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A genomic approach to alcoholism

Un abordaje genómico del alcoholismo

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Genomic technologies based on DNA chips (microarrays) permit the simultaneous analysis of hundreds of thousands of single nucleotide polymorphisms (SNP), and this has revolutionized case-control association studies. Research has moved on from studies of candidate genes, in accordance with previous etiopathogenic hypotheses, to genome-wide association studies (GWAS), which analyze the vast majority of the common variation throughout the genome. The impact of this on our knowledge about the genetic bases of predisposition to complex multifactorial diseases has been substantial.

Psychiatric disorders have not been immune to these advances, and this applies especially to schizophrenia, with 37,000 cases and 113,000 controls analyzed through GWAS by the Psychiatric Genomics Consortium (PGC) (Schizophrenia Working Group PGC, 2014). Even so, in the case of other psychiatric disorders, including alcohol dependence, the sample sizes of GWAS are much more modest, though the pioneering studies in schizophrenia are showing the potential contributions of GWAS, which are now being confirmed with other disorders. The most obvious of such contributions concerns the ability to detect common variants associated with the disorder under study, employing the established criterion for genomic significance ($p < 5x10^{-8}$, equivalent to a Bonferroni correction for a million tests). In alcohol dependence, GWAS have confirmed the already-known involvement of *ALDH2* or the *ADH* family, and have identified a few additional genes, such as *PECR* or *NKAIN1-SERINC2* (Frank et al., 2012; Treutlein et al., 2009; Zuo et al., 2013). Experience with other complex disorders indicates that these studies, which analyze fewer than 2000 patients and a similar number of controls in the GWAS phase, have very limited power for identifying vulnerability SNPs, since their individual effect is very small (odds ratio < 1.25). Thus, in schizophrenia, we have moved on from identifying a maximum of three independent significant associations in analyses with sample sizes similar to those currently employed in alcohol dependence research, to 108 in the latest GWAS by the PGC, referred to above (Schizophrenia Working Group PGC, 2014; Stefansson et al., 2009). Hence, the significant results at the genome level represent just the tip of the iceberg. For example, the gene *SLC39A8*, initially associated with schizophrenia in a study led by our group and based on 4545 patients and 15,575 controls ($p = 2.7x10^{-6}$), reached the level of genomic significance in the PGC mega-GWAS ($p = 7.98x10^{-15}$) (Carrera et al., 2012; Schizophrenia Working Group PGC, 2014).

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Given that numerous variants of vulnerability fail to reach significance at the genome level, the next logical step would be the detection of groups of functionally related genes that are over-represented among the most significant values of a GWAS. By way of example, Biernacka et al. (2013) identified a possible association (pending confirmation in new samples) with the pathway of synthesis and degradation of ketone bodies. Excessive alcohol use can increase levels of ketone bodies in the blood, leading to alcoholic ketoacidosis. Ketoacidosis involves symptoms such as nausea, vomiting, or abdominal pain, which can cause aversion to heavy drinking.

In addition to advancing our understanding of the biological bases that predispose people to the onset of a disorder, GWAS could be applied for estimating individual genetic risk of developing a disorder. Such estimates have clear limitations, since they are based solely on common variants (though this may improve as new-generation sequencing studies begin to identify rare variants with larger effects). Moreover, genetic risk explains only a part of total risk. In the case of alcoholism, it is estimated that genetic factors explain 40-60% of populational variation in risk (heritability). But despite these limitations, the data for schizophrenia (heritability ~65%) suggest that the calculation of individual genetic risk from GWAS data may be useful for stratification of risk groups. Thus, the decile at highest risk presents an odds ratio of between 8 and 20 with reference to that of lowest risk (Schizophrenia Working Group PGC, 2014).

Currently, the estimate of polygenic risk is made in simple way. From the GWAS data of a discovery sample, a risk model is generated that includes all the independent SNPs below a lax significance threshold and their effect (logarithm of odds ratio). In each individual in a target sample, the number of risk alleles for each SNP of the model is count, weighted by their effect. The sum of this value for all the SNPs considered constitutes the polygenic risk score of a target individual. Frank et al. (2012) were the first to apply this method to alcohol dependence, based on 1333 cases and 2168 controls divided at random into discovery and target samples of equal size. Using a significance threshold of $p < 0.5$ in the GWAS of the discovery sample (equivalent to analyzing the ~84.000 most significant independent SNPs), they found a difference in the polygenic risk score between cases and controls in the target sample in the expected direction ($p = 1.28\text{x}10^{-6}$). Considering the entire sample as a discovery sample, they also found significant differences when the target samples came from other, previous GWAS.

Among the SNPs included in the calculation of polygenic risk there will be both SNPs with real effects and SNPs unrelated to the disorder, which will generate noise. Thus, there is plenty of room for improvement in the estimate through increasing the size of the discovery sample, which would reduce sampling error in the construction of the polygenic risk model. Another option for improvement would involve prioritizing the SNPs of the model according to additional, a priori biological criteria, such as prediction of functionality or results of GWAS in related phenotypes. Indeed, using discovery and target samples of different phenotypes, it has been possible to confirm shared genetic vulnerability (Cross-Disorder Group PGC, 2013). This type of analysis will improve our understanding of dual pathology.

Finally, the confirmation that there are persons more vulnerable to becoming drug-dependent from the biological point of view can be relevant both to the reduction of stigma associated with alcoholism and to adolescents' and young people's attitude to alcohol. Various studies have indicated a fair degree of interest in a potential genetic test for individual risk of presenting alcohol dependence, and that the belief in a high individual genetic predisposition constitutes an incentive for changing one's drinking pattern (Dar-Nimrod, Zuckerman, & Duberstein, 2013; Scott et al., 2014).

In sum, GWAS have shown that genetic predisposition to alcoholism is due to multiple genes with a very small individual effect. The study of these genes will have consequences in the medium-term, both increasing our understanding of the biological mechanisms involved in vulnerability to alcoholism, and permitting the stratification of individuals according to their genetic risk of suffering from alcoholism, and this represents an important step in the direction of selective prevention. For example, stratification of adolescents with a use pattern involving risk and/or problematic behaviours (delinquency, violence) based on genetic tests could facilitate more sharply focused interventions. Given the seriousness of the problem, with more than 25,000 people seeking treatment for alcoholism annually in Spain (according to the Spanish Observatory for Drugs and Substance Dependence), any approach that can make a difference should be welcomed. In such a context, work on drug dependence in the coming years should pay attention to the progress made through the use of genomic technologies, given their potential utility. For such potential to be unleashed it will be essential to employ multidisciplinary approaches.

Conflicts of interest

The author declares that there are no conflicts of interest in relation to this work.

References

Biernacka, J. M., Geske, J., Jenkins, G. D., Colby, C., Rider, D. N., Karpyak, V. M., . . . Fridley, B. L. (2013). Genome-wide gene-set analysis for identification of pathways associated with alcohol dependence. *International Journal of Neuropsychopharmacology, 16*, 271-278. doi: 10.1017/s1461145712000375.

Carrera, N., Arrojo, M., Sanjuan, J., Ramos-Rios, R., Paz, E., Suarez-Rama, J. J., . . . Costas, J. (2012). Association Study of Nonsynonymous Single Nucleotide Polymorphisms in Schizophrenia. *Biological Psychiatry, 71*, 169-177. doi: 10.1016/j.biopsych.2011.09.032.

Cross-Disorder Group of the Psychiatric Genomics Consortium (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet, 381*, 1371-1379. doi: 10.1016/S0140-6736(12)62129-1.

Dar-Nimrod, I., Zuckerman, M. & Duberstein, P. R. (2013). The effects of learning about one's own genetic susceptibility to alcoholism: a randomized experiment. *Genetics in Medicine, 15*, 132-138. doi: 10.1038/gim.2012.111.

Frank, J., Cichon, S., Treutlein, J., Ridinger, M., Mattheisen, M., Hoffmann, P., . . . Rietschel, M. (2012). Genome-wide significant association between alcohol dependence and a variant in the ADH gene cluster. *Addiction Biology, 17*, 171-180. doi: 10.1111/j.1369-1600.2011.00395.x.

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*, 421-427. doi: 10.1038/nature13595.

Scott, D. M., Nwulia, E., Kwagyan, J., Cain, G., Marshall, V. J., Kalu, N., . . . Taylor, R. E. (2014). Genetic Testing for the Susceptibility to Alcohol Dependence: Interest and Concerns in an African American Population. *Genetic Testing and Molecular Biomarkers, 18*, 538-545. doi: 10.1089/gtmb.2013.0417.

Stefansson, H., Ophoff, R. A., Steinberg, S., Andreassen, O. A., Cichon, S., Rujescu, D., . . . Collier, D. A. (2009). Common variants conferring risk of schizophrenia. *Nature, 460*, 744-747. doi: 10.1038/nature08186.

Treutlein, J., Cichon, S., Ridinger, M., Wodarz, N., Soyka, M., Zill, P., . . . Rietschel, M. (2009). Genome-wide association study of alcohol dependence. *Archives of General Psychiatry, 66*, 773-784. doi: 10.1001/archgenpsychiatry.2009.83.

Zuo, L., Wang, K., Zhang, X. Y., Krystal, J. H., Li, C. S., Zhang, F., . . . Luo, X. (2013). NKAIN1-SERINC2 is a functional, replicable and genome-wide significant risk gene region specific for alcohol dependence in subjects of European descent. *Drug and Alcohol Dependence, 129*, 254-264. doi: 10.1016/j.drugalcdep.2013.02.006.

Clinical and Demographic Characteristics of Binge Drinkers Associated with Lack of Efficacy of Brief Intervention and Medical Advice

Características clínicas y demográficas de bebedores "por atracones" que se relacionan con una falta de eficacia de la intervención breve y el consejo médico

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Abstract

Brief Counseling Intervention (BCI) and Medical advice (MA) are psychotherapeutic approaches used for the treatment of binge drinkers in Primary Care. Although binge drinking is a common pattern of alcohol misuse in Europe and in the US, no studies have evaluated those subjects who do not respond to Brief Counseling Interventions or Medical Advice. ***Objective.*** To determine the clinical and demographic characteristics of binge drinkers in whom BCI or MA are not effective in reducing harmful alcohol use. ***Methods.*** This is a secondary analysis of data from a randomized alcohol brief intervention trial with a 12-month follow-up period. A total of 674 subjects (89%) participated right through to the end of the study. The primary outcome measure was change in harmful alcohol use from baseline to 12 months. ***Results.*** The strongest baseline predictors of harmful alcohol use during follow-up were educational status, young adults, and high number of cigarettes smoked, present family history of alcoholism, treatment condition and number of drinks per episode of binge drinking. ***Conclusions.*** Binge drinkers are a heterogeneous group that responds to brief intervention or MA but in a subgroup of them these interventions fail to prevent harmful alcohol use. Other interventions should be implemented for these subjects.

Key words: Brief intervention, Medical advice, Binge drinking, Harmful alcohol consumption.

Resumen

La Intervención Breve (IB) y el Consejo Médico simple (CM) son intervenciones psicoterapéuticas usadas para el tratamiento del consumo de alcohol por atracones en Atención Primaria. A pesar de la frecuencia de este patrón de abuso en Europa y en los Estados Unidos, ningún estudio ha evaluado las características de los sujetos que no responden a esas dos técnicas. ***Objetivo.*** Determinar las características demográficas y clínicas de los bebedores por atracones en los que la IB y el CM no son efectivos para la reducción del consumo perjudicial de alcohol. ***Métodos.*** Se trata de un análisis secundario de los datos obtenidos en un ensayo aleatorizado de intervención breve en alcohol con un período de seguimiento de 12 meses. Un total de 674 sujetos (89%) participaron durante todo el estudio hasta el final. La variable principal fue el cambio en el uso perjudicial de alcohol tras 12 meses de seguimiento. ***Resultados.*** Para ambos grupos de tratamiento las variables que predecían la continuidad en el consumo perjudicial tras el seguimiento eran: bajo nivel educativo, ser jóvenes, el número de cigarrillos fumados, la historia familiar de alcoholismo y la gravedad del consumo de alcohol basalmente. ***Conclusiones.*** Las características clínicas y sociodemográficas de los sujetos con un patrón de consumo de alcohol por atracones atendidos en Atención primaria influyen en el pronóstico de las Intervenciones breves y del Consejo Médico.

Palabras clave: Intervención breve, Consejo médico, Atracones, Consumo perjudicial.

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The pattern of binge drinking is characterized in men by the consumption of five or more standard drink units (SDU) (50gr. of alcohol), and in women by more than four SDUs in a period of 2 hours (NIAAA, 2004). In the European Union, one in five adults consumes this amount at least once per week (Anderson and Baumberg, 2006).

This pattern of alcohol use is associated with traffic accidents, medical complications, tobacco consumption, and various social complications (NIH, 2000, Naimi et al., 2003).

Brief Counseling Interventions (BCI) constitute a group of approaches designed to reduce the damage linked to alcohol consumption among subjects who are heavy or binge drinkers (Fleming, 2003, Kaner et al., 2007). Their efficacy, however, is moderate and there is much variability in their effectiveness (Bertholet et al., 2013). Results of trials which included binge drinkers are not conclusive. Therefore, the findings of the Project Trial for Early Alcohol Treatment (TrEAT) (Fleming et al., 1997; 1999; Grossberg et al., 2004) and our own group (Rubio et al., 2010) indicate that subjects exposed to BCI significantly reduce the number of binge drinking episodes compared with control groups. Nevertheless, other studies did not find any significant differences (Ockene et al., 1999; Curry et al., 2003; Reiff-Hekking et al., 2005).

In the opinion of some authors, disagreement as to the efficacy of BCIs could be due to the heterogeneity of the subjects included, which implies the necessity to evaluate the influence of the socio-democratic variables in the prognoses of these approaches (Littlejohn, 2006). Other authors posit that the neurological damage associated with alcohol diminishes the results of these therapies with this type of subject and increases the number of relapses (Soler-González et al, 2014).

In terms of controlled studies carried out among binge drinkers, the project implemented by our group is the only one centered exclusively on this population (Rubio et al., 2010). In this article, therefore, we have carried out a second analysis of the earlier results in an attempt to determine the clinical and socio-demographic characteristics which might influence the lack of efficacy of BCI or medical advice (MA) after a twelve month follow-up. As the principal variable, we have chosen the fact that at the end of the follow-up our patient evidenced a pattern of harmful use of alcohol (HUA), whether through continued binge drinking or a risky level of consumption, given that the goal of each intervention (BCI or MA) was to achieve a reduction in any type of harmful consumption.

Methods

As the methodology of this study has been described in a separate article (Rubio et al., 2010), only the most salient aspects are described here.

Subjects and procedures

The subjects of the study were adult patients between 18 and 65 years of age attended in primary care centers in the city of Madrid between March 2003 and March 2006. If, after the completion of the AUDIT questionnaire (Alcohol Use Disorders Identification Test, AUDIT [Rubio et al., 1998]), they displayed a binge drinking pattern and scored 15 points or less in the AUDIT, they were considered to be candidates for randomization. The percentage of patients who declined to complete the questionnaire was 2.4%. The characteristics of the sample are described in Table 1.

Criteria of inclusion and exclusion. Binge drinking patients included are defined thus: males who drank five or more standard drink units (SDU, 10gr. of alcohol per unit) at a single sitting on one or more occasions in the previous month; women who drank four SDUs or more at a single sitting on one or more occasions in the previous month.

Intervention protocol. The CBI was carried out by primary care staff and consisted of two sessions, four weeks apart. Each face-to-face session lasted between 10 and 15 minutes and was carried out during normal clinic hours. The intervention included a checkup of the effects related to alcohol consumption, a conversation about the methods of reducing alcohol consumption and planning what the patient was ready to do before the next interview.

The subjects assigned to the MA group received a leaflet covering the general health problems caused by alcohol consumption. Any doubts about the leaflets or the IB could be dealt with in the usual way by speaking with their doctor or a nurse.

Monitoring. A total of 751 people fulfilled the criteria for brief counseling intervention (BCI, N=371) or medical advice (MA, = 381), of which 89.62% (N= 674) completed the follow-up after 12 months. Of the 78 who did not complete the follow-up after 12 months, 49 declined to take part in the interview and 29 disappeared during the year.

The follow-up interviews were carried out by "blind" researchers not linked to the patient's treatment center.

Principal variable. For this study, we chose a pattern of harmful alcohol use (HAU) in the previous month as the outcome variable. This included subjects with binge drinking episodes (>5 SDU for men, >4 for women per sitting) and/or consuming more than 18 (men) or 13 (women) drinks per week.

Other variables. A history of family alcohol consumption was established after the interview with the participants and by applying the diagnostic criteria of family history research (Endicott, Andreasen & Spitzer 1989). The age of alcohol consumption onset was the age the subject claimed to have started drinking.

Table 1
Clinical and demographic characteristics of the population classified by the persistence of harmful alcohol use (HAU) in the last month of follow-up.

Demographic characteristics	**HAU (-) N=274 No. (%)**	**HAU (+) N=400 No. (%)**	**p-value**
Intervenion Group			
Control	106(31.7)	228(68.3)	0.000
CBI	168(49.4)	172(50.6)	
Sex			
Male	150 (36.1)	283(63.9)	0.001
Female	114 (49.4)	117 (50.6)	
Marital Status			
Never Married	44(27.2)	118 (72.8)	
Widow(er)/Divorced/Estranged	4(25.0)	12 (75.0)	0.000
Married/Living with Partner	226 (45.6)	270 (54.4)	
Educational Level			
Secondary school or lower	110(26.7)	302(73.3)	
High school diploma	144 (60.3)	95(39.7)	0.000
University or higher	20 (87.0)	3 (13.0)	
Employment Situation			
Working	231(38.7)	366 (61.3)	
Unemployed	3 (9.7)	28 (90.3)	0.000
Domestic Work	40(87.0)	6(13.0)	
Family History of Alcohol Dependence			
NO	244(49.9)	245(50.1)	0.000
YES	30(16.2)	155(83.8)	

Clinical Characteristics	**Mean (SD)**	**Mean (SD)**	**p-value**
Current Age, year	39.49(6.03)	35.67(4.02)	0.000
Number of cigarettes/day	9.52(5.36)	16.55(9.24)	0.000
Onset age	14.50(2.45)	13.41(1.58)	0.000
Age when smoking became habitual (More than once a week)	14.81(2.38)	13.66(1.81)	0.000
Baseline pattern of alcohol consumption			
Days of consumption per month	18.38(4.92)	19.98(4.15)	0.000
Number of Standard Drink Units (SDU) per week	26.11(10.42)	30.36(8.31)	0.000
Number of binge drinking episodes per month	2.95(2.08)	3.46(2.45)	0.000
Number of SDUs per binge drinking episode	8.98(2.08)	10.80(2.95)	0.000

HAU(+) = Persistence of harmful drinking in the last month.
HAU(-) = Absence of harmful drinking in the last month.

Statistical analysis

Categorical variables were described using the frequency distribution and continuous variables in the form of means and standard deviations. The comparisons among categorical variables were realized with the chi square homogeneity test, and the Mann-Whitney U test was used for comparisons among continuous variables.

The principal variable "harmful alcohol use in the previous month" was characterized by the answer "I had harmful alcohol consumption in the last month / I did not have harmful alcohol consumption in the last month" (1/0).

Univariate analysis. Initially, a univariate logistic regression analysis was run to determine the risk of association with the principal variable. Following the recommendations of Hosmer & Lemeshow (2000), we used the likelihood ratio test (LRT) as a screening criterion to select the candidate variables for each multivariate model. Taking into account that the criteria for binge drinking patterns were different for men than for women, and that men and women differed in baseline patterns of consumption ($p<0.031$), we chose to carry out separate regression analyses for men and women. In the case of the model for the women's group, only one variable (number of binge drinking episodes per month

p=0.944) did not achieve predictive capacity in the univariate model.

Values greater than 1 of the odds ratio indicated a higher likelihood of "harmful alcohol consumption", while values below 1 reduced this probability.

Multivariate analysis. A multivariate logistic regression analysis was run, following the method proposed by Hosmer & Lemeshow (2000). The degree of fit of the prediction equation was measured using Nagelkerke's R2 coefficient. The area under the ROC curve was also calculated. Data analysis was carried out using SPSS 19 and Statgraphics Centurion.

Results

The subjects included in the BCI or MA groups did not display significant differences in clinical or demographic characteristics (p value > 0.197), which demonstrates that the groups were well balanced.

During the 12 month follow-up period, 78 subjects abandoned the study, 47 of them in the medical advice group and 31 in the group which received BCI. Comparing these percentages, we found a greater drop-out ratio among the MA group (p=0.036).

During the final month of the study, 59.34% (N=400) of the total sample continued to have a harmful alcohol use pattern (HAU+), while the rest (40.65%, N= 274) had broken this pattern (CPA-). No statistically significant differences were observed between the two groups.

Univariate logistic regression analysis models adjusted by sex

Given the small number of women in some of the categories, we reformulated the following variables: "employment situation" which changed to "domestic work (YES / NO)" and "marital status" was changed to "married (YES / NO)".

Table 2 shows the odds ratio of the univariate regression models with their 95% confidence interval, and the likelihood ratio by sex. The probability of harmful alcohol consumption was reduced for both men and women by BCI, while a family history of alcohol abuse increased it. It was observed that the younger the subject and the earlier the onset of alcohol use, the greater the probability of harmful alcohol consumption persisting at the end of the study. Having alcohol and tobacco consumption patterns at the start of the study was associated with a worse prognosis at the end of it. In terms of socio-demographic variables, the worst prognosis was for single people, the unemployed and those with lower educational levels.

Multivariate regression models to explain the presence of Harmful Alcohol Use (HAU) at the end of the study

Table 3 shows the regression models by sex. For men, the selected variables were treatment group, educational level, alcoholic father/mother, age, cigarette consumption, days of baseline consumption, number of drinks per binge drinking sitting. After a study of the linearity of the following variables: age, cigarette consumption, days of baseline consumption, number of drinks per binge drinking sitting, it was found that "cigarette consumption" and "days of baseline consumption" did not have a linear effect and therefore, following Hosmer & Lemeshow (2000) the transformations Tobacco*LN (Tobacco) and Days*LN (Days) were added.

For women, the chosen variables were: treatment group, educational level, age, cigarette consumption, number of SDUs consumed per week. Similarly in this case, the number of cigarettes smoked and the number of SDUs consumed did not have a linear effect, and therefore the following transformations were carried out: Cigarettes*LN (Cigarettes) and Drinks*LN (Drinks).

For both men and women, the possible interaction of all variables were checked for type of treatment (BCI or MA) and none showed statistical significance (all p values were > 0.194 for men and >0.135 for women), which means that the clinical and socio-demographic variables included in the models explained the lack of efficacy of both BCI and medical advice.

In summary, the risk for subjects treated under BCI as well as those receiving medical advice of continuing harmful alcohol use after twelve months of follow-up increased among subjects with low educational level (primary school), young people (<37), heavy smokers (>25 cigarettes), having a family history of alcoholism and consuming a greater number of SDUs before starting the therapeutic intervention (drinking more than 10 SDUs per sitting in the case of men, or having high levels of alcohol consumption during the baseline week in the case of women).

Discussion

This is the first study to be carried out exclusively with subjects with a binge drinking pattern, treated in primary care centers in which the influence of clinical and socio-demographic variables is shown on the prognosis of the interventions (Brief Counseling Intervention and Medical Advice) after a 12 month follow-up. The variables linked to the "harmful alcohol use" pattern in both treatment groups were smoking a high number of cigarettes (>25), having a family history of alcoholism, being young (<37 year of age), low educational level, heavy baseline consumption (more than 10 SDUs per binge drinking sitting for men and high weekly consumption for women).

The influence of high number of cigarettes on harmful alcohol use found in our study matches the findings in earlier studies (Murray et al. 1995, Fleming et al., 1997). In another study which attempted to show the effectiveness of an integrated therapy for smokers and drinkers with a binge drinking pattern, it was shown that while the treatment significantly reduced the number of cigarettes, the effect

Table 2
Results of the univariate logistic regression models, by sex

	Male			Female		
	Odds ratio	**95% interval**	**p-value**	**Odds ratio**	**95% interval**	**p-value**
Group (Reference group: control) IB	0.597	0.402 - 0.884	0.009	0.303	0.176- 0.520	0.000
Marital Status: (Reference group: never married) Widow(er)/Divorced/Estranged Married/Living with partner	0.497 0.681	0.313 -0.789 0.191- 2.421	0.009			
Marital Status: (Reference group: not married) Currently married				0.374	0.178-0.781	0.009
Educational level (Reference group: Secondary or lower) High school, vocational training University students	0.219 0.024	0.142-0.337 0.003-0.191	0.000	0.286 0.139	0.163- 0.503 0.028-0.680	0.000
Employment Situation (Reference group: Working) Unemployed	4.411	1.295-15.026	0.005			
Employment situation (Reference group: not domestic work) Domestic Work				0.100	0.040-0.248	0.000
Family History of Alcohol Dependence (Reference group: without family history) With	6.703	3.887- 11.556	0.000	2.310	1.093- 4.876	0.023
Current age, years	0.877	0.844- 0.912	0.000	0.725	0.655- 0.801	0.000
Number of cigarettes per day	1.134	1.096-1.173	0.000	1.162	1.103- 1.224	0.000
Onset age	0.747	0.673-0.829	0.000	0.809	0.708 -0.942	0.002
Age when consumption became continuous (more than one day per week)	0.754	0.684-0.832	0.000	0.823	0.718-0.942	0.003
Days of consumption per month	1.074	1.027- 1.121	0.001	1.093	1.026- 1.164	0.005
Number of standard drinks units per week	1.050	1.028- 1.073	0.000	1.041	1.007-1.075	0.014
Number of binge drinking episodes per month	1.132	1.040-1.231	0.003	0.968	0.841-1.112	0.644
Number of SDUs per binge drinking episode	1.354	1.238-1.480	0.000	1.244	1.114- 1.387	0.000

Table 3
Results of the multivariate logistic regression models by sex

	Male		Female	
	Coefficients	**ODDS**	**Coefficients**	**ODDS**
Group				
BCI	-0.900	0.407	-2.253	0.105
Education level				
Primary or Secondary	-0.894	0.409	-0.898	0.407
High school or higher	-2.827	0.059	-1.951	0.142
Family History of Alcohol Dependence				
Yes	1.825	6.201		
Current Age	-0.072	0.930	-0.354	0.702
Number of cigarettes smoked per day (Cigarettes)	-0.454	0.635	-0.332	0.717
Days of alcohol use per month (Days)	2.930	18.714		
Number of Standard Drink Units per Week (Drinks)			2.116	8.296
Number of Standard Drink Units per binge drinking episode (Drinks)	0.240	1.271		
Cigarettes*LN(Cigarettes)	0.178	1.195	0.157	1.171
Days*LN(Days)	-0.768	0.464		
Drinks*LN(Drinks)			-0.514	0.598
Constant	-11.155		2.507	
Nagelkerke's R^2	0.547		0.665	
ROC area	0.898		0.928	

was not repeated on the number of binge drinking episodes (Ames et al., 2010). Nevertheless, the expectation that both can be reduced was confirmed in a pilot clinical trial to test the efficacy of an intervention aimed at decreasing both (Ames et al, 2014) in which it was observed that when the treatment was realized simultaneously and was also focused on smoking, after three and six months the patients continued not to smoke and also reduced the consumption of alcohol. Therefore, and despite the heterogeneous nature of these results, the existence of a special relationship between smoking and binge drinking appears to be consistent (Blazer and Wu, 2009). In our sample, the subjects at greater risk of continuing harmful alcohol use were smokers of 25 or more cigarettes per day, followed by ex-smokers and finally smokers of fewer than 10 cigarettes per day. Our data support the need to design interventions for binge drinkers which integrate treatment for tobacco addiction.

