessary for the network of examiners.

The supervisor-examiner invitation network provides a closer view of the existence of close connections among academics since it represents the number of times that a supervisor invites, recommends or asks for the presence of an academic to participate as an examiner on the committee of a doctoral thesis that he or she has supervised. The invitation by the thesis supervisor to different academics to sit on the examining committee understood as the establishment of a relationship. This has been done following the regulations governing submission, assessment and defense of the thesis of various universities, including the Complutense University of Madrid and the University of Valencia, which require alongside the thesis submission a list of six experts for its assessment. While ten experts were previously required, this was modified with the publication of Royal Decree 99/2011, January 28, 2011, regulating the official doctoral education (Royal Decree 99/2011, 2011). This stipulates that the selection of academics for the thesis examining committee is carried out by its supervisor(s) and therefore reveals a relationship between supervisors and examiners. Inclusion criterion for this network was sitting on three examining committees or more.

Results

Global data

The first doctoral thesis on drug addiction to be included in TESEO is "*Psychological and evaluative aspects of the alcoholic personality*" by Flora Paniagua Cárdenas, defended in 1978 at the Complutense Universidad of Madrid. The most productive five-year period is 2013-2017, with 208 (28.6%)

doctoral theses (Figure 1). Although doctoral thesis output is increasing overall, it slowed significantly to 5.2% of the total during the quinquennium 2003-2007, 11.4 percentage points less than in the previous five years (16.6%). It can be noted that 11.7% of thesis authors also participate later as supervisors or examiners, and that 22 have been author, supervisor and examiner.

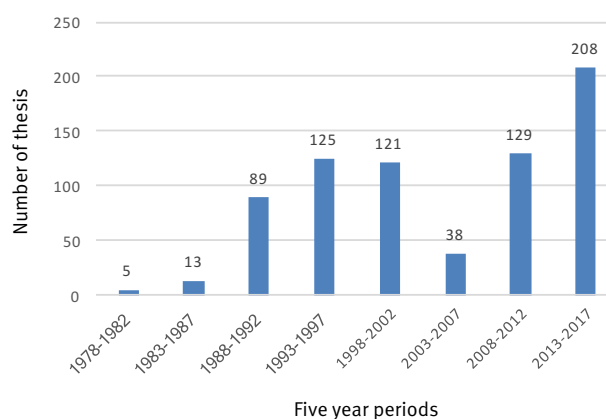


Figure 1. Development over five-year periods of doctoral thesis output in Spain on the subject of drug addiction.

The largest number of doctoral theses have been defended in Catalonia (16.8%), followed by Madrid and the Community of Valencia (15.7% and 15.4%, respectively), while Andalusia registered 13.9%. The theses were defended at 51 universities. Valencia University has contributed most to the study ($n = 69$), followed by Autònoma University of Barcelona ($n = 57$) and the University of Valladolid with 51 theses; the Complutense University of Madrid is also in the top positions with 46 theses. Table 1 shows the universities where 10 or more theses have been defended.

Analysis of thesis supervisors

The analysis of thesis supervisors yields 664 different supervisors or co-supervisors. This analysis was carried out with those theses which included the relevant information in the TESEO database registry ($n = 663$, 91.1% of total theses). The co-supervision index is 1.54 supervisors. The academic supervising the most theses is Alfonso Velasco Martín ($n = 26$), professor of pharmacology at Valladolid University; followed at a significant distance by Emilio González Reimers, professor of internal medicine at La Laguna University, who supervised 11 theses. Of the total number of supervisors, 75.9% have overseen only one thesis, 20% between two and four theses and 4.1% five or more theses. Table 2 presents the academics who have supervised five or more doctoral theses.

The supervisor-examiner network shows that 106 academics participated and 22 groups were created, with the

Table 1. *Distribution of Spanish doctoral theses on drug addiction by university ($\geq$ of 10 theses ordered by number of theses defended).*

University in which defended	Nº of theses	%
Universitat de València (Estudi General)	69	9.5%
Universidad Autónoma de Barcelona	57	7.8%
Universidad de Valladolid	51	7.0%
Universidad Complutense de Madrid	46	6.3%
Universidad de Santiago de Compostela	38	5.2%
Universidad de Barcelona	36	4.9%
Universidad de Granada	34	4.7%
Universidad de Murcia	29	4.0%
Universidad del País Vasco/ Euskal Herriko Unibertsitatea	29	4.0%
Universidad Autónoma de Madrid	25	3.4%
Universidad de La Laguna	24	3.3%
Universidad de Salamanca	23	3.2%
Universidad de Sevilla	23	3.2%
Universidad de Málaga	19	2.6%
Universidad Miguel Hernández de Elche	18	2.5%
Universidad de Zaragoza	17	2.3%
Universidad Pompeu Fabra	17	2.3%
Universidad Nacional de Educación a Distancia	15	2.1%
Universidad de Cádiz	13	1.8%
Universidad de Oviedo	12	1.6%
Universidad de Navarra	10	1.4%
Universidad Jaume I de Castellón	10	1.4%

largest group consisting of 28 people (Figure 2). It shows that there is no reciprocity when recommending supervisors to other academics for examining committees, but there is a conspicuous relationship around Alfonso Velasco Martín, who on 11 occasions recommends that Luis San Román del Barrio (Salamanca University) and Fernando Fernández de la Gandara (Complutense University of Madrid) sit on the examining committees in which he is supervisor. The relationships around Pedro Sánchez García (Autonomous University of Madrid) or Antonio Dueñas Laita (Valladolid University) also stand out, and the figure shows vertices (academics) that act as a link with other academics such as, for example, Cecilio Álamo González (Alcalá de Henares University) or Francisco Javier Álvarez González (Valladolid University).

Figure 3 shows four groups of six or seven components, where reciprocity is observed in the relationship formed by Emilio González Reimers and Francisco Javier Santolaria Fernández of La Laguna University, who invite each other to sit on examining committees when they are supervisors. There is a similar reciprocity in the relationship

Table 2. *Distribution of supervisors of Spanish doctoral theses on drug addiction ($\geq$ of 5 theses supervised, ordered by number of theses directed and alphabetically).*

Name	Supervisor	Co-supervisor	Nº of theses supervised
Velasco Martín, Alfonso	25	1	26
Gonzalez Reimers, Emilio	10	1	11
Bermejo Barrera, Ana María	8	1	9
Luna Maldonado, Aurelio	8	1	9
Miñarro López, José	6	3	9
Álvarez González, Javier	8		8
Farré Albaladejo, Magí	6	2	8
Romero Gómez, Francisco Javier	7	1	8
Santolaria Fernández, Francisco Javier	7	1	8
de la Torre Fornell, Rafael	3	3	7
García Del Castillo Rodríguez, José Antonio	6	1	7
Ambrosio Flores, Emilio	5	1	6
Cadaveira Mahía, Fernando	4	2	6
Fernández Gómez, Purificación	3	3	6
García Algar, Oscar	4	2	6
Maldonado López, Rafael	1	5	6
Pérez García, Miguel	4	2	6
Rodríguez Arias, Marta	3	3	6
Domingo Salvany, Antònia	4	1	5
Espada Sánchez, José Pedro	5		5
Espí Martínez, Fernando	5		5
González Aragón, Carlos Manuel	4	1	5
Graña Gómez, José Luis	4	1	5
Luengo Martín, María Ángeles	4	1	5
Miquel Salgado-Araujo, Marta Asunta	3	2	5
Tabernero Duque, María Jesús	2	3	5
Torrens Melich, Marta	4	1	5

between José Antonio García del Castillo Rodríguez and José Pedro Espada Sánchez of the Miguel Hernández University in Elche.

Analysis of examining committees

We found that 2,055 different doctors have participated as examiners. Table 3 shows that Emilio Ambrosio Flores is the researcher who has sat on committees most frequently, 20 times in total, (five times as chair, once as secretary and 14 times as member), followed by Miguel Sánchez Turet, on 17 committees (eight as chair and nine as member).

Taking into account that the capacity in which one sits on an examining committee can differ in importance, it is notable that Francesc Jané (n = 10) has participated most

often as committee chair, followed by Vicente Simón Pérez ($n = 9$) and Miguel Sánchez Turet ($n = 8$). The majority of academics who sit on committees do so only once (74%), with only 22 (1.1%) sitting on 10 or more committees (Table 3).

The network analysis of examiners yields a network formed of 67 committee members and 21 groups. The largest group consists of 16 members (Figure 4) and shows how Luis San Román del Barrio (University of Salamanca) is the academic who most frequently coincides with other

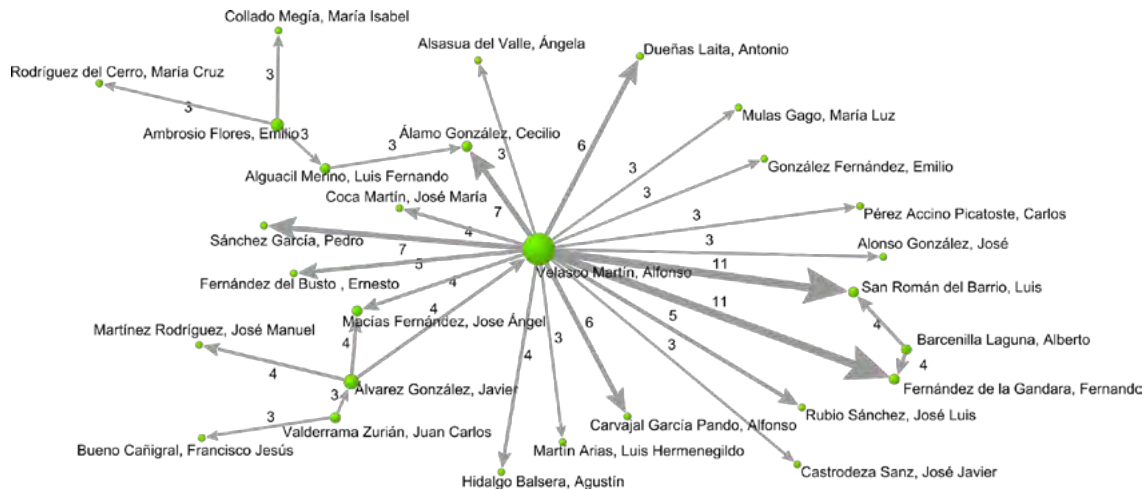


Figure 2. Supervisor-examiner invitation network in Spanish doctoral theses on drug addiction (group of 28 members).

Note. The vertices represent academics acting as supervisors or examiners. The size of the vertices reflects the direct connections with other vertices. The thickness of the arrows represents the total number of times a supervisor has invited an academic to participate in a thesis.

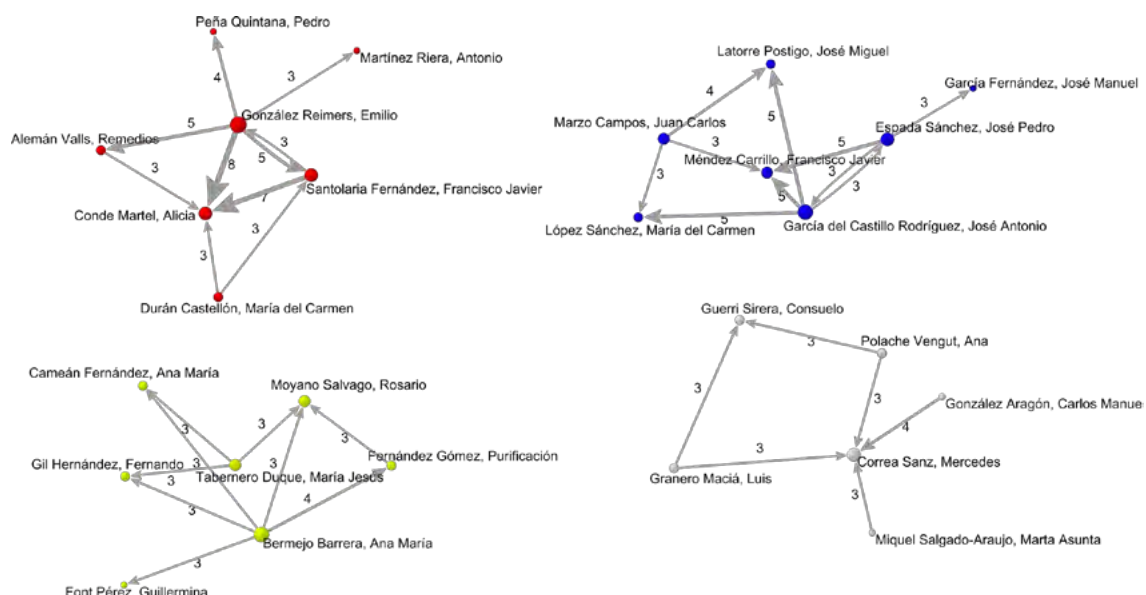


Figure 3. Chair-examination committee invitation network in Spanish doctoral theses on drug addiction (groups of 7-6 members).

Note. The vertices represent academics acting as chair or examiner. The size of the vertices determines the direct connections with other vertices. The thickness of the arrows reflects the total number of times the chairperson has asked an academic to participate in a thesis.

Table 3. Distribution of the committees examining Spanish doctoral theses on drug addiction (≥ 10 appearances on committees ordered by number of appearances and alphabetically).