From our point of view, the impact of family history of alcoholism on harmful alcohol use is of special interest. This variable has been linked to a higher risk of developing alcohol dependence (Rubio et al., 1999) and to a bad prognosis to pharmaceutical treatment of alcohol-dependent people (Rubio et al., 2005; Keifer et al., 2008). It is possible that these patients require more intensive therapeutic strategies, which is why we consider that more studies focused on this issue are necessary.

The association between educational level and the prognosis of brief interventions has been pointed out in different studies (Fleming et al., 1997; Ockene et al., 1999; Aalto & Sullanauke, 2000). As in our study, the subjects who dropped out of school before finishing secondary education were at greater risk of harmful alcohol use after the treatment. These results therefore support the need to adapt treatment strategies to the educational level of the population at whom the intervention is aimed.

Our findings regarding the lower efficacy of the treatments among young subjects does not support the results of earlier research (Monti et al., 1999; Grossberg et al., 2004). The reasons for these differences are not clear. It is possible that younger binge drinkers are less aware of the possible consequences of this pattern of consumption (Okoro et al., 2004), which could explain that treatments based on motivational interventions are more efficacious, especially with those who experienced certain negative consequences linked to alcohol (Daeppen et al., 2011).

In our study, consumers with a baseline pattern of heavy consumption had greater problems giving up harmful consumption. This fact may be explained in different ways. It has been shown that compared to non-drinkers, binge drinkers have a greater deficit of inhibitory control performed by the frontal lobe (Townshend & Duka, 2005), this damage of the brain also being partly related to accumulated alcohol (So-

ler González et al, 2014). Furthermore, moderate drinkers who consume alcohol occasionally have a higher likelihood of being classified as subjects with alcohol disorder (abuse or dependence) than those who drink moderately but daily (Knight et al., 2002).

This has led to the hypothesis that binge drinking episodes provoke withdrawal symptoms, which can make it difficult to control consumption (Stephen et al, 2005) and, furthermore, contribute to heightening the adaptive processes underlying the development of alcohol dependence (Breese et al, 2005). In summary, drinkers who have frequent binge drinking episodes may represent a group of drinkers with greater difficulties in modifying their drinking patterns (Cournet & Polich, 2009), and for whom a more intensive therapeutic treatment than medical advice or BCI needs to be proposed.

One of the limitations of our study is that the measure of efficacy is based on the self-reports of patients. Unfortunately, there are no efficient biological measurements to demonstrate the reduction of alcohol ingested. In this study, ethyl glucuronide (EtG) in urine or ethyl sulphate was used, but their high cost makes them unfeasible for this type of study. Nevertheless, research indicates that self-reports are more reliable than other methods of measuring alcohol consumption (Harrison et al, 1997). In order to reduce the limitation of the self-report, we have used different strategies such as, for example, informing the patients that they are participating in a research project and that their data will not appear in their medical records. Furthermore, the questions relating to alcohol consumption were masked, mixed in among others on health habits. We have also used standardized methods of reporting on consumption and information gathering. Of binge drinkers who scored 15 points or less on the AUDIT, 29% declined to take part in the initial interview. As we do not know whether they could have fulfilled the inclusion criteria, we must be cautious when generalizing from our results. The majority of our sample was white, which also limits generalization from our findings to other populations.

Conclusions

In general, our results show that a substantial proportion of binge drinkers continues harmful alcohol use after undergoing Brief Counseling Intervention or Medical Advice. Therefore, we believe that other treatment strategies should be adopted for other specific groups, such as people with a family history of alcoholism, smokers, young adults or drinkers with frequent bingeing episodes.

Conflict of Interests

In the name of all authors, the first signatory of the reference manuscript declares that no potential conflict of interests exists in connection with this article.

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References

Aalto, M., & Sillanaukee, P. (2000). Compliance rate and associated factors for entering an alcohol brief intervention treatment programme. *Alcohol and Alcoholism*, *35*, 372–376. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10906003

Ames, S. C., Pokorny, S. B., Schroeder, D. R., Tan, W., & Werch, C. E. (2014). Integrated smoking cessation and binge drinking intervention for young adults: a pilot efficacy trial. *Addictive Behaviors*, *39*, 848–853. doi:10.1016/j.addbeh.2014.02.001

Ames, S. C., Werch, C. E., Ames, G. E., Lange, L. J., Schroeder, D. R., Hanson, A. C., & Patten, C. A. (2010). Integrated smoking cessation and binge drinking intervention for young adults: a pilot investigation. *Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine*, *40*, 343–349. doi:10.1007/s12160-010-9222-4

Anderson, P., & Baumberg, B. (2008). *Alcohol in Europe*. London: Institute of Alcohol Studies.

Bertholet, N., Palfai, T., Gaume, J., Daeppen, J. B., & Saitz, R. (2014). Do brief alcohol motivational interventions work like we think they do? *Alcoholism, Clinical and Experimental Research*, *38*, 853–859. doi:10.1111/acer.12274

Blazer, D. G., & Wu, L. T. (2009). The epidemiology of at-risk and binge drinking among middle-aged and elderly community adults: National Survey on Drug Use and Health. *The American Journal of Psychiatry*, *166*, 1162–1169. doi:10.1176/appi.ajp.2009.09010016

Breese, G. R., Overstreet, D. H., & Knapp, D. J. (2005). Conceptual framework for the etiology of alcoholism: a "kindling"/stress hypothesis. *Psychopharmacology*, *178*, 367–380. doi:10.1007/s00213-004-2016-2

Courtney, K. E., & Polich, J. (2009). Binge drinking in young adults: Data, definitions, and determinants. *Psychological Bulletin*, *135*, 142–156. doi:10.1037/a0014414

Curry, S. J., Ludman, E. J., Grothaus, L. C., Donovan, D., & Kim, E. (2003). A randomized trial of a brief primary-care-based intervention for reducing at-risk drinking practices. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *22*, 156–165.

Daeppen, J.-B., Bertholet, N., Gaume, J., Fortini, C., Faouzi, M., & Gmel, G. (2011). Efficacy of brief motivational intervention in reducing binge drinking in young men: A randomized controlled trial. *Drug and Alcohol Dependence*, *113*, 69–75. doi:10.1016/j.drugalcdep.2010.07.009

Endicott, J., Andreasen, N., & Spitzter, R. (1989). *Research Diagnostic Criteria (Spanish version by Hubert M.S.)*. Madrid: E. Médicos, Ed.

Fleming, M. F. (2003). Brief interventions and the treatment of alcohol use disorders: current evidence. *Recent Developments in Alcoholism : An Official Publication of the American Medical Society on Alcoholism, the Research Society on Alcoholism, and the National Council on Alcoholism*, *16*, 375–390.

Fleming, M. F., Barry, K. L., Manwell, L. B., Johnson, K., & London, R. (1997). Brief physician advice for problem alcohol drinkers. A randomized controlled trial in community-based primary care practices. *JAMA*, *277*, 1039–1045. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9091691

Fleming, M. F., Manwell, L. B., Barry, K. L., Adams, W., & Stauffacher, E. A. (1999). Brief physician advice for alcohol problems in older adults: a randomized community-based trial. *The Journal of Family Practice*, *48*, 378–384. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10334615

Grossberg, P. M. (2004). Brief physician advice for high-risk drinking among young adults. *The Annals of Family Medicine*, *2*, 474–480. doi:10.1370/afm.122

Harrison, L. (1997). The validity of self-reported drug use in survey research: an overview and critique of research methods. *NIDA Research Monograph*, *167*, 17–36.

Hosmer, D., & Lemeshow, S. (2000). *Applied Logistic Regression*. John Wiley & Sons Ltd.

Kaner, E. F. S., Beyer, F., Dickinson, H. O., Pienaar, E., Campbell, F., Schlesinger, C., … Burnand, B. (2007). Effectiveness of brief alcohol interventions in primary care populations. *The Cochrane Database of Systematic Reviews*, CD004148. doi:10.1002/14651858.CD004148.pub3

Kiefer, F., Jiménez-Arriero, M. A., Klein, O., Diehl, A., & Rubio, G. (2008). Cloninger's typology and treatment outcome in alcohol-dependent subjects during pharmacotherapy with naltrexone. *Addiction Biology*, *13*, 124–129. doi:10.1111/j.1369-1600.2007.00073.x

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

Littlejohn, C. (n.d.). Does socio-economic status influence the acceptability of, attendance for, and outcome of, screening and brief interventions for alcohol misuse: a review. *Alcohol and Alcoholism*, *41*, 540–545. doi:10.1093/alcalc/agl053

Monti, P. M., Colby, S. M., Barnett, N. P., Spirito, A., Rohsenow, D. J., Myers, M., … Lewander, W. (1999). Brief intervention for harm reduction with alcohol-positive older adolescents in a hospital emergency department. *Journal of Consulting and Clinical Psychology*, *67*, 989–994.

Murray, R. P., Istvan, J. A., Voelker, H. T., Rigdon, M. A., & Wallace, M. D. (1995). Level of involvement with alcohol and success at smoking cessation in the lung health study. *Journal of Studies on Alcohol*, *56*, 74–82.

Naimi, T. S., Brewer, R. D., Mokdad, A., Denny, C., Serdula, M. K., & Marks, J. S. (2003). Binge drinking among US adults. *JAMA*, *289*. doi:10.1001/jama.289.1.70

National Institute of Alcohol Abuse and Alcoholism, A. (2004). NIAAA Council Approves Definition of Binge Drinking. *NIAAA Newsletter*.

NIH, US Department of Health and Human Services, PHS y NIAAA. (2000). *The tenth special report to the U.S. Congress on alcohol and health from the Secretary of Health and Human Services*. Washington DC: U.S. Department of Health and Human Services.

Ockene, J. K., Adams, A., Hurley, T. G., Wheeler, E. V, & Hebert, J. R. (1999). Brief physician- and nurse practitioner-delivered counseling for high-risk drinkers: does it work? *Archives of Internal Medicine*, *159*, 2198–205.

Okoro, C. A., Brewer, R. D., Naimi, T. S., Moriarty, D. G., Giles, W. H., & Mokdad, A. H. (2004). Binge drinking and health-related quality of life: do popular perceptions match reality? *American Journal of Preventive Medicine*, *26*, 230–233. doi:10.1016/j.amepre.2003.10.022

Reiff-Hekking, S., Ockene, J. K., Hurley, T. G., & Reed, G. W. (2005). Brief physician and nurse practitioner-delivered counseling for high-risk drinking. Results at 12-month follow-up. *Journal of General Internal Medicine*, *20*, 7–13. doi:10.1111/j.1525-1497.2005.21240.x

Rubio, G., Jiménez-Arriero, M. A., Martínez, I., Ponce, G., & Palomo, T. (2010). Efficacy of physician-delivered brief counseling intervention for binge drinkers. *The American Journal of Medicine*, *123*, 72–78. doi:10.1016/j.amjmed.2009.08.012

Rubio, G., León, G., Pascual, F. F., & Santo-Domingo, J. (1998). Clinical significance of Cloninger's classification in a sample of alcoholic Spanish men. *Addiction*, *93*, 93–101.

Rubio, G., Ponce, G., Rodriguez-Jiménez, R., Jiménez-Arriero, M. a, Hoenicka, J., & Palomo, T. (2005). Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? *Alcohol and Alcoholism*, *40*, 227–233. doi:10.1093/alcalc/agh151

Rubio Valladolid, G., Bermejo Vicedo, J., Caballero Sánchez-Serrano, M. C., & Santo-Domingo Carrasco, J. (1998). Validation of the Alcohol Use Disorders Identification Test (AUDIT) in primary care. *Revista Clínica Española*, *198*, 11–14.

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

Stephens, D. N., Ripley, T. L., Borlikova, G., Schubert, M., Albrecht, D., Hogarth, L., & Duka, T. (2005). Repeated ethanol exposure and withdrawal impairs human fear conditioning and depresses long-term potentiation in rat amygdala and hippocampus. *Biological Psychiatry*, *58*, 392–400. doi:10.1016/j.biopsych.2005.04.025

Town, M., Naimi, T. S., Mokdad, A. H., & Brewer, R. D. (2006). Health care access among U.S. adults who drink alcohol excessively: missed opportunities for prevention. *Preventing Chronic Disease, 3*, A53.

Townshend, J. M., & Duka, T. (2005). Binge drinking, cognitive performance and mood in a population of young social drinkers. *Alcoholism: Clinical & Experimental Research, 29*, 317–325. doi:10.1097/01.ALC.0000156453.05028.F5

Exposure to tobacco, alcohol and drugs of abuse during pregnancy. A study of prevalence among pregnant women in Malaga (Spain)

Exposición a tabaco, alcohol y drogas de abuso en gestantes. Estudio de prevalencia en gestantes de Málaga (España)

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Abstract

The prevalence of substance abuse in women who become pregnant is similar to that of the general population, resulting in a high fetal exposure rate during the most vulnerable period regarding neurodevelopment and organogenesis. The present study was intended to assess the level of prenatal exposure to tobacco, alcohol or illicit drugs in the city of Málaga (Spain). It was designed as a cross-sectional study, and based on the anonymous self-reports of participants. A total of 451 pregnant women were recruited in the first, second or third trimester. The prevalence in each of the quarters respectively was 21.2%, 18.5% and 13.3% for smoking, 40.7%, 23.1% and 17.1% for alcohol and 4.8%, 1.9% and 1.2% for cannabis. We also found that a higher educational level was associated with a lower consumption of tobacco (RR 0.659 [0.537-0.810] p<0.0001) and greater exposure to alcohol (RR 1.87 [1.30-2.69] p<0.0007). These results, particularly in regard to alcohol intake, are sufficiently alarming to alert obstetric care providers about the need to implement preventive measures.

Key words: Prenatal exposure, Maternal alcohol intake, Maternal smoking, Prevalence, Drug abuse during pregnancy, High risk pregnancy.

Resumen

La prevalencia de hábitos tóxicos en la población de mujeres que quedan embarazadas es similar a la de la población general, por lo que la exposición fetal a tóxicos es elevada en el período de mayor vulnerabilidad, sobre todo en relación al neurodesarrollo y la organogénesis. El presente estudio ha sido desarrollado para conocer el nivel de exposición prenatal a tabaco, alcohol u otras drogas en la ciudad de Málaga (España). El trabajo responde a un diseño observacional de corte transversal sobre el consumo de tóxicos durante el embarazo, y se basa en la autodeclaración de las gestantes mediante la cumplimentación de un cuestionario. Se reclutaron 451 gestantes de primer, segundo y tercer trimestre. La prevalencia de consumo en cada uno de los trimestres resultó ser respectivamente del 21.2%, 18.5% y 13.3% para el tabaco, 40.7%, 23.1% y 17.1% para el alcohol y del 4.8%, 1.9% y 1.2% para cannabis. En los tres trimestres, un mayor nivel de estudios se asoció a un menor consumo de tabaco (RR 0,659 [0.537-0.810] p< 0.0001) y una mayor exposición al alcohol (RR 1.87 [1.30-2.69] p< 0.0007). Los resultados obtenidos, sobre todo en relación al consumo de alcohol, son suficientemente llamativos como para alertar a los proveedores de atención obstétrica sobre la necesidad de poner en marcha medidas preventivas.

Palabras clave: Exposición prenatal, Consumo materno de alcohol, Tabaquismo materno, Prevalencia, Drogas ilícitas durante el embarazo, Alto riesgo obstétrico.

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According to data obtained by the National Plan for Drugs (Government Delegation for the National Plan for Drugs, 2011) in a household survey of Spanish citizens between 15 and 64 years of age, 35.1% of those questioned consumed tobacco daily and 15.3% drank alcohol. Consuming cannabis in the last 30 days was reported by 6.5%; the figures for cocaine and amphetamines were 1.4% and 0.6% respectively. Data gathered by the National Health Survey in 2012 showed that 61.4% of women of fertile age drank alcohol during the previous year (Ministry for Health, Social Services and Equality, 2013). The prevalence of substance abuse among women who become pregnant is similar to that in the general population, signifying high fetal exposure during the first trimester, with a large group of patients still maintaining a high level of exposure at the end of pregnancy (Cnattingius, 2004).

Although it is very difficult to estimate all the consequences of the consumption of these substances, we at least know that the effects on the fetus depend fundamentally on the moment and intensity of exposure, with the first trimester being the most vulnerable, above all with respect to the neurodevelopment and organogenesis. The consumption of toxic substances has also been linked to intrauterine growth retardation, placental abruption, premature birth (Bernstein, Plociennik, Stahle, Badger & Secker-Walker, 2000; Bouras et al., 2013), miscarriage, ectopic pregnancy, and sudden infant death (National Committee for the Prevention of Smoking, 2007; Genbacev, Blass, Joslin & Fisher, 1995; Toothily, Stewart, Coles, Andrews & Cartlidge, 1999). Not a great deal of information has been gathered in Spain regarding the prevalence of substance abuse during pregnancy. Studies of tobacco consumption show a prevalence of between 27% (Doz-Mora et al., 2002) and 34% of pregnant women at the end of pregnancy (Pichini et al., 2002). Furthermore, Martínez-Frías, Rodríguez-Pinilla & Bermejo (2005) have observed a tendency towards increased smoking among pregnant women since 1975, with a prevalence of 30% between 1995 and 2002. With regard to alcohol consumption, the Eurocare group (2011) reports that in our country, 25% of women consume alcohol during pregnancy, and that there is an incidence of fetal alcohol syndrome of 0.46 per 1000 births (Eurocat, 2014). There are no national data regarding the prevalence of fetal alcohol spectrum disorder, but in other countries these figures can be up to ten times more frequent. Data on the consumption of illicit drugs is scarce. In a study carried out in Barcelona on samples of meconium, 5.3% tested positive for cannabis, 4.7% for heroin and 2.6% for cocaine (García-Algar et al., 2009).

This study has been designed with the aim of discovering prenatal levels of exposure to tobacco, alcohol and other drugs in the city of Malaga, and to propose public health strategies which can be added to existing ones in order to reduce the negative impact of the consumption of these substances during pregnancy and on the health of newborns. The systematization of obstetrical care through the design of care procedures enables the development of interventions towards this end. Based on scientific evidence, the clinical practice guide for normal births (Working group of the Clinical Practice Guide on Pregnancy and Infant Care, 2014) establishes some recommendations and suggestions as to the detection of risk behavior linked to substance abuse, although the integration of such recommendations in health care practice depends on local factors related to the organizational context and to the motivation of the staff involved, and no data exists regarding compliance at the national level. The efficacy of educational intervention on the reduction of consumption during pregnancy has already been evaluated in previous studies (Chang, Wilkins-Haug, Berman & Goetz, 1999; O´Connor & Whaley, 2007; Reynolds, Coombs, Lowe, Peterson & Gayoso, 1995), although none of these were carried out in Spain.

Our study is positioned within a line of research into reproductive health aimed at avoiding exposure of pregnant women to tobacco, alcohol and other drugs.

Method

To study the prevalence of exposure to tobacco, alcohol or other substance abuse among pregnant women in Malaga, an observational, descriptive, transversal study of prevalence was designed. Before the study was initiated, the corresponding authorization of the Ethics and Research Committee of Northeast Malaga was obtained.

Participants

The population of the study consisted of pregnant women who attended obstetric check-ups at our hospital during the months of November and December 2101.

Our maternity unit is the reference center for specialized obstetric and gynecological care in 14 primary care centers in the Malaga health district, with more than 5000 deliveries in 2013. Although there are other centers with obstetric services in Malaga, the volume of activity means that the population attended to in our center is highly representative of the general population of pregnant women in the city.

In the organization of obstetric care in Andalucía it is normal that women with low-risk pregnancy attend

primary care centers to control their pregnancy, coming to our hospital once in every trimester for a clinical evaluation and ultrasound scan carried out by the obstetric and gynecological specialist. These visits are programmed for weeks 12, 20 and 32.

The population of the study was made up of patients who attended the obstetric control center in weeks 12, 20 or 32. Given the empirical prevalence (Cnattingius, 2004) of smoking between 20% and 40% and a frequency of alcohol consumption (García-Algar et al., 2008) among pregnant women of up to 45%, we estimated that for a 95% confidence interval and 5% accuracy it would be necessary to recruit at least 350 pregnant women to obtain a representative sample.

Consecutive sampling was carried out on pregnant women who attended obstetric controls at our maternity ward in the last quarter of 2013, generating a final sample of 451 participants. Of these, 184 were in the first, 121 in the second and 146 in the third trimester.

Procedure

The patients who agreed to participate in this study answered questions about tobacco, alcohol and other drugs presented in a consumption questionnaire. Alongside the questionnaire, an informational consent form was handed out which, as well as explaining the reasons for the study, highlighted the fact that responses would be treated anonymously. The pregnant women deposited the completed questionnaire in a sealed box themselves, ensuring the impossibility of tracing any of the forms since they lacked all personal data. In order to safeguard the anonymity of the patients, no signature was required at any time, on the understanding that the completion of the questionnaire and posting it in the collection box constituted implicit agreement to being included in the study. All patients could refuse to participate before, during or after completion of the questionnaire, right up to the moment of posting it in the collection box. Nevertheless, the number of pregnant women who refused to participate was less than 3.2%.

Instruments

Participants answered a self-administered and anonymous questionnaire (Appendix 1) on substance consumption, based on direct questions focused on assessing whether substances were consumed, as well as frequency and intensity. These questions were in turn adapted from questionnaires validated and used in previous studies of prenatal exposure to substance abuse during pregnancy (Gómez, Conde & Aguiar, 2001). In terms of tobacco consumption, patients had to state the number of cigarettes smoked daily or weekly, at the moment of response and also before pregnancy, as well as the age of smoking onset. At the same time, the patient was asked about the smoking habits of her partner. For data referring to alcohol consumption, patients were asked whether or not they drank, about the absolute quantity consumed (number and type of drinks) as well as frequency. Items were incorporated from the domain of high-risk alcohol consumption of the AUDIT test (Babor, Higgins-Biddle, Saunders & Monteiro, 2001). With reference to other substance abuse, the women were presented with questions about the consumption of cannabis, cocaine, ecstasy, methadone, heroin or amphetamines, and the frequency of such, whether daily, weekly, monthly or occasional. The questionnaire also included questions regarding the socio-demographic and family context of the women relating to occupation, educational level, number of pregnancies, assisted reproduction, nationality, home postal code, consumption of tobacco, alcohol or drugs of abuse prior to pregnancy and consumption of the same by their partners.

Data analysis

The dependent variables considered referred to socio-demographic and health aspects: the woman's age, trimester of pregnancy, educational level, occupation, number of pregnancies, use of assisted reproduction techniques, nationality, postal code, consumption of tobacco, alcohol or drugs of abuse prior to pregnancy and by her partner.

The principal outcome variables studied were consumption of tobacco, alcohol and other drugs of abuse. The three variables were coded as dichotomous variables (consumption or non-consumption). Information regarding the frequency of consumption in the three cases was collected in the shape of categorical variables (daily, weekly, monthly, occasional consumption or non-consumption). The intensity of tobacco consumption was studied through the outcome variable of number of cigarettes consumed (ranging from 0 to n).

To study the intensity of alcohol consumption, we measured the volume of alcoholic drinks consumed (shot glass, standard glass, can, bottle) daily, weekly or monthly, according to each woman's declared drinking pattern, and distinguishing between consumption of beer, wine or spirits (straight or mixed). For subsequent coding and analysis, the volumes were converted into standard drink units (SDU). An SDU in Spain contains 10 grams of pure alcohol, with the conversion from volume to SDU done in the following way: a standard serving of beer or wine equals 1 SDU, and a standard serving of spirits equals 2 SDUs (Llopis, Gual & Rodríguez-Martos, 2000).

Finally, to analyze the consumption of drugs of abuse, a variable was coded to gather the frequency (dai-

ly, weekly or occasional) of cannabis, cocaine, ecstasy, methadone, heroin or amphetamine consumption. A descriptive analysis of the variables was initially carried out. The analysis of the independent variables enabled stratification of the sample on the basis of its different categories. To test for possible significant differences in the observed frequencies across the different stratification groups, the Chi-squared test was applied when the dichotomous variables of tobacco, alcohol and other substance consumption was analyzed. For bi-dimensional tables we have calculated the risk ratios and their 95% confidence intervals. Having checked for the normality of the distribution, to analyze the differences among the values of the continuous variables (intensity of consumption) the Student's t-test was applied to two independent samples or single-factor ANOVA when the number of categories of the independent variable was superior to two. The statistical analyses were carried out using SPSS 15.0 (SPSS Inc., Chicago, IL).

Results

The main demographic characteristics of the women in the study are reflected in Table 1. The average age was 31.4 (SD 5.2), 55.16 were first-time pregnancies and 92.7 were Spanish nationals. Of the non-Spanish patients, those from the Maghreb were the most numerous.

In terms of tobacco consumption, 152 pregnant women stated they were smokers (33.7%), of which 68 continued smoking during pregnancy; we thus found a 15.07% prevalence of smoking during pregnancy. In our sample, tobacco consumption was lower at the end of pregnancy, with third trimester smoking down significantly compared to first and second trimesters (÷2 = 13.114 and 18.715, p<0.0003 and p <0.0001, respectively). The distribution by trimester can be seen in Table 2.

A total of 123 pregnant women admitted to drinking or having drunk alcohol during pregnancy, resulting in global exposure prevalence of 27.2% during pregnancy, and an average of 16.5 SDUs (SD 20.5). Consumption was significantly greater (÷2 = 9.48 p<0.002) in the first trimester group (40.7%), and progressively lower in the other trimesters (23.1% in the second trimester group, and 17.1% in the third). In the group of women exposed to alcohol, 52.8% declared a consumption of 1 or 2 weekly SDUs, with 3.1% admitting a consumption of more than 10 SDUs.

The type of drink most frequently consumed was beer (68.8% of women), followed by spirits (26.9%) and wine (20.8%).

Table 1
Principal socio-demographic characteristics of the sample

Caracteristics	1st Trimester (N = 184)	2nd Trimester (N = 121)	3rd Trimester (N = 146)
Age			
Age in years	30.4	33.6	30.2
First pregancy	108 (58.7%)	62 (51.2%)	55 (55.6%)
Employment situation			
No schooling	46 (25.3%)	26 (21%)	47 (32.1%)
Working	104 (57.1%)	77 (63%)	69 (37.5%)
Looking for work	32 (17.6%)	18 (14.5%)	29 (19.8%)
Educational level			
No schooling	13 (7.1%)	4 (3.3%)	11 (7.5%)
Compulsory	64 (34.8%)	29 (24%)	46 (31.5%)
High school diploma or equivalent	44 (23.9%)	39 (32.2%)	34 (23.2%)
University	57 (31%)	47 (38.8%)	31 (21.2%)
Nationality			
Spanish	163 (90.1%)	113 (95.0%)	91 (91.7%)
Eastern European	2 (1.1%)	-	1 (0.6%)
South American	5 (2.8%)	2 (1.7%)	5 (4.1%)
Chinese	1 (0.6%)	-	1 (0.6%)
African	1 (0.6%)	-	2 (1.2%)
Maghreb	8 (4.4%)	2 (1.6%)	3 (1.8%)
Assisted Reproduction			
No	175 (95.6%)	106 (88.3%)	142 (97.2%)
Yes	7 (3.8%)	13 (10.8%)	4 (2.8%)

Table 2
Exposure to tobacco during pregnancy

Tobacco	1st Trimester (N = 184)	2nd Trimester (N = 124)	3rd Trimester (N = 146)
Onset age			
Age in years	16.7 (DT 2.9)	17.2 (DT 3.3)	17 (DT 2.7)
Before pregnancy			
Smoked	67 (36%)	37 (29.6%)	48 (35.7%)
Did not smoke	117 (63.6%)	87 (69.6%)	98 (64.3%)
During pregnancy			
Smoke	39 (21.2%)	23 (18.5%)	6 (13.3%)
Does not smoke	145 (78.8%)	101 (81.5%)	140 (86.7%)
No. of cigarettes			
Before	13.0 (DT 6.2)	14.3 (DT 7.7)	14.8 (DT 9.0)
During	4.9 (DT 3.3)	6.3 (DT 4.4)	7.9 (DT 8.0)
Her partner smokes			
Yes	60 (32.6%)	32 (26%)	34 (34.3%)
No	116 (63%)	89 (73%)	64 (64.6%)
Passive smoking			
At home	39 (21.3%)	18 (15.1%)	14(14.7%)
At work	9 (4.9%)	7 (6%)	4 (4.2%)

The number of consumers increased significantly among women in the first and second trimesters of pregnancy, at the weekend (÷2 = 9.8 and 9.56, p<0.0017 and p<0.002 respectively), rising 29.1% above weekday levels. Of pregnant women who drank, 11.3% did so daily, 35.3% weekly and 54.3% on a monthly basis. Table 3 shows the main results by trimester of pregnancy.