Name	Chair	Secretary	Member	Nº of committee appearances	Place of work
Ambrosio Flores, Emilio	5	1	14	20	Universidad Nacional de Educación a Distancia
Sánchez Turet, Miguel	8		9	17	Universitat de Barcelona
Becoña Iglesias, Elisardo	4		12	16	Universidad de Santiago de Compostela
Casas Brugue, Miquel	4	3	9	16	Fundación Hospital Universitario Vall d'Hebron
Conde Martel, Alicia	1		13	14	Universidad de Las Palmas de Gran Canaria
Alguacil Merino, Luis Fernando	4		9	13	Universidad San Pau CEU
San Román Del Barrio, Luis	2		11	13	Universidad de Salamanca
Torrens Melich, Marta	4	3	6	13	Institut Hospital del Mar d'Investigacions Mèdiques
Álamo González, Cecilio	4	1	7	12	Universidad de Alcalá de Henares
Beneit Montesinos, Juan Vicente	3	1	8	12	Universidad Complutense de Madrid
Collado Megía, María Isabel	2	2	8	12	Universidad Complutense de Madrid
Fernández De La Gandara, Fernando	5		7	12	Universidad Complutense de Madrid
Simón Pérez, Vicente	9	1	2	12	Universidad de Valencia
Valverde Granados, Olga	4	3	5	12	Universitat Pompeu Fabra
Álvarez González, Javier	2	3	6	11	Universidad de Valladolid
Dueñas Laita, Antonio		2	9	11	Universidad de Valladolid
Jané Carrenca, Francesc	10		1	11	Universitat Autònoma de Barcelona
Leal Cercós, Carmen	3		8	11	Universitat de València
Mendez Carrillo, Francisco Javier	7		4	11	Universidad de Murcia
Vega Fuente, Amando	3		8	11	Universidad del País Vasco
Echeburua Odriozola, Enrique	7		3	10	Universidad del País Vasco
Velasco Martín, Alfonso	6	2	2	10	Universidad de Valladolid

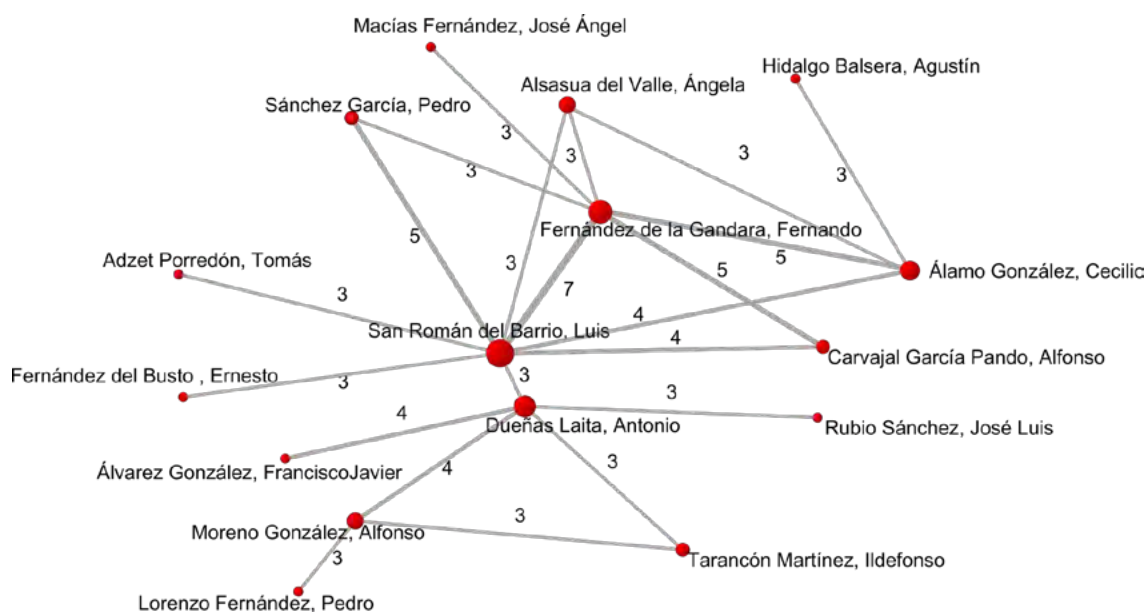


Figure 4. Network of committees examining Spanish doctoral theses on drug addiction (group of 16 members).

Note. The vertices represent the academics who act as chairs or examiners. The size of the vertices determines the direct connections with other vertices. The thickness of the lines represents the total number of times that two committees co-occur in the same thesis.

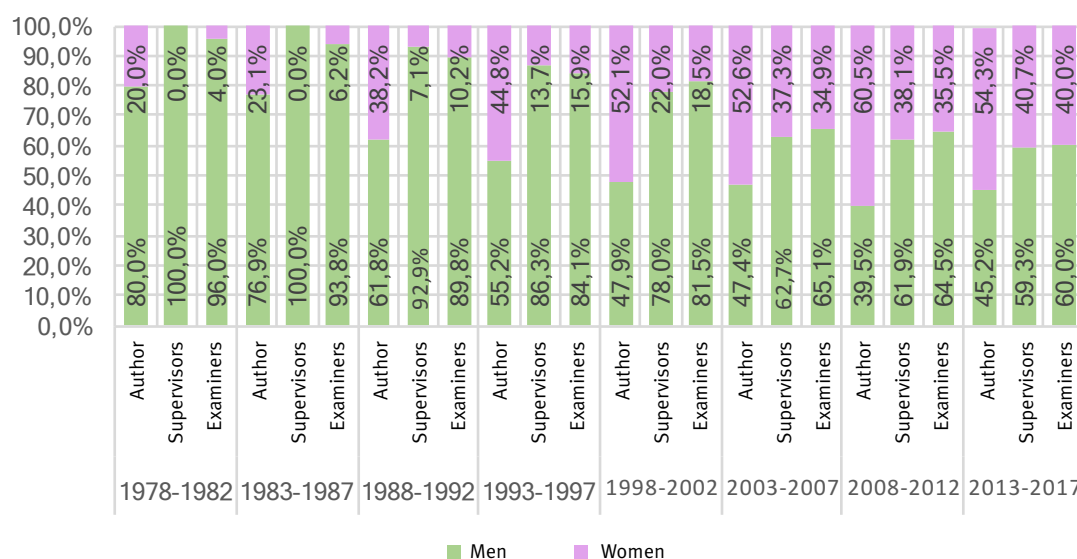


Figure 5. Comparison by sex of participants in doctoral theses on drug addiction

academics on examining committees. Moreover, this co-occurs more often on the committees with Fernando Fernández de Gandara (Complutense University of Madrid) and they, in turn, form two triangles of co-occurrence with Cecilio Álamo González (Alcalá de Henares University) and Alfonso Carvajal García Pando (Valladolid University).

Comparison by sex of thesis process participants

Men comprised 49.5% of authors and women 50.5%. In the first four five-year periods, men make up the greater proportion of authors, while from the five-year period 1998-2002 the situation reverses to women submitting the most theses, with the most significant difference occurring in the period 2008-2012, when women's output makes up 60.5% (Figure 5) of the total.

With respect to supervisors, 68.2% are men and 31.8% are women. Figure 5 shows that there is a constant and gradual growth in the participation of women as doctoral thesis supervisors, rising from zero in the first and second quinquennia to 40.7% in the last five years.

In the case of examining committees, men make up 74.4% of members and women 25.6%, with a growing trend in the percentage of women sitting on committees being observable. During the first two decades, the percentage of women sitting on committees was greater than the percentage of theses supervised by women, with values of 4% and 6.2% as committee members and zero as supervisors. These differences are steadily disappearing, with the percentage of women supervisors already exceeding the percentage of women examiners in the five-year period 1998-2002.

Thematic analysis of theses

In general, the subjects dealt with in the doctoral theses are psychology, pharmacology and medical sciences. Within the field of psychology, the following subjects stand out: psychopharmacology ($n = 385$) and psychology ($n = 379$), psychopathology ($n = 31$), experimental psychology ($n = 23$) and clinical and social psychology, with 21 theses each. In the medical sciences, the keyword medical sciences ($n = 223$), psychiatry ($n = 52$), internal medicine ($n = 37$) and public health ($n = 35$) are prominent. The specific keywords related to addiction are drug abuse ($n = 304$), followed by alcoholism ($n = 200$), drug effects ($n = 196$) and drug addiction treatment ($n = 126$). Table 4 shows keywords appearing in more than 10 doctoral theses.

Figure 6 shows the six most frequent keywords in each five-year period. It can be observed that in the first five-year period, doctoral theses focus on aspects related to psychology, peaking in the two central quinquennia from 1993 through 2002, while in the subsequent five-year periods it undergoes a very significant decline until it almost disappears. Drug effects emerges strongly in the years from 1998 to 2002, and although they subsequently decline slightly, in the last five years it becomes the most researched aspect alongside drug abuse, thus reflecting the greatest concern, together with alcoholism.

Figures 7 and 8 show the relationships between keywords occurring jointly in the same thesis in the periods 1978-1997 and 1998-2017. The network of the first period (1978-1997) shows that psychology and psychopharmacology appear more often in theses with other keywords. These, in turn, are frequently found alongside drug abuse, alcoholism and medical sciences. Keywords such as the drug

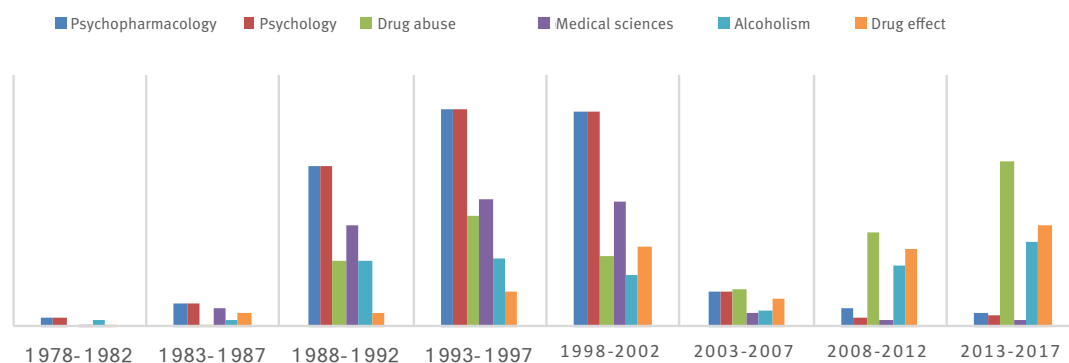


Figure 6. Changes by five-year period in the six most used keywords in doctoral theses on drug addiction

Table 4. Frequency of keywords in Spanish doctoral theses on drug addiction (>10 theses).

Keyword	Frequency	%
Psychopharmacology	385	12.6%
Psychology	379	12.4%
Drug abuse	304	9.9%
Medical sciences	223	7.3%
Alcoholism	200	6.5%
Effect of drugs	196	6.4%
Drug addiction treatment	126	4.1%
Psychiatry	52	1.7%
Pharmacodynamics	42	1.4%
Pharmacology	40	1.3%
Internal medicine	37	1.2%
Public health	35	1.1%
Mechanisms of drug action	33	1.1%
Psychopathology	31	1.0%
Epidemiology	28	0.9%
Neurosciences	27	0.9%
Psychotropic drugs	27	0.9%
Toxicology	26	0.8%
Experimental psychology	23	0.8%
Clinical psychology	21	0.7%
Social psychology	21	0.7%
Psychology of children and adolescents	20	0.7%
Preventive medicine	19	0.6%
Clinical sciences	18	0.6%
Personality	18	0.6%
Life sciences	17	0.6%
Psychology of abnormality	16	0.5%
Physiological psychology	16	0.5%
Evaluation and diagnosis in psychology	13	0.4%
Behavioral responses	13	0.4%
Pathology	13	0.4%
Sociology	13	0.4%
Action of drugs	11	0.4%
Neurology	11	0.4%

effects, pharmacodynamics or psychiatry are very closely connected, while keywords related to behavior, law or sociology, among others, are found on the network's periphery.

In the network of the second period (1998-2017), drug abuse becomes the keyword that is most strongly linked to other drugs, followed by psychology and psychopharmacology. It is observed that the keyword drug effects becomes more relevant in this second period, since it grows in co-occurrence with a variety of other keywords and in the frequency of their connections. The treatment of drug addiction and alcoholism continues to be of importance in this network. In this second network and the period covered, the keyword acquired immunodeficiency syndrome disappears and new terms appear, such as occupational health, neurosciences, clinical genetics, emotion, motivation, neurochemistry and personality measurement.

Discussion

The most substantial limitation of this work is due to the shortcomings of the TESEO database itself; although it features the most complete level of thesis coding, it should be noted that the data records for thesis registration are completed by the doctoral candidates or in the faculty or department office (Delgado et al., 2006). For this reason, the records sometimes contain errors and lack relevant information, such as, for example, examining committee or supervisor. In addition, there are deficiencies in terms of completeness, quality or the complete text, among others (Fuentes & Arguimbau, 2010). A further limitation of the study involves the fact that, although all the UNESCO keywords on drug abuse have been used, it should be noted that there may be biases, since it is possible that there are theses dealing with addiction which have not have been indexed with these keywords, or that theses from another field of study were included. Such aspects of deficient coding make it difficult to recover valuable information

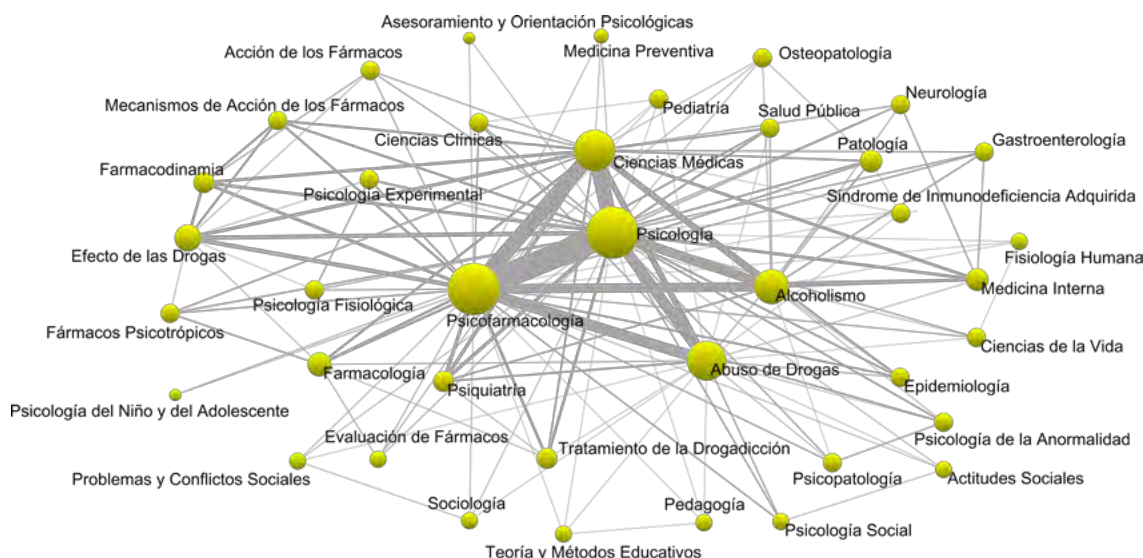


Figure 7. Network showing co-occurrence of keywords with three or more co-occurrences in doctoral theses on drug addiction (1978-1997).

Note. The size of the vertices is proportional to the number of direct relationships with other keywords, and the thickness of the lines represents the number of times that two keywords co-occurred in the same thesis.

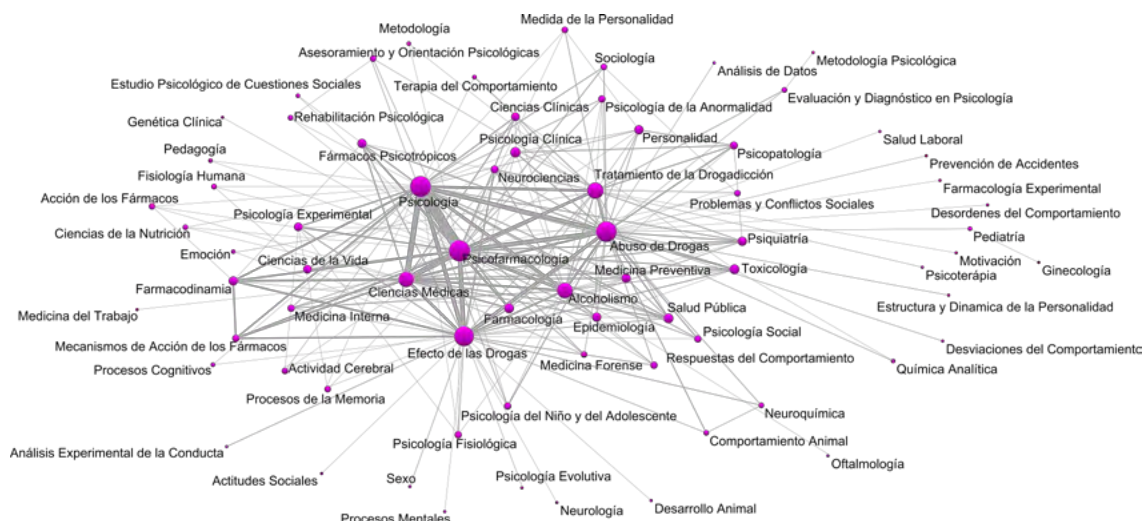


Figure 8. Network showing co-occurrence of keywords with three or more co-occurrences in doctoral theses on drug addiction (1998-2017).

Note. The size of the vertices is proportional to the number of direct relationships with other keywords, and the thickness of the lines represents the number of times that two keywords co-occurred in the same thesis.

linked to addiction or result in its loss (Curiel et al., 2018) and thus obscure or hinder the possibilities of a better knowledge of the field. However, despite such limitations, the TESEO database is an effective source for analyzing doctoral thesis output at Spanish universities since it has more records than any other (Machan & Sendra, 2018; Ramos-Pardo & Sánchez-Antolín, 2017).

Since the beginning of this century, studies of doctoral theses have gained momentum because they provide useful

indicators when analyzing the evolution of a science, lines of research and research trends, or the most productive academics in thesis supervision, which is important since these are original pieces of work and subject to a rigorous examination (Arguimbau-Vivó & Fuentes-Pujol, 2009; Curiel-Marín & Fernández-Cano, 2015; Delgado et al., 2006; Fuentes & Arguimbau, 2010; Fuentes-Pujol & González, 2002; Miguel, 2000; Repiso, Torres-Salinas & Delgado, 2011b). Furthermore, a study of theses in a given discipline

provides an overview of its structure and the most influential academics working in it; students often seek to have their theses supervised by the most prestigious or powerful academics in the field, aiming to link the prestige of the academic to their work, since “the simple number of theses supervised is sufficient to distinguish the great promoters in the different disciplines” (Bourdieu, 2008).

Thesis output in the field of addiction during the period studied is similar to that found in most areas of science, with the trend of sustained growth in the number of defended theses only broken by a drop during the academic year 2004/2005 (Fuentes & Arguimbau, 2010). This decrease in almost all fields can be explained by a weakness in TESEO in relation to keyword labelling: during the period 2001-2005 there are numerous records with no keywords assigned (Sánchez et al., 2017), resulting in a loss of records when running searches in the affected field, as is our case. However, in other fields, such as sociology, the growth in the number of doctoral theses defended is constant (Castelló-Cogollos, 2016). Where our subject does resemble sociology is in the exponential growth over the most recent five-year periods, a phenomenon that does not occur in other fields such as, for example, otolaryngology (Diego & Prim, 2008), psychology (Agudelo et al., 2003; Osa-Lluch, Haba, Fonseca, Civera & Tortosa, 2013) or the field of radiology (Repiso et al., 2011b). This growth could be due to the evident concern generated by the problem of drug addiction in recent years.

With regard to the authors of the theses, it was found that 11.7% of the total has continued an academic career, subsequently participating as supervisors or examiners; this is 1.6% lower than in the field of sociology, where 13.4% continue their academic careers (Castelló-Cogollos, 2016). One possible explanation can be found in the profile of the successful candidates in this area, since after graduation most doctors and psychologists dedicate themselves to clinical work rather than university teaching or research.

The university producing the most theses on drug addiction is the University of Valencia, probably because it offers several master's degrees in this field, as well as running specific research groups such as the Psychobiology Research Unit of Drug Dependence attached to the Psychology Department, or the Neuropharmacology of Addiction group (NEUROPHARAD) at the Pharmacy Department. The University of Valencia, the University of Valladolid and the University of Santiago de Compostela are among the most productive universities, more so than the top five universities in overall doctoral thesis output in Spain, namely the Complutense University of Madrid, the Autonomous University of Madrid, the University of Barcelona, the Autonomous University of Barcelona and the University of Granada (Sánchez et al., 2017).

With regard to supervision, the noticeably wide range of people who have supervised theses is significant, since

75.9% of supervisors have only overseen a single thesis, a value almost 14 percentage points below that observed in the doctoral theses of women's studies at national level in the period 1976-2002 (Torres & Torres, 2005). However, in areas such as librarianship and documentation, almost 50% of the theses defended in Spain in the period 1992-2006 are led by just six supervisors (Olmeda-Gómez, Perianes-Rodríguez, Ovalle-Perandones & de Moya-Anegón, 2009). This spread may be related to the thematic diversity observed in the field of addiction since substance use affects a multitude of health, family and social aspects and can therefore be analyzed from a variety of methodological and theoretical aspects.

Analyzing the data regarding thesis supervisors and examiners can identify the most important academics in the field of addiction. At the level of supervision, the difference between Alfonso Velasco Martín and other supervisors is clear. Velasco has dedicated his entire career to the study of drugs and poisons at the University of Valladolid, becoming an authority in his field. The woman who has supervised most doctoral theses is Ana María Bermejo Barrera, who has developed her career in the field of toxicology at the University of Santiago de Compostela. The fact that she is the only woman among the top ten supervisors may be a result of gender bias because, as various investigations have shown, women encounter gender-based career obstacles in their professions (Alonso-Arroyo, Bolaños-Pizarro, González-Alcaide, Villamón & Aleixandre-Benavent, 2010; Vicente, 2003; García de Cortázar & García de León, 1997; García, 1990; Gonzalez-Alcaide, Agullo-Calatayud, Valde-rama-Zurián & Aleixandre-Benavent, 2009; Lluch, 2012).

With regard to sitting on examining committees, substantial differences were found because the same value cannot be assigned to taking part as chair, secretary, or member. The role of chairperson carries more responsibility and prestige and, for this reason, it is customary to appoint a renowned academic in the field. While it is true that this model of chair appointment is the most common, it should be noted that the chair is occasionally chosen according to the age of the committee's members. If these differences in weighting are considered, the positions regarding greatest participation would change; while Emilio Ambrosio is the academic who has sat on most examining committees, this was mostly as a normal member; Francesc Jané Carrenca, on the other hand, almost always sat on committees as chairman, given his long career in medicine and his position as emeritus professor of pharmacology at the Universitat Autònoma de Barcelona.

The study of supervisors and examiners thus shows that, having consolidated or finished their academic career, Alfonso Velasco and Francesc Jané possess greater prestige and capacity for action, which confirms Bourdieu's theory (2008) that the accumulation of academic capital and prestige is directly linked to the number of years in academia

and to age. The names of Miguel Sánchez Turet, a professor in the Department of Psychiatry and Clinical Psychology and founder of the master's degree in drug addiction at Barcelona University, and Elisardo Becona Iglesias, professor of clinical psychology at the University of Santiago de Compostela also stand out.

Regarding the number of invitations a single academic receives to join a committee, the maximum is eleven, and the maximum reciprocity is five and three petitions, figures which are very similar in the field of sociology, where the maximum number of invitations received by the same academic is ten (Castelló-Cogollos, 2016). These data regarding number of invitations add to the existing spread in the participation on committees and confirms that in the area of drug addiction the level of inbreeding is not particularly high and is similar to that found in sociology. Therefore, we may consider that it is a field of science open to other disciplines and the exchange of theories and methods. Nevertheless, the fact that there are connections between academics could suggest a system of obligations, because "he who invites a colleague to sit on the examining committee of a thesis that he has supervised tacitly agrees to reciprocity and thus enters a cycle of continuous exchanges" (Bourdieu, 2008).

With regard to a comparison of the sex of authors, the proportion of women successfully completing the doctorate is greater than that of men from the quinquennium 1998-2002 onwards. This fact can also be observed in other areas such as experimental sciences and health, in which the percentage ranged from 51% to 56% per year during the quinquennium 2006-2010 (Instituto Nacional de Estadística; INE, 2011) or in psychology, where in the period from 1978 to 2012 women submitted 56.52% of the theses (Osca-Lluch et al., 2013). Also in the field of sociology, in the period 2010-2013 the percentage of women rises to 57.81% (Castelló-Cogollos, 2016).

In the case of supervisors and examiners, however, the percentages change, with men reaching higher quotas throughout the period studied; here, women make up 25.6% of examining committee members and 31.8% of supervisors. These data are similar to those found in other fields such as sociology, where the percentage of women examiners was 26.8% and that of supervisors 17.2% (Castelló-Cogollos, 2016), education, where 32.7% of examiners and 36.4% of supervisors were women (Moreno-Fernández & Moreno-Crespo, 2016), and psychology, with 26% and 30%, respectively (Osca-Lluch et al., 2013).

Although there is a gradual increase in the presence of women as thesis supervisors and examiners, their representation is still 20 percentage points lower than that of men in the last five years. These data confirm that the participation of women in education is progressively increasing and their consolidation as students and graduates is a reality (Barona, 2013; Bermúdez et al., 2011; Lluch,

2012). However, after this stage the academic careers of women slow down and a large number of women abandon an academic trajectory. (Castelló-Cogollos, 2016). In other words, while "the overall educational performance" of women is higher at all educational levels (Manassero & Vázquez, 2003), this advantage is not reflected in the academic positions held by women (Escribano, 2010; Lluch, 2012; Vicente, 2003), and it has been observed that there is a lack of gender equality among the most productive authors in the area of drug addiction (González-Alcaide et al., 2007). Much has been written on the causes of this situation, such as, for example, "bottleneck", "leaky pipeline", "hysteresis" or "hidden discrimination" (Díaz, 2008; Gonzalez-Alcaide et al., 2009). However, the metaphor most often used to clarify this phenomenon is "glass ceiling", the invisible barriers discriminating against women and difficult to pinpoint since they are not found in any law or clearly identifiable social code (García de Cortázar & García de León, 1997).