In terms of illicit substance use (Table 4), 11 patients admitted having consumed cannabis during pregnancy, equivalent to 2.43%. No other pregnant women admitted to taking any other type of illicit drug.

Table 3
Exposure to alcohol during pregnancy

Alcohol	1st Trimester (N = 184)	2nd Trimester (N = 121)	3rd Trimester (N = 146)
Consumption			
Yes	75 (40.7%)	28 (23.1%)	25 (17.1%)
No	109 (59.3%)	93 (76.5%)	121 (82.9%)
Type of drink on weekdays			
Beer	40 (57%)	11(39.3%)	18 (70%)
Wine	20 (28.6%)	11 (39.3%)	7 (25%)
Spirits	13 (18.6%	2 (7.1%)	1 (5%)
Type of drink on weekend/holidays			
Beer	47 (67.1%)	20 (71.4%)	17 (68%)
Wine	29 (41.4%)	14 (50%)	7 (28%)
Spirits	27 (38.6%)	4 (14.3%)	7 (28%)
Frequency of consumption			
Daily	9 (12.8%)	2 (7.1%)	3 (12%)
Weekly	24 (34.2%)	10 (35.7%)	9 (36%)
Monthly	40 (57.1%)	14 (50%)	14 (56%)
SDUs weekly			
<2 SDUs	36 (51.4%)	18 (64.2%)	11 (55%)
2-10 SDUs	28 (40%)	9 (32.1%)	9 (32.1%)
>10 SDUs	6 (8.6%)	1 (5%)	
SDUs weekly			
Average	16.7 (DT 20.6)	8.5 (DT 11.1)	12 (DT 9.9)

Table 4
Exposure to cannabis during pregnancy

Illicit drugs	1st Trimester (N = 184)	2nd Trimester (N = 121)	3rd Trimester (N = 146)
Marihuana consumption			
Yes	7 (4.8%)	2 (1.9%)	2 (1.2%)
No	137 (85.2%)	103 (98.1%)	83 (98.8%)

Table 5
Association of high education level and partner smoking habits with tobacco and alcohol consumption (RR: relative risk)

	First T	Second T	Third T
High education level			
Tobacco consumption			
RR	0.341	0.455	0.778
IC95%	(0.187-0.623)	(0.206-1.00)	(0.345-1.756)
Signif.	p<0.0001	p<0.039	p<0.39 NS
Alcohol consumption			
RR	2.455	4.091	3.143
IC95%	(1.298-4.641)	(1.134-14.759)	(0.95-10.21)
Signif.	p<0.004	p<0.017	p< 0.042
Partner smoking habits			
Tobacco consumption			
RR	17.208	24.364	5.576
IC95%	7.648-38.721	(7.749-76.606)	(2.272-13.685)
Signif.	p<0.0001	p<0.0001	p<0.0001

We did not observe differences in the consumption of tobacco, alcohol or other drugs in any of the trimesters linked to age, number of pregnancies, employment situation, nationality, or district of residence. We did however find a significant difference between educational level and the consumption of tobacco and alcohol, globally and by trimester. It is worth noting that smoking was less prevalent among pregnant women with higher educational level (RR 0.659 [0.537-0.810] p< 0.0001), while in contrast alcohol consumption was more frequent among those with higher educational level (RR 1.87 [1.30-2.69] p< 0.0007). Table 5 contains the risk ratios for each of the trimesters.

We have observed a significant association between smoking during pregnancy and the smoking habits of partners, with RR 3.091 [2.501-3.820] p< 0.0001. Furthermore, alcohol consumption in the first trimester was linked to smoking (RR 2.357 [1.243-4.469] p<0.006). This association did not prove significant en the second or third trimester.

Discussion

This study investigates the consumption of toxic substances during pregnancy in a cross-sectional observational design. The limits of a study based on self-reports of pregnant women has been shown in previous studies (Aranda, Mateos, González,

Sánchez & Luna, 2008). In our study, an anonymous self-administered questionnaire was applied in which the responses were untraceable, and which the women

themselves posted in a sealed collection box, thus providing a guarantee of confidentiality and increasing the reliability of the responses. Furthermore, despite the need to take possible under-reporting into account (Castellanos et al., 2000), the results obtained are striking enough, especially in terms of alcohol consumption, to alert the providers of obstetric care of the need to introduce preventive measures.

Pregnancy appears to have a modulating effect on tobacco consumption, given that the proportion of pregnant women who smoked prior to pregnancy was 36% while only 21.2% continued smoking during pregnancy. The proportion of smokers in the second and third trimester groups was also smaller, with the women in the third trimester exhibiting the lowest consumption (13.3%) as well as the greatest difference between women who smoked before pregnancy (35.7%) and those who continued to do so. The physical demands of third trimester, alongside the health promotion measures carried out in primary care are the most influential factors in this trend. It is nevertheless striking that levels of smoking reported in the first trimester are similar to those described 30 years ago (Herrera, 1989). The information campaigns developed over recent years have had a limited effect in reducing consumption, especially during the initial stages of pregnancy. In fact, despite various studies showing a decreasing pattern of habitual smokers among young Spanish people, the onset of smoking is getting noticeably earlier among women, as are their numbers, in comparison to men of the same age (Villalbí et al., 2012), a fact which may be linked to the marketing strategies of the tobacco multinationals or to aspects related to gender identity (Amos & Bostock, 2007). Although health surveys show that the prevalence of smoking is similar in both sexes, or slightly higher among males, the number of smokers of reproductive age is very high, with the proportion of women smokers who become pregnant reaching 36% in our study.

In addition, we have observed significantly higher consumption of alcohol among women with higher educational level in the first and second trimesters. The existence of social, educational, and occupational gradients in the consumption of alcohol has been shown previously in studies of the overall female population; the National Health Survey 2011-2012 for example, showed that while 52.05% of women between 25 and 64 years of age with higher education had drunk alcohol in the 2 weeks prior to the survey, only 33.86% of women with lower educational level had done so. Furthermore, 71.1% of female university graduates had drunk alcohol in the previous year, in contrast with 27.9% of women without a degree, with the same difference in all age groups (National Statistics Institute, 2013).

It is remarkable that women with a higher level of education, and therefore greater access to information regarding the potential effects of alcohol during pregnancy should display a higher tendency to drink. It is possible that the social habits of these women are different from those with a lower educational level, thus conditioning differences in consumption. Although there is no agreement in the international literature on tolerable levels of alcohol intake during pregnancy, the health care authorities in Spain recommend abstaining. Indeed, the Spanish Ministry of Health, Social Policy and Equality (2010) uses the slogans "Pregnancy: zero alcohol" or "If you're pregnant, there's no excuse" in its campaign to prevent alcohol consumption during pregnancy. Although the messages of such prevention programs are getting through, since alcohol consumption does decrease during pregnancy, it would be important to discover better ways of communicating with the groups at greater risk. The systematization of obstetric care with monthly visits to health centers or hospitals to control pregnancy represents an opportunity to offer pregnant women information referring to the need to avoid alcohol, in our view an ideal method of communication with the susceptible population.

Pre-conception counseling and the first obstetric check-up offer the ideal framework for communicating the unequivocal message that toxic substances must be avoided and starting educational strategies specifically integrated in maternal education.

The efficacy of educational intervention in reducing consumption during pregnancy has been variously studied (Chang et al., 1999; O´Connor, 2007; Reynolds et al., 1995), and, although results are mixed, it appears that psychological and educational interventions may help to reduce alcohol consumption or help women to abstain during pregnancy. To this end, health care staff involved in the interventions need to be motivated and prepared. In our context, neither the effect of such interventions on alcohol consumption during pregnancy nor the level of implementation in the different autonomous communities has been assessed.

The first trimester of pregnancy, at least the first half of it, goes unnoticed by many women, especially in cases of unplanned pregnancy. This leads to first trimester alcohol consumption of 40.7%, in line with data published for Spanish cities of a similar profile, such as Barcelona (García-Algar et al., 2008). It is worth noting in this context that alcohol consumption is also linked to sexual risk behaviors in unplanned pregnancies as has recently been revealed in Spain by Espada, Morales, Orgilés, Piqueras & Carballo (2013), indicating that the use of contraceptives is 1.4 times less frequent among adolescents having sex under the influence of alcohol.

As we have pointed out previously, pregnancy itself may modify consumption, with the proportion of drinkers being lower among second and third trimester patients. Nevertheless, levels of consumption of 23.1% and 17% among second and third trimester groups respectively are excessively high if we take into account the 2010 Health Ministry target of abstention during pregnancy (Ministry of Health Social Policy and Equality, 2010).

Although half of the pregnant women report a sporadic drinking pattern (monthly), 12.8% of first trimester, 7% of second trimester and 12% of third trimester patients admit drinking daily. Furthermore, although somewhat more than half the pregnant women declare a weekly intake of below 2 SDUs, more than a third admit to drinking up to 10 SDUs. It needs to be pointed out that while there is no consensus as to what may be considered a harmless level of alcohol, the potential effects on the fetus, in both perinatal results (prematurity, low weight, or fetal alcohol syndrome) (Patra et al., 2011), as well as fetal alcohol syndrome disorder in the longer term (López & Arán, 2010) dictate that women be strongly dissuaded from alcohol consumption during pregnancy (Working group of the Clinical Practice Guide on Pregnancy and Infant Care, 2014; Ministry of Health, Social Policy and Equality, 2010; Poli et al., 2013). The WHO highlights the advantages of advocating complete abstinence during pregnancy as well as developing intervention measures for pregnant women who drink.

We have found that 2.43% of pregnant women admit to using cannabis, although none of the women reported consuming other illegal drugs. The Collaborative Spanish Study of Congenital Malformations 1976-1996 showed how the consumption of drugs varied depending on the ethnic group of the pregnant woman, ranging from 5.5% among ethnic Gypsies and 1.1% among white Caucasians (Martínez-Frías, 1999). It is possible that potential legal and socio-health connotations associated with illicit drugs are obstacles preventing the women included in our study from admitting the consumption of drugs other than cannabis. Nevertheless, the fetal and neonatal morbidity associated with the consumption of such drugs emphasizes the need to include information about these substances in the educational intervention measures during pregnancy with the aim of reducing consumption.

There is a variety of aspects which limit the interpretation of the results of our study. The application of a self-administered questionnaire involves a potential bias factor derived from under-reporting by patients. In addition, no laboratory tests have been carried out which would allow objective corroboration of consumption levels found, with the result that real levels may well be even higher than those claimed by the patients. Furthermore, the aim of simultaneously examining the consumption of tobacco, alcohol and other drugs, as well as their intensity, led to the use of a single questionnaire, developed with questions which had been previously validated, although the questionnaire as a whole has not been subjected to the relevant validation process. Finally, given the transversal nature of the study, we have obtained data about the prevalence and intensity of substance use without being able to analyze the progression of consumption during the course of the different trimesters. Nevertheless, the results obtained are sufficiently conclusive to urge that health education campaigns aimed at preventing substance use during pregnancy be intensified by providing suitable information for pregnant women and incorporating specific educational strategies which cover all stages from pre-conception to nursing. The implementation of pre-conception counseling, and the design of pregnancy training programs with sessions aimed at achieving abstinence during pregnancy (and nursing) are proposed as necessary strategies in our environment. In putting such measures into practice, the role of health professionals both in the areas of primary and specialized care is fundamental in the diffusion of unequivocal messages.

Conflict of interests

The authors declare that there is no conflict of interests.

References

Amos, A., & Bostock, Y. (2007). Young people, smoking and gender – a qualitative exploration. *Health Educational Research, 22,* 770-781. doi: 10.1093/her/cyl075.

Aranda, J. M., Mateos, P., González, A., Sánchez, F. y Luna, J. D. (2008). Validez de distintas medidas de consumo de tabaco durante el embarazo: especificidad, sensibilidad y puntos de corte dónde y cuándo. *Revista Española de Salud Pública, 82,* 535-545.

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., & Monteiro, M. G. (2001). *Cuestionario de identificación de los transtornos debidos al consumo de Alcohol.* Ginebra: Organización Mundial de la Salud. Recuperado de http://www.who.int/substance_abuse/activities/en/AUDITmanualSpanish.pdf

Bernstein, I. M., Plociennik, K., Stahle, S., Badger, G. J., & Secker-Walker, R. (2000). Impact of maternal cigarette smoking on fetal growth and body composition. *American Journal Obstetrics and Gynecology, 183,* 883-886. doi: 10.1067/mob.2000.109103

Bouras, G., Theofanopoulou, N., Mexi-Bourna, P., Poulios, A., Michopoulos, I., Tassiopoulou, I.,... Christodoulou, C. (2013). Preterm birth and maternal psychological health. *Journal of Health Psychology*. doi: 10.1177/1359105313512353.

Castellanos, M. E., Muñoz, M. I., Nebot, M., Payá, A., Rovira, M. T., Planasa, S.,… Carreras, R. (2000). Validez del consumo declarado de tabaco en el embarazo. *Atención Primaria, 9,* 629-632. doi: 10.1016/S0212-6567(00)78736-1.

Chang, G., Wilkins-Haug, L., Berman, S., & Goetz, M. A. (1999). Brief intervention for alcohol use in pregnancy: randomized trial. *Addiction, 94,* 1499-1508. doi: 10.1046/j.1360-0443.1999.941014996.x.

Cnattingius, S. (2004). The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics and pregnancy outcomes. *Nicotine and Tobacco Research, 6,* 125-140. doi: 10.1080/14622200410001669187.

Comité Nacional para la Prevención del Tabaquismo (CNPT). (2007). *Libro blanco sobre mujeres y tabaco*. Madrid: Ministerio de Sanidad y Consumo. Recuperado de http://www.cnpt.es/doc_pdf/mujerestabaquismo.pdf

Delegación del Gobierno para el Plan Nacional sobre Drogas. (2011). *Plan Nacional sobre drogas. Memoria del Ministerio de Sanidad, Servicios Sociales e Igualdad*. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved from http://www.pnsd.msc.es/Categoria2/publica/pdf/oed-2007.pdf.

Doz-Mora, J. F., Gasulla-Pascual, G., Cárceles-Jurado, S., Guerrero-Bartolín, I., Tintó-Padró, A., Prat-Asensio, C., & Rosell-Murphy, M. (2004). Evolución del hábito tabáquico durante el embarazo y el posparto. *Atención Primaria, 34,* 465-471.

Espada, J. P., Morales, A., Orgilés, M., Piqueras, J. A., & Carballo, J. L. (2013). Sexual behaviour under the influence of alcohol among Spanish adolescents. *Adicciones, 25*, 55-62.

Eurocare. (2011). *Protecting the unborn baby from alcohol. Policy debate*. Brussels: European Alcohol Policy Alliance. Retrieved from http://www.eurocare.org/resources/policy_issues/alcohol_and_pregnancy

Eurocat. (2014). *European surveillance of congenital anomalies prevalence tables*. Derry: University of Ulster. Retrieved from http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables

García-Algar, O., Kulaga, V., Gareri, J., Koren, G., Vall, O., Zuccaro, P.,… Pichini S. (2008). Alarming prevalence of fetal alcohol exposure in a Mediterranean city. *Therapeutic Drug Monitoring, 30,* 249-254.

Garcia-Algar, O., Vall Combelles, O., Puig Sola, C., Mur Sierra, A., Scaravelli, G., Pacifici, R., & Pichini, S. (2009). Exposición prenatal a drogas de abuso a través del análisis de meconio en una población de bajo nivel socioeconómico en Barcelona. *Anales de Pediatría, 70,* 151-158. doi: 10.1097/FTD.0b013e31816a8657.

Genbacev, O., Blass, K. E., Joslin, S. J., & Fisher, S. J. (1995). Maternal smoking inhibts early human cytothrofoblast differentiation. *Reproductive Toxicology, 9,* 245-255.

Gómez, A., Conde, A., & Aguiar, J. A. (2001). Utilidad Diagnóstica del cuestionario Alcohol Use Disorders Identification Test (AUDIT) para detectar el consumo de alcohol de riesgo en atención primaria. *Medicina Clínica, 116,* 121-124.

Grupo de trabajo de la Guía de Práctica Clínica de Atención en el Embarazo y Puerperio. (2014). *Guía de práctica clínica de atención en el embarazo y puerperio*. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved from http://www.juntadeandalucia.es/salud/servicios/contenidos/nuevaaetsa/up/AETSA_2011_10_GPC_Embarazo.pdf

Herrera, J. (1989). *El tabaco y su relación con aspectos perinatales*. [Unpublished doctoral dissertation]. Madrid: Universidad Complutense de Madrid.

Instituto Nacional de Estadística. (2013). *Encuesta Nacional de salud 2011-2012*. Madrid: Instituto Nacional de Estadística. Retrieved from http://www.ine.es/jaxi/menu.do?type=pcaxis&path=/t15/p419/a2011/p06/&file=pcaxis

Llopis, J. J., Gual, A., & Rodríguez-Martos A. (2000). Registro del consumo de bebidas alcohólicas mediante la unidad de bebida estándar. Diferencias geográficas. *Adicciones, 12,* 11-19.

Lopez, M. B., & Arán, V. (2010). Perfiles ejecutivos en niños y adolescentes con trastornos del espectro fetal alcohólico. *Acta Psiquiátrica y Psicológica de América Latina, 56*, 294-304.

Martínez-Frías, M. L. (1999). Análisis del riesgo de defectos congénitos debidos a la ingesta de drogas durante el embarazo. *Medicina Clínica, 112,* 41-44.

Martínez-Frías, M. L., Rodríguez-Pinilla, E., & Bermejo, E. (2005). Consumo de tabaco durante el embarazo en España: análisis por años, comunidades autónomas y características maternas. *Medicina Clínica, 124,* 86-92.

Ministerio de Sanidad, Política Social e Igualdad. (2010). *Embarazadas cero alcohol*. Madrid: Ministerio de Sanidad, Política Social e Igualdad. Retrieved from http://www.embarazadasceroalcohol.es/embarazadas_cero_alcohol.htlm

Ministerio de Sanidad Servicios Sociales e Igualdad. (2013). Encuesta Nacional de Salud. España 2011/12. *Serie informes monográficos nº 1. Consumo de alcohol*. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved from http://www.pnsd.msc.es

O'Connor, M., & Whaley, S. (2007). Brief intervention for alcohol use by pregnant women. *American Journal of Public Health, 97,* 252-258. doi: 10.2105/AJPH.2005.077222

Annex 1. *Consumption questionnaire*

DATOS DEMOGRÁFICOS

Edad: ..... Profesión: ..... Semana de gestación: .....

¿Trabaja actualmente fuera de casa?: ❑ Sí ❑ No ❑ Está en paro busca empleo

Estudios: ❑ No estudios ❑ Obligatorios (ESO) ❑ Bachillerato ❑ Universitarios

Nacionalidad: ❑ España /Europa ❑ Europa Este ❑ Asia-Filipinas
❑ Centro-Sudamérica ❑ España etnia gitana ❑ África-Caribe
❑ India-Pakistán ❑ China ❑ Magreb

¿Tiene hijos? ❑ Sí ❑ No ¿cuántos? .....

¿Ha tenido abortos? ❑ Sí ❑ No ¿cuántos? .....

Este embarazo ha sido ❑ Natural ❑ Inseminación ❑ In vitro

Código postal del domicilio: ..... Código postal del .....

TABACO

¿Fumaba antes del embarazo? ❑ Sí ❑ No

¿Ha fumado algo en estas últimas 2 semanas? ❑ Sí ❑ No

¿Cuántos cigarrillos al día o a la semana está fumando? al día .....
a la semana .....

¿Su marido/pareja fuma? ❑ Sí ❑ No ❑ Lo ha dejado antes del embarazo

¿Cuántos cigarrillos al día fumaba antes del embarazo? .....

¿A qué edad empezó a fumar? .....

ALCOHOL

De Lunes a viernes. Indique con qué frecuencia consume bebidas alcohólicas entre semana. Especifique también el tipo de bebida.

	RECIPIENTE (elegir uno)	**DIARIAMENTE** Número de veces: 0, 1, 2,...	**SEMANALMENTE** Número de veces: 0, 1, 2,...	**MENSUALMENTE** Número de veces: 0, 1, 2,...
CERVEZA	Vaso, lata, jarra, botella mediana, quinto			
VINO	Vaso, copa, botella			
LICORES	Chupito, copa, combinados Licores			

En sábado, domingos y festivos. Indique con qué frecuencia consume bebidas alcohólicas el fin de semana. Especifique también el tipo de bebida.

	RECIPIENTE (elegir uno)	**DIARIAMENTE** Número de veces: 0, 1, 2,...	**SEMANALMENTE** Número de veces: 0, 1, 2,...	**MENSUALMENTE** Número de veces: 0, 1, 2,...
CERVEZA	Vaso, lata, jarra, botella mediana, quinto			
VINO	Vaso, copa, botella			
LICORES	Chupito, copa, combinados Licores			

OTRAS SUSTANCIAS

Indique si consume alguna sustancia como las que se describen a continuación

MARIHUANA	❑ DIARIO	❑ SEMANAL	❑ OCASIONAL	❑ NUNCA
COCAÍNA	❑ DIARIO	❑ SEMANAL	❑ OCASIONAL	❑ NUNCA
HEROÍNA	❑ DIARIO	❑ SEMANAL	❑ OCASIONAL	❑ NUNCA
METADONA	❑ DIARIO	❑ SEMANAL	❑ OCASIONAL	❑ NUNCA
ANFETAMINAS	❑ DIARIO	❑ SEMANAL	❑ OCASIONAL	❑ NUNCA
EXTASIS	❑ DIARIO	❑ SEMANAL	❑ OCASIONAL	

Motivational interviewing group at inpatient detoxification, its influence in maintaining abstinence and treatment retention after discharge

Grupo motivacional en unidad hospitalaria desintoxicación, su influencia en mantenimiento de la abstinencia y retención al tratamiento tras alta

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Abstract

The relapse rate after discharge from inpatient detoxification is high. The objective of this pilot study is to assess the sociodemographic, clinical and therapeutic factors associated with maintaining abstinence in patients who participated in a brief motivational interviewing group during admission for detoxification.

A total of 46 patients, diagnosed substance dependent according to DSM –IV, and admitted to the Hospital Detoxification Unit, participated in a brief motivational interviewing group. Sociodemographic, clinical, motivation to change (University of Rhode Island Change Assessment, URICA) and satisfaction with the treatment group (Treatment Perceptions Questionnaire, CPT) data were collected. Abstinence and treatment retention two months after discharge were assessed by weekly telephone calls. A survival analysis was performed. Being male, having more cognitions of the maintenance stage of change at discharge, being satisfied with group therapy and therapist during hospitalization are associated with longer abstinence after discharge.

The brief motivational interviewing group approach with patients admitted for detoxification is related to greater likelihood of maintaining abstinence and subsequent treatment retention.

Key words: Motivational Interviewing, substance-related disorders, relapse, inpatient detoxification, group therapy.

Resumen

La tasa de recaída en el consumo al alta de una Unidad de Desintoxicación Hospitalaria es elevada. El objetivo de este estudio piloto es valorar los factores sociodemográficos, clínicos y terapéuticos asociados al mantenimiento de la abstinencia de pacientes que han participado en un grupo psicoterapéutico breve de corte motivacional durante su ingreso para la desintoxicación.

Un total de 46 pacientes con diagnóstico de trastorno por dependencia a sustancias, según DSM-IV, ingresados en Unidad de Desintoxicación Hospitalaria participaron en un grupo breve de corte motivacional. Se midieron variables sociodemográficas y clínicas, así como la motivación al cambio (University of Rhode Island Change Assessment, URICA) y la satisfacción con el tratamiento grupal (Cuestionario de Percepciones de Tratamiento, CPT). El mantenimiento de la abstinencia y la retención al tratamiento, dos meses tras el alta, se evaluaron mediante llamadas telefónicas semanales. Se realizó un análisis de supervivencia. Los resultados muestran que ser varón, tener cogniciones del estadio de mantenimiento del cambio al alta y tener una buena satisfacción con la terapia grupal y su terapeuta durante el ingreso, se asocia con mayor tiempo en abstinencia tras el alta.

El abordaje psicoterapéutico grupal breve de corte motivacional, en pacientes ingresados para la desintoxicación, se relaciona con mayor probabilidad de mantenimiento de abstinencia y de retención al tratamiento posterior.

Palabras clave: Entrevista Motivacional, trastorno por uso de sustancias, recaída, desintoxicación hospitalaria, terapia grupal.

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Addiction is a chronic and recurrent psychological disorder. The relapse rate after inpatient detoxification is very high (Santa Ana, Wulfert & Nietert, 2007). Six months after discharge, between 12.5% and 27.8% remain abstinent from various substances, rising to 32% in the case of cocaine (Grau-López et al., 2012; Shaw, Waller, Latham, Dunn & Thomson, 1998), while only 17.4% continue without consuming alcohol after one year (John, Veltrup, Driessen, Wetterling & Dilling, 2003).

Sociodemographic and clinical variables which have been linked to relapse include sex, living arrangements, education level, employment situation, legal record, family history of substance abuse, comorbidity with other mental disorders (dual diagnosis), the type of addictive substance, years of addiction, polydrug use, previous admissions or binge consumption prior hospitalization for detoxification. These variables may be indicators of the seriousness of the addiction (Arias et al., 2013; García Rodríguez et al., 2005; Goeb, Coste, Bigot & Ferrand, 2000; Grau-López et al., 2012; John et al., 2003; Márquez-Arrico & Adán, 2013; Schellekens, de Jong, Buitelaar & Verkes, 2014).

Low motivation to change is a further important factor which has been linked to post-discharge relapse (Loeber, Kiefer, Wagner, Mann & Croissant., 2009). To address this issue, motivational interviewing, developed by Miller and Rollnick (2002), focuses the treatment of addiction on raising the patient's internal motivation to change. Intervention with such a therapeutic focus has been linked to a reduction in substance abuse, a positive effect on the process of change and an improvement in treatment retention (Wagner & Ingersoll, 2012). The efficacy of a short version of motivational interviewing has also been demonstrated, and depends on the variables of the patient associated with the severity of the addiction, variables on which more research needs to be done (Vasilaki, Hosier & Cox, 2006).