Universities must not stop incorporating such highly qualified women, who would contribute to excellence in teaching and research. To improve this situation and to make sure the equality of women is more than a formal and rhetorical goal (Lluch, 2012), some studies (Díaz & Dema, 2013; Lluch, 2012) advocate solutions such as the need to apply general corrective measures (in terms of maternity and affirmative action). An example would be the supervision of appointment procedures, career breaks in tune with the biological clock or the active recruitment of women (Díaz & Dema, 2013), in addition to effectively applying and monitoring laws regarding gender, and projecting them across all public domains (Lluch, 2012).

In terms of collaboration between subjects, the most significant, as expected, is between psychology and psychopharmacology and drug abuse, since historically "the intervention of psychology in drug addiction has developed in parallel to the specialization in this area" (Colegio Oficial de Psicólogos, 1998). While the field of addiction has benefited from psychologists' professionalism and their versatility in interventions, psychology has found an emerging field in which to develop its techniques (Martín González, 2000).

Nevertheless, when attention is turned to the development of research into drug addiction, drastic changes in focus are apparent. Whereas the initial focus is on psychopharmacology and the ability to create drugs to treat the problem of addiction and its effects, since 2000 the trend has changed and research into this question drops completely, while the interest in researching the effect of drugs on the brain and how they affect human behavior gradually increases. This change can be explained by the influence of different entities and institutions such as NIDA (National Institute on Drug Abuse), which, thanks

to Nora Volkow, favored the creation of a model of “brain disease in addiction”. This new model was consolidated in 2007 when NIDA defined addiction as “a chronic brain disease [...] It is considered a brain disease because drugs change the brain: they modify its structure and how it works” (Secades-Villa, García-Rodríguez, Fernández-Hermida & Carballo, 2007) and has led to an increase in research in neuroscience, neurochemistry and clinical genetics.

In conclusion, the results confirm that bibliometric analysis of theses and the related academic networks in terms of supervision and assessment provides an instrument that facilitates an overview of the structure of a specific field of science, as well as of the academics with most influence and the greatest capacity for action (Bourdieu, 2008).

Conclusions

The realization of this study has made it clear that an analysis of the theses of a discipline provides an overview of its structure and the most influential academics involved in it. Likewise, it has been observed that the TESEO database has some limitations, the most significant of which are related to deficiencies in the coding of the data.

Regarding thesis output, it is noted that the increase in social concern over the consequences of addiction and the increase in the creation of groups and research units analyzing this problem is reflected in the growing number of doctoral theses in the field of addiction.

The results indicate that the positions with greatest power of action and academic prestige are occupied by professors such as Alfonso Velasco or Frances Jané, which was to be expected since in some cases they have either finished their teaching career or consolidated it well. Emilio Ambrosio Flores, Miguel Sánchez Turet and Elisardo Becoña Iglesias have also been or still are important academics in the field of drug addiction.

The analysis by institution shows that the leading universities in this field are the University of Valencia, the Autònoma University of Barcelona and the University of Valladolid.

Regarding the study of gender, the promotion of women to positions of great academic responsibility or power is slow since the levels of participation both as supervisors and examiners continues to be lower than that of men. It can thus be said that universities also suffer from a “glass ceiling”, which makes it difficult for women to progress in the workplace, obstructing access to higher positions of responsibility.

Regarding research trends in drug addiction, a change has been observed from an initial focus on psychopharmacology and its effects to a focus on the effects of drugs on the brain. Similarly, the large number of keywords found in this study is an example of the rich diversity of issues that affect drug addiction.

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Conflict of interests

The authors of this article declare that there is no conflict of interest.

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What to do when drivers test positive for methadone in roadside drug tests? The Spanish Experience

¿Que hacer en los casos que dan positivo a metadona en los controles de drogas en carretera? La experiencia de España

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Driving under the influence of illicit drugs, as well as some legal substances, is against the law internationally (WHO, 2016). To prevent such risky behaviour, Spain is one of the European Union countries with a zero tolerance policy, where driving with any amount of drugs in the body is illegal. Roadside drug screening or testing is mandatory (the law penalises all those who refuse to undergo such tests believing they would turn out positive), and are performed on oral fluid. When a driver tests positive, a second sample of oral fluid is obtained and sent to accredited laboratories for confirmation and quantification analysis of the detected substances (Álvarez, Gonzalez-Luque & Seguí, 2016).

Spanish legislation establishes that when the substance detected is a medical drug which requires a doctor's prescription and is used in accordance with its marketing authorisation (as indicated in the summary of product characteristics), the standard penalties are not applied provided that no other 'non-permitted' substance is detected. This requires a (medical) report to confirm the prescription of the drug detected (Fierro, Colas, González-Luque & Álvarez, 2017): such could be the case of patients in a methadone maintenance program.

In a recent article, we revealed the presence of opioids in the confirmation analysis of those drivers with a positive result in road drug tests between 2011 and 2016 (Herrera-Gómez, García-Mingo, Colas, González-Luque & Álvarez, 2018). In this period, a total of 179,645 tests were carried out, of which 65,244 were positive. Methadone was confirmed present in 4.1% of all these positive cases, with

most drivers being male (94%) and middle-aged (mean $\pm$ standard deviation (SD) 41.90 $\pm$ 7.61 years). In almost all cases, other illicit drugs were also detected (99.6%), such as heroin (81.9%), cocaine (45%), cocaine and cannabis (33%), or cannabis alone (6%). Table 1 shows the figures for positive tests during the period covered by the study.

Table 1. *Presence of methadone in road drug controls in Spain, 2011–2016*

Year	Number of tests carried out in roadside controls*	Number of drivers testing positive in roadside controls**	Number of cases confirmed by toxicology labs	
			Methadone only	Methadone and other substances
2011	743	62	0	10
2012	3487	1087	1	169
2013	4563	2017	1	132
2014	29643	9991	2	465
2015	76040	25966	3	933
2016	65169	26121	5	935
Total	179645	65244	12	2644

Note. * Data correspond to number of tests per year

** Data refer to positive cases in roadside screening controls or drug detection tests.

The results of this study emphasise the serious problem of the use of multiple psychoactive substances by Spanish drivers. Methadone and other opioids authorised as medical drugs are often used abusively in the population, generally in combination with other psychoactive substances (Guardia, 2018; Volkow & McLellan, 2016).

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A key question is what should be done when a driver-patient requests a (medical) report confirming the prescription of methadone (and other drugs) to avoid a traffic fine following a positive result in a drug control. It should be the norm to request that these patients present the document they received from the traffic authorities with the result of the confirmation analysis, before issuing the report confirming the prescription of methadone (and other drugs), if indeed this is the case. It should not be forgotten that the driver-patient will be penalised if other psychoactive substances not legally authorised are detected in his/her body. In any case, we must always report what we know: the prescribed medication and the patient's clinical status.

The kits currently used in roadside drug controls in Spain do not detect methadone; it should thus not be surprising that a large percentage of drivers testing positive for methadone in the confirmation analysis were also positive for other opioids (heroin) and illicit drugs (cocaine, cannabis). However, the high percentages of combined use surprised us, and we consider them alarming.

Of the patients in opioid substitution programmes in Europe, 63% are under methadone treatment, while 35% are being treated with buprenorphine and buprenorphine/naloxone (EMCDDA, 2017, pp: 68-69). In Spain, 91.2% were on methadone treatment in 2016, while only 8.8% were on buprenorphine/naloxone (Plan Nacional sobre Drogas, 2018, pp: 109-110). Buprenorphine and methadone can both provoke moderate to severe deterioration in the ability to drive safely (Ravera et al, 2013), and, like other medications which affect driving, the packaging of these drugs in Spain carries a specific pictogram: the "medicines and driving" pictogram (and the leaflets contain patient information on these effects).

The data do not allow us to determine whether or not these methadone-positive cases in roadside drug controls involve drivers who "abuse" this opioid or drivers on methadone maintenance programmes. The frequent comorbidity of these opioid-dependent patients, which could also affect their driving ability, must also be taken into account. In these cases, it is particularly relevant to prescribe those drug(s) which cause less deterioration in the driver's abilities.

Patients should be informed that driving under the influence of drugs means putting themselves and other road users at risk, that the devices currently in use will detect the presence of drugs (and certain medications) in saliva, and that they could be penalised (Álvarez, González-Luque & Seguí, 2016; Gutiérrez-Abejón, Herrera-Gómez, Criado-Espejel & Álvarez, 2017).

Conflict of interests

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Smoking cessation interventions in substance use treatment facilities: clinical implications and recommendations for implementation

Tratamiento del tabaquismo en centros de tratamiento de drogodependencias: implicaciones clínicas y recomendaciones para su implementación

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There exists mounting evidence stating the positive impact of smoking cessation over substance use abstinence outcomes. While quitting smoking is related to a 25% greater likelihood of long-term abstinence from drugs (Prochaska, Delucchi, & Hall, 2004), smoking leads to 4.86 times greater odds of substance use relapse (Weinberger et al., 2018). Despite consensus having been reached in favor of the implementation of smoking cessation services in substance treatment facilities (Cohn, Elmasry, & Niaura, 2017), the integration of quitting aids within these contexts has been scarcely adopted. In Spain, the organizational culture of substance use treatments is considered the major barrier to integrating smoking cessation services (Nieva & Gual, 2005). Both staff and patients typically perceive tobacco as a less harmful drug than alcohol. The belief that smoking cessation will compromise substance abuse recovery deters patients from quitting.

This study sought to advance knowledge on the provision of smoking cessation treatments within substance use disorder SUD treatment facilities in Spain. It also sought to identify barriers to effectively implementing smoking cessation treatments.

A total of 20 SUD treatment facilities from the Principality of Asturias (located in the north-west of Spain with 1,034 million habitants), were identified using a guide on substance use resources (Health Council of the Principal-

ity of Asturias, 2016). Of 20 existing facilities, 15 agreed to participate (7 out of 12 ambulatory, 5 out of 5 residential and 3 out of 3 mixed facilities). Treatment modality was primarily mixed (14/15), followed by female-centered (1/15). Most of the treatment programs were focused on three or more substances (10/15), followed by cocaine only (2/15), cocaine and opiates (1/15), cannabis only (1/15), and alcohol only (1/15). An ad hoc survey (fully accessible at <https://docs.google.com/forms/d/1y1Mt-PzmQQptSHVHOpRsd2dBOaAGmf9NzRJw5Ih9UFkA/edit?ts=5c86aee2>) comprising 34 items was provided to the principal coordinator of each facility between July-October 2018 to collect data on the availability/provision of resources to support patients' quit attempts and normative tobacco use. The coordinators were also queried on their opinion about providing patients reporting SUD with quitting aids.

Of the 15 surveyed centers, only 3 (20%) systematically offered smoking cessation. A total of 10 out of 15 centers (66.66%) self-reported any tobacco control measure: banning cigarette exchange (4/10; 40%), limiting time for rolling cigarettes (4/10; 40%), and using cigarettes as a prize/punishment (2/10; 20%). Barriers to effectively implementing smoking cessation treatments are reported in Table 1.

The low provision of quitting aids within SUD treatment facilities is substantially lower than the one reported by a similar study indicating that 55.6% of 142 Spanish drug

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centers provide cessation support (Becoña Iglesias et al., 2006). Delaying offering quitting aids results in a lack of treatment for some patients who would otherwise have been interested in attempting to quit.

Table 1. *Barriers to effectively implementing smoking cessation treatments (N = 15)*

Staff level (n/%)	Negative beliefs of the effect of quitting smoking on SUD abstinence	11 (73,3%)
	Lack of specific training	2 (13,3%)
Resource level (n/%)	Lack of financial and time resources	3 (20%)
Organizational level (n/%)	Lack of recognition of smoking cessation as part of the therapeutic plan	9 (60%)
	Lack of restrictions on the daily CPD	7 (46,6%)

Note. SUD = Substance use disorder; CPD = Cigarettes per day.

We have identified several factors that reduce the chance of addressing patients' smoking behavior: negative beliefs regarding the impact of quitting over drug abstinence, lack of smoke-free policies, no staff training, and a permissive smoking culture.

Organizational change approaches have been increasingly developed and assessed within drug treatment settings and shown to be cost-effective for increasing provision of cessation counselling (Skelton et al., 2018). Implementing organization change models pursuing "denormalization" of tobacco use, providing staff with education on smoking cessation treatment and eliminating negative beliefs of the effect of quitting smoking on SUD abstinence are all highly advisable measures.

Limitations need to be mentioned. The fact that we did not collect data on patients and staff might have negatively impacted the center's representativeness. Also, the fact that the study was restricted to Asturias prevents its generalization to other communities. Finally, hospitalization centers were not included, and the results cannot be extrapolated to these contexts.

In sum, these findings add substantially to the current situation on the provision of quitting aids within SUD facilities. Changes at patient, staff, and organizational levels should be approached in order to effectively integrate smoking cessation treatments into SUD treatment facilities.

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Conflict of interest

No conflict declared.

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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 "Sponsorship, 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.

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

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.
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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 resume 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.

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

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

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1. NOMBRE DEL MEDICAMENTO. Xepilon 25 mg suspensión inyectable de liberación prolongada. Xepilon 50 mg suspensión inyectable de liberación prolongada. Xepilon 75 mg suspensión inyectable de liberación prolongada. Xepilon 100 mg suspensión inyectable de liberación prolongada. Xepilon 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 117 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. 75 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 176 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. 100 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 234 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. 150 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 293 mg de palmitato de paliperidona equivalentes a 150 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1.3. **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.** Xepilon 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, Xepilon puede ser utilizado sin necesidad de estabilización previa con tratamiento oral si los síntomas psíquicos son leves o moderados y es necesario un tratamiento con un inyectable de acción prolongada. **4.2. Posología y forma de administración.** Posología. Se recomienda iniciar Xepilon con una dosis de 50 mg en el día 1 de tratamiento y 100 mg una semana después (día 8), ambos administrados en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). La tercera dosis se debe administrar un mes después de la segunda dosis de inicio. La dosis de mantenimiento mensual recomendada es de 75 mg; algunos pacientes pueden beneficiarse de dosis inferiores o superiores dentro del rango recomendado de 25 a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. Los pacientes con sobrepeso u obesas 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 Xepilon (ver sección 5.2), dado que el pleno efecto de las dosis de mantenimiento puede no resultar evidente durante varios meses. **Cambio desde paliperidona oral de liberación prolongada a risperidona oral a Xepilon.** El tratamiento con Xepilon se debe iniciar según se describe al comienzo de esta sección 4.2. Durante el tratamiento de mantenimiento mensual con Xepilon, los pacientes previamente estabilizados con diferentes dosis de paliperidona comprimidos de liberación prolongada, pueden alcanzar una exposición similar a paliperidona en estado estacionario por vía inyectable. La dosis de mantenimiento de Xepilon necesaria para alcanzar una exposición similar en el estado estacionario se muestra a continuación:

Dosis de paliperidona comprimidos de liberación prolongada y Xepilon necesaria para alcanzar una exposición a paliperidona similar en estado estacionario durante el tratamiento de mantenimiento	
Dosis previa de paliperidona comprimido de liberación prolongada	Inyección de Xepilon
3 mg diarios	25-50 mg mensualmente
6 mg diarios	75 mg mensualmente
9 mg diarios	100 mg mensualmente
12 mg diarios	150 mg mensualmente

El tratamiento recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con Xepilon. Algunos pacientes se pueden beneficiar de una retirada gradual. Algunos pacientes que cambian de dosis orales más altas de paliperidona (p. ej., 9,12 mg diarios) o inyecciones en el glúteo con Xepilon pueden tener una exposición plasmática menor durante los primeros 6 meses después del cambio. Por lo tanto, alternativamente, se puede considerar administrar inyecciones en el deltoides durante los primeros 6 meses. **Cambio desde Risperidona inyectable de acción prolongada a Xepilon.** Al realizar el cambio de tratamiento de los pacientes desde risperidona inyectable de acción prolongada, inicie el tratamiento con Xepilon en lugar de la primera inyección programada. A partir de entonces, Xepilon se debe continuar en intervalos mensuales. No es necesario seguir el régimen de dosificación inicial de una semana incluyendo las inyecciones intramusculares (días 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 Xepilon según se describe a continuación:

Dosis de risperidona inyectable de acción prolongada y Xepilon necesaria para alcanzar una exposición a paliperidona similar en estado estacionario	
Dosis previa de risperidona inyectable de acción prolongada	Inyección de Xepilon
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 Xepilon, 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 iniciación de Xepilon 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 Xepilon (día 8 ± 4 días), el momento de reinicio recomendado depende del tiempo que haya transcurrido desde la primera inyección de 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 Xepilon de 75 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. **Omisión de la segunda dosis de iniciación (entre 4 y 7 semanas desde la primera inyección).** Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xepilon, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. **Omisión de la segunda dosis de iniciación (>7 semanas desde la primera inyección).** Si han transcurrido más de 7 semanas desde la primera inyección de Xepilon, inicie la administración según los pautas recomendadas para la iniciación de Xepilon recogidas anteriormente. **Omisión de la dosis de mantenimiento mensual (1 mes a 6 semanas).** Tras la omisión, el ciclo de inyección recomendado de Xepilon es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. **Omisión de la dosis de mantenimiento mensual (>6 semanas o 6 meses).** Si han transcurrido más de 6 semanas desde la última inyección de Xepilon, 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 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. **Omisión de la dosis de mantenimiento mensual (>6 meses).** Si han transcurrido más de 6 meses desde la última inyección de Xepilon, inicie la administración según los pautas recomendadas para la iniciación de Xepilon 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 Xepilon 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 Xepilon 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 Xepilon con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg en función de la tolerabilidad y/o eficacia individual del paciente. Xepilon 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 se prescribió aquí las dosis en los pacientes con insuficiencia hepática leve o moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes (ver sección 5.2). **Población pediátrica.** No se ha establecido la seguridad y la eficacia de Xepilon en niños y adolescentes < 18 años de edad. No hay datos disponibles. **Forma de administración.** Xepilon 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 Xepilon, 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 Xepilon 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 Xepilon 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, o 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.** Xepilon no se debe utilizar para el tratamiento de estados agitados o psicóticos graves cuando está 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 conciencia y elevación de los niveles séricos de creatina fosfoquinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiólisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de paliperidona. **Disfunción tardía/síntomas extrapiramidales.** 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. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno a ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). **Leucopenia, neutropenia y agranulocitosis.** Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xepilon. 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 Xepilon si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos $< 1 \times 10^9/L$) se debe discontinuar el tratamiento con Xepilon y controlar los niveles de GB hasta la recuperación. **Reacciones de hipersensibilidad.** Durante la experiencia post-comercialización se han notificado raras reacciones alérgicas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xepilon, 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). **Hiper glucemia y diabetes mellitus.** Se ha notificado hiper glucemia, diabetes mellitus y exacerbación de diabetes pre-existente que incluye como diabético y cetoadicosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antidiabéticas utilizadas. A los pacientes tratados con Xepilon se les deben monitorizar los síntomas de la hiperglucemia (tales como polidipsia, poluria, polifagia y debilidad) y a los pacientes con diabetes mellitus se les debe monitorizar regularmente el empeoramiento del control de glucosa. **Aumento de peso.** Se ha notificado un aumento de peso significativo con el uso de

Xepilon. 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. **Hipertensión ortostática.** Paliperidona puede inducir hipotensión ortostática en algunos pacientes sobre la base de su actividad alfa-1 bloqueante. Según los datos agrupados de los tres ensayos controlados con placebo, de dosis fijas y 6 semanas de duración con comprimidos orales de paliperidona de liberación prolongada (3, 6, 9 y 12 mg), el 2,5% de los pacientes tratados con paliperidona oral comunicaron hipotensión ortostática, en comparación con el 0,8% de los sujetos tratados con placebo. Xepilon 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 efusiones que predispongan al paciente a la hipotensión (p. ej., deshidratación e hipovolemia). **Convulsiones.** Xepilon puede 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. Xepilon 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 (diseño C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en dichos pacientes. **Pacientes de edad avanzada con demencia.** No se ha estudiado Xepilon en pacientes de edad avanzada con demencia. Xepilon se debe utilizar con precaución en pacientes de edad avanzada con demencia y con factores de riesgo de poder caer. La experiencia con risperidona citada más adelante se considera válida también para paliperidona. **Mortalidad global.** En un metanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, tales como risperidona, aripiprazol, olanzapina y quetiapina, tenían un mayor riesgo de mortalidad en comparación con placebo. Entre los pacientes tratados con risperidona, la mortalidad fue del 4% frente al 3,1% con placebo. **Reacciones adversas cerebrovasculares.** Se ha observado un aumento de aproximadamente 3 veces del riesgo de reacciones adversas cerebrovasculares en los ensayos clínicos aleatorizados controlados con placebo en la población con demencia al utilizar algunos antipsicóticos atípicos, tales como risperidona, aripiprazol y olanzapina. Se desconoce el mecanismo de este aumento del riesgo. **Enfermedad de Parkinson y demencia con cuerpos de Lewy.** Los médicos deben sopesar los riesgos y los beneficios de prescribir Xepilon a los pacientes con enfermedad de Parkinson o Demencia con Cuerpos de Lewy (DLQ), ya que ambos grupos pueden tener mayor riesgo de padecer Síndrome Neuroléptico Maligno, así como tener una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, abulia, inestabilidad postural con caídas frecuentes, además de síntomas extrapiramidales. **Pirapismo.** Se ha notificado que los medicamentos antipsicóticos (incluida risperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Durante la vigilancia post-comercialización, también se han notificado casos de priapismo con paliperidona oral, que es el metabolito activo de risperidona. Se ha de informar a los pacientes de la necesidad de acudir al médico urgentemente en caso de que el priapismo no haya sido resuelto en el transcurso de 4 horas. **Regulación de la temperatura del organismo.** Se ha atribuido a los medicamentos antipsicóticos la interrupción de la capacidad del organismo para reducir la temperatura corporal central. Se aconseja proceder con especial cautela cuando se prescribe Xepilon a pacientes que vayan a experimentar circunstancias que puedan conllevar a una elevación de la temperatura corporal central, p. ej., ejercicio físico intenso, exposición a calor extremo, que reciban medicamentos concomitantes con actividad anticolinérgica o que estén sujetos a deshidratación. **Tromboembolismo venoso.** Se han notificado casos de tromboembolismo venoso (TEV) con medicamentos antipsicóticos. Dado que los pacientes tratados con antipsicóticos suelen presentar factores de riesgo adquiridos de TEV, se han de identificar todos los posibles factores de riesgo de TEV antes y durante el tratamiento con Xepilon y adoptar medidas preventivas. **Efecto antiemético.** Se observó un efecto antiemético en los estudios preclínicos con paliperidona. Este efecto, si se produce en humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de enfermedades como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. **Administración.** Se debe tener cuidado para evitar la inyección involuntaria de Xepilon en un vaso sanguíneo. **Síndrome del iris flácido intraoperatorio.** Se ha observado síndrome del iris flácido intraoperatorio (IFS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa-1-adrenérgico, como Xepilon (ver sección 4.8). El IFS 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 alfa-1-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloques alfa-1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **Excipientes.** Este medicamento contiene menos de 1 mmol (23 mg) de sodio por dosis; esto es, esencialmente "exento de sodio" para el paciente. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir Xepilon con medicamentos que prolonguen el intervalo QT, p. ej., antiarrítmicos de clase III (p. ej., quinidina, disopiridamida) y antiarrítmicos de clase III (p. ej., amiodarona, sotalol), algunos antihipertensivos, algunos otros antipsicóticos y algunos antipsicóticos (p. ej., mellequin). Esta lista es indicativa y no exhaustiva. **Posibilidad de que Xepilon 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 farmacológicos de paliperidona se ejercen sobre el sistema nervioso central (SNC) (ver sección 4.8), Xepilon debe utilizarse con precaución en combinación con otros medicamentos de acción central, p. ej., ansiolíticos, la mayoría de los antipsicóticos, hipnóticos, opiáceos, etc. o con el alcohol. Paliperidona puede antagonizar el efecto de levodopa y otros agonistas de dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se debe recetar la dosis mínima eficaz de cada tratamiento. Debido a la posibilidad de que induzca hipotensión ortostática (ver sección 4.4), se puede observar un efecto aditivo si se administra Xepilon con otros tratamientos que también tengan esta posibilidad, p. ej., otros antipsicóticos, tróficos. Se recomienda precaución cuando se coordina minipaliperidona junto con otros medicamentos que disminuyen el umbral convulsivo (es decir, fenitoína o barbitúricos, tricólicos o IRS, tramadol, mellequin, 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 2.000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xepilon y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. **Posibilidad de que otros medicamentos afecten a Xepilon.** Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vivo* ni *in vivo* de que esas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paracetamol, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{max} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad del principio activo inicialmente excretado en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP en la biodesposición 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 Xepilon, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xepilon, 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 Xepilon. Esta interacción no se ha estudiado con Xepilon. **Uso concomitante de Xepilon y risperidona a paliperidona oral.** Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando Xepilon sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xepilon con otros antipsicóticos son limitados. **Uso concomitante de Xepilon y psicoestimulantes.** El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia. Embarazo.** No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron teratogénicos 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 síntomas de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hiperventilación, hipotensión, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xepilon 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. Xepilon no debe utilizarse durante la lactancia. **Fertilidad.** No se observaron efectos relevantes en estudios en humanos. **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 Xepilon. **4.8. Reacciones adversas. Resumen del perfil de seguridad.** Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acritia, agitación, síndrome/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estas, la acritia y la infección/somnolencia parecen estar relacionadas con la dosis. **Tabla de reacciones adversas.** A continuación se recogen todos los RAMs notificados 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* ($\geq 1/10$); *frecuentes* ($\geq 1/100$ a $< 1/10$); *poco frecuentes* ($\geq 1/1.000$ a $< 1/100$); *raras* ($\geq 1/10.000$ a $< 1/1.000$); *muy raras* ($< 1/10.000$); y *fre-*