Treatment retention is an important factor in preventing relapses, thus incorporating strategies to improve retention will improve the prognosis (NIDA, 2010). Nevertheless, low treatment retention is commonplace among patients with addictions (Chutuape, Katz & Stitzer, 2001), more so than with other mental disorders, (Wierzbicki & Pekarik, 1993). Rates of detoxification treatment take-up after discharge improve with the introduction of groups during hospitalization and group information at discharge (Frydrych, Greene, Blondell & Purdy, 2009).

In addition, satisfaction with the psychological treatment received during hospitalization is a further important factor in retention and subsequent abstention, although the number of studies relating to this is limited (Ino, Saka, Yamashiro, Cho & Torituka, 2006).

For these reasons, inpatient detoxification should not be limited to pharmaceutical management, but should promote psychotherapeutic interventions which support abstinence maintenance and the continuation of post discharge treatment (Driessen, Veltrup, Junghanns, Przywara & Dilling, 1999; Myrick, Anton & Kasser, 2003, O´Farrell, Murphy, Alter & Fals-Stewart, 2008). However, not a great deal of research has been done on the introduction of therapy groups in detoxification units (Berman, Forsberg, Durbeej, Kallmen & Hermansson, 2010; John et al., 2003; Loeber et al., 2009; Santa Ana et al., 2007; Schilling, El-Bassel, Finch, Roman & Hanson., 2002; Stetter, Zahres, Batra & Mann, 1995).

The goal of this pilot study is, therefore, to describe which sociodemographic, clinical and therapeutic factors are associated with abstinence maintenance two months after follow-up in patients participating in a motivation group during hospitalization. We hypothesize that there are differences in the clinical and sociodemographic variables linked to abstinence. In terms of therapeutic variables, the hypothesis is that the greater the motivation to change when leaving hospital, and the greater the satisfaction with group therapy, the longer abstinence will last and the higher the likelihood of subsequent treatment retention.

Method

Study design

A descriptive longitudinal study of a two month follow-up period was carried out among 46 patients.

Participants

Of the 58 patients in the Hospital Detoxification Unit (HDU) of Vall d'Hebron University Hospital from May to September 2012 who were diagnosed with substance abuse disorders according to DSM-IV-TR criteria, 46 participated voluntarily in the therapeutic group and agreed to take part in the two month post-discharge follow-up (Figure 1). The patients signed the informed consent form, approved by the hospital ethics committee.

Patients who did not complete hospitalization, those who were participating in other research protocols (clinical trials), and those who declined to participate in the therapeutic groups or the study were excluded. Of the 46 subjects included, 43 completed the follow-up period.

Patients were not remunerated in any form for the data provided.

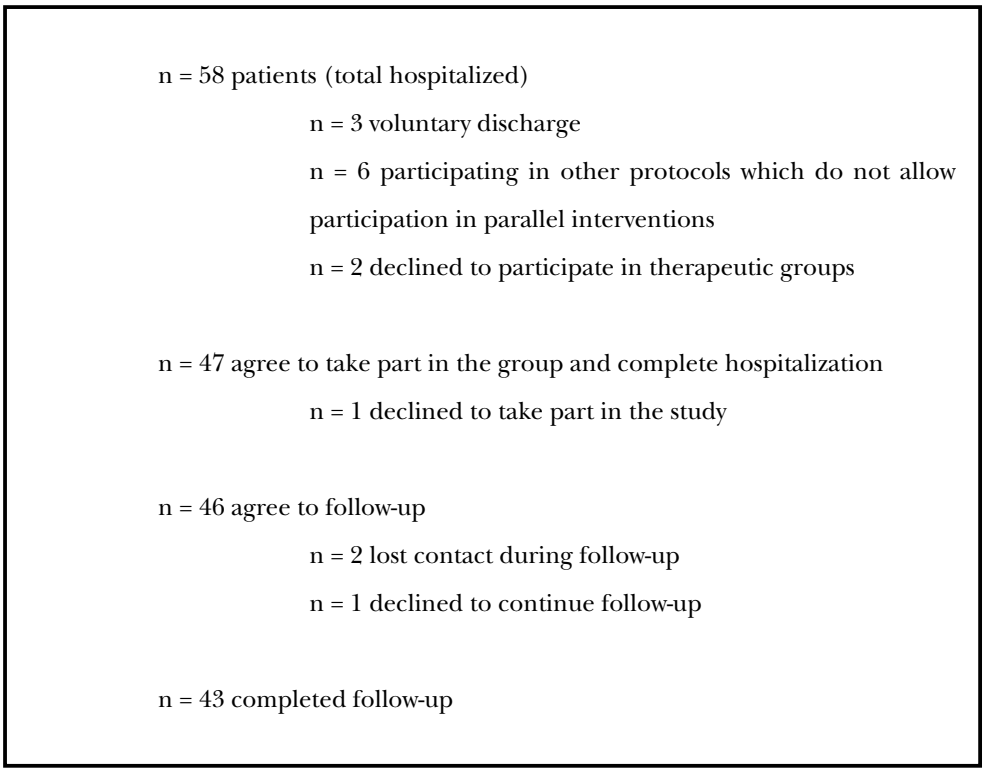

Figure 1. Study sample flow

Instruments

Therapeutic pre-group measures.

Ad-hoc registration design. Data were collected on sociodemographic (sex, age, nationality, living arrangements, education, employment situation, legal record) and clinical variables (family history of substance abuse, number of substances involved in current abuse or dependency, type of substance principally causing hospitalization, years of development of dependency on this substance, previous hospitalizations, whether for dependence or psychopathological destabilization, binge consumption prior to hospistalization).

To check for dual diagnosis, the following instruments were used:

- ***SCID-I***. Structured interview for DSM-IV axis I disorders, in its Spanish adaptation (First, Spitzer, Gibbon & Williams, 1999).
- ***SCID-II***. Structured clinical interview for DSM-IV axis II personality disorders, in its Spanish adaptation (First, Spitzer, Gibbon & Williams, 1999).

Therapeutic post-group measures.

URICA scale. A scale for the evaluation of change, Universidad of Rhode Island (McConnaughy, Prochaska & Velicer, 1983); Spanish version by Rojas and Espinoza (2008). This instrument assesses to what extent the subject presents behaviors or cognitions of each state of change, according to Prochaska and DiClemente's (1982) theory of change. It measures four subscales: precontemplation, contemplation, action, and maintenance. The higher the score, the greater one's own cognition of each stage. The Readiness to Change (RTC) score, obtained from the four previous, measures the global willingness of the individual to change. The scale has an acceptable internal consistency of 0.69-0.89 (McConnaughy et al., 1983; McConnaughy, DiClemente, Prochaska & Velicer, 1989).

TPQ. The Treatment Perception Questionnaire (Marsden et al., 1998), Spanish version (Mandersen et al., 2001). This is a short questionnaire with scores ranging from 0 to 40. It comprises two factors, with scores between 0 and 20: perception of the therapists and perception of the therapy. The higher the score, the more satisfied with the treatment. This instrument has an acceptable inter-class correlation of 0.57 in the Spanish sample (Mandersen et al., 2001).

Follow-up measures.

Self-reported information about abstinence and detoxification treatment retention carried out by weekly telephone calls over a two month period. The following criteria were used for each variable:

- ***Abstinence from the substance principally causing hospitalization.*** In terms of alcohol, abstinence was considered broken by drinking on five consecutive days, or by consuming more than five units of alcohol in one day (Vol-

picelli et al., 1997). For other substances, abstinence was considered broken when the patient admitted to consuming three times in one week or following a pattern similar to pre-admission (Grau-López et al., 2012).

- ***Subsequent treatment retention***
- Having attended, or having appointments to attend treatment sessions, in at least six of the eight weeks of the telephone follow-up.

Procedure

While hospitalized in the HDU, patients followed pharmaceutical detoxification treatment. The psychiatrist prescribed decreasing doses of benzodiazepines down to their withdrawal for detoxification from each substance, as well as contributory pharmaceuticals to help treat comorbid symptoms. In some cases of addiction, specific medicines were also prescribed, such as antabuse o methadone.

Patients were informed about the nature of the study and were asked to participate in the brief therapy group. Declining to take part in the study did not prevent them from joining the group.

The psychotherapeutic treatment which was carried out is based on motivational interviewing (Miller et al., 2002; Wagner et al., 2012). The therapy's main aims were twofold: to raise motivation for abstinence maintenance after discharge, and to motivate subsequent treatment retention. Sessions lasted for 45 minutes, and took place three times a week. Group size varied from four to five participants. Groups were open, with sessions independent of each other and not limited by protocol in order to facilitate entry and exit of group members and adapt to the context of the hospital unit. If the therapist felt that a patient was not in a suitable condition owing to symptoms of intoxication or withdrawal, sedative effects of medicines, or as a negative consequence of a physical illness, they did not participate in the session. The role of the group leaders (a clinical psychologist in co-therapy with an internal resident psychologist) was to stimulate lively discussion of the topics brought up by the group itself. The psychotherapists have had standard training in motivational interviewing and wide-ranging experience in group therapy with drug addicts.

Patients were hospitalized in the HDU for an average of 12.2 days (SD = 5.42; range 5 - 36). The average number of motivational group treatment sessions was 4.07 (SD = 2.45; range 2 - 16).

We asked patients for their authorization to carry out pre-program, post-group, and two month post-discharge follow-up evaluations. At discharge, each was given a follow-up appointment at their reference health center. Evaluation during the follow-up phase consisted of a weekly telephone call for two months to assess whether they were keeping up abstinence from the principal substance, and whether they were continuing their treatment.

Statistical analysis

Firstly, the sociodemographic and clinical variables of the simple are described. For the analysis of how the sociodemographic, clinical and therapeutic variables are linked to post-discharge abstinence, the comparison of means is carried out using the Mann-Whitney U test for continuous variables. For categorical values, the chi-square test is used, except when at least one box displays an expected frequency of less than 5, in which case Fisher's correction is applied. Using the Pearson correlation, the possible associations between the variables resulting from this analysis are tested before including them in logistic regression, and the one with greatest effect size is chosen for Cohen's d. Logistic regression is run, with the forward stepwise inclusion of variables, to determine whether the variables associated with relapse do so independently. Finally, as a likelihood test the Cox model is applied, forward stepwise, to discover the predictive capacity of these factors for duration of abstinence.

Kaplan-Meier is used for the survival function. The statistical package SPSS 20.0 was used to analyze the data.

Results

The sociodemographic and clinical characteristics of the subjects participating in the study are described (*Table 1*). Average age is 44.9 years (*SD* = 10.60; range 25 - 68).

Table 1
Sample description (n=46). Sociodemographic and clinical variables

Sociodemographic variables	
Sex	
Male	58.7%
Female	41.3%
Living arrangements	
Alone	17.4%
With family	82.6%
Education	
Compulsory	69.6%
Higher	30.4%
Employment	
Working	8.7%
Unemployed	91.3%
Legal record (yes)	17.4%
Clinical variables	
Family history of substance abuse (yes)	73.9%
Dual pathology (yes)	71.7%
No. of substances currently dependent	
1	52.2%
2 or more (polydrug abuse)	47.8%
Substance type[a]	
Depressant	78.3%
Stimulant	21.7%
Years of principal substance addiction development	(21.26, 10.45) (range, 3-50)
Previous hospitalizations[b] (yes)	67.4%
Overdose prior to admission (yes)	50%

NOTES: [a] depending on its effect on the central nervous system; [b] whether for detoxification or psychopathologial destabilization.

Table 2
Description of the variables associates with abstinence two months after discharge (n=43)

Sociodemographic and clinical variables				
	ABSTINENT n = 22	NOT ABSTINENT n = 21	Test	p
Sex				
Male	77.3%	38.1%	6.78[a]	.009*
Female	22.7%	61.9%		
Dual pathology (yes)	81.8%	61.9%	2.12[a]	.146
Polydrug abuse (yes)	54.5%	52.4%	0.20[a]	1[b]
Principal drug type (Depressive)	77.3%	85.7%	0.51[a]	.698[b]
Years of principal substance addiction disorder development	(22.14, 10.10)	(19.95, 11.01)	0.74[c]	.458
Previous hospitalization (yes)	77.3%	57.1%	1.98[a]	.159
Overdose prior to admission (yes)	22.7%	71.4%	10.24[a]	.001*
Variables terapéuticas				
	ABSTINENT	NOT ABSTINENT	Test	p
URICA Post-Group				
Precontemplation	(15.81, 5.59)	(14.27, 3.37)	0.47[c]	.641
Contemplation	(35.33, 2.90)	(33.60, 3.13)	1.49[c]	.137
Action	(35.57, 3.68)	(33.27, 3.57)	1.81[c]	.071
Maintenance	(32.86, 3.21)	(30.00, 4.14)	2.11[c]	.035*
RTC	(11.01, 1.24)	(10.16, 1.53)	1.85[c]	.064
TPQ				
Total	(31.24, 6.07)	(27.69, 5.99)	1.71[c]	.088
Therapist	(15.57, 3.07)	(13.25, 3.45)	2.26[c]	.024*
Therapy	(16.62, 2.97)	(14.44, 3.42)	2.04[c]	.041*

NOTES: [a] Chi-square; [b] Fisher correction; [c] z scores; * (p< .05); URICA: University of Rhode Island Change Assessment; RTC: Disposition to Change; TPQ: Treatment Perception Questionnaire.

The sample is composed completely of Spanish nationals. Alcohol is the principal substance for 56.5%, cocaine for 21.7%, cannabis for 8.7%, heroin for 6.5%, methadone for 4.3% and benzodiazepines for 2.2%.

The scores obtained by the therapy participants on the TPQ's global scale have a mean of 29.35 (*SD* = 6.28), 14.52 (*SD* = 3.30) on the therapist subscale, and 15.32 (*SD* = 3.69) for therapy.

With regard to the principal substance causing their hospitalization, 48.8% of the patients relapsed after 2 months. The dependent variables of abstinence and subsequent treatment retention are linked. It is observed that 4.5% of abstinent patients abandon treatment, while this figure rises to 38.1% of those who relapsed. The difference is statistically significant (*X2* = 7.31, *p* = .009). Therefore, it is more likely at discharge from the HDU that those who maintain treatment retention will also continue abstinence, and vice-versa, while those who do not continue treatment subsequent to discharge are more likely to suffer a relapse.

Results of the bivariate analysis are described to determine the association with abstinence, sex (sociodemographic variable) and the clinical and therapeutic variables considered in the study (*Table 2*). Being female (*X2* = 6.78; *p* = .009) and taking an overdose prior to admission (*X2* = 10.24; *p* = .001) are significantly associated with relapse after two months.

With respect to therapeutic variables, having greater cognition of the stages of abstinence maintenance (maintenance scale), acquired in the HDU, significantly increases the likelihood of remaining abstinent over the two months following discharge (z = 2.11; *p* = .035). In contrast to the global TPQ scale, where none are detected, significant results are found on both subscales separately. Given that the variables of satisfaction with the therapy and the therapist correlate with each other (*r* = 0.59 *p*<.001), both effect sizes are compared using Cohen's d (*d* = 0.68 for satisfaction with the therapy and *d* = 0.71 for the therapist). The second of these two variables is selected for the logistic regression. Multivariate analysis is run to determine if the variables associated with abstinence, bivariately at two months, do so independently.

Being male (Wald = 6.45, *p* = .011, OR = 0.015, 95% CI = 0.001 – 0.38), not taking an overdose prior to admission (Wald = 4.61, *p* = .032, OR = 0.52, 95% CI = 0.004 – 0.77), higher therapist satisfaction scores (Wald = 4.38, *p* = .036, OR = 0.60, 95% CI = 0.37 – 0.97) and higher scores on the URICA maintenance scale (Wald = 4.47, *p* = .034, OR = 0.69, 95% CI = 0.49 – 0.97) are associated independently with abstinence two months after discharge.

The Cox regression is applied to determine whether the above factors predict an increase in the length of time before relapse (Table 3).

Tabla 3
Modelo de Cox de permanencia de la abstinencia

Variable	Wald	OR	95% CI	p
Sex (Male)	7.18	0.20	0.06 - 0.65	.007
Maintenance stage	5.14	0.84	0.72 - 0.98	.023
Satisfaction with therapist	8.10	0.77	0.64 - 0.92	.004

NOTE: Sex (1 = varón; 2 = mujer)

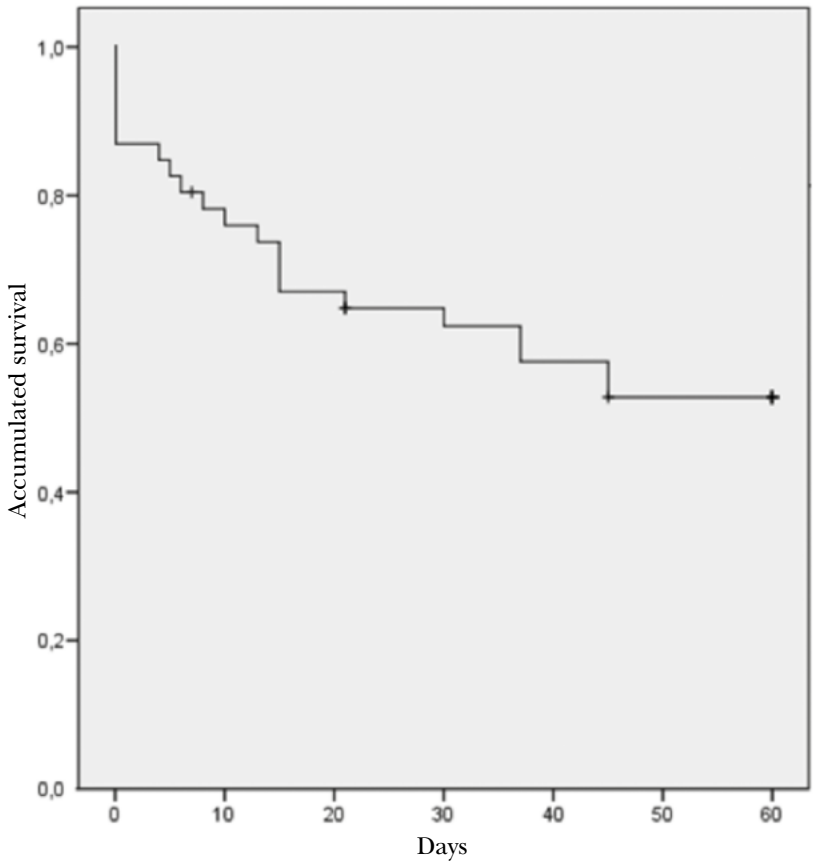

Figure 2. Kaplan-Meier estimator of survival function

The survival function is shown graphically in Figure 2. Being male reduces the risk of relapse by five times. Having greater cognition and more behaviors associated with the motivational stage of maintenance and high satisfaction with the group therapist also increases survival, controlling for other associated variables. Binge consumption of the principal substance of addiction prior to admission does not predict shorter survival time two months after discharge.

Discussion

Participation in therapeutic groups of a motivational type during hospitalization for detoxification is associated with positive effects on the likelihood of continuing abstinence and the retention of addiction treatment in a two month follow-up. Results show that being male, having more motivation to change (understood as cognitions of the maintenance stage) and greater satisfaction with the psychological treatment during hospitalization (with the motivational therapy or the therapist), is linked to a longer period before relapse after detoxification.

The data therefore suggest that a satisfactory experience while hospitalized favors subsequent abstinence and retention. There are not many studies on detoxification in this regard (Kornreich, Dan, Fryns, Gozlan & Verbanck, 1992). Similar to our results, high rates of satisfaction with motivational therapy have also been found elsewhere (Borsari & Carey, 2000), which could be linked to motivational interviewing therapists being perceived as having the ability to empathize and listen (Vasilaki et al., 2006).

Furthermore, the results demonstrate that a greater post-treatment readiness to global change (RTC on the URICA scale) prior to discharge is not associated with a greater duration of abstinence. This finding has already been discussed by Diclemente, Carbonari, Zweben, Morrel & Lee (2001), who link it to the fact that self-evaluation with regard to potential post-treatment consumption may be optimistic, influenced by the restrictions and sense of security in a hospital ward. Therefore, this measure loses its predictive capacity in our context. Nevertheless, we find that a high score in the maintenance subscale is associated with abstinence, a result congruent with that of another earlier study (Henderson, Saules & Galen, 2004). Having said this, the influence of motivation to change on the efficacy of motivational interviewing, and how it mediates the change of behaviour, is not known (Berman et al., 2010; Dunn, Deroo & Rivara, 2001; Maisto et al., 2001; Vasilaki et al., 2006), thus highlighting the need for more research in this area.

One of the main aims of the therapeutic group was to motivate post-discharge retention. This may explain why detoxification treatment was continued by 73.9% of patients, an above average figure but in line with the good results obtained in other programs designed specially with the same goals (Sánchez et al. 2011; Secades-Vila, García-Rodríguez, Higgins, Fernández-Hermida, & Carballo, 2008), and those achieved by the introduction of motivational groups in detoxification units (Santa Ana et al., 2007). It is possible that retention is influenced by the weekly telephone call, although this was not the goal (McKay, Lynch, Shepard & Pettinati, 2005). In any case, it is an important result given that retention is a predictive factor in abstinence (Frydrych et al., 2009; Moggi, Ouimette, Moos & Finney, 1999; Secades Villa & Fernández Hermida, 2000; Vaillant, 1966) and highlights once again the need to introduce this type of motivational intervention with the aim of improving the prognosis for these patients.

In terms of results obtained concerning other variables linked to relapse, these indicate that women present greater problems in maintaining abstinence, matching the results found by Maehira et al., (2013). Nevertheless, future studies should be carried out with the aim of clarifying whether women really do suffer higher relapse rates (Tuchman, 2010).

In terms of the clinical variables examined, the majority, such as presenting dual diagnosis, having a family history of addiction, the length of addiction, previous hospitalizations, the type of substance, or a pattern of polydrug consumption, are not associated with a shorter duration of abstinence. These results are congruent with those found by Loeber et al., (2009), who discovered that the time until the first relapse was delayed independently of the length of the period of alcohol addiction, previous hospitalizations and sex of those who participated in the group therapy during their hospital stay. Nevertheless, in contrast with the results found by these authors, the present study has found that sex does have a link to abstinence duration.

Although by itself it does not predict a shorter period of abstinence, overdosing was the only clinical variable which was linked to relapse two months after detoxification. The results of an earlier study (Grau-López et al., 2012) are confirmed, which described this link after six months. However, it appears that the association is not maintained in longer follow-ups, at least in the case of alcoholism (Monrás Arnau, Gual Solé, Freixa & Lligoña, 2004).

This preliminary study is subject to various limitations which should be taken into account. First of all, no control group was used to determine if the results obtained in terms of motivation at discharge, treatment retention, and subsequent abstinence are due to participation in group therapy. Nevertheless, the relapse rate among motivational group participants (48,8%) was found to be similar to that discovered by Loeber et al. (2009) two months after discharge: 42,4% in comparison with the control group's 68,3%. Furthermore, due to the small sample size and a high percentage of females included, it is difficult to generalize to the population of substance abusers, which is normally distributed with a greater proportion of males (EMCDDA, 2012). As an open therapeutic group, it was not possible to limit the sessions by protocol, although this more flexible format allowed the treatment to be adapted to the context of the unit with constant new entries and discharges. Another possible limitation is that laboratory parameters were not used in measuring abstention owing to data protection regulations since patients belong to different centers; nevertheless, it has been found in other studies that these parameters do not add greater veracity to the information (Babor, Steinberg, Anton & Del Boca, 2000).

This study provides different contributions. Firstly, as far as we are aware, this is the first to evaluate the level of satisfaction with motivational-type groups and with the therapist, and how this is related to post-treatment. It is, furthermore, a study with high ecological validity, given that it is a group intervention, applicable in a clinical detoxification context with a heterogeneous group in terms of sex, age, and principal substance.

Different lines of research can be derived from these results. As well as measuring emotional state, future studies should also consider more implicit cognitive aspects, for example nuclear beliefs about addiction (Martínez González & Verdejo García, 2012).

In addition, the most basic components of satisfaction with the therapy or the therapist and their influence on the efficacy of psychological treatment of drug addicts should be investigated to enable improvements to be made in such interventions.

Finally, these data have relevant clinical implications, since they show the importance of offering psychological treatment in addition to pharmaceutical treatment from the first stages of intervention with addicts in order to improve their efficacy (Berner et al., 2008; Loeber et al., 2009; Stetter & Mann, 1997).

In conclusion, aspects related to motivational-type group intervention, such as satisfaction with therapist and therapy, and having cognitions at discharge associated with maintaining abstinence, operate as protective factors, since they are associated with longer abstinence after admission.

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Conflict of interests

There are no conflicts of interest.

References

Arias, F., Szerman, N., Vega, P., Mesias, B., Basurte, I., Morant, C.,… Babín, F. (2013). Estudio Madrid sobre prevalencia y características de los pacientes con patología dual en tratamiento en las redes de salud mental y de atención al drogodependiente. *Adicciones, 25,* 118-127.

Babor, T. F., Steinberg, K., Anton, R., & Del Boca, F. (2000). Talk is cheap: measuring drinking outcomes in clinical trials. *Journal of Studies on Alcohol, 61,* 55-63.

Berman, A. H., Forsberg, L., Durbeej, N., Kallmen, H., & Hermansson, U. (2010). Single-session motivational interviewing for drug detoxification inpatients: effects on self-efficacy, stages of change and substance use. *Substance Use & Misuse, 45,* 384-402. doi: 10.3109/10826080903452488

Berner, M., Günzler, C., Frick, K., Kriston, L., Loessl, B., Brück, R.,… Mann, K. (2008). Finding the ideal place for a psychotherapeutic intervention in a stepped care approach–a brief overview of the literature and preliminary results from the Project PREDICT. *International Journal of Methods in Psychiatric Research, 17 (Supl. 1),* 60-64. doi: 10.1002/mpr.250

Borsari, B., & Carey, K. B. (2000). Effects of a brief motivational intervention with college student drinkers. *Journal of Consulting and Clinical Psychology, 68,* 728-733.

Chutuape, M. A., Katz, E. C., & Stitzer, M. L. (2001). Methods for enhancing transition of substance dependent patients from inpatient to outpatient treatment. *Drug and Alcohol Dependence, 61,* 137-143.

DiClemente. C. C., Carbonari, J., Zweben, A, Morrel, T., & Lee, R. L. (2001). Motivation Hypotheis Causal chain Analysis. In R. Longabaugh, & P. W. Wirtz (Eds.), *Project MATCH Hipotheses: Results and Causal Chain Analyses. Project MATCH Monograph Series, Volume 8.* (pp. 239-259). Rockville, MD: National Institute on Alcohol Abuse and Alcoholism.

DiClemente, C. C., Schlundt, D., & Gemmell, L. (2004). *Readiness and stages of change in addiction treatment. The American Journal on Addictions, 13,* 103-119.

Driessen, M., Veltrup, C., Junghanns, K., Przywara, A., & Dilling, H. (1999). Cost-efficacy analysis of clinically evaluated therapeutic programs. An expanded withdrawal therapy in alcohol dependence. *Der Nervenarzt, 70,* 463-470.

Dunn, C., Deroo, L., & Rivara, F. P. (2001). The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. *Addiction, 96,* 1725-1742. doi: 10.1080/09652140120089481

First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B. W., & Benjamin, L. S. (1999). *Entrevista clínica estructurada para los trastornos de la personalidad del Eje II del DSM-IV (SCID-II).* Barcelona: Masson.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1999). *Entrevista clínica estructurada para los trastornos del Eje I del DSM-IV, versión clínica (SCID-I-VC).* Barcelona: Masson.