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	No conocidas*
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, infección de oídos, amigdalitis, otitis media, celulitis	infección de ojos, eritema, 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 alérgica
Trastornos endocrinos		hiperprolactinemia ^a		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 ^b , hipercalcemia, aumento del apetito, anorexia, aumento de los triglicéridos en sangre, aumento del colesterol en sangre	retinopatía diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos		insomnio ^c	agitación, depresión, ansiedad	catatonia, estado confusional, somnolencia, embolamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo ^d , acritia ^e , sedación/somnolencia, distonía ^f , mareos, discinesia ^g , temblor, cefalea	discinesia tardía, síncope, hiperventilación, mareos, postural, alteración de la atención, disartria, disgeusia, hipostesia, parestesia		como diabético, temblor catálico en reposo
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos		síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, 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 sinusual	
Trastornos vasculares	hipertensión	hipotensión, hipertensión ortostática	trombosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, tórax y mediastínicos	tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringolaringeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, distonia
Trastornos gastrointestinales	dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	molestia abdominal, gastroenteritis, disfgia, sequedad de boca, flatulencia	pneumonitis, hinchazón de la lengua, incontinencia fecal, fecaloma, queratitis	obstrucción del intestino, íleo
Trastornos hepatobiliares	aumento de las transaminasas	aumento de la gamma-glutamyltransferasa, 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, escopa	angioedema, decoloración de la piel, dermatitis seborreica
Trastornos musculoesqueléticos y del tejido conjuntivo	dolor musculoesquelético, dolor de espalda, artralgia	aumento de la creatina fosfatasa en sangre, espasmos musculares, rigidez en las articulaciones, debilidad muscular, dolor de cuello	reumatoidismo, inflamación de las articulaciones	anomalía postural
Trastornos renales y urinarios		incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales				síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama	amenorrea, galactorrea	disfunción eréctil, trastorno de la eyaculación, trastornos menstruales, ginecomastia, disfunción sexual, dolor de mamas	molestia de las mamas, congestión de las mamas, aumento de las mamas, secreción vaginal	priapismo
Trastornos generales y alteraciones en el lugar de administración	pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema*, aumento de la temperatura corporal, alteración de la marcha, dolor de pecho, malestar de pecho, molestia, endurecimiento	hipotermia, escalofríos, sed, síndrome de abstinencia a medicamentos, absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección, hematoma en el lugar de la inyección	disminución de la temperatura corporal, necrosis en el lugar de la inyección, úlcera en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos		caídas		

*La frecuencia de estas reacciones adversas se clasifica como "no conocidas" porque no fueron observadas en los ensayos clínicos con palmitato de paliperidona. Proceden de notificaciones espontáneas poscomercialización y la frecuencia no se puede determinar, o proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral y/o de informes poscomercialización. *Referido a "Hiperalcemia" a continuación. *Referido a "Síntomas extrapiramidales" a continuación. *En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con Xepion 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 fovea. **Trastornos menstruales incluyen:** retraso en la menstruación, menstruación irregular, oligomenorrea.

Reacciones adversas notificadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de risperidona, por lo tanto, los perfiles de las reacciones adversas de estos compuestos (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. **Descripción de algunas reacciones adversas.** **Reacción analéptica.** Durante la experiencia post-comercialización, en raras ocasiones se han notificado casos de una reacción analéptica después de la inyección de Xepion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). **Reacciones en el lugar de la inyección.** La reacción adversa relacionada con el lugar de la inyección notificada con mayor frecuencia fue el dolor. La mayoría de estas reacciones se notificaron con gravedad de leve a moderada. Las evaluaciones del dolor en el sitio de la inyección en los sujetos, basadas 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 Xepion. 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 incluyen eritema (frecuente), prurito (poco frecuente) y nódulos (raro). **Síntomas extrapiramidales (SEP).** SEP incluye un análisis agrupado de los siguientes términos: parkinsonismo (incluye hipersalivación salival, rigidez musculoesquelética, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, fúas en máscara, tensión muscular, acinesia, rigidez de la nuca, rigidez muscular, modo de andar parkinsoniano, reflejo de la glabella anormal y temblor en reposo parkinsoniano), acinesia (incluye acinesia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (discinesia, coreas musculares, coreoatetosis, atetosis y mioclonía), distonia (incluye distonia, hipertonía, tortolice, contracciones musculares involuntarias, contracciones musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringospasmo, miotenia, opistótonos, espasmo orofaríngeo, pleurotorácicos, espasmo ligal y trismo) y temblor. Hay que destacar que se incluye un espectro más amplio de síntomas que no tienen necesariamente 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 normal de peso $\geq 7\%$ 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% de los grupos tratados con 25 mg, 100 mg y 150 mg de Xepion, respectivamente. Durante el periodo abito de transición/mantenimiento de 33 semanas de duración del ensayo de prevención de recaídas a largo plazo, el 12% de los pacientes tratados con Xepion cumplieron este criterio (aumento de peso de $\geq 7\%$ desde la fase doble ciego hasta el final del estudio); la media (DE) del cambio de peso desde el nivel basal del periodo abito fue de $+0.7$ (4,79) kg. **Hiperalcemia.** En ensayos clínicos, se observaron mediones de aumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xepion. Las reacciones adversas que pueden surgir con aumentos de los niveles de prolactina (p. ej., amenorrea, galactorrea, alteraciones de la menstruación, ginecomastia) se notificaron en $<1\%$ de los sujetos. **Efectos de dosis.** Con antipsicóticos puede aparecer prolongación del QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicable, parada cardíaca y torsades de pointes. Se han notificado casos de tromboembolismo venoso, incluidos casos de embolismo pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). **Notificación de sospechas de reacciones adversas.** Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: <https://www.aefma.es>. **4.9. Subpoblaciones.** **Síntomas.** En general, los signos y síntomas presentes son los resultados de la exogénesis de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipertensión, prolongación del intervalo QT y síntomas extrapiramidales. Se han notificado torsades de pointes y fibrilación ventricular en un paciente en relación con la subpoblación de paliperidona oral. En caso de subpoblaciones, se debe tener en cuenta la posibilidad de que estén implicados varios medicamentos. **Administración.** Al evaluar el tratamiento necesario y la recuperación hay que tener en cuenta la naturaleza de liberación prolongada del medicamento y la prolongada vida media de eliminación de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el tórax circulatorio deben tratarse con las medidas terapéuticas adecuadas, como administración de líquidos por vía intravenosa y/o de simpatomiméticos. En caso de síntomas extrapiramidales, 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: Psicofármacos, otros antipsicóticos. Código ATC: N05AX13. Xepion contiene una mezcla racémica de paliperidona (+) y (-). **Mecanismo de acción.** Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas, cuyos propiedades farmacológicas son diferentes de las de los neurolepticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT₂ y dopaminérgicos D₂. Paliperidona también bloquea los receptores adrenérgicos α_1 y α_2 , en menor medida, los receptores histaminérgicos H₁ y los adrenérgicos α_2 . La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D₂ potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos atropínicos y reduce las funciones motoras en menor medida que los neurolepticos tradicionales. La preponderancia del antagonismo central de la serotoninina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. **Eficacia clínica.** **Tratamiento agudo de la esquizofrenia.** La eficacia de Xepion en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Los dos tipos de Xepion en estos estudios se administraron en los días 1, 8, y 36 en el estudio de 9 semanas de duración, y, además, el día 64 en los estudios de 13 semanas de duración. No fue necesario administrar suplementos antipsicóticos orales adicionales durante el tratamiento agudo de la esquizofrenia con Xepion. El criterio principal de eficacia del estudio se definió como una reducción de las puntuaciones totales de la Escala de los Síndromes Positivo y Negativo (PANSS), como se muestra en la siguiente tabla. La PANSS es un inventario multi-elemento validado compuesto por cinco factores destinados a evaluar los síntomas positivos, los síntomas negativos, el pensamiento desorganizado, la hostilidad/excitación incontrolada y la ansiedad/depresión. La función se evaluó mediante la escala de Funcionamiento Personal y Social (PSP). La PSP es una escala homologada que mide la capacidad del paciente para desempeñar sus actividades personales y sociales en cuatro áreas del comportamiento: las actividades sociales íntimas (incluidas el trabajo y el estudio), las relaciones personales y sociales, el cuidado personal y los comportamientos disruptivos y agresivos. En el estudio de 13 semanas de duración (n=636) que comparó tres dosis fijas de Xepion (inyección inicial en el deltoides de 150 mg seguida por tres dosis en el glúteo o en el deltoides de cualquiera de 25 mg o 100 mg, 100 mg/4 semanas o 150 mg/4 semanas) con placebo, las tres dosis de Xepion fueron superiores a placebo en términos de la mejora de la puntuación total de la PANSS. En este estudio, todos los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntuación de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejora de la PANSS, que se observaron ya en el día 4, con una superioridad significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de Xepion en el día 8. Los resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de Xepion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

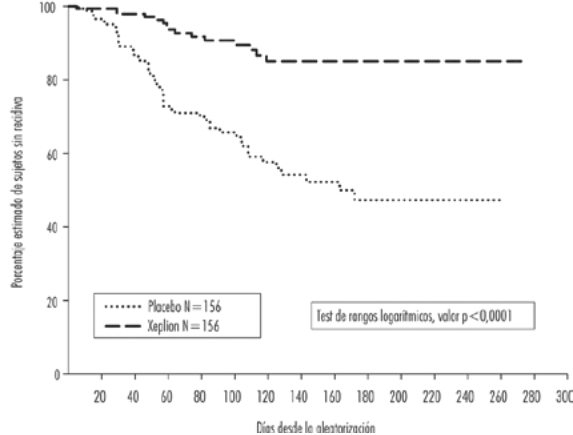
Puntuación total de la escala de los síntomas positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración de la eficacia					
	Placebo	25 mg	50 mg	100 mg	150 mg
R092670-PSY-3007*					
n=	160	155		161	160
Media basal (DE)	86,8 (10,31)	86,9 (11,99)		86,2 (10,77)	88,4 (11,47)
Variación media (DE)	-2,9 (19,26)	-8,0 (19,99)		-11,6 (17,63)	-13,2 (18,48)
Valor p (frente a placebo)		0,034		<0,001	<0,001
R092670-PSY-3003					
n=	132		93	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	129	128	131	
Media basal (DE)	90,7 (12,22)	90,7 (12,25)	91,2 (12,02)	90,8 (11,70)	
Variación media (DE)	-7,0 (20,07)	-13,6 (21,45)	-13,2 (20,14)	-16,1 (20,36)	
Valor p (frente a placebo)		0,015	0,017	<0,001	

R092670-SCH-201	n=66	n=63	n=68	
Media basal (DE)	87,8 (13,90)	88,0 (12,39)	85,2 (11,09)	
Variación media (DE)	6,2 (18,25)	-5,2 (21,52)	-7,8 (19,40)	
Valor p (frente a placebo)		0,001	<0,0001	

*En el estudio R092670-PSY-3007, se administró una dosis de iniciación de 150 mg a todos los sujetos de los grupos de tratamiento con Xepion 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 Xepion en el mantenimiento del control de los síntomas y el retraso de la recidiva de la esquizofrenia se determinó en un estudio doble ciego, controlado con placebo, de dosis flexible, con un plazo más largo, en el que participaron 849 sujetos adultos no ancianos que cumplían los criterios para la esquizofrenia del DSM-IV. Este estudio incluyó un tratamiento abierto agudo de 33 semanas de duración y una fase de estabilización, una fase aleatorizada, en promedio, se observó una C_{tr} un 28% superior en comparación con la inyección en el músculo deltoides. Las dos inyecciones iniciales intramusculares de una dosis aleatorizada, en promedio, se observó una C_{tr} un 28% superior en comparación con la inyección en el músculo deltoides. Los dos tipos de Xepion 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 Xepion durante un periodo de transición de 9 semanas de duración, seguida 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 Xepion (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 tiempo por motivos de eficacia, dado que se observó un tiempo significativamente más largo hasta la recidiva (p<0,0001, Figura 1) en los pacientes tratados con Xepion 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 Xepion 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 farmacodinámicas.** **Absorción y distribución.** Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrolizabilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{tr} un 28% superior en comparación con la inyección en el músculo deltoides. La dosis de la vida media aparente de paliperidona en los deltoides de 150 mg el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xepion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xepion 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_{tr} para dosis superiores a 50 mg. El promedio del pico en el estudio estacionario: a través del ratio para una dosis de 100 mg de Xepion 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 Xepion 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 Xepion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. **Biointerconversión y eliminación.** Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C¹⁴, el 59% de la dosis fue eliminado intacta 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 benzotiazol. Aunque en estudios in vitro se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos in vivo que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por los 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. **Liberación de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada.** Xepion 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 Xepion (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 plásmicos de iniciación con Xepion se encuentran 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 Xepion 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 (día 8 y día 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos de los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. **Insuficiencia hepática.** Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xepion 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 y la vida media de eliminación se prolonga. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (CL_{cr}=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (CL_{cr}=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (CL_{cr}=10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{0-∞}) 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 Xepion en sujetos con insuficiencia renal leve y de los resultados de los 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. **Indice 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.** 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 Xepion. **Sexo.** No se han observado diferencias clínicamente significativas entre hombres y mujeres. **Tobaquismo.** Segundos 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 Xepion el efecto del consumo de tabaco en la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensil) inyectado por vía intramuscular y paliperidona administrado 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 mayoritariamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las ratas cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratas), de los adenomas del páncreas endocrino (ratas) y los de adenomas de las glándulas mamarias (en ambos especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D₂ con el hipofalmarismo. Se desconoce la transgénesis de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACOLÓGICOS.** **6.1. Lista de excipientes.** Polisorbato 20, Polietilenglicol 400, Ácido cítrico monohidrato, Fosfato ácido disódico anhidro, Fosfato ácido disódico monohidrato, Hidróxido de sodio (para ajustar el 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 (diltio-olefina-copolímero) con un tapón de tipo émbolo, tipo troyano y un protector para la punta (goma de brombutilo) con un agujero de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 31 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaño de envase: El envase contiene 1 jeringa precargada y 2 agujeros. **Presentaciones y precios.** Xepion 50 mg suspensión inyectable de liberación prolongada PVL: 168,18 €; PVP (IVA): 214,09 €; PVP (IVA): 222,65 €. Xepion 75 mg suspensión inyectable de liberación prolongada PVL: 218,62 €; PVP: 269,53 €; PVP (IVA): 280,31 €. Xepion 100 mg suspensión inyectable de liberación prolongada PVL: 269,10 €; PVP: 320,01 €. PVP (IVA): 332,81 €. Xepion 150 mg suspensión inyectable de liberación prolongada PVL: 403,64 €; PVP: 454,55 €; PVP (IVA): 473,75 €. **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. NUMERO(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 renovación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. 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.** TREVICTA 175 mg suspensión inyectable de liberación prolongada. TREVICTA 263 mg suspensión inyectable de liberación prolongada. TREVICTA 350 mg suspensión inyectable de liberación prolongada. TREVICTA 525 mg suspensión inyectable de liberación prolongada. 2. **COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** 175 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 273 mg de palmitato de polipéridona equivalentes a 175 mg de polipéridona. 263 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 410 mg de palmitato de polipéridona equivalentes a 263 mg de polipéridona. 350 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 546 mg de palmitato de polipéridona equivalentes a 350 mg de polipéridona. 525 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 819 mg de palmitato de polipéridona equivalentes a 525 mg de polipéridona. 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 o blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). 4. **DATOS CLÍNICOS.** 4.1. Indicaciones terapéuticas. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de polipéridona (ver sección 5.1). 4.2. **Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de polipéridona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a TREVICTA. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de polipéridona inyectable mensual (± 7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de polipéridona inyectable mensual, utilizando una dosis 3.5 veces más alta como se indica en la tabla siguiente:

Dosis de TREVICTA en pacientes tratados adecuadamente con palmitato de polipéridona inyectable mensual	
Si la última dosis de palmitato de polipéridona inyectable mensual es de	TREVICTA se iniciará en la dosis siguiente
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

No se ha estudiado la dosis de TREVICTA equivalente a la dosis de 25 mg de palmitato de polipéridona 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 polipéridona preferiblemente durante cuatro meses o más. Cambio desde TREVICTA a otros medicamentos antipsicóticos. Si se suspende la administración de TREVICTA, se deben tener en cuenta sus características de liberación prolongada. Cambio desde TREVICTA a palmitato de polipéridona inyectable mensual. Para cambiar desde TREVICTA a palmitato de polipéridona inyectable mensual, este se administrará en el momento en que se debe administrar la dosis siguiente de TREVICTA, dividiendo la dosis por 3.5 según se indica en la tabla siguiente. No es necesario la dosis de inicio según se describe en la ficha técnica de palmitato de polipéridona inyectable mensual. El palmitato de polipéridona inyectable mensual se seguirá administrando una vez al mes tal como se describe en su ficha técnica.

Dosis de palmitato de polipéridona inyectable mensual en los pacientes que cambian desde TREVICTA	
Si la última dosis de TREVICTA es de	Iniciar palmitato de polipéridona inyectable mensual 3 meses después en la dosis siguiente
175 mg	50 mg
263 mg	75 mg
350 mg	100 mg
525 mg	150 mg

Cambio desde TREVICTA a los comprimidos diarios de liberación prolongada de paliperidona oral. Para cambiar desde TREVICTA a los comprimidos de palmitato de polipéridona 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 polipéridona 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 liberación prolongada.

Dosis de los comprimidos de paliperidona de liberación prolongada para los pacientes que cambian desde TREVICTA*			
Última dosis de TREVICTA (semana 0)	Tiempo transcurrido desde la última dosis de TREVICTA		
	de la semana 12 a 18, incluida	de la semana 19 a 24, incluida	desde la semana 25 y en adelante
Dosis diaria de los comprimidos de polipéridona 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 polipéridona de liberación prolongada diarios se deben adaptar siempre al paciente individual, teniendo en cuenta variables como los motivos del cambio, la respuesta al tratamiento previo con paliperidona, la gravedad de los síntomas psiquiátricos y/o la tendencia a presentar efectos adversos.

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

Dosis omitidas	
Si se ha omitido la dosis programada y el tiempo transcurrido desde la última inyección es de	Medida
> 3 meses y medio a 4 meses	Se administrará la inyección lo antes posible y a continuación se reanudará el calendario de inyecciones trimestrales.
de 4 meses a 9 meses	Se seguirá la pauta de reanudación recomendada que se indica en la tabla siguiente.
> 9 meses	Se reanudará el tratamiento con palmitato de polipéridona 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 polipéridona preferiblemente durante cuatro meses o más.

Pauta recomendada de reanudación del tratamiento después de 4 a 9 meses de interrupción de TREVICTA		
Si la última dosis de TREVICTA fue de	Se administrarán dos dosis de palmitato de polipéridona inyectable mensual con un intervalo de una semana (en el deltoides)	A continuación se administrará TREVICTA (en el deltoides o el glúteo)
175 mg	Día 1 50 mg	Día 8 175 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 dosis 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 polipéridona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina < 50 ml/min). Insuficiencia hepática. No se ha estudiado el uso de TREVICTA en pacientes con insuficiencia hepática. Según la experiencia con paliperidona oral no es necesario ajustar la dosis en pacientes con insuficiencia hepática leve o moderada. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, por lo que se recomienda precaución en estos pacientes (ver sección 5.2). Población pediátrica. No se ha establecido la seguridad y eficacia de TREVICTA en niños y adolescentes menores de 18 años. No se dispone de datos. Forma de administración. TREVICTA está indicado para administración intramuscular únicamente. No se debe administrar por ninguna otra vía. Cada inyección se administrará solo por un profesional sanitario, que administrará la dosis completa en una sola inyección. Se debe inyectar lenta y profundamente en el músculo deltoides o en el glúteo. Si apo-

recen 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 polipéridona ni otros agujas comercialmente disponibles (ver Información reservada para médicos o profesionales sanitarios). Se inspeccionará visualmente el contenido de la jeringa precargada para descartar la presencia de cuerpos extraños o decoloración antes de la administración. Es importante agitar energicamente la jeringa con la punta hacia abajo y la mezcla relajada durante al menos 15 segundos para garantizar una suspensión homogénea. TREVICTA debe ser administrado dentro de los 5 minutos siguientes a la agitación. Si transcurren más de 5 minutos antes de la inyección, agitar otra vez energicamente 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 1/2 (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). No se debe administrar en el centro del músculo deltoides. Las inyecciones deltoides 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 1 1/2 (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 energicamente 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 dada la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará diligentemente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. 4.3. **Contraindicaciones.** Hipersensibilidad al principio activo, a respondedor o a alguno de los excipientes incluidos en la sección 6.1. 4.4. **Advertencias y precauciones especiales de empleo.** Uso en estados psíquicos graves o de agitación aguda. No se debe utilizar TREVICTA para tratar estados psíquicos graves o de agitación aguda en los que es necesario un control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se usa a la vez que otros medicamentos que se sepan que prolongan el intervalo QT. Síndrome neuroléptico maligno (SNM). Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonoma, alteración de la conciencia y elevación de la creatinofosfatasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rhabdomiólisis) 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/síntomas extrapiramidales. Los medicamentos con propiedades anticolinérgicas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, que se caracteriza por movimientos rítmicos involuntarios, predominantemente de la lengua y/o de la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la posibilidad de suspender la administración de todos los antipsicóticos, incluido el paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Se requiere precaución en pacientes que reciben tanto psicostimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno a ambos medicamentos. Se recomienda la retirada gradual del tratamiento estético (ver sección 4.5). Leucopenia, neutropenia y granulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y granulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo clínicamente relevante o de leucopenia/neutropenia inducido 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 que intervienga 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 $< 1 \times 10^9$) 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 respondedor oral o paliperidona oral (ver sección 4.8). Hiperuricemia y diabetes mellitus. Se han notificado hiperuricemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso como diabético y cetoacidosis en el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica clínica habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polipisia, polifuria y estenuo) 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 significativo de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipertensión ortostática. Paliperidona puede inducir hipertensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipertensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o esquema de micción, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipertensión (p. ej., deshidratación e hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥ 50 a < 80 ml/min), se ajustará la dosis y se estabilizará al paciente con palmitato de polipéridona 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 respondedor indica que se describe o continuación se considera aplicable también a paliperidona. Mortalidad global. En un metaanálisis de 17 ensayos clínicos controlados, las dosis de dosis de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como respondedor, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con respondedor, 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 respondedor, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplicó por 3 aproximadamente. Se desconoce el mecanismo de este aumento de riesgo. Enfermedad de Parkinson o 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 (DL), 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. Precaución. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa-adrenérgico inducen hipotensión. Se indicará al paciente que solicite asistencia médica urgente si el paciente no se ha resuelto en el transcurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de regular la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescriba TREVICTA a pacientes que vayan a experimentarse intervenciones que puedan contribuir a una elevación de la temperatura corporal (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 atribuido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transcurso del tratamiento con TREVICTA y se adoptarán medidas preventivas. Efecto antitrombótico. En los estudios preclínicos con paliperidona se observó un efecto antitrombótico. Si se produce este efecto en los seres humanos, puede enmascarar los signos y síntomas de la subevidencia de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Raye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA en un vaso sanguíneo. Síndrome del iris fijado intrapupilar. Se ha observado síndrome del iris fijado intrapupilar (IFS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antipéptico alfa-1-adrenérgico, como TREVICTA (ver sección 4.8). El IFS 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 antipéptico alfa-1-adrenérgico antes de la cirugía. El beneficio potencial de la intervención 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. Excipientes. Este medicamento contiene menos de 1 mmol de sodio (23 mg) por dosis; esto es, esencialmente "exento de sodio". 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 disipiramida) y antiarrítmicos de la clase III (por ejemplo, amiodarona o sotalol), algunos antipsicóticos, antibióticos (por ejemplo, fluoroquinolonas), algunos antipsicóticos y algunos antipsicóticos (por ejemplo, melagatrina). 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 los 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 antihipertensivos tríficos. Se recomienda precaución al combinar la paliperidona con otros medicamentos que disminuyen el umbral convulsivo (por ejemplo, fenitoína o barbitúricos), antihipertensivos tríficos o SRS, tramadol, melagatrina, 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 farmacocí-

nica en el estado estacionario del valproato. No se han llevado a cabo estudios de interacción entre TREVICTA y el lin, sin embargo, no es probable que se produzcan una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a TREVICTA. Los estudios in vivo indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios in vivo de que esos isoenzimas desempeñen un papel importante en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paracetamol, 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 por carbamazepina. Una disminución menor de la probabilidad de principio activo excretado inducido en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el adormiento sistémico, no se preveía 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 respondedor o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de respondedor, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con respondedor o con paliperidona oral durante periodos prolongados de tiempo. Las dosis de seguridad relacionadas con el uso concomitante de TREVICTA con otros antipsicóticos son limitadas. Uso concomitante de TREVICTA y psicostimulantes. El uso concomitante de psicostimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). 4.6. **Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de polipéridona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratogénicos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para el desarrollo (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, hipertonia, hipotonia, temblor, somnolencia, dificultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición materna a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo 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 en 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 somnolencia, síncope o visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a TREVICTA. 4.8. **Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas al medicamento observadas con mayor frecuencia notificadas en $\geq 5\%$ de los ensayos clínicos con ensayos clínicos controlados a doble ciego de TREVICTA, fueron aumento de peso, infección de las vías respiratorias altas, ansiedad, cefalea, insomnio y náuseas en el lugar de inyección. Tabla de reacciones adversas. A continuación se recogen todos los RAM notificados con paliperidona en función de la frecuencia estimada en los ensayos clínicos de paliperidona tratados con palmitato de polipéridona. Se aplican los siguientes términos y frecuencias: muy frecuentes ($\geq 1/10$), frecuentes ($\geq 1/100$ a $< 1/100$), poco frecuentes ($\geq 1/1000$ a $< 1/100$), raras ($\geq 1/10000$ a $< 1/1000$), muy raras ($< 1/10000$) 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 infecciones	infección de vías respiratorias altas, infección urinaria, gripe	neumonía, bronquitis, infección de vías respiratorias, sinusitis, cistitis, otitis, amigdalitis, onicomicosis, celulitis	infección oftálmica, acorodermis, absceso subcutáneo		
Trastornos de la sangre y del sistema linfático		disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, aumento del recuento de eosinófilos	granulocitosis	
Trastornos del sistema inmunológico		hipersensibilidad		reacción anafiláctica	
Trastornos endocrinos		hiperprolactinemia ^a		secreción inadecuada de hormona antidiurética, glucosuria	
Trastornos del metabolismo y de la nutrición	hiperglucemia, aumento de peso, pérdida de peso, apetito disminuido	diabetes mellitus ^b , hipersensibilidad, aumento del apetito, anorexia, náuseas, triglicéridos en sangre elevados, colesterol en sangre elevado	retardación diabética, hipoglucemia, polidipsia	intoxicación por agua	
Trastornos psiquiátricos	insomnio ^c	agitación, depresión, ansiedad	trastornos del sueño, menor disminución de la libido, neurosis, pesadillas	catatonia, estado de confusión, somnolencia, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso	parkinsonismo ^d , síndrome, sedación, ataxia, disfonía, mareo, discinesias ^e , temblor, cefalea	discinesia tardía, síncope, hipersensibilidad psicóptica, mareo postural, trastornos de la atención, disartria, disgeusia, hipotensión, parosismo		síndrome neuroléptico maligno, isquemia cerebral, fallo de respuesta a los estímulos, pérdida del conocimiento, reducción del nivel de conciencia, convulsiones ^f , trastornos del equilibrio, coordinación anormal	como diabético, 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 fijado (intraoperatorio)	
Trastornos del oído y del laberinto		vértigo, acúfenos, dolor de oídos			
Trastornos cardíacos	taquicardia	bloqueo aurículoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibрилación auricular, arritmia sinusal		
Trastornos vasculares	hipertensión	hipotensión, hipertensión ortostática	trombosis venosa, rubor	embolia pulmonar, isquemia	