Frydrych, L. M., Greene, B. J., Blondell, R. D., & Purdy, C. H. (2009). Self-help program components and linkage to aftercare following inpatient detoxification. *Journal of Addictive Diseases, 28,* 21-27. doi: 10.1080/10550880802544799

García Rodríguez, O., Secades Villa, R., Fernández Hermida, J. R., Carballo Crespo, J. L., Errasti Pérez, J. M., & Al-halabí Díaz, S. (2005). Comparación de pacientes cocainómanos y heroinómanos en el EuropASI. *Adicciones,* 17, 33-42.

Goeb, J. L., Coste, J., Bigot, T., & Ferrand, I. (2000). Prospective study of favorable factors in follow-up of drug addicted patients–apropos of 257 patients of the Cassini Center in Paris. *L'Encéphale, 26,* 11-20.

Grau-López, L., Roncero, C., Daigre, C., Gonzalvo, B., Bachiller, D., Rodriguez-Cintas, L.,… Casas, M. (2012). Factores de riesgo de recaída en pacientes drogodependientes tras desintoxicación hospitalaria. *Adicciones, 24,* 115–122.

Henderson, M. J., Saules, K. K., & Galen, L. W. (2004). The predictive validity of the University of Rhode Island Change Assessment Questionnaire in a heroin-addicted polysubstance abuse sample. *Psychology of Addictive Behaviors, 18,* 106-112. doi: 10.1037/0893-164X.18.2.106

Ino, A., Saka, Y., Yamashiro, K., Cho, T., & Torituka, M. (2006). Alcohol dependence syndrome and Before-Discharge Intervention Method (BDIM)–No. 5. Patients' evaluation of BDIM by questionnaire survey. *Japanese Journal of Alcohol Studies & Drug Dependence, 41,* 358-367.

John, U., Veltrup, C., Driessen, M., Wetterling, T., & Dilling, H. (2003). Motivational intervention: an individual coun-

selling vs a group treatment approach for alcohol-dependent in-patients. *Alcohol and Alcoholism, 38,* 263-269.

Kornreich, C., Dan, B., Fryns, A., Gozlan, S., & Verbanck, P. (1992). Cognitive-behavioral approach to alcoholism: preliminary report of the realization of a therapeutic group. *Acta Psychiatrica Belgica, 92,* 279-293.

Loeber, S., Kiefer, F., Wagner, F., Mann, K., & Croissant, B. (2009). Treatment outcome after inpatient alcohol withdrawal: impact of motivational interventions: a comparative study. *Der Nervenarzt, 80,* 1085-1092. doi: 10.1007/s00115-009-2724-2

Maehira, Y., Chowdhury E.I., Reza, M., Drahozal, R., Gayen, T.K., Masud, I.,… Azim, T. (2013). Factors associated with relapse into drug use among male and female attendees of a three-month drug detoxification-rehabilitation programme in Dhaka, Bangladesh: a prospective cohort study. *Harm Reduction Journal, 10,* 1-14. doi: 10.1186/1477-7517-10-14

Maisto, S. A., Conigliaro, J., McNeil, M., Kraemer, K., Conigliaro, R. L., & Kelley, M. E. (2001). Effects of two types of brief intervention and readiness to change on alcohol use in hazardous drinkers. *Journal of Studies on Alcohol, 62,* 605-614.

Mandersen, J., Nizzoli, U., Corbelli, C., Margaron, H., Torres, M.A.,… Gossop, M. (2001). Fiabilidad del "Maudsley addiction profile" (MAP, ERIR-Versión) y del "Treatment perceptions questionnaire (TPQ) en Italia, España y Portugal para la evaluación de tratamientos. *Adicciones, 13,* 217-227.

Márquez-Arrico, J. E., & Adán, A. (2013). Patología dual y rasgos de personalidad: situación actual y líneas futuras de trabajo. *Adicciones, 25,* 195-202.

Marsden, J., Bacchus, L., Stewart, D., Griffiths, P., Clarke, K. Gossop, M., & Strang, J. (1998). *The Treatment Perceptions Questionnaire (TPQ): A brief questionnaire for assessing service satisfaction* Unpublished manuscript. London: National Addiction Centre.

Martínez González, J. M.,, & Verdejo García, A. (2012). Evolución de las creencias nucleares relacionadas con la adicción en drogodependientes con y sin trastornos de personalidad. *Adicciones, 24,* 229-238.

McConnaughy, E. A., DiClemente, C. C., Prochaska, J. O.,, & Velicer, W. F. (1989). Stages of change in psychotherapy: A follow-up report. *Psychotherapy, 26,* 494-503. doi: 10.1037/h0085468

McConnaughy, E. A., Prochaska, J. O., & Velicer, W. F. (1983). Stages of change in psychotherapy: Measurement and sample profiles. *Psychotherapy: Theory, Research, and Practice, 20,* 368-375. doi: 10.1037/h0090198

McKay, J. R., Lynch, K. G., Shepard, D. S., & Pettinati, H. M. (2005). The effectiveness of telephone-based continuing care for alcohol and cocaine dependence: 24-month outcomes. *Archives of General Psychiatry, 62,* 199-207. doi: 10.1001/archpsyc.62.2.199

Miller, W. R., & Rollnick, S. (2002). *Motivational Interviewing: Preparing people for change* (2nd ed.). New York: Guilford Press.

Moggi, F., Ouimette, P. C., Moos, R. H., & Finney, J. W. (1999). Dual diagnosis patients in substance abuse treatment: relationship of general coping and substance-specific coping to 1-year outcomes. *Addiction, 94,* 1805-1816. doi: 10.1046/j.1360-0443.1999.941218056.x

Monrás Arnau, M., Gual Solé, A., Freixa, N., & Lligoña, A. (2004). El último consumo de alcohol previo al ingreso de desintoxicación como predictor a largo plazo de la abstinencia. *Adicciones, 16,* 117-122.

Myrick, H., Anton, R., & Kasser. C. (2003). Management of intoxication and withdrawal; general principles. In: A.W. Graham, T. K. Schultz, M. F. Mayo-Smith, R. K. Ries, & B. B. Wilford (Eds.), *Principles of addiction medicine* (3rd ed.) (pp. 611-618). Chevy Chase, MD: American Society of Addiction Medicine.

National Institute on Drug Abuse. (2010). *Principios de tratamientos para la drogadicción: Una guía basada en las investigaciones* (2nd ed.). Washington, DC: National Institute on Health. Retrieved from http://www.drugabuse.gov/sites/default/files/podatsp.pdf

Observatorio Español de Drogas y Toxicomanías (OEDT) para el Plan Nacional sobre Drogas (2012). *Informe Nacional 201 al OEDT por el punto focal nacional Retoix* Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved from http://www.pnsd.msc.es/Categoria2/publica/pdf/Informe_Nacional_REITOX2012.pdf

O'Farrell, T. J., Murphy, M., Alter, J., & Fals-Stewart, W. (2008). Brief family treatment intervention to promote aftercare among substance abusing patients in inpatient detoxification: Transferring a research intervention to clinical practice. *Addictive Behaviors 33,* 464-471.

Prochaska, J. O., & DiClemente, C. C. (1982). Trans-theoretical therapy - toward a more integrative model of change. *Psychotherapy: Theory, Research and Practice 19,* 276-288.

Rojas, M. J., & Espinoza, L. S. (2008). Consejo psicológico y psicoterapia motivacional en drogodependencias: evaluación de las intervenciones del programa "Lugar de Escucha". *Adicciones, 20,* 185-196.

Sánchez, L., Díaz-Morán, S., Grau-López, L., Moreno, A., Eiroa-Orosa, F. J., Roncero, C.,… Casas, M. (2011). Tratamiento ambulatorio grupal para dependientes de cocaína combinando terapia cognitiva conductual y entrevista motivacional. *Psicothema, 23,* 107-113.

Santa Ana, E. J., Wulfert, E., & Nietert, P. J. (2007). Efficacy of group motivational interviewing (GMI) for psychiatric inpatients with chemical dependence. *Journal of Consulting and Clinical Psychology, 75,* 816-822. doi: 10.1037/0022-006X.75.5.816

Schellekens, A. F., de Jong, C. A., Buitelaar, J. K., & Verkes, R. J. (2014). Co-morbid anxiety disorders predict early

relapse after inpatient alcohol treatment. *European Psychiatry*. Advanced on-line publication. doi: 10.1016/j.eurpsy.2013.08.006

Schilling, R. F., El-Bassel, N., Finch, J. B., Roman, R. J., & Hanson, M. (2002). Motivational Interviewing to encourage self-help participation following alcohol detoxification. *Research on Social Work Practice, 12,* 711-730. doi: 10.1177/104973102237469

Secades Villa, R., & Fernández Hermida, J. R. (2000). Cómo mejorar las tasas de retención en los tratamientos de drogodependencias. *Adicciones, 12,* 353–63.

Secades-Villa, R., García-Rodríguez, O., Higgins, S. T., Fernández-Hermida, J. R., & Carballo, J. L. (2008). Community reinforcement approach plus vouchers for cocaine dependence in a community setting in Spain: six month outcomes. *Journal of Substance Abuse Treatment, 34,* 202-207.

Shaw, G. K., Waller, S., Latham, C. J., Dunn, G., & Thomson, A. D. (1998). The detoxification experience of alcoholic in-patients and predictors of outcome. *Alcohol and Alcoholism, 33,* 291-303.

Stetter, F., & Mann, K. (1997). Dependency outcome of alcohol-dependent patients after inpatient detoxification and motivation treatment. *Der Nervenarzt, 68,* 574-581.

Stetter, F., Zahres, S., Batra, A., & Mann, K. (1995). Results of integrated inpatient detoxification and motivation treatment of alcohol dependent patients. *Psychiatrische Praxis, 22,* 189-192.

Tuchman, E. (2010). Women and addiction: the importance of gender issues in substance abuse research. *Journal of Addictive Diseases, 29,* 127-138. doi: 10.1080/10550881003684582

Vaillant, G. E. (1966). A twelve-year follow-up of new york narcotic addicts: I. The relation of treatment to outcome. *American Journal of Psychiatry, 122,* 727-737.

Vasilaki, E. I., Hosier, S. G., & Cox, W. M. (2006). The efficacy of motivational interviewing as a brief intervention for excessive drinking: a meta-analytic review. *Alcohol and Alcoholism, 41,* 328-335. doi: 10.1093/alcalc/agl016

Volpicelli, J. R., Rhines, K. C., Rhines, J. S., Volpicelli, L. A., Alterman, A. I., & O'Brien, C.P. (1997). Naltrexone and alcohol dependence. Role of subject compliance. *Archives of General Psychiatry, 54,* 737-742.

Wagner, C. C., & Ingersoll, K. S., (2012). *Motivational Interviewing in groups.* New York: Guilford Press.

Wierzbicki, M., & Pekarik, G. (1993). A meta-analysis of psychotherapy dropout. *Professional Psychology: Research and Practice, 24*, 190-195. doi: 10.1037//0735-7028.24.2.190.

Predictors of weekly alcohol drinking and alcohol-related problems in binge-drinking undergraduates

Predictores del consumo semanal de alcohol y sus consecuencias asociadas en universitarios consumidores intensivos de alcohol

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Abstract

The important implications generated by binge drinking among university students justify the interest to determine which factors predict its occurrence. Specifically, this study aims to assess the role of personality and drinking onset in predicting weekly alcohol consumption, and the impact of the whole set of variables in predicting the number of consequences associated with consumption in undergraduates. Two hundred and thirteen freshmen who were intensive consumers (binge drinkers) from the University Complutense of Madrid were evaluated. All of them filled in a self-registration of consumption, the BIS-11, the NEO-FFI and the IECI consequences associated with intake. The hierarchical regression analysis shows that the drinking onset appears to be a relevant predictor variable in explaining weekly consumption and the number of consequences. The same can be said of the weekly consumption variable with regard to the number of consequences. In general, the influence of personality is quite limited. It is interesting to point out that responsibility and impulsivity, along with age, explain most of the weekly consumption behavior among males. With respect to the consequences of consumption, only impulsivity and neuroticism contribute to explain them, but with less strength than age and weekly consumption. Our results justify the need to plan tighter interventions and consider new predictors that help to explain further weekly consumption in women.

Key words: binge drinking, consequences, personality, drinking onset, university students.

Resumen

Las importantes implicaciones que genera el consumo intensivo de alcohol entre los jóvenes justifican el interés por determinar qué factores predicen su aparición. Concretamente, en este estudio se analiza el papel de la personalidad y edad de inicio en el consumo de alcohol en la predicción del consumo semanal de alcohol, y de todas estas variables en la predicción del número de consecuencias asociadas al consumo en jóvenes universitarios.

Se evalúan 213 consumidores intensivos de primer curso de la Universidad Complutense de Madrid. Todos ellos cumplimentaron un autoregistro de consumo, el BIS-11, el NEO-FFI y el IECI de consecuencias asociadas a la ingesta.

Los análisis de regresión de orden jerárquico muestran que la edad de inicio resulta ser una variable predictora relevante tanto en la explicación del consumo semanal como del número de consecuencias. Lo mismo puede decirse de la variable consumo semanal respecto a la del número de consecuencias.

En líneas generales, el influjo de las variables de personalidad es bastante limitado. Tan sólo mencionar la responsabilidad e impulsividad, que junto con la edad, llegan a explicar gran parte de la conducta de consumo semanal entre varones. En lo que respecta a las consecuencias derivadas del consumo, sólo resultan explicativas, aunque en menor medida que la edad y el consumo semanal, la impulsividad y el neuroticismo.

Esto justifica la necesidad de planificar intervenciones más ajustadas y de analizar nuevos predictores en el caso de las mujeres que permitan explicar en mayor medida su conducta de consumo semanal.

Palabras clave: consumo intensivo de alcohol, consecuencias, personalidad, edad inicio, universitarios.

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Intensive Alcohol Consumption, otherwise known as binge drinking, the consumption of 60 grams or more in men and 40 grams or more in women, over a period of between 2 and 3 hours – (Hingson, Assailly and Williams MSC, 2008; NIAAA, 2004) is a generalized practice among young people (Anderson and Baumberg, 2006), one that occurs widely among university students (Arata, Stafford and Tims, 2003; Calafat, 2007; Danielsson, Wennberg, Tengström and Romelsjö, 2010; March et al., 2010; Parada et al., 2011). Despite the fact that the number of males and females who binge drink is ever more homogenous, the former group continue to show higher indices both in the amount and frequency of consumption (Cortés, Giménez, Motos and Cadaveira, 2014; Gliksman, Adlaf, Demers and Newton, 2003; O'Malley and Johnston, 2002; Wechsler, Dowdall, Davenport and Castillo, 1995).

This pattern of consumption is associated with multiple biopsychosocial problems (Martens et al., 2005; Neighbors, Walker and Larimer, 2003; Park, 2004; Ray, Turrisi, Abar and Peters, 2009), among which the most important are symptoms of intoxication, problems with studies and at work, interpersonal problems, engaging in unprotected and unplanned sexual practices, driving under the influence of alcohol, becoming involved in fights, suffering injuries, having legal problems and even causing harm to third parties (Cortés, 2010; Devos-Comby and Lange, 2008; Hingson, Zha and Weitzman, 2009; Kahler, Strong and Read, 2005; Mallett et al., 2011; Shield, Gmel, Patra y Rehm, 2012; Wechsler and Nelson, 2010). The range and importance of these consequences show clearly the need to identify more accurately those young people who are at risk, which would provide a basis for interventions that are tailored to their needs (Cortés et al., 2014; Ibáñez, Ruipérez, Villa, Moya and Ortet, 2008).

One of the aspects of this problem that has aroused much interest in recent years is the relationship between personality variables in binge drinkers of varying intensity and frequency (Adan, 2012; Ibáñez et al., 2008; Woicik, Stewart, Pihl and Conrod, 2009) and the appearance of associated biopsychosocial problems (Cooper, Agocha and Sheldon, 2000; Ibáñez et al., 2008; Magid, MacLean and Colder, 2007; Mezquita, Stewart and Ruipérez, 2010; Ruipérez, Ibáñez, Villa and Ortet, 2006; Sher, Grekin and Williams, 2005). Specifically, it has been shown that traits included in the Five Factors of Personality (Costa and McCrae, 1992), are linked to problems associated with consumption, both in the population of clinical dependents (Hopwood et al., 2007; Sher, Trull, Bartholow and Veith, 1999), and in alcohol abusers (Littlefield, Sher and Wood, 2010; Flory, Lynam, Milich, Leukefeld and Clayton, 2002) and binge drinkers (Martin, 2011; Ruiz, Pincus and Dickinson, 2003). Among the factors that are most analyzed in the different types of consumers are Neuroticism and Extraversion (Martin, 2011; Mezquita et al., 2010; Read y O'Connor, 2006; Ruiz et al., 2003). Specifically, among the binge drinkers, high levels of Neuroticism correlate with a greater number of problems caused by alcohol consumption (Conrod, Stewart, Comeau and Maclean, 2006; Cooper, et al., 2000), which contributes significantly to the explanation of the variance of these problems (Cooper et al., 2000; Ruiz et al., 2003). On the other hand, Extraversion is shown to be directly related to variables that are relative to the pattern of consumption -the amount of alcohol consumed, the frequency- and contributes a specific weight to the prediction of the binge drinker (Hussong, 2003; Martin, 2011; Ruiz et al., 2003).

In other traits defined in the model, such as Agreeableness, previous research shows that a low score is usually associated with an increase in the amount of alcohol consumed by binge drinkers (Kubicka, Matjcek, Dytrych and Roth, 2001; Ibáñez et al., 2010; Mestre, Viñas, Dutil and Moya, 2004; Ruiz et al., 2003) as well as with the problems derived from this consumption among young university students (Ruiz et al., 2003). Nevertheless, some studies show contradictory results concerning the influence of Agreeableness on the consumption of binge drinkers (Hussong, 2003). The Consciousness trait shows similar behavior to that of Agreeableness, since the research also indicates an association between low scores in the dimension and an increase in consumption among binge drinkers (Ruiz et al., 2003). On the other hand, among binge drinkers, the Openness trait does not appear to be a significant predictor either of the amount of alcohol consumed or the problems caused by the same (Hussong, 2003; Ibáñez et al., 2010; Ruiz et al., 2003; Stewart, Loughlin and Rhyno, 2001). Thus, the personality profile that is characteristic of young binge drinkers could be defined by high scores in Neuroticism (Conrod et al., 2006; Cooper et al., 2000; Hussong, 2003; Littlefield, Sher and Wood, 2009; Martín, 2011; Ruiz et al., 2003; Stewart et al., 2001) and Extraversion (Cooper et al., 2000; Hussong, 2003; Martin, 2011; Littlefield et al., 2009; Ruiz et al., 2003) and low scores in Conscientiousness (Ibáñez et al., 2010; Ruiz et al., 2003; Stewart et al., 2001) and Agreeableness (Hussong, 2003; Ibáñez et al., 2010; Ruiz et al., 2003; Stewart et al., 2001).

One of the personality tools that has been most used in research related to alcohol consumption, including binge drinking, is the short form of the NEO Five-Factor Inventory (NEO-FFI, Costa y McCrae, 1992, 1999), which evaluates the personality traits of the Five Factor Model (Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness), (Boyle, Matthews and Saklofske, 2008; Hussong, 2003; Mezquita et al., 2010; Ruiz et al., 2003; Stewart et al., 2001). Many researchers, however, warn of the need to complement this evaluation with a tool that takes into account the multidimensionality of the Impulsivity trait (Cyders, Flory, Rainer and Smith, 2009; Henges and Marczinski, 2012; Magid et al., 2007; Meda et al., 2009; Quilty and Oakman, 2004; Stanford et al., 2009; Whiteside and Lynam, 2001).

The literature has shown that there is a significant relationship between impulsivity and binge drinking (Adan, 2012; Field, Schoenmakers and Wiers, 2008; Goudriaan, Grekin, Sher, 2007, 2011; MacKillop, Mattson, Anderson, Castelda and Donovick, 2007; Prado, Crespo, Brenlla and Páramo, 2007; Simons, Carey and Gaher, 2004; White et al., 2011) and between this trait and the experience of negative consequences as a result of this consumption (Fischer and Smith, 2008; Littlefield et al., 2009; Ruiz et al., 2003; Simons, Gaher, Correia, Hunsen and Christopher, 2005; Simons et al., 2004). For all of that, together with the NEO-FFI, the application of Barratt's Impulsivity Scale (BIS-11, Patton, Stanford and Barratt, 1995) is recommended, as this is a tool that is used among consumers of this type (Balodis, Potenza and Olmstead, 2009; Carlson and Johnson, 2012).

As well as this, the role of gender in the relationship between personality and alcohol should not be omitted. Some studies indicate that the traits typical of Neuroticism are more characteristic among female consumers of different intensity levels, including binge drinkers, who tend to experience a greater number of alcohol-related problems (Locke and Newcomb, 2001; Martin, Lynch, Pollock and Clark, 2000; Schuckit, Tipp, Bergman and Reich, 1997; Schutte, Hearst and Moos, 1997). On the other hand, traits corresponding to Impulsivity seem to be more relevant among male consumers, including binge drinkers (Adan, 2012; Cortés et al., 2014; Fischer and Smith, 2008; Waldeck and Miller, 1997; Zuckermann and Kuhlman, 2000).

However, many studies suggest there are no statistically significant differences between male and female binge drinkers in terms of Neuroticism (Ruiz et al., 2003) and Impulsivity (Balodis et al., 2009; Magid et al., 2007; Ruiz et al., 2003; Simons et al., 2004). These results show the need to continue evaluating the role of gender in the relationship between different aspects of personality and alcohol consumption.

Finally, another additional variable to consider, owing to its link to the appearance of problematic consumption, including binge drinking, is the drinking onset, that is, the age at which consumption is initiated (Hingson, Heeren and Winter, 2006; Jenkins et al., 2011; Lo, 1996; Pitkänen, Lyyra and Pulkkinen, 2005; Warner and White, 2003; Warner, White and Johnson, 2007). In that regard, one can find studies that appear to demonstrate that relationship (Bonomo, Bowes, Coffey, Carlin and Patton, 2004; DeWit, Adlaf, Offord and Ogborne, 2000; Grant, Stinson and Harford, 2001; Hingson and Zha, 2009; Livingston, Laslett and Dietze, 2008; Muthen and Muthen, 2000; Pilatti, Caneto, Garimaldi, Del Valle and Pautassi, 2013), and others that cast doubts on it, linking it instead to other variables, among which are included personality traits (Afitska, Plant, Weir, Miller and Plant, 2008; Dawson, Goldstein, Chou, Ruan and Grant, 2008; Harford, 2003; Rossow and Kuntsche, 2013). This has meant that, at present, research continues into the influence of the drinking onset as a factor that possibly contributes to the increase in the probability of consequences appearing.

This paper aims, firstly, to analyze the predictive weight of the drinking onset and personality traits on the amount of alcohol that young, binge-drinking university students consume weekly. Secondly, the predictive weight of these same variables -age and personality traits- will be seen, together with that of the weekly alcohol consumption on the number of consequences experienced. At all times, the gender perspective will be considered.

Method

Participants and procedures

To select the sample group, a stratified sampling was carried out of the first-year student population at the Universidad Complutense de Madrid (Complutense University of Madrid, or UCM) during the 2011-2012 academic year, using data provided by the vice-chancellor's office of the university. Degree courses from each area of knowledge (Basic Sciences, Social Sciences, Health Sciences, Humanities and Educational Sciences) were selected based on the number of students enrolled, the campus on which the degree course was studied, and distributed by gender. In all cases at least one morning and one evening group was included. The questionnaires were completed in the classrooms and during class time (both morning and evening), with members of the research team always present. Participation in the study was voluntary, and participants were asked for a contact telephone number in order to call them in for the following stage. From all of the students surveyed, some 440 subjects were selected, none of whom had any history of psychopathological or neurological disorders; abuse or substance dependence (including alcohol), or a family history of first-degree relative with alcoholism. Half of them were binge drinkers and the rest were either non-drinkers or consumers of small amounts, well below what is considered a binge drinker. After signing an informed consent form, among all of the multiple aspects evaluated, their consumption patterns were recorded, along with their cognitive and personality determinants. The data presented here form part of a longitudinal cohort study as neuropsychological evaluation was also included, even though, as this paper focuses solely on data obtained in the first stage of the research it could be said that information from a cross-sectional analysis is also used. Specifically, the results obtained from the 123 students who engage in binge drinking (MSC, 2008) are evaluated. 56.8% of the sample group are female (n = 21). The average age is 18.20 years (SD = .414).

Variables

Drinking onset. The age at which alcohol consumption begins is indicated.

Consumption patterns. The number of times in which alcohol is consumed over the last six months is registered. The number of drinks consumed each day of a week of habitual consumption over those six months is noted in an ad hoc table, following a procedure that is similar to that employed by Neighbors, Lee, Lewis, Fossos and Larimer (2007). The type of alcohol consumed and the time of day at which each consumption occurs are also registered. All of this information allows for the grams of alcohol consumed with each drink to be calculated, taking as a reference the Standard Drink Units in Spain (Rodríguez-Martos, Gual and Llopis, 1999). From these data, different variables are generated: total of alcohol consumed per week (the result of adding together the grams of alcohol consumed each day of the week, extracted from the self-register of consumption) and type of consumption (binge drinking-non-binge drinking). To obtain this last variable, the maximum number of grams consumed over a period of two to three hours of greatest consumption is calculated, with those males who drink 60 or more grams of alcohol, and the females who reach 40 or more grams being labelled as binge drinkers (MSC, 2008).

Personality traits. The Spanish version (Cordero, Pamos and Seisdedos, 2008) of Costa and McCrae's short form of the NEO-FFI Personality Inventory (1999). It consists of 60 items which evaluate the Five-Factor Model of personality (Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness), by means of a 5-point Likert response scale ranging from 0 (totally disagree) to 4 (strongly agree). In this study, the T scores of the 5 scales have been used (the range of these scores varies between 25 and 75; a score of over 55 is considered high and one of over 65 is very high). This tool obtains good internal consistency in a great many studies of the binge-drinking university population – a Cronbach alpha of between 0.71 and 0.85- (Mezquita et al., 2010; Ruiz et al., 2003; Sanz, Silva and Avia, 1999). Impulsivity is measured by means of Barratt's BIS-11 tool (Patton et al., 1995; Spanish adaptation by Oquendo et al., 2001), made up of 30 4-point Likert-type items: 0 (never/rarely), 1 (occasionally), 3 (often) and 4 (almost always) that measure Cognitive, Motor and Unplanned Impulsivity. The sum of the scores of the latter three constitutes the Total Impulsivity scale used in this study (with a range of scores from 0 to 120). This tool has shown good internal robustness in the student drinking population –a Cronbach alpha of between 0.79 and 0.83- (Hair and Hampson, 2006; Patton et al., 1995; Stanford et al., 2009).

Consequences. These are evaluated with the corresponding section of the IECI tool (Cortés et al., 2012). The scale includes 30 items which refer to the different consequences that each young person says they experience as a result of drinking. They refer to physical symptoms (I have had a hangover, felt dizzy, vomited; etc.); loss of control (I have drunk more than planned; etc.); risky behavior (I have had unsafe sex; etc.); physical dependency (I need more alcohol than I did a few years ago; etc.); self-perception (Drinking alcohol makes me feel guilty; etc.); academic or professional consequences (I have neglected my responsibilities because of drinking; etc.); socio-interpersonal consequences (When I drink I say things that I later regret; etc.) and other consequences (I have money problems because of drinking; etc.). All of them respond by means of a dichotomous scale (Yes/No). This scale has shown goodness of fit in previous studies, reaching a Cronbach alpha of over .807 (Cortés et al., 2012; Motos, 2013). In this paper the sum of all the consequences that each young person says they have experienced in the last six months is used, and this constitutes the number of consequences variable (with a range of scores of between 0 and 30).