Trastornos respiratorios, torácicos y mediastínicos	tos, congestión nasal	disnea, congestión respiratoria, síndrome, dolor torácico, rinitis, epistaxis	Síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, distorsión
Trastornos gastrointestinales	dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, odontalgia	molestias abdominales, gastroenteritis, disagra, sequedad de boca, flatulencia	pancreatitis, edema lingual, incontinencia fecal, flegma, queilitis	obstrucción intestinal, íleo
Trastornos hepatobiliares	niveles elevados de transaminasas	niveles elevados de gamma-glutamilo-transferasa y de enzimas hepáticas		ictericia
Trastornos de la piel y del tejido subcutáneo			erupción farmacológica, hiperqueratosis, escoria	angioedema, trastornos de la pigmentación, dermatitis seborreica
Trastornos osteomusculares y del tejido conjuntivo	dolor osteomuscular, dolor lumbodorsal, artalgia	valores elevados de creatinina/serumato en sangre, espasmos musculares, rigidez articular, debilidad muscular, dolor cervical	abdominalidad, hinchazón de las articulaciones	alteraciones posturales
Trastornos renales y urinarios		incontinencia urinaria, poliuria, 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, trastornos de la eyaculación, trastornos menstruales, ginecomastia, disfunción sexual, dolor mamario	hinchazón o molestia mamaria, aumento del tamaño de las mamas, flujo vaginal	prurito
Trastornos generales y alteraciones en el lugar de administración	fiebre, estenosis, fatiga, reacciones en el lugar de inyección	edema facial, edema*, aumento de la temperatura corporal, alteraciones de la marcha, dolor torácico, molestias en el pecho, malestar general, induración	hipotermia, escalofríos, 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 dermatológicas, intoxicaciones y complicaciones de procedimientos terapéuticos		caídas		

*La frecuencia de estas reacciones adversas se clasifica como "no conocida" porque no se observaron en los ensayos clínicos con paliperidona. Proceden de notificaciones espontáneas poscomercialización y la frecuencia no se puede determinar, o proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral y/o de informes poscomercialización. *Ver el apartado "Hiperproliferación" a continuación. *Ver el apartado "Síntomas extrapiramidales" a continuación. *En ensayos clínicos con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con paliperidona inyectable mensual comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,45% en todos los pacientes tratados con paliperidona inyectable mensual. **Insomnio incluye:** Insomnio inicial e insomnio medio. **Convulsiones incluye:** convulsiones del gran mal. **Edema incluye:** edema generalizado, edema periférico, edema con fiebre. **Trastornos menstruales incluye:** retrasos de la menstruación, menstruación irregular, oligomenorrea.

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 paliperidona inyectable 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 TREVICA, 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 induración, ruborización e hinchazón no se presentaron o fueron leves en $\geq 95\%$ de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. **Síntomas extrapiramidales (SEP).** En los ensayos clínicos de TREVICA se notificaron acatisia, discinesia, distonias, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyen los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, tics en máscara, trémulo muscular, acinesia, rigidez rural, rigidez muscular, marcha parkinsoniana, reflejo labial 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), distonia (incluye distonia, espasmo cervical, ampollosos, crisis oculárgicas, distonias, distonias, brucismos, risis sardónica, tetania, hipertonia, tortícolis, contracciones musculares involuntarias, contractura muscular, blefarospasmo, oculogiración, tortícolis lingual, espasmo facial, laringoespasmo, miotonia, opistótonos, espasmo bucodentario, pleurotorax, espasmo lingual y trismus) y temblor. **Aumento de peso.** En el estudio a largo plazo de retiro aleatorizado, se notificaron aumentos anormales de $\geq 7\%$ 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 TREVICA y el 1% de los pacientes del grupo de placebo. A la inversa, se notificaron reducciones anormales del peso corporal ($\geq 7\%$) desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, en el 1% de los pacientes del grupo de TREVICA 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 $+2.28$ kg en los grupos de TREVICA y placebo, respectivamente. **Hiperproliferación.** Durante la fase de doble ciego del estudio a largo plazo de retiro aleatorizado, 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 TREVICA que del grupo placebo (9% frente a 3% y 5% frente a 1%, respectivamente). En el grupo de TREVICA, 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 TREVICA tuvo una reacción adversa de amenorrea, mientras que no se observaron reacciones adversas potencialmente relacionadas con la prolactina en ninguno del grupo de 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 inesperada, paro cardíaco y torsades de pointes. Se han notificado casos de tromboembolismo venoso, entre ellos de embolia 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 Farmovigilancia de Medicamentos de Uso Humano: <https://www.notificaram.es>. **4.9. Subefectos.** **Síntomas.** En general, los signos y síntomas previstos son los resultados de la exposición 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 sobrados de paliperidona oral. En caso de sobrados agudos se debe tener en cuenta la posibilidad de que estén implicados varios fármacos. **Tratamiento.** Al evaluar las medidas terapéuticas y de recuperación, se tendrán en cuenta la naturaleza de liberación prolongada del medicamento, así como la prolongada vida media de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio se deben tratar con las medidas adecuadas, como administración de líquidos por vía intravenosa y/o de simpatomiméticos. En caso de síntomas extrapiramidales graves, se debe administrar medicación antipsicótica. Se debe mantener una supervisión y un control estícticos y continuos

hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicofármacos, otros fármacos antipsicóticos, código ATC: N05AX13. TREVICA contiene una mezcla racémica de paliperidona (+) y (-). **Mecanismo de acción.** Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolepticos 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 cataplexia y menos reducción de las funciones motoras que los neurolepticos tradicionales. La preponderancia del antagonismo central de la serotoninina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. **Eficacia clínica.** La eficacia de TREVICA 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 paliperidona de paliperidona y los últimos dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retiro 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 retiro aleatorizado, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles 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 TREVICA en el músculo deltoides o glúteo durante la fase de estabilización abierta (la dosis era 3,5 veces la última dosis de paliperidona de paliperidona mensual). Los pacientes que se consideraban clínicamente estabilizados al final de la fase de estabilización de 17 semanas se aleatorizaron en proporción 1:1 para recibir TREVICA o un placebo en una fase doble ciego de duración variable (la dosis de TREVICA 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 TREVICA (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 puso fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 283 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,81 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICA 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 TREVICA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

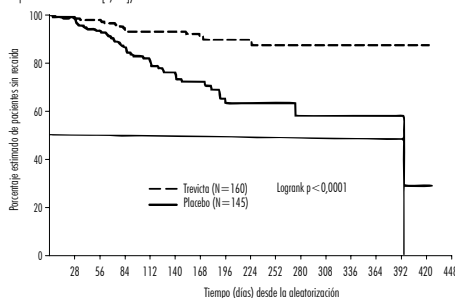


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída – Análisis final

En el estudio de no inferioridad, 1.429 pacientes con enfermedad aguda (puntación 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 paliperidona inyectable mensual durante 17 semanas. Se permitió ajustar la dosis (esto es, 50 mg, 75 mg, 100 mg o 150 mg) después de 5 semanas y 9 inyecciones y el lugar de inyección podía ser el deltoides o el glúteo. De los pacientes que cumplían los criterios de aleatorización en las semanas 14 y 17, 1.016 fueron aleatorizados en proporción 1:1 para seguir recibiendo una vez al mes la inyección de paliperidona de paliperidona mensual o bien cambiar a TREVICA, multiplicando por 3,5 la dosis de las semanas 9 y 13 de paliperidona inyectable mensual, durante un periodo de 48 semanas. Los pacientes recibieron TREVICA una vez cada 3 meses y una medicación inyectable placebo durante los meses restantes para mantener el ciego. En este estudio, el criterio de valoración de la eficacia principal era el porcentaje de pacientes sin recaída al final de la fase de doble ciego de 48 semanas, basado en la estimación de Kaplan-Meier de las 48 semanas (TREVICA: 91,2%, paliperidona inyectable mensual: 90,9%). 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 2,2% (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 TREVICA fue no inferior al grupo tratado con paliperidona inyectable mensual. Las medidas farmacológicas, determinadas según la Escala de Funcionamiento Personal y Social (FSP), que se observaron durante la fase de estabilización abierta se mantuvieron durante la fase de doble ciego en ambos de tratamiento.

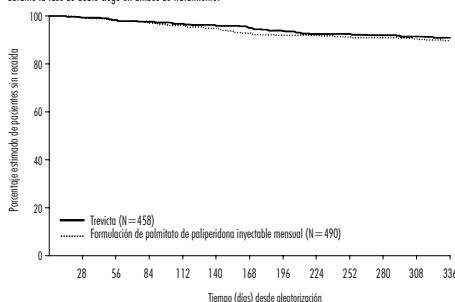
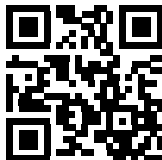


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICA y paliperidona inyectable mensual

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 examinado al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICA 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 paliperidona de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidratarse 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 TREVICA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas mínimas en una mediana de T_{1/2} de 30-33 días. Tras la inyección intramuscular de TREVICA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-26% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la profilaxis de administración de TREVICA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICA 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-valor en el estado estacionario para una dosis de TREVICA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICA, 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 ¹⁴C paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ¹⁴C paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con el orina, indicando que la paliperidona no se metaboliza masivamente 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 oxidación de benzazepina. Aunque en estudios in vitro se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del comportamiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6,

CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. Estudios in vitro han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos in vivo y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICA 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. **Composición de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona.** TREVICA está diseñado para liberar paliperidona durante un periodo de 3 meses, mientras que la inyección mensual de paliperidona de paliperidona se administra una vez al mes. TREVICA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de paliperidona de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de paliperidona de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICA 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 TREVICA 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 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 (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl=10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC₀₋₂₄) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con personas sanas. **Población de edad avanzada.** El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con la edad. **Índice de masa corporal (IMC/peso corporal).** En los pacientes obesos y con sobrepeso se observaron valores de C_{max} más bajos. En el estudio estacionario aparente de TREVICA, 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 TREVICA. Un análisis de farmacocinética poblacional basado en los datos obtenidos con comprimidos de liberación prolongada de paliperidona demostró una exposición a paliperidona ligeramente más alta en los fumadores que en los no fumadores. No es probable que esta diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de paliperidona 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 paliperidona de paliperidona se observó una reacción inflamatoria en el lugar de inyección intramuscular. Se produjo la formación ocular 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 los críos. No se han observado embriotoxicidad ni malformaciones después de la administración intramuscular de paliperidona de paliperidona a dosis repetidas a dosis máximas (160 mg/kg/día), equivalentes a 2,2 veces el nivel de exposición de los humanos a la dosis máxima recomendada de 525 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la motricidad y del aprendizaje en los críos cuando se administraron a animales gestantes. Ni el paliperidona 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 las adenomas hipofisarios (ratas), de los adenomas del páncreas endocrino (ratas) y de los adenomas de las glándulas mamarias (en ambos sexos). Se evaluó el potencial carcinogénico del 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 hiperproliferación. Se desconoce la relevancia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20, Polietilenglicol 400, Ácido cítrico monohidratado, Dihidrogenofosfato sódico monohidratado, Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina clídica) con émbolo, tope trócan y capuchón protector (goma bromobutilica), equipada con una aguja de seguridad de pared fina de 22 G 1 1/2 pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 1/2 pulgadas (0,72 mm x 25,4 mm). Tamaño del envase: Envases con 1 jeringa precargada y 2 agujas. Presentaciones y precios. Treviso 175 mg suspensión inyectable de liberación prolongada: PVL 489,25 €, PVP: 540,16 €, PVP (IVA): 561,77 €. Treviso 263 mg suspensión inyectable de liberación prolongada: PVL 636,50 €, PVP: 692,41 €, PVP (IVA): 720,11 €. Treviso 350 mg suspensión inyectable de liberación prolongada: PVL 782,80 €, PVP: 838,71 €, PVP (IVA): 872,26 €. Treviso 525 mg suspensión inyectable de liberación prolongada: PVL 1.174,20 €, PVP: 1.230,11 €, PVP (IVA): 1.279,31 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visita 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 el se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICA (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/14/971/007, EU/14/971/008, EU/14/971/009, EU/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.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos <http://www.ema.europa.eu>.



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