Data analysis

By means of the IBM SPSS Statistics 19 pack, descriptive analysis of the binge drinking, weekly consumption, drinking onset, personality traits and number of consequences variables for the general sample and by gender were carried out. In addition, in order to check for possible differences according to gender, mean comparisons were carried out (by means of the Student t test) on these same variables. Then, the zero-order correlations between number of consequences, weekly consumption, drinking onset, gender, the five NEO-FFI personality traits and Total Impulsivity were examined (by means of the Pearson correlation coefficient). This made it possible to confirm which elements were most strongly associated with consumption and its consequences and to identify variables that presented unforeseen bivariate relationships. As a prior step to the regression analyses, the Blom transformation (1958) was applied to all of the continuous variables used in the same (except the NEO-FFI), with the aim of avoiding bias in the frequency of the measurements and to maintain the coherence of the data. By this means the cases are ordered by range, each case's range becomes a percentile and the measures are finally normalized. The result is a *z* score of ranges, which reduces to a minimum the spurious impact of the extreme cases. Finally, three hierarchical regression analyses were carried out (one for the whole sample, and one for each gender) in order to detect the unique contributions of the *drinking onset, gender, Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness* and *Total Impulsivity* variables on the amount of alcohol consumed per week. These variables were introduced in eight separate steps. On the other hand, in order to predict the percentage of variance on the consequences, another hierarchical regression analysis was carried out. In this case, for the whole of the sample, owing to the fact that no differences by gender had been observed in the *t* tests or in the correlations. Specifically, the *drinking onset, grams per week, Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness* and *Total Impulsivity* variables were introduced in eight separate steps.

Results

Table 1 shows how both the males (121.63g) and the females (89.09g) consume double the grams of alcohol that define a binge drinker (60g-40g respectively). In addition, as can be appreciated in the difference between this intake and that reflected in the weekly grams of alcohol variable, they complement this intake with others, of smaller amounts, throughout the week. When the total weekly intake is considered, a third of the women and a quarter of the men exceed the limit fixed by the WHO (2007) to define the harmful weekly amount (280g in men, 170g in women). Looking at the gender differences, the same table shows how men consume a significantly larger amount of alcohol per week (209.24g *vs.* 152.77g; t=-4.042; p<.000), and during one binge-drinking session, than women (121.63g *vs.* 89.09g; t=-4.988; p<.000).

Contrary to this, no significant differences are appreciated either in the drinking onset or the number of consequences experienced. Looking at the personality traits, it is the males who obtain a significantly higher mean in Agreeableness (58.82 *vs.* 53.23; t=-6.209; p<.000) and Impulsivity (47.43 vs. 43.64; t=-2.201; p<.029). In general, the personality scale scores may be considered as high, with Neuroticism, whose profile is defined as very high, standing out from the rest, according to the NEO-FFI scale. No gender differences are observed in Neuroticism, Openness, Extraversion or Conscientiousness.

Table 1.
Consumption variables, number of consequences and personality traits, differentiated by gender.

Item	Mean	Sd	Males (M, sd)		Females (M, sd)		t	p
Drinking onset	14.94	1.25	15.10	1.37	14.83	1.13	-1.538	.126
Weekly grams of alcohol	177.16	99.89	209.24	115.14	152.77	78.65	-4.042	.000
Grams in one binge-drinking session	103.15	47.37	121.63	54.35	89.09	35.54	-4.988	.000
Number of consequences	7.79	3.53	8.22	3.58	7.47	3.46	-1.534	.126
Personality traits								
Neuroticism	69.77	4.48	70.30	3.69	69.38	4.97	-1.540	.125
Extraversion	58.95	5.35	59.28	4.96	58.70	5.64	-0.783	.435
Openness	62.22	6.51	62.62	6.22	61.92	6.74	-0.778	.437
Agreeableness	55.63	7.04	58.82	6.32	53.23	6.61	-6.209	.000
Conscientiousness	58.44	6.60	57.98	6.83	58.79	6.42	0.878	.381
Total Impulsivity	45.28	12.58	47.43	11.83	43.64	12.94	-2.201	.029

The first column of Table 2 shows the correlations of the amount of alcohol consumed weekly with the drinking onset, gender and the NEO-FFI and BIS-11 personality traits, for the general sample. The drinking onset shows a negative correlation with the amount of alcohol consumed in a week. By contrast, gender correlates in a positive way with consumption. For that reason, hierarchical regression analyses by gender were carried out. The second column of Table 2 shows the correlations between the consequences experienced with the drinking onset, gender, grams consumed weekly and the NEO-FFI and BIS-11 personality traits, for the general sample. Weekly consumption correlates positively and significantly with the number of consequences experienced. Against this, the drinking onset shows a negative relationship, as in the previous case. Impulsivity, for its part, correlates more strongly with consequences derived from consumption. In this case no differences appear in terms of gender, for which reason no further separate hierarchical regression analyses were performed.

Tabla 2.
Correlations between consumption and personality traits with weekly consumption and the number of consequences.

	Weekly grams	No. of consequences
Drinking onset	-.267**	-.288**
Gender	.281**	.091
Weekly grams	-	.332**
Personality traits		
Neuroticism	-.040	.154*
Extraversion	.078	.135*
Openness	.120*	.008
Agreeableness	.180**	.152*
Conscientiousness	-.111	-.061
Total Impulsivity	.185**	.310**

Note: * .01 < $p \leq$ .05 ** .001 < $p \leq$ .01

Tables 3, 4 and 5 present the results of the hierarchical regression analyses carried out to predict the amount of alcohol consumed weekly, both for the overall sample and for each of the sexes. Only the drinking onset and gender variables turn out to be significant for the overall sample, which explains variances of 4.8% and 9.6% respectively. In the case of the first variable, the contribution of the variance is also significant for both sexes, being greater in males (10.6%). As well as this, Conscientiousness and Impulsivity are significant for males. The amount of variance that they contribute to the prediction of weekly consumption is of 9.4% and 6.9% respectively. Among the females, only the drinking onset, with an explained variance of 3.8%, stands out. The highest percentage of explained variance of weekly consumption is that obtained by the males (30.4%). This percentage is eleven points higher than that of the overall sample (19.4%) and ten points higher when compared with that of the females (9.5%).

Table 3.
Hierarchical regression analyses to predict weekly consumption in the overall sample.

						Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7		Step 8	
	R	R^2	Error estimation	ΔR^2	$F\Delta R^2$	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β
1	.218	.048	.798	.048	10.266**	-.218	-3.204**														
2	.380	.144	.759	.096	22.968***	-.254	-3.895***	.312	4.793***												
3	.394	.155	.756	.011	2.608	-.239	-3.643***	.295	4.480***	.106	1.615										
4	.402	.161	.755	.006	1.555	-.246	-3.738***	.262	3.709***	.097	1.465	.088	1.247								
5	.412	.170	.753	.009	2.063	-.253	-3.844***	.269	3.801***	.084	1.266	.066	.909	.096	1.436						
6	.421	.177	.751	.008	1.843	-.252	-3.848***	.262	3.704***	.073	1.085	.073	1.010	.100	1.501	-.08	-1.35				
7	.427	.182	.751	.005	1.132	-.259	-3.932***	.262	3.700***	.060	.877	.070	.963	.090	1.341	-.11	-1.564	.073	1.064		
8	.441	.194	.747	.012	3.002	-.262	-3.990***	.264	3.754***	.069	1.011	.088	1.212	.093	1.379	-.09	-1.460	.096	1.386	-.12	-1.733

Note: *Step 1. Drinking onset; Step 2. Gender; Step 3. Total Impulsivity; Step 4. Agreeableness; Step 5. Openness; Step 6. Consciousness; Step 7. Extraversion; Step 8. Neuroticism*
* $.01 < p \leq .05$ ** $.001 < p \leq .01$ *** $p \leq .001$

Table 4.
Hierarchical regression analyses to predict weekly alcohol consumption in males.

						Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7	
	R	R^2	Error estimation	ΔR^2	$F\Delta R^2$	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β
1	.326	.106	.8137	.106	10.204**	-.326	-3.194**												
2	.448	.200	.7741	.094	10.014**	-.302	-3.106**	-.308	-3.164**										
3	.519	.270	.7442	.069	7.976*	-.220	-2.241*	-.313	-3.347**	.276	2.824**								
4	.535	.286	.7403	.016	1.897	-.225	-2.306*	-.296	-3.153**	.298	3.024**	-.131	-1.377						
5	.548	.301	.7371	.015	1.718	-.235	-2.408*	-.273	-2.878**	.296	3.020**	-.167	-1.696	.128	1.311				
6	.549	.302	.7411	.001	.112	-.236	-2.408*	-.275	-2.878**	.295	2.985**	-.168	-1.689	.123	1.239	.032	.335		
7	.551	.304	.7445	.002	.257	-.239	-2.423*	-.283	-2.909**	.289	2.895**	-.176	-1.743	.124	1.242	.036	.377	.050	.507

Note: *Step 1. Drinking onset; Step 2. Consciousness; Step 3. Total Impulsivity; Step 4. Neuroticism; Step 5. Openness; Step 6. Agreeableness; Step 7. Extraversion*
* $.01 < p \leq .05$ ** $.001 < p \leq .01$ *** $p \leq .001$

Table 5.
Hierarchical regression analyses to predict weekly alcohol consumption in females.

						Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7	
	R	R^2	Error estimation	ΔR^2	$F\Delta R^2$	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β
1	.195	.038	.7158	.038	4.619*	-.195	-2.149*												
2	.248	.062	.7100	.024	2.922	-.217	-2.386*	.155	1.709										
3	.259	.067	.7109	.006	.701	-.221	-2.428*	.132	1.386	.079	.837								
4	.274	.075	.7110	.008	.956	-.220	-2.411*	.158	1.597	.074	.776	-.092	-.978						
5	.297	.088	.7092	.013	1.594	-.225	-2.467*	.149	1.505	.043	.436	-.119	-1.239	.123	1.262				
6	.306	.094	.7101	.006	.699	-.220	-2.410*	.134	1.333	.033	.330	-.122	-1.274	.122	1.252	.078	.836		
7	.309	.095	.7126	.002	.228	-.223	-2.430*	.142	1.390	.041	.412	-.120	-1.239	.125	1.280	.065	.661	-.047	-.478

Note: *Step 1. Drinking onset; Step 2. Extraversion; Step 3. Openness; Step 4. Neuroticism; Step 5. Agreeableness; Step 6. Conscientiousness; Step 7. Total Impulsivity*
* $.01 < p \leq .05$ ** $.001 < p \leq .01$ *** $p \leq .001$

Table 6 presents the results for the overall sample of the hierarchical regression analyses to predict the consequences derived from the consumption of alcohol. The total model contributes 20.2% to the prediction of the variance. The variable that explains the greater percentage of variance is the drinking onset (6.9%). This is followed by weekly consumption (5.2%) and the Impulsivity and Neuroticism traits with 4.4% and 1.8% respectively.

Table 6.
Hierarchical regression analyses to predict the number of consequences derived from binge drinking, in the overall sample

						Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7		Step 8		Step 9	
	R	R^2	Error estimation	ΔR^2	$F\Delta R^2$	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β	β	p value for β
1	.263	.069	.8744	.069	15.177***	-.263	-3.896***																
2	.348	.121	.8517	.052	12.048**	-.212	-3.145**	.234	3.471**														
3	.405	.164	.8324	.044	10.567**	-.193	-2.925**	.199	2.994**	.213	3.251**												
4	.428	.183	.8252	.018	4.565*	-.195	-2.977**	.208	3.148**	.192	2.930**	.137	2.137*										
5	.435	.190	.8239	.007	1.658	-.209	-3.153**	.190	2.824**	.183	2.776**	.120	1.828	.087	1.288								
6	.441	.194	.8234	.005	1.230	-.218	-3.265**	.184	2.725**	.173	2.604**	.103	1.532	.084	1.253	.074	1.109						
7	.441	.194	.8255	.000	.003	-.218	-3.225**	.183	2.611**	.173	2.585**	.103	1.524	.083	1.165	.074	1.108	-.070	-1.067				
8	.443	.197	.8264	.002	.524	-.220	-3.249**	.178	2.521*	.165	2.436*	.105	1.557	.087	1.209	.085	1.240	.002	.026	-.05	-.724		
9	.449	.202	.8259	.005	1.267	-.214	-3.145**	.186	2.621**	.173	2.537*	.108	1.590	.102	1.401	.095	1.367	-.005	-.068	-.047	-.699	-.076	-1.126

Step 1. Drinking onset; Step 2. Weekly consumption; Step 3. Total Impulsivity Total; Step 4. Neuroticism; Step 5. Agreeableness; Step 6. Extraversion; Step 7. Gender; Step 8. Conscientiousness; Step 9. Openness
* $.01 < p \leq .05$ ** $.001 < p \leq .01$ *** $p \leq .001$

Discussion

The data concerning consumption analyzed in this sample confirm the tendency that had been observed in previous papers (Cadaveira, 2010; Cortés, 2012; Cortés et al., 2014; White, Kraus and Swartzwelder, 2006), which point to the homogenization of a pattern of binge drinking among young people that reaches double the grams of alcohol required to define it. It is important to point out that these young binge drinkers do not consider themselves to be consumers at weekly risk as defined by the WHO (2007), hence, it is difficult to be able to identify them if weekly consumption is considered (Cortés, Motos and Giménez, 2013). The young people present high scores in the five factors evaluated, so two aspects can be highlighted. On the one hand, a relationship between all of them that is similar to that outlined in the introduction is observed (Conrod et al., 2006: Cooper et al., 2000; Hussong, 2003; Ibáñez et al., 2010; Littlefield et al., 2009; Martín, 2011; Ruiz et al., 2003; Stewart et al., 2001), since the highest scores are to be found in Neuroticism and Extraversion, with those of Agreeableness and Conscientiousness being secondary. This means that the binge drinker can be defined as a person with emotional reactions that may unbalance him, making him act in an irrational and even rigid manner. In addition, he would be sociable, a party-lover, with a need to talk to people but, at the same time, impulsive, carefree and with a tendency to be aggressive on occasions.

Altruism, sensitivity towards others, self-discipline and efficiency, while present, would not tend to represent these young people with the same level of intensity. The other aspect to highlight is that, unlike in other research projects (Hussong, 2003; Ibáñez et al., 2010; Ruiz et al., 2003; Stewart et al., 2001), in this case the evaluation of the influence of the Openness trait is not ruled out, as it shows itself to be as relevant as the rest. This result is not surprising if it is borne in mind that the sample studied was a group of first-year university students, for which reason one might expect of them attitudes and competences which are in keeping with a wide range of interests and critical thought.

In attempting to elucidate possible gender differences among the personality factors evaluated, the result obtained in Neuroticism tends to confirm the research carried out by Ruiz et al. (2003), indicating in this way the well-known importance of this trait among all binge drinkers. In addition, the difference found between males and females in Agreeableness means that new information that allows for a more precise description of the male binge drinkers as young persons with a more trusting and altruistic character than the female binge drinkers of the same age can be nuanced. On the other hand, the differences observed in Impulsivity support part of prior research (Adan, 2012; Cortés et al., 2014; Fischer y Smith, 2008; Waldeck y Miller, 1997; Zuckermann y Kuhlman, 2000) that highlights the greater probability that young male binge drinkers behave without thinking, live for the moment and have a short attention span. One of the most important contributions of this study has been the attempt to determine the weight or value that each of these dimensions may have when it comes to explaining consumption behavior among binge drinkers and the psychosocial consequences derived from the same.

Until now, most research has been limited to identifying dimensions in which these young people are conspicuous, but without attempting to assess the predictive level of each of them. For this reason, the primary objective of this study was to determine the predictive value of the drinking onset for drinking and of the personality traits on the weekly consumption of alcohol. Taking the sample as a whole, the drinking onset stands out as a variable with a greater predictive influence, while no explanatory value is obtained for any of the personality traits evaluated, unlike what is sustained by other research (Hussong, 2003; Ibañez et al., 2010; Martin, 2011; Ruiz et al., 2003). But it would be a mistake to focus only on this result and not give importance to the relevance of the gender variable in this prediction. Not to nuance the comment made regarding the function of gender would be to mask the weight that some personality traits do have. In this case the explicative importance that both the drinking onset and the Consciousness and Impulsivity traits have among males should be highlighted. Specifically, the explanatory weight of both exceeds that obtained in other research (Ibáñez et al., 2008, 2010; Martín, 2011). A different situation can be appreciated among females, since despite obtaining high scores for the personality dimensions none of them appear to have a relevant weight when it comes to explaining and justifying their alcohol consumption. These results warn of the importance of encouraging among males activities that work on their sense of duty, improve their time-management and establish limits or self-control on impulsive or aggressive responses.

On the other hand, it is useful to continue looking into new variables that will allow the explained variance of the consumption pattern among females to be increased, thus making it easier to lay down guidelines that guarantee a more optimal intervention. In addition, given that it has been shown that the drinking onset has an important influence on the amount of alcohol consumed weekly by binge drinkers, and bearing in mind that this is the main pattern of consumption among university students at the moment (OED, 2012, 2013), this supports the need to continue fostering the use of all those measures which prove to be universally effective in prevention to achieve the goal of delaying the drinking onset of alcohol consumption. Among these measures are those referring to alcohol consumption policies, be they legal controls, the raising of prices and taxes, or the reduction of the amount of advertising (Babor et al., 2003; EMCDDA, 2009; Villalbí and Gual, 2009), as well as those that foster the development of interpersonal relationship skills, resistance to peer pressure, improving conflict resolution or increasing self-esteem (CSAP, 2004). The importance of intervening at the same time in the social agents that surround young people, especially the parents, cannot be left aside, with the aim of encouraging changes in attitudes that are favorable to alcohol and the improvement of communication within families (CSAP, 2004; SMAHSA, 2010).

Another of the aims of this study was to evaluate the predictive capacity of the age of onset of alcohol consumption, the personality traits and the grams of alcohol consumed weekly on the number of consequences experienced. The result obtained defines, as was expected, that the drinking onset of alcohol consumption (Benton et al., 2006; Grant et al., 2001; Larimer, Turner, Mallett and Geisner, 2004; Muthen and Muthen, 2000), and the amount of this substance consumed (Neighbours et al., 2007) are the variables with the greatest explanatory power. But, together with these variables, although of less weight, the explanatory importance of Impulsivity and also Neuroticism is confirmed, clearly indicating the tendency observed in the papers reviewed (Conrod et al., 2006: Cooper et al., 2000; Fisher y Smith, 2008; Littlefield et al., 2009; Ruiz et al., 2003; Simons et al., 2005; Simons et al., 2004). This reality shows the need to work on, for all types of binge drinkers, with the aim of diminishing the incidence of negative consequences, a set of proposals concerning the management of skills to face situations of stress, among which could be activities that reinforce impulse control and foster the capacity to deal with anxiety, hostile reactions and negative emotional states.

An example of an intervention program that directly impacts on some of the variables included in the Neuroticism trait is that carried out by Conrod et al. (2006) and Conrod, Castellanos-Ryan and Mackie (2008, 2011) with young binge drinkers. The efficacy of this program in reducing the amount of alcohol consumed, in binge drinking and in the probability of experiencing problems derived from consumption has been shown on numerous occasions (Conrod et al., 2006; Conrod et al., 2008, 2011; O'Leary-Barrett, Mackie, Castellanos-Ryan, Al-Khudhairy and Conrod, 2010). However, Conrod himself warns that despite the growing evidence to support a personality-based approach to the prevention of alcohol consumption, there are still significant gaps, principally concerning everything that surrounds the generalization that short-term effects on alcohol consumption can be translated into a reduction of the risk of experiencing long-term problems (Conrod et al., 2011). This study presents a series of limitations that must be pointed out. Firstly, the participants are university students, which means questioning the generalization of its results to all young people of a similar age. It would be useful to carry out studies with young people who are both university students and not university students, although the difficulties of gaining access to the latter group should not be dismissed.

Secondly, estimations of alcohol consumption are based on self-reporting and not on objective measurements, with the bias that this may introduce. There is, in addition, a limitation that goes beyond the scope of this paper but which may be important to bear in mind, and that is that there is still no international consensus on a definition of binge drinking. This heterogeneity leads to some to estimate binge drinking in terms of a number of drinks but wi-

thout specifying the period of time over which consumption takes place or whether the alcohol drunk is of low or high graduation; others to estimate it according to the number of grams consumed but over a 2-3-hour period, and still others to calculate it in terms of the number of times binge drinking has occurred in recent months, etc. This situation often leads to comparisons being made of results obtained from highly heterogeneous subjects, who have been included all together under the same denomination. This points to the need to reach agreement on the definition of the binge drinker in as rigorous way as is possible. Finally, given that the variables included in this study only allow for part of the consumption patterns and the consequences derived from the same to be understood, it would be interesting to look into other possible explanatory variables, such as the perceived norms regarding alcohol intake within the ambit of the drinker (Neighbors et al., 2007) or the motives for consumption (Martín, 2011; Mezquita et al., 2010), which have shown their efficacy independently.

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Conflict of interests

There are no conflicts of interests in connection with this article.

References

Adan, A. (2012). Impulsividad funcional y disfuncional en jóvenes con consumo intensivo de alcohol. *Adicciones, 24*, 17-22.

Afitska, N., Plant, M. A., Weir, I., Miller, P. & Plant, M. L. (2008). The relationship between teenage 'binge' drinking, age of first alcohol consumption and intoxication. *Journal of Substance Use, 13*, 205–218. doi: 10.1080/14659890701740663

Anderson, P. & Baumberg, B. (2006). *Alcohol in Europe*. London: Institute of Alcohol Studies.

Arata, C. M., Stafford, J. & Tims, M. S. (2003). High school drinking and its consequences. *Adolescence, 38*, 567-579.

Babor, T., Caetano, R., Casswell, S., Edwards, G., Giesbrecht, N., Graham, K.,... & Rossow, I. (2003). Alcohol: no ordinary commodity: Research and Public policy. Oxford University Press.

Balodis, I. M., Potenza, M. N. & Olmstead, M. C. (2009). Binge drinking in undergraduates: relationships with sex, drinking behaviours, impulsivity, and the perceived effects of alcohol. *Behavioral Pharmacology, 20*, 518-526. doi: 10.1097/FBP.0b013e328330c779

Benton, S. L., Downey, R. G., Glider, P. S., Benton, S. A., Shin, K., Newton, D. W.,… Price, A. (2006). Predicting negative drinking consequences: Examining descriptive norm perception. *Journal of Studies on Alcohol, 67*, 399–405.

Blom, G. (1958). *Statistical estimates and transformed beta–variables*. New York: John Wiley and Sons.

Bonomo, Y. A., Bowes, G., Coffey, C., Carlin, J. B. & Patton, G. C. (2004). Teenage drinking and the onset of alcohol dependence: a cohort study over seven years. *Addiction, 99*, 1520–1528. doi: 10.1111/j.1360-0443.2004.00846.x

Boyle, G. J., Matthews, G. & Saklofske, D. H. (2008). Personality theories and models: An overview. En G. J. Boyle, G. Matthews & D. H. Saklofske (Eds.), *Personality theory and assessment. Personality theories and models* (Vol. 1, pp. 1–29). London: SAGE.

Cadaveira, F. (2010). *Consecuencias neurocognitivas: estudio de seguimiento en jóvenes españoles que realizan binge drinking*. Presented at the meeting Consumo Intensivo de Alcohol en Jóvenes: conocimiento, alternativas y viabilidad. Valencia.

Calafat, A. (2007). El abuso de alcohol de los jóvenes en España. *Adicciones, 19*, 217-224.

Carlson, S. R. & Johnson, S. C. (2012). Impulsivity is not always associated with student drinking: A moderation study of impulsivity and drinking by positive alcohol expectancies. *Addictive Behaviors, 37*, 556–560. doi: 10.1016/j.addbeh.2011.12.007

Center for Substance Abuse Prevention (2004). *SAMHSA Model Programs. Effective Substance Abuse and Mental Health Programs for Every Community*. Retrieved from http://modelprograms.samhsa.gov/.

Conrod, P. J., Castellanos, N. & Mackie, C. (2008). Personality-targeted interventions delay the growth of adolescent drinking and binge drinking. *Journal of Child Psychology and Psychiatry, 49*, 181–190.

Conrod, P. J., Castellanos-Ryan, N. & Mackie, C. (2011). Long-Term Effects of a Personality-Targeted Intervention to Reduce Alcohol Use in Adolescents. *Journal of Consulting and Clinical Psychology, 79*, 296-306. doi: dx.doi.org/10.1037/a0022997

Conrod, P. J., Stewart, S. H., Comeau, N. & Maclean, A. M. (2006). Efficacy of Cognitive-Behavioral Interventions Targeting Personality Risk Factors for Youth Alcohol Misuse. *Journal of Clinical Child and Adolescent Psychology, 35*, 550–563. doi: 10.1207/s15374424jccp3504_6

Cooper, M. L., Agocha, V. B. & Sheldon, M. S. (2000). A motivational perspective on risky behaviors: The role of personality and affect regulatory processes. *Journal of Personality, 68*, 1059–1088. doi:10.1111/1467-6494.00126

Cordero, A., Pamos, A. & Seisdedos, N. (2008). *NEO PI-R Manual. Adaptación Española*. Madrid: TEA Ediciones.

Cortés, M. T. (2010). *Debates en drogodependencias: Aspectos sociales y de salud en el botellón: obligados a entenderse*. Valencia: Plan Municipal de Drogodependencias. Ayuntamiento de Valencia.

Cortés, M. T. (2012). *Determinantes psico-sociales relacionados con el consumo intensivo de alcohol de mujeres*. Presented at the meeting XIV Jornadas asociación Proyecto hombre. Jóvenes y alcohol: enfocando una realidad, Madrid.

Cortés, M. T., Giménez, J. A., Motos, P. & Cadaveira, F. (2014). The importance of expectations in the relationship between impulsivity and binge drinking among university students. *Adicciones, 26*, 134-145.

Cortés, M. T., Giménez, J. A., Tomás, I., Espejo, B., Pascual, F., Pedrero, E. & Guardia, J. (2012). *Instrumento de Evaluación del Consumo Intensivo de Alcohol*. Presented at the Plan Nacional sobre Drogas.

Cortés, M. T., Motos, P. & Giménez, J. A. (2013). *Adjustment of different ways of measuring alcohol binge drinking in Spanish youngsters*. Poster presented at the Congreso Internacional Global Addiction, Pisa.

Costa, P. T. & McCrae, R. R. (1992). *Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) professional manual*. Odessa, FL: Psychological Assessment Resources.

Costa, P. T. & McCrae, R. R. (1999). *Inventario de Personalidad NEO Revisado (NEO PIR) e Inventario NEO Reducido de Cinco Factores (NEO-FFI). Manual profesional*. Madrid: TEA.

Cyders, M. A., Flory, K., Rainer, S. & Smith, G. T. (2009). The role of personality dispositions to risky behavior in predicting first-year college drinking. *Addiction, 104*, 193–202. doi:10.1111/j.1360-0443.2008.02434.x

Danielsson, A. K., Wennberg, P., Tengström, A. & Romelsjö, A. (2010). Adolescent alcohol use trajectories: Predictors and subsequent problems. *Addictive Behaviors 35*, 848–852. doi: 10.1016/j.addbeh.2010.05.001

Dawson, D. A., Goldstein, R. B., Chou, S. P., Ruan, W. J. & Grant, B. F. (2008). Age at first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. *Alcoholism Clinical Experimental Research, 32*, 2149–2160. doi: 10.1111/j.1530-0277.2008.00806.x

Devos-Comby, L. & Lange, J. E. (2008). Standardized Measures of Alcohol-Related Problems: A Review of Their Use Among College Students. *Psychology of Addictive Behaviors, 22*, 349-361. doi: 10.1037/0893-164X.22.3.349

DeWit, D. J., Adlaf, E. M., Offord, D. R. & Ogborne, A. C. (2000). Age at first alcohol use: a risk factor for the development of alcohol disorders. *American Journal of Psychiatry, 157*, 745-750. doi: 10.1176/appi.ajp.157.5.745

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2009). Annual Report 2009. Retrieved from http://www.emcdda.europa.eu/attachements.cfm/att_93236_EN_EMCDDA_AR2009_EN.pdf

Field, M., Schoenmakers, T. & Wiers, R. W. (2008). Cognitive processes in alcohol binges: a review and research agenda. *Current Drug Abuse Reviews, 1*, 263–279.

Fischer, S. & Smith, G. T. (2008). Binge eating, problem drinking, and pathological gambling: Linking behavior to shared traits and social learning. *Personality and individual Differences, 44*, 789-800. doi: 10.1016/j.paid.2007.10.008

Flory, K., Lynam, D., Milich, R., Leukefeld, C. & Clayton, R. (2002). The relations among personality, symptoms of alcohol and marijuana abuse, and symptoms of comorbid psychopathology: results from a community sample. *Experimental and clinical psychopharmacology, 10*, 425-434. doi: 10.1037/1064-1297.10.4.425

Gliksman, L., Adlaf, E. M., Demers, A. & Newton, B. (2003). Heavy Drinking on Canadian Campuses. *Canadian Journal of Public Health, 94*, 17-21.

Goudriaan, A. E., Grekin, E. R. & Sher, K. J. (2011). Decision making and response inhibition as predictor of heavy alcohol use: a prospective study. *Alcoholism: Clinical and Experimental Research, 35*, 1-8. doi: 10.1111/j.1530-0277.2011.01437.x

Grant, B. F., Stinson, F. S. & Harford, T. C. (2001). Age at onset of alcohol use and DSM-IV alcohol abuse and dependence: a 12-year follow-up. *Journal of Substance Abuse, 13*, 493–504. doi: 10.1016/S0899-3289(01)00096-7

Hair, P. & Hampson, S. E. (2006). The role of impulsivity in predicting maladaptative behaviour among female students. *Personality and Individual Differences, 40*, 943-952. doi: 10.1016/j.paid.2005.10.002

Harford, T. C. (2003). Early onset of alcohol use and health problems: spurious associations and prevention. *Addiction, 98*, 1483–1484. doi: 10.1046/j.1360-0443.2003.00555.x

Henges, A. L. & Marczinski, C. A. (2012). Impulsivity and alcohol consumption in young social drinkers. *Addictive Behaviors, 37,* 217–220.

Hingson, R. W., Assailly, J. P. & Williams, A. F. (2004). Underage drinking: Frequency, consequences, and interventions. *Traffic Injury Prevention, 5,* 228-236. doi: 10.1080/15389580490465256

Hingson, R. W., Heeren, T. & Winter M. R. (2006). Age at drinking onset and alcohol dependence: age at onset, duration, and severity. *Archives of pediatrics & adolescent medicine, 160*, 739-746. doi: 10.1542/peds.2006-0223

Hingson, R. W. & Zha, W. (2009). Age of drinking onset, alcohol use disorders, frequent heavy drinking, and unintentionally injuring oneself and others after drinking. *Pediatrics, 123*, 1477–1484. doi: 10.1542/peds.2008-2176

Hingson, R., Zha, W. & Weitzman, E. R. (2009). Magnitude of and trends in alcohol-related mortality and morbidity among US college students ages 18-24. *Journal of Study on Alcohol and Drugs, supl. 16*, 12-20.

Hopwood, C. J., Morey, L. C., Skodol, A. E., Stout, R. L., Yen, S., Ansell, E. B.,… McGlashan, T. H. (2007). Five-factor model of personality traits associated with alcohol-related diagnoses in a clinical sample. *Journal of Studies on Alcohol and Drugs, 68*, 455-460.

Hussong, A. M. (2003). Social Influences in Motivated Drinking Among College Students. *Psychology of Addictive Behaviors, 17*, 142–150. doi: 10.1037/0893-164X.17.2.142

Ibáñez, M. I., Moya, J., Villa, H., Mezquita, L., Ruipérez, M. A. & Ortet, G. (2010). Basic personality dimensions and alcohol consumption in Young adults. *Personality and Individual Differences, 48*, 171-176. doi: 10.1016/j.paid.2009.09.017

Ibáñez, M. I., Ruipérez, M. A., Villa, H., Moya, J. & Ortet, G. (2008). Personality and alcohol use. En G. J. Boyle, G. Matthews & D. H. Saklofske (Eds.), *Personality theory and assessment. Personality theories and models* (Vol. 1, pp. 677–697). London: SAGE.

Jenkins, M. B., Agrawal, A., Lynskey, M. T., Nelson, E. C., Madden, P. A., Bucholz, K. K. & Heath, A. C. (2011). Correlates of Alcohol Abuse/Dependence in Early-Onset Alcohol-Using Women. *The American Journal on Addictions, 20*, 429-434. doi: 10.1111/j.1521-0391.2011.00151.x.

Kahler, C. W., Strong, D. R. & Read, J. P. (2005). Toward efficient and comprehensive measurement of the alcohol problems continuum in college students: The Brief Young Adult Alcohol Consequences Questionnaire. *Alcoholism: Clinical and Experimental Research, 29*, 1180-1189.doi:10.1097/01.ALC.0000171940.95813.A5

Kubicka, L., Matjcek, Z., Dytrych, Z. & Roth, Z. (2001). IQ and personality traits assessed in childhood as predictors of drinking and smoking behaviour in middle-aged adults: a 24-year follow-up study. *Addiction, 96,* 1615-1628. doi: 10.1111/j.1467-6494.1996.tb00816.x

Larimer, M. E., Turner, A. P., Mallett, K. A. & Geisner, I. M. (2004). Predicting drinking behavior and alcohol-related problems among fraternity and sorority members: Examining the role of descriptive and injunctive norms. *Psychology of Addictive Behaviors, 18*, 203–212. doi: 10.1037/0893-164X.18.3.203

Littlefield, A. K., Sher, K. J. & Wood, P. K. (2009). Is the "maturing out" of problematic alcohol involvement related to personality change? *Journal of Abnormal Psychology, 118,* 360–374. doi: 10.1037/a0015125

Littlefield, A. K., Sher, K. J. & Wood, P. K. (2010). A personality-based description of maturing out of alcohol problems: Extension with a five-factor model and robustness to modeling challenges. *Addictive Behaviors, 35*, 948–954. doi: 10.1016/j.addbeh.2010.06.008

Livingston, M., Laslett, A. M. & Dietze, P. (2008). Individual and community correlates of young people's high-risk drinking in Victoria, Australia. *Drug Alcohol Depend, 98*, 241–248. doi: 10.1016/j.drugalcdep.2008.06.002

Lo, C. C. (1996). Are women heavier drinkers than we thought they were? *Journal of Studies on Alcohol, 57*, 531-535.

Locke, T. F. & Newcomb, M. D. (2001). Alcohol involvement and dysphoria: A longitudinal examination of gender differences from late adolescence to adulthood. *Psychology of Addictive Behaviors, 15*, 227–236. doi: 10.1037/0893-164X.15.3.227

MacKillop, J., Mattson, R. E., Anderson, E. J., Castelda, B. A. & Donovick, P. J. (2007). Multidimensional assessment of impulsivity in undergraduate hazardous drinkers and controls. *Journal of Studies on Alcohol and Drugs, 68*, 785–788.

Magid, V., MacLean, M. G. & Colder, C. R. (2007). Differentiating between sensation seeking and impulsivity through their mediated relations with alcohol use and problems. *Addictive Behaviors, 32*, 2046–2061. doi: 10.1016/j.addbeh.2007.01.015

March, J. C., Prieto, M. A., Danet, A., Escudero, M., López, M. & Luque, N. (2010). El consumo de alcohol en los adolescentes: una aproximación cualitativa desde los docentes. *Trastornos Adictivos, 12*, 65-71. doi: 10.1016/S1575-0973(10)70013-1

Mallett, K. A., Marzell, M., Varvi-Weld, L., Turrisi, R., Guttman, K. & Abar, C. (2011). One-Time or Repeat Offenders? An Examination of the Patterns of Alcohol-Related Consequences Experienced by College Students Across the Freshman Year. *Addictive Behaviors, 36*, 508-511. doi: 10.1016/j.addbeh.2010.12.022

Martens, M. P., Ferrier, A. G., Sheehy, M. J., Corbett, K., Anderson, D. A. & Simmons, A. (2005). Development of the protective behavioral strategies survey. *Journal of Studies on Alcohol, 66*, 698–705.

Martin, J. L. (2011). *Examination of the interaction of drinking motives and personality on alcohol use and alcohol-related problems among college students.* (Order No. 3464655, State University of New York at Albany). ProQuest Dissertations and Theses, 157. Retrieved from http://search.proquest.com/docview/886751150?accountid=14777. (886751150).

Martin, C. S., Lynch, K. G., Pollock, N. K. & Clark, D. B. (2000). Gender differences and similarities in the personality correlates of adolescent alcohol problems. *Psychology of Addictive Behaviors, 14,* 121–133. doi: 10.1037/0893-164X.14.2.121

Meda, S. A., Stevens, M. C., Potenza, M. N., Pittman, B., Gueorguieva, R., Andrews, M. M., … Pearlson, G. D. (2009). Investigating the behavioral and self-report constructs of impulsivity domains using principal component analysis. *Behavioral Pharmacology, 20*, 390–399. doi: 10.1097/FBP.0b013e32833113a3

Mestre, H., Viñas, M., Dutil, V. & Moya, J. (2004). *Personalidad y consumo de alcohol en adolescentes.* PResented at the meeting Jornadas de fomento de la investigación de la Universitat Jaume I, Castellón de la Plana.

Mezquita, L., Stewart, H. S. & Ruipérez, M.A. (2010). Big-five personality domains predict internal drinking motives in Young adults. *Personality and Individual Differences, 49*, 240–245. doi: 10.1016/j.paid.2010.03.043

Ministerio de Sanidad y Consumo (2008). *Prevención de los problemas derivados del alcohol. 1ª Conferencia de prevención y promoción de la salud en la práctica clínica en España.* Madrid: Ministerio de Sanidad y Consumo.

Motos, P. (2013). *Determinantes del consumo intensivo de alcohol en jóvenes universitarios* (dissertation). Valencia: Universitat de València.

Muthen, B. & Muthen, L. (2000). The development of heavy drinking and alcohol-related problems from ages 18 to 37 in a U.S. national sample. *Journal of Studies on Alcohol, 61*, 290–300.

National Institute on Alcohol Abuse and Alcoholism (2004). Council approves definition of binge drinking. *NIAAA Newsletter, 3*(3).

Neighbors, C., Lee, C. M., Lewis, M. A., Fossos, N. & Larimer, M. E. (2007). Are Social Norms the Best Predictor of Outcomes Among Heavy-Drinking College Students? *Journal on Studies on Alcohol and Drugs, 68*, 556–565.

Neighbors, C., Walker, D. D. & Larimer, M. E. (2003). Expectancies and evaluations of alcohol effects among college students: Self-determination as a moderator. *Journal of Studies on Alcohol, 64*, 292–300.

Observatorio Español sobre Drogas del Plan Nacional Sobre Drogas (2012). *Encuesta Domiciliaria sobre Alcohol y Drogas en España, EDADES 2011-2012*. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved from http://www.pnsd.msssi.gob.es/Categoria2/observa/pdf/EDADES2011.pdf

Observatorio Español sobre Drogas del Plan Nacional Sobre Drogas (2013). *Encuesta Estatal sobre el Uso de Drogas en Enseñanzas Secundarias, ESTUDES 2012-2013, España.* Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad. Retrieved from http://www.pnsd.msssi.gob.es/Categoria2/observa/pdf/PresentESTUDES2012_2013.pdf

O'Leary-Barrett, M., Mackie, C. J., Castellanos-Ryan, N., Al-Khudhairy, N. & Conrod, P. J. (2010). Personality-targeted interventions delay uptake of drinking and decrease risk of alcohol-related problems when delivered by teachers. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*, 954-963. doi: 10.1016/j.jaac.2010.04.011

O'Malley, P. M. & Johnston, LL. D. (2002). Epidemiology of Alcohol and Other Drug Use among American College Students. *Journal of Studies on Alcohol, 14*, 23- 39.

Oquendo, P. A., Baca-García, E., Graver, R., Morales, M., Montalbán, V. & Mann, J. J. (2001). Spanish Adaptation of Barrat Impulsiveness Scale (BIS). *European Journal of Psychiatry, 15*, 147-155.

Parada, M., Corral, M., Caamaño-Isorna, F., Mota, N., Crego, A., Rodríguez, S. & Cadaveira, F. (2011). Definición del concepto de consumo intensivo de alcohol adolescente (binge drinking). *Adicciones, 23*, 53-63.

Park, C. L. (2004). Positive and negative consequences of alcohol consumption in college students. *Addictive Behaviors, 29*, 311–321. doi: 10.1016/j.addbeh.2003.08.006

Patton, J. H., Stanford, M. S. & Barratt, E. S. (1995). Factor structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology, 51*, 768–774. doi: 10.1002/1097-4679(199511)51: 6<768::AID-JCLP2270510607>3.0.CO;2-1

Pilatti, A., Caneto, F., Garimaldi, J. A., Del Valle, B. & Pautassi, R. M. (2013). Contribution of Time of Drinking Onset and Family History of Alcohol Problems in Alcohol and Drug Use Behaviors in Argentinean College Students. *Alcohol and Alcoholism, 49*, 128–137. doi: 10.1093/alcalc/agt176

Pitkänen, T., Lyyra, A. L. & Pulkkinen, L. (2005). Age of onset of drinking and the use of alcohol in adulthood: a follow-up study from age 8–42 for females and males. *Addiction, 100*, 652–61. doi:10.1111/j.1360-0443.2005.01053.x

Prado, V., Crespo, J. M., Brenlla, J. & Páramo, M. (2007). Relación entre consumo de alcohol y rasgos patológicos de personalidad en una muestra de alumnos universitarios. *Trastornos Adictivos*, 9, 126-131.

Quilty, L. C. & Oakman, J. M. (2004). The assessment of behavioral activation: The relationship between impulsivity and behavioral activation. *Personality and Individual Differences, 37*, 429–442. doi: http://dx.doi.org/10.1016/j.paid.2003.09.014

Ray, A. E., Turrisi, R., Abar, B. & Peters, K. E. (2009). Social-cognitive correlates of protective drinking behaviors and alcohol-related consequences in college students. *Addictive Behaviors, 34*, 911–917. doi: 10.1016/j.addbeh.2009.05.016

Read, J. P. & O'Connor, R. M. (2006). High-and low-dose expectancies as mediators of personality dimensions and alcohol involvement. *Journal of Studies on Alcohol and Drugs, 67*, 204-214.

Rodríguez-Martos, A., Gual, A. & Llopis, J. J. (1999). La unidad de bebida estándar como registro simplificado del consumo de bebidas alcohólicas y su determinación en España. *Medicina Clínica, 112*, 446-450.

Rossow, I. & Kuntsche, E. (2013). Early onset of drinking and risk of heavy drinking in young adulthood-a 13-year prospective study. *Alcoholism: Clinical and Experimental Research, 37*, E297–E304. doi: 10.1111/j.1530-0277.2012.01924.x

Ruipérez, M. A., Ibáñez, M. I., Villa, H. & Ortet, G. (2006). Factores biopsicosociales en el consumo de alcohol. En L.A. Oblitas (Ed.), *Atlas de psicología de la salud*. Bogotá: PSICOM editores.

Ruiz, M. A., Pincus, A. L. & Dickinson, K. A. (2003). NEO PI-R Predictors of Alcohol Use and Alcohol-Related Problems. *Journal of Personality Assessment, 81*, 226-236. doi: 10.1207/S15327752JPA8103_05

Sanz, J., Silva, F. & Avia, M. D. (1999). La evaluación de Personalidad desde el modelo de los "Cinco Grades": El Inventario de Cinco- Factores NEO (NEO-FFI) de Costa y McCrae. En F. Silva (Ed.), *Avances en Evaluación Psicológica* (pp. 171–234). Valencia: Promolibro.

Schuckit, M. A., Tipp, J. E., Bergman, M. & Reich,W. (1997). Comparison of induced and independent major depressive disorders in 2,945 alcoholics. *American Journal of Psychiatry, 154*, 948–957.

Schutte, K. K., Hearst, J. & Moos, R. H. (1997). Gender differences in the relations between depressive symptoms and drinking behavior among problem drinkers: a three-wave study. *Journal of consulting and clinical psychology, 65*, 392.

Sher, K. J., Grekin, E. R. & Williams, N. A. (2005). The development of alcohol use disorders. *Annual Review of Clinical Psychology, 1*, 493–523. doi: 10.1146/annurev.clinpsy.1.102803.144107

Sher, K. J., Trull, T. J., Bartholow, B. D. & Veith, A. (1999). Personality and alcoholism: Issues, methods, and etiological processes. En K. E. Leonard & H. T. Blane (Eds.), *Psychological theories of drinking and alcoholism* (2nd ed., pp. 54–105). New York: Guilford Press.

Shield, K. D., Gmel, G., Patra, J. & Rehm, J. (2012). Global burden of injuries attributable to alcohol consumption in 2004: a novel way of calculating the burden of injuries attributable to alcohol consumption. *Population Health Metrics, 9*, 1-14.

Simons, J. S., Carey, K. B. & Gaher, R. M. (2004). Lability and impulsivity synergistically increase risk for alcohol-related problems. *The American Journal of Drugs and Alcohol Abuse, 30,* 685-694. doi:10.1081/ADA-200032338

Simons, J. S., Gaher, R. M., Correia, C. J., Hansen, C. L. & Christopher, M. S. (2005). An affective-motivational model of marijuana and alcohol problems among college students. *Psychology of Addictive Behaviors, 19*, 326-334. doi: 10.1037/0893-164X.19.3.326

Stanford, M. S., Mathias, C. W., Dougherty, D. M., Lake, S. L., Anderson, N. E. & Patton, J. H. (2009). Fifty years of the Barratt impulsiveness scale: An update and review. *Personality and Individual Differences, 47*, 385–395. doi: 10.1016/j.paid.2009.04.008

Stewart, S. H., Loughlin, H. L. & Rhyno, E. (2001). Internal drinking motives mediate personality domain-drinking relations in young adults. *Personality and Individual Differences, 30*, 271–286. doi: 10.1016/S0191-8869(00)00044-1

Substance Abuse and Mental Health Services Administration (2010). *Town Hall Meeting. Mobilizing Communities to Prevent and Reduce Underage Alcohol Use.* Retrieved from http://store.samhsa.gov

Villalbí, J. R. & Gual, A. (2009). Las políticas preventivas del consumo de sustancias adictivas y la responsabilidad de los profesionales. *Adicciones, 21*, 5-8.

Waldeck, T. L. & Miller, L. S. (1997). Gender and impulsivity differences in licit substance use. *Journal of Substance Abuse, 9*, 269–275.

Warner, L. A. & White, H. R. (2003). Longitudinal effects of age at onset and first drinking situations on problem drinking. *Substance Use and Misuse, 38*, 1983–2016. doi: 10.1081/JA-120025123

Warner, L. A., White, H. R. & Johnson, V. L. (2007). Alcohol initiation experiences and family history of alcoholism as predictors of problem drinking trajectories. *Journal of Studies on Alcohol, 68*, 56–65.

Wechsler, H., Dowdall, G. W., Davenport, A. & Castillo, S. (1995). Correlates of student binge drinking. *American Journal of Public Health, 85*, 921-926. doi: 10.2105/AJPH.85.7.921

Wechsler, H. & Nelson, T. F. (2010). Will increasing alcohol availability by lowering the minimum legal drinking age decrease drinking and related consequences among youths? *American Journal of Public Health, 100*, 986-992. doi: 10.2105/AJPH.2009.178004

White, A. M., Kraus, C. L. & Swartwelder, H. S. (2006). Many College Freshman Drink at Levels Far Beyond the Binge Threshold. *Alcoholism: Clinical and Experimental Research, 30*, 1006-1010. doi: 10.1111/j.1530-0277.2006.00122.x

White, H. R., Marmorstein, N. R., Crews, F. T., Bates, M. E., Mun, E. Y. & Loeber, R. (2011). Associations between heavy episodic drinking and changes in impulsive behavior among adolescent boys. *Alcoholism: Clinical and Experimental Research, 35,* 295–303.

Whiteside, S. P. & Lynam, D. R. (2001). The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. *Personality and Individual Differences, 30*, 669–689. doi: 10.1016/S0191-8869(00)00064-7

Woicik, P. A., Stewart, S. H., Pihl, R. O. & Conrod, P. J. (2009). The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles. *Addictive Behaviors, 34*, 1042-1055. doi: 10.1016/j.addbeh.2009.07.001

World Health Organization (2007). *WHO Expert Committee on Problems Related to Alcohol Consumption. Second report.* Geneva (WHO Technical Report Series, No. 944).

Zuckerman, M. & Kuhlman, D. M. (2000). Personality and risk-taking: common biosocial factors. *Journal of Personality, 68*, 999–1029.

Epidemiology of Alcohol Abuse Among Spanish Immigrant Populations

Epidemiología del abuso de alcohol entre la población inmigrante en España

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Abstract

In recent years, the immigrant population has substantially increased in Spain. However, there is a lack of information in the knowledge of alcohol abuse among Spanish immigrants. We describe the epidemiology of alcohol abuse among foreign-born immigrants versus Spanish natives. We carried out a cross-sectional study that uses data from the European Survey of Health on the General Population of Spain of 2009. A sample of 22,188 subjects was analyzed (of whom, 3,162 were foreign). Proxies of problematic alcohol consumption were the prevalence of excessive average consumption and the prevalence of excessive episodic consumption (*binge drinking*). Descriptive analysis of the population, determination of area of origin with major alcohol consumption and related factors for each kind of consumption, separating immigrant and native population, were performed. The immigrant profile was heterogeneous, though predominantly aged between 35 and 54, and were living with their family and working. 3.4% of immigrants and 3.2% of natives were considered excessive drinkers; 8.9% and 10%, respectively, reported binge drinking in the last year. Immigrants from Northern and Western Europe, and Latin America, Andean countries had significantly a higher report of frequent alcohol consumption and/or binge drinking compared to native. On the contrary, born in Africa was a protective factor. Unemployment was the most relevant related factor, being more important in the immigrant population. The excessive alcohol consumption in immigrants is dissimilar; the interventions must be adapted to their social situation, environments and areas of origin.

Key words: Immigrant status; Alcohol abuse; Alcohol dependence; Excessive drinking.

Resumen

A pesar del gran incremento de la población inmigrante en los últimos años, su uso de alcohol está poco estudiado. Se describe la epidemiología del consumo de riesgo de alcohol en la población inmigrante residente en España, frente a la nativa. Se emplearon datos de 22188 respondentes a la Encuesta Europea de Salud de 2009, de los que 3162 eran extranjeros. Como indicadores de consumo problemático se usó la prevalencia de consumo excesivo promedio y el consumo excesivo episódico. Se realizaron análisis descriptivo de la población, determinación de zonas de procedencia con mayor consumo de alcohol y factores relacionados para cada tipo de consumo separando población inmigrante de autóctona. El perfil sociodemográfico del inmigrante fue heterogéneo, aunque predominantemente de entre 35 y 54 años, que vive en familia y trabaja. Se consideraron bebedores excesivos promedio al 3,4% de los inmigrantes por el 3,2% de los nativos, y bebedores excesivos episódicos en el último año el 8,9% frente al 10%. Los inmigrantes procedentes de Europa del Norte y del Oeste, y América latina, países andinos, fueron aquellos que presentaron mayores razones de prevalencia de bebedores de riesgo que la población nativa. Por el contrario, proceder de África fue un factor protector. De los factores relacionados con un mayor consumo, destaca el desempleo, siendo más relevante en la población inmigrante. El consumo excesivo de alcohol en inmigrantes es muy heterogéneo, debiendo adecuarse las intervenciones sobre el mismo a su situación social, diferentes entornos y áreas de procedencia.

Palabras clave: Inmigración, Uso de alcohol, Dependencia de alcohol, Consumo excesivo de alcohol.

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Alcohol consumption is one of the principal factors of risk of illness and early death worldwide (World Health Organization (WHO), 2014; Lim et al., 2012). It is related to the risk of dependency, hepatic cirrhosis, high accident rates and other major health problems (Anderson P, 2012). However, despite the enormous weight of illnesses associated with alcohol consumption, public health interventions to reduce its impact continue to be insufficient (WHO, 2014). Many consequences of problematic alcohol consumption depend on the patterns of quantity or volume, and on the frequency with which it occurs. Basically, two types of harmful alcohol consumption (HAC) are differentiated: high weekly excessive average consumption (EAC) (WHO, 2000), and excessive episodic consumption (EEC), known also in the literature as binge drinking, which implies heavy alcohol consumption over short periods (Valencia-Martin, Galan, and Rodriguez-Artalejo, 2007). Although both types of consumption have common consequences, such as hypertension, pancreatitis and hepatic pathology, EEC is more closely related to traffic accidents and episodes of violence (WHO, 2014). The factors that determine alcohol consumption are multiple; either individual, such as educational levels or genetic traits (Martínez-Hernáez, Mari-Klose, Julia, Escapa, and Mari-Klose, 2012), group or contextual. Among the latter, economic development, cultural level, the availability of alcohol or the effectiveness of social or health policies of each country are important (WHO, 2010; Babor et al., 2007; Rehm, Rehm, Shield, Gmel and Gual, 2013). These factors determine the differences in the level of consumption among population groups or nations (Anderson P, 2012). In this sense, the enormous geographic mobility between countries observed in recent years poses new social and health challenges. There are often inequalities in the level and the determining health factors between the country of origin of the immigrant and the host country. These differences have variable effects on the health of immigrants and natives (MacPherson and Gushulak, 2001). While it is often assumed that immigrants have a poorer level of health, the "healthy immigrant effect" is well documented: the recently-arrived who have mean levels of health that are higher than their peers in the country of origin or even better than that of their peers in the host country (De Maio, 2010). Nevertheless, this is not necessarily so for the most mutable factors that determine health such as alcohol use patterns (Gutmann, 1999). The epidemiology of alcohol consumption among immigrants in Spain has scarcely been studied despite the significant increase in this population. In recent years, the non-autochthonous population has quadrupled to the extent that they now represent 10% of the population resident in Spain (Permanent Immigration Observatory [OPI in its Spanish initials], 2006). Some studies indicate that immigrants have a lower prevalence of alcohol consumption than the native population (Carrasco-Garrido, de Miguel, Barrera, and Jimenez-Garcia, 2007). At the same time they point out that this is not homogeneous and that it depends on the country of origin (Marsiglia, Kulis, Luengo, Nieri, and Villar, 2008). Regarding their risk factors, studies carried out outside Spain show that they are heterogeneous. Immigrants acquire patterns of their country of origin, while at the same time their alcohol consumption may increase owing to processes of maladaptation, such as the process of acculturation or migratory stress, related to the new host country (Mills and Caetano, 2012; Zamboanga, Schwartz, Jarvis, and Van, 2009).

The objective of this study is to determine, separately for the autochthonous population and for immigrants in Spain, the prevalence of excessive average and episodic alcohol consumption, as well as socio-demographic factors associated with these indicators.

Method

Design, population and data collection

The data analyzed in this study come from the 2009 European Survey of Health, framed within the proposal of the European Commission to create a European system of health information. The survey has as an objective to provide information on the health of the population resident in Spain in a way that is harmonized and comparable with the rest of Europe, with the aim of planning and evaluating interventions in matters of health (National Statistics Institute (INE in its Spanish initials), 2009).

The survey was aimed at the overall group of persons resident in main family households throughout Spain. The participants were selected by means of a three-stage sampling with stratification of the units in the first stage. These were the census tracts that existed in January of 2008, whose selection was carried out by probability proportional to their size. The second-stage units were the main family households of the selected sections and were obtained from the Continuous Register Statistics. The selection of households was carried out by means of a systematic sampling with random start and equal selection probabilities for each household in the tract. Finally, within each household one adult person (over the age of 16) was selected (with the same probability) from those that comprised the household. To facilitate estimations with an acceptable degree of reliability at national and regional (that of autonomous communities) level, 1927 census tracts, and 12 households per tract, were selected. Data collection took place between April 2009 and March 2010 by means of computer assisted personal interviews (CAPI), except for the questions concerning "spending from your own pocket", and consumption of tobacco, alcohol and drugs, which were self-administered with the aim of preserving confidentiality and facilitating truthfulness in responses. The present study was carried out on all the participants in the survey with the exception of those whose country of origin and/or their alcohol consumption were unknown (n=22.188).

Variables and Definitions

Of the five sections on the questionnaire, for this study the modules concerning socio-demographic characteristics, state of health and factors determining the same were analyzed. Regarding variables of interest, an "immigrant" was considered to be a person whose country of origin (of birth) was not Spain. In view of the -heterogeneity of the countries of origin and the impossibility of carrying out a country-by-country analysis of the data, these were grouped into areas of origin following the classification used by the United Nations Organization (WHO, 2006): Europe (subdivided into North, South, East and West); Latin America (subdivided into the Southern Cone and the Andean Region); Central America, the Caribbean and Mexico; Africa; other countries and Spain. The dependent variables were: excessive average consumption, defined as the average consumption over the last 12 months >40g/day (men) or >20g/day (women) of pure alcohol, and excessive episodic consumption, defined as the consumption at least once in the last 12 months of six alcoholic drinks or more on the same occasion.

The independent variables analyzed were: gender, age (16-34, 35-54 and 55 or over), area of residence in Spain (South: Andalusia, Murcia, the Canary Islands, Ceuta and Melilla; East, Region of Valencia, Catalonia and the Balearic Islands; Centre, Madrid, Castilla-La Mancha and Extremadura; and North), size of the municipality of residence, domestic or familial situation (living alone, with a partner, with or without children, and others), educational level, employment situation, perceived state of health, self-referred bouts of anxiety or depression over the last 12 months, exposure to violence or vandalism, smoking and consuming cannabis, cocaine, amphetamines, ecstasy or similar substances over the last 12 months.

Analysis

Firstly, a descriptive analysis of the characteristics of the sample group, stratifying by area of origin, was carried out. The relationships between the different areas (including Spanish origin) and between foreign and autochthonous origin were analyzed by means of Chi-square test correlations (Table 1). Later, to evaluate the influence of the area of origin on the indicators of alcohol consumption (EAC and EEC), Poisson regression models with robust variance were adjusted, obtaining adjusted prevalence ratios (aPR) for each area of origin in relation to the autochthonous population and the corresponding confidence intervals at 95% (CI95%) (Spiegelman and Hertzmark, 2005). The adjustment variables that were introduced for each of the models (EAC and EEC) were those that showed $p<0.10$ in the bivariate analysis with the overall sample group. Finally, and separately for immigrants and autochthonous population, the factors related to each one of the indicators of alcohol consumption considered were identified, using once again Poisson regression models with robust variance and the aPR as a measure of effect. The independent variables included in each of the models were those that showed a $p<0.05$ in the previous bivariate analyses. In the regression models for samples of immigrants, additional adjustments were made by area of origin.

Results

Characteristics of the Sample

The immigrants who live in Spain, analyzed as a whole, are above all young people aged between 16 and 34, who reside in the east of Spain, in large urban areas, with their families, who work and have secondary-level studies; approximately half of them are women. Their state of health is good or very good, with a self-referred prevalence of depression in the last year that is lower than that of the autochthonous population (55.5% and 10.1% respectively) and are little exposed to violence. If we compare this profile with that of the autochthonous populations, what is highlighted is their low age (16.1% were over 55 as opposed to 36.1% of the autochthonous population) and a higher educational level (22.6% had studied at university level as opposed to 11.7% of the autochthonous population).

Stratifying by area of origin, more heterogeneous characteristics are observed, with the areas that are furthest away from the average profile described being: Northern Europe –where the population over 55 (53.4%), residency in smaller populations of fewer than 10,000 inhabitants and the inactive employment situation predominated- and Africa, where the immigrants with only primary studies predominated.

Disparities in alcohol consumption between natives and immigrants of different origins

The prevalence of excessive average consumption (EAC) of alcohol among immigrants and natives was of 3.4% and 3.2% respectively while the prevalence of excessive episodic consumption (EEC) was of 8.9% among immigrants as opposed to 10.0% among natives. The differences in these prevalences according to the area of origin were notable, with the first varying between 7.0% for Northern Europe and 0.5% for Africa (in fact only two people from this area indicated EEC), and the second between 15.0% and 2.7% for the same areas of origin (Table 1). Adjusting for the confounding factors identified in the bivariate analysis, immigrants from Northern and Eastern Europe were those who presented a greater risk of EEC than the autochthonous population (aPR=0.16%; CI95% 0.04-0.67). regarding EAC, the areas of origin with a risk that was significantly greater than that of the natives were Northern Europe (aPR1.81 CI95% 1.25-2.62); and those with a significantly lower risk were from Africa (aPR=0.20 CI95% 0.11-0.37) and Eastern Europe (aPR=0,74 CI95% 0.58-0.96) (Tabla 2).

Table 1. *Socio-demographic characteristics and prevalence of risky alcohol consumption of the whole population by country of origin*

	Area of origin													
	Eastern Europe[1] (n=524)	**Northern Europe[2] (n=220)**	**Southern Europe[3] (n=126)**	**Western Europe[4] (n=243)**	**Latin America Southern Cone[5] (n=383)**	**Latin America Andean Region[6] (n=854)**	**Central America, Caribbean and Mexico[7] (n=184)**	**Africa[8] (n=475)**	**Other countries[9] (n=153)**	**Spain (n=19025)**	**Abroad (n=3162)**	**Total (n=22188)**	**p-value* between areas****	**p-value* Spain Vs. Abroad**
Male	47,1%	51,8%	67,2%	44,9%	50,4%	42,2%	31,0%	56,9%	54,2%	49,2%	49,5%	49,0%	<0,001	0,117
Age														
16-34 years	56,5%	19,5%	35,7%	25,1%	59,3%	54,6%	40,2%	59,4%	52,9%	27,8%	44,8%	31,0%		
35-54 years	39,3%	27,1%	42,1%	49,4%	35,2%	40,6%	46,2%	34,9%	36,6%	36,1%	39,1%	36,5%		
55 and over	4,2%	53,4%	22,2%	25,5%	5,5%	4,8%	13,6%	5,7%	10,5%	36,1%	16,1%	32,6%	<0,001	<0,001
Area of residence in Spain														
South of Spain[I]	16,0%	41,6%	22,2%	22,6%	20,4%	18,7%	23,2%	32,6%	22,2%	25,4%	24,4%	25,1%		
East of Spain[II]	34,4%	52,1%	35,7%	51,9%	46,5%	34,4%	28,6%	39,8%	48,4%	27,6%	41,3%	29,3%		
North of Spain[III]	17,9%	2,3%	23,8%	11,1%	13,1%	13,8%	21,1%	14,1%	14,4%	27,0%	14,6%	25,2%		
Centre of Spain[IV]	31,7%	4,1%	18,3%	14,4%	20,1%	33,1%	27,0%	13,5%	15,0%	20,0%	19,7%	20,4%	<0,001	<0,001
Size of town/city of residence														
<10 000 inhabitants	18,3%	34,8%	19,0%	18,1%	6,3%	6,6%	6,0%	18,1%	3,9%	21,7%	14,6%	20,5%		
10 000 - 50 000 inhabitants	30,2%	30,3%	39,7%	34,2%	32,1%	23,8%	27,7%	27,1%	26,8%	25,6%	30,2%	26,0%		
>50 000 inhabitants	51,5%	34,8%	41,3%	47,7%	61,6%	69,7%	66,3%	54,8%	69,3%	52,7%	55,2%	53,5%	<0,001	<0,001
Living situation														
Alone	6,9%	16,4%	16,7%	16,0%	7,3%	4,7%	8,2%	7,1%	7,8%	9,0%	10,1%	8,9%		
With partner and/or children	66,9%	78,6%	67,5%	73,3%	64,2%	63,9%	66,8%	62,2%	54,9%	79,2%	66,5%	77,3%		
Other	26,3%	5,0%	15,9%	10,7%	28,5%	31,5%	25,0%	30,7%	37,3%	11,7%	23,4%	13,7%	<0,001	<0,001
Educational level														
Primary studies or lower	17,6%	9,5%	32,0%	11,2%	14,4%	18,2%	17,4%	50,8%	24,8%	39,2%	21,8%	36,8%		
Secondary	67,4%	55,0%	50,8%	53,9%	65,4%	65,7%	60,3%	43,0%	39,2%	44,1%	55,7%	46,2%		
University studies	15,1%	35,5%	17,2%	34,9%	20,2%	16,0%	22,3%	6,1%	35,9%	16,7%	22,6%	17,0%	<0,001	<0,001
Employment situation														
Employed	60,5%	36,7%	54,4%	50,8%	60,0%	60,7%	52,2%	42,3%	68,0%	46,5%	54,0%	47,7%		
Unemployed	22,1%	10,4%	17,6%	14,9%	18,9%	22,0%	26,6%	30,2%	21,3%	11,6%	20,5%	13,0%		
Other[β]	17,4%	52,9%	28,0%	34,3%	21,1%	17,3%	21,2%	27,4%	10,7%	41,9%	25,6%	39,3%	<0,001	<0,001
Excessive Average Consumption[a]	4,8%	7,0%	1,7%	6,9%	1,7%	3,4%	4,5%	0,5%	0,0%	3,2%	3,4%	3,2%	<0,001	0,362
Excessive Episodic Consumption[b]	10,4%	15,0%	5,0%	11,7%	11,8%	13,3%	7,8%	2,7%	2,1%	10,0%	9,9%	10,0%	<0,001	0,478
Perceived state of health[α]														
Good or very good	76,0%	86,8%	78,6%	79,0%	83,3%	79,6%	78,9%	85,5%	81,7%	69,2%	81,0%	70,9%		
Regular, poor or very poor	24,0%	13,2%	21,4%	21,0%	16,7%	20,4%	21,1%	14,5%	18,3%	30,8%	19,0%	29,1%	<0,001	<0,001
Bouts of Anxiety or Depression[α]	4,2%	0,9%	8,7%	3,7%	7,6%	7,1%	8,2%	4,2%	3,3%	10,1%	5,3%	9,4%	<0,001	<0,001
Exposure to delinquency, violence or vandalism[α]														
Very exposed	2,9%	2,7%	4,0%	1,3%	2,9%	7,0%	4,3%	3,8%	5,9%	3,5%	3,9%	3,6%		
Somewhat exposed	12,5%	17,3%	19,8%	15,8%	12,3%	13,4%	16,2%	11,3%	14,4%	14,8%	14,8%	14,6%		
Not exposed	84,7%	80,0%	76,2%	82,9%	84,9%	79,6%	79,5%	84,8%	79,7%	81,7%	81,4%	81,8%	<0,001	0,032
Smokes every day	52,4%	18,0%	40,8%	34,2%	27,1%	12,0%	19,2%	18,4%	14,8%	26,3%	26,3%	25,3%	<0,001	0,144
Consumption of cannabis, cocaine, amphetamines, ecstasy o similar[α]														
Yes	3,0%	9,4%	21,4%	8,9%	9,0%	4,1%	1,1%	5,1%	4,4%	5,4%	7,4%	5,4%		
No	97,0%	90,6%	78,6%	91,1%	91,0%	95,9%	98,9%	94,9%	95,6%	94,6%	92,6%	94,6%	←0,001	0,031

* Note. For Chi-square tests; **Spain was analyzed as an area; α In the last 12 months; β Students or persons in training with unpaid internship, retired, declared .unfit for work, homemakers and others
. a male drinker of >40g/day or female drinker of >20g/day of Alcohol; b Has drunk 6 or more alcoholic drinks on the same occasion at least once in the last 12 months.
1 Czec Rep, Bulgaria, Hungary, Poland, Rumania, Rep. of Moldavia, Russian Federation, Ukraine; 2 Denmark, Finland, Iceland, Lithuania, Norway, Sweden, United Kingdom of Great Britain and Northern Ireland, Isle of Man; 3 Andorra, Bosnia-Herzegovina, Croatia, Greece, Italy, Portugal, Serbia and Montenegro, Slovenia; 4 Belgium, France, Germany, Switzerland; 5 Argentina, Brazil, Chile, Uruguay, Paraguay; 6 Colombia, Ecuador, Peru, Venezuela; 7 Belize, Costa Rica, Cuba, Dominica, Guatemala, Honduras, Martinique, Mexico, Nicaragua, Panama, Puerto Rico, Dominican Republic, Trinidad and Tobago; 8 South Africa, Algeria, Burkina Faso, Burundi, Cameroon, Cabo Verde, Ivory Coast, Egypt, Gabon, Gambia, Ghana, Guinea, Equatorial Guinea, Guinea-Bissau, Mauritania, Mali, Morocco, Mozambique, Nigeria, Senegal, Western Sahara, Tunisia; 9 Afghanistan, Armenia, Bangladesh, Belarus, Canada, China, United States of America, The Philippines, Georgia, India, Iran, Iraq, Israel, Japan, Jordan, Pakistan, Republic of Korea, Syria, Sri Lanka, Uzbekistan.
I Andalusia, Murcia, Canarias, Ceuta-Melilla; II Valencia, Baleares, Cataluña; III Aragón, Rioja, Navarra, País Vasco, Cantabria, Asturias, Galicia, Castilla-León; IV Madrid, Castilla-La Mancha, Extremadura.

Table 2.
Disparity in prevalences of excessive alcohol consumption (average and episodic) between native Spaniards and immigrants of different origins

	Excessive average drinker							Excessive episodic drinker						
	N	%	cPR	aPR[1,2]	95%	CI	p-value	N	%	cPR	aPR[1]	95%	CI	p-value
Area of Country of Origin														
Spain	566	3,1	1	1				1814	10,0	1	1			
Eastern Europe	23	4,8	1,33	1,02	0,65	1,59	0,934	52	10,4	1,00	0,74*	0,58	0,96	0,021
Northern Europe	13	7	2,14**	2,28**	1,29	4,05	0,005	31	15,0	1,30	1,81**	1,25	2,62	0,002
Southern Europe	2	1,7	0,53	0,27	0,06	1,11	0,069	6	5,0	0,51	0,15**	0,05	0,46	0,001
Western Europe	15	6,9	2,16**	2,12**	1,29	3,49	0,003	26	11,7	1,17	1,10	0,78	1,55	0,576
Latin America Southern Cone	6	1,7	0,6	0,55	0,26	1,16	0,115	44	11,8	1,22	0,87	0,67	1,12	0,279
Latin America Andean Region	27	3,4	1,1	1,36	0,93	1,99	0,113	110	13,3	1,32**	1,24*	1,03	1,50	0,020
Mexico, Central America and Caribbean	8	4,5	1,37	1,77	0,90	3,48	0,101	14	7,8	0,82	1,04	0,64	1,70	0,865
Africa	2	0,5	0,16	0,16	0,04	0,67	0,012	11	2,7	0,25**	0,20**	0,11	0,37	0,000
Other countries	0	0		N.A			N.A	3	2,1	0,21**	0,20**	0,07	0,61	0,005

Note. cPR: Crude Prevalence Ratio; aPR: Adjusted Prevalence Ratio. 95% CI: Confidence Interval at 95%. * p>0,05, **p<0,01 N.A: Non-applicable
Analysis adjusted by: (1) Gender, Age, Area of Residence, Size of Municipality, Domestic/Family Situation, Educational Level, Employment Situation, Perceived State of Health, Anxiety or Depression, Smokes daily and has consumed other substances in the last year. (2): Exposure to vandalism or delinquency.

Factors associated with alcohol consumption in natives and immigrants

Several factors are associated with a greater prevalence of EAC in both natives and immigrants: being under the age of 34 and taking illegal drugs. A greater exposure to violence, living in the Centre of Spain and being unemployed are associated with a greater prevalence in the immigrant population but not so in the native population (Table 3).

Regarding EEC, four factors related to a greater prevalence of the same were identified in both populations: being a man, being below the age of 35, smoking every day and taking other drugs. In addition, solely in the immigrant population were these factors identified as being related to a greater prevalence: living in urban areas with more than 50,000 inhabitants as opposed to those of fewer than 10,000, being unemployed, enjoying good health, living alone and being exposed to vandalism (Table 4).

Discussion

The prevalence of excessive average alcohol consumption is greater among the native population, while that of excessive episodic consumption is greater among the immigrant population, even though neither of these differences are significant. There are, however, great disparities within the immigrant population if the area of origin is looked at in detail. Then it can be observed that the immigrants from European countries, especially those from Western and Northern Europe, show prevalences that are greater than those of the autochthonous population while the prevalences of those coming from Africa are lower. These disparities, which coincide with the findings of other studies (Adrian, 1996; Conde and Herranz, 2004), persist after adjusting for other possible confounding factors, for which reason they would not be attributable simply to different socio-demographic patterns.

This heterogeneity in consumption in the so-called "immigrant population" is one of the principal messages of this study. The arrival of immigrants to Spain, which has occurred in a way that could hardly be described as staggered, has given rise to an image of a "collective" with very few differences within it. This does not correspond to reality and does not help when it comes to setting up social intervention programs that are adjusted to the different subgroups (Conde and Herranz, 2004). The profiles of these persons vary greatly from one to another area of origin. From the profile of the older person, possibly already retired, essentially originating from European countries, with a good socio-economic level that predominates in Spain's coastal regions to the profile of the young, male immigrant who has come from a developing country and who belongs to what has been called the category of "economic immigrant" (OPI, 2006). It is highly possible that these profiles have a correlation with alcohol consumption, for which reason it would be necessary to confirm this by means of studies designed ad hoc to adjust policies to the needs of the most vulnerable groups.

This study also focused on the factors related to the patterns of consumption studied. Highlighted globally is the scarce coincidence between the factors associated with EAC between immigrants and natives, while the number of common factors that are associated with EEC is much greater between the two populations. The greater vulnerability of the over-35s for each patterns is clear, both among immigrants and among natives. This is the age at which alcohol consumption has most risen, especially in the form of EEC (Donath et al., 2011; Valencia-Martin et al., 2007). For that reason this study does nothing more than emphasize the need to prioritize interventions aimed at young people, whatever their origin. As well as this, there are other specific aspects that contribute to the vulnerability of the immigrant population in relation to the consumption of alcohol, and that

Table 3.
Factors associated with excessive average alcohol consumption between immigrants and natives

	Immigrants					Natives				
	n	%	cPR	aPR	CI95%	n	%	cPR	aPR	CI95%
Gender										
Man	43	3,2	1			355	4,1	1		
Woman	54	3,5	1,2	1,1	0,7-1,7	211	2,3	0,6*	0,8*	0,7-1
Age										
16-34	57	3,9	1			210	4,2	1		
35-54	28	2,5	0,6*	0,5*	0,3-0,9	226	3,5	0,8*	0,8	0,6-1,1
55 and over	12	3,8	0,9	0,9	0,5-1,6	131	2,1	0,4*	0,7*	0,5-1
Area of residence in Spain										
South[I]	17	2,5	1			160	3,5	1		
East[II]	36	3,2	1,4	1,3	0,7-2,4	75	1,6	0,4*	0,4*	0,3-0,6
North[III]	13	3,0	1,3	1,7	0,9-3,8	184	3,8	1,1	1,1	0,8-1,3
Centre[IV]	30	4,7	1,9*	2*	1,1-3,9	147	4,2	1	1,0	0,8-1,3
Size of town/city of residence										
<10 000 inhabitants	14	3,6	1			148	3,8	1		
10 000 - 50 000 inhabitants	23	2,7	0,7			121	2,7	0,7*	0,8	0,6-1,0
>50 000 inhabitants	60	3,6	1,0			297	3,2	0,9	0,8	0,6-1,0
Living Situation										
Alone	15	6,2	1			61	3,8	1		
Other forms of co-habitation	28	3,7	0,6	0,6	0,3-1,1	80	4,2	1,1	1,0	0,7-1,4
With partner and/or children	54	2,9	0,5*	0,8	0,4-1,6	426	3,0	0,8*	0,8*	0,6-1
Educational level										
Primary studies or lower	10	1,6	1			172	2,6	1		
Secondary (including baccalaureate and professional studies)	64	3,7	2,2*	1,4	0,7-2,7	290	3,7	1,5*	1,2	1-1,5
University studies	23	4,2	2,5*	1,5	0,7-3,1	104	3,5	1,5*	1,4*	1-1,8
Employment situation										
Employed	48	3,0	1			319	3,8	1		
Unemployed	37	6,0	2*	2,2*	1,5-3,3	106	5,1	1,3*	1,1	0,9-1,4
Others[β]	12	1,9	0,7	0,4*	0,2-0,8	137	1,9	0,5*	0,7*	0,6-0,9
Perceived state of health[α]										
Good or very good	84	3,6	1			443	3,6	1		
Regular, poor or very poor	12	2,2	0,6			123	2,4	0,7*	0,9	0,7-1,1
Bouts of anxiety or depression[α]										
Si	3	2,0	1			24	1,4	1		
No	93	3,4	1,7			543	3,4	2,4*	1,9*	1,3-3,0
Exposure to delinquency, violence or vandalism[α]										
A lot	9	7,8	1			23	3,8	1		
Some	11	2,9	0,3*	0,4*	0,2-0,5	100	3,9	0,8	0,8	0,5-1,3
None	75	3,2	0,4*	0,5	0,2-1,1	443	3,1	0,7*	0,8	0,5-1,2
Smokes daily										
No	63	2,9	1			226	1,7	1		
Yes	33	5	1,4			340	7	5*	3,1*	2,6-3,8
Consumption of cannabis, cocaine, amphetamines, ecstasy or similar[α]										
No	81	3,0	1			409	2,5	1		
Yes	15	9,4	2,94*	2,1*	1,5-3,3	150	15,7	9,3*	4,2*	3,3-5,2

Note. cPR: Crude Prevalence Ratio; aPR: Adjusted Prevalence Ratio; * $p<0,05$; α In the last 12 months; β Students or persons in training with unpaid internship, pensioners or retired, unfit for work, homemakers and others. I Andalucía, Murcia, Canarias, Ceuta-Melilla; II Valencia, Baleares, Cataluña; III Aragón, Rioja, Navarra, País Vasco, Cantabria, Asturias, Galicia, Castilla-León; IV Madrid, Castilla-La Mancha, Extremadura.

have to be borne in mind: 1) As has been seen in other studies (Spanish Ministry of Health, Social Services and Equality), immigrants living in the Centre of Spain constitute a target group for messages aimed at the prevention of EAC. 2) Among immigrants, unemployment is associated to heavier consumption, although the strength of association is greater in EAC. The most important reason for emigrating is usually to work (Skarlund, Ahs, and Westerling, 2012), and the impact of being employed, or not, seems to influence notably on the alcohol consumption of this population, as has already been indicated (So and Wong, 2006). The relationship between deteriorating health, alcohol consumption and unemployment is multidirectional. Each one of these factors may be a cause or a consequence of the others (Skarlund et al., 2012). And if this occurs in any population, it is particularly important in that of immigrants, whose employment situation and support networks are usually more unstable (Gutmann, 1999). 3) Among the non-natives, exposure to violence is associated with a heavier alcohol consumption both in EAC and in EEC. It is appropriate to ask once again whether this factor is a cause or an effect, but it could give rise to an interpretation of greater vulnerability. 4) The prevalence of EEC is greater among immigrants who live in large cities. It is possible that this is because it is in them that immigrants find environments with more people of the same origin as them, which would increase their social network and, as a consequence, their EEC. In any case, it does lead to reflect on whether the leisure options that are available in Spain may not meet the demands of the immigrant population.

Table 4.
Factors associated with excessive episodic alcohol consumption between immigrants and natives

	Immigrants					Natives				
	n	%	cPR	aPR	CI95%	n	%	cPR	aPR	CI95%
Gender										
Man	194	13,7	1			1405	15,7	1		
Woman	102	6,5	0,4*	0,5*	0,4-0,6	408	4,4	0,2*	0,3*	0,3-0,4
Edad										
16-34	176	11,8	1			957	18,0	1		
35-54	106	9,1	0,8*	0,8*	0,6-0,9	684	10,2	0,5*	0,7*	0,6-0,8
55 and over	15	4,6	0,4*	0,3*	0,2-0,6	173	2,7	0,1*	0,3*	0,2-0,3
Area of residence in Spain										
South[I]	66	9,4	1			462	10,0	1		
East[II]	107	9,1	0,9	1,0	0,8-1,6	339	6,8	0,7*	0,7*	0,6-0,8
North[III]	37	8,4	0,9	0,9	0,7-1,5	528	10,8	1,1	1,2*	1-1,3
Centre[IV]	87	13,0	1,4*	1,1	0,8-1,6	485	13,5	1,4*	1,3*	1,1-1,5
Size of town/city of residence										
<10 000 inhabitants	24	6,1	1			398	10,1	1		
10 000 - 50 000 inhabitants	78	9,0	1,4	1,3	0,8-2,1	430	9,3	0,9		
>50 000 inhabitants	195	11,3	1,8*	1,6*	1,1-2,5	986	10,3	1,0		
Living Situation										
Alone	35	13,8	1			143	8,7	1		
Other forms of co-habitation	92	11,9	0,9	0,9	0,6-1,3	1464	10,1	1,2*	0,9	0,8-1,1
With partner and/or children	169	8,6	0,7*	0,7*	0,5-0,9	207	10,5	1,2*	1,0	0,8-1,3
Educational level										
Primary studies or lower	34	5,4	1			369	5,4	1		
Secondary (including baccalaureate and professional studies)	206	11,6	2,2*	1,4	0,9-2	1045	12,7	2,4*	1,4*	1,2-1,6
University studies	54	9,6	1,8*	1,3	0,8-2	400	12,8	2,5*	1,8*	1,5-2,0
Employment situation										
Employed	153	9,2	1			1099	12,7	1		
Unemployed	88	14,0	1,5*	1,4*	1,1-1,8	302	14,0	1,1	1,0	0,8-1,1
Others[β]	54	8,0	0,8	1,1	0,8-1,7	400	5,5	0,4*	0,9	0,8-1,1
Perceived state of health[α]										
Good or very good	252	10,4	1			1535	11,9	1		
Regular, poor or very poor	44	7,7	0,6*	0,7*	0,5-0,9	279	5,3	0,4*	0,9	0,8-1
Bouts of anxiety or depression[α]										
Yes	10	6,4	1			72	4,1	1		
No	286	10,1	1,6			1742	10,6	2,8*	1,4*	1,1-1,9
Exposure to delinquency, violence or vandalism[α]										
A lot	21	17,6	1			52	8,4	1		
Some	41	10,1	0,5*	0,6	0,3-1	301	11,2	1,2		
None	233	9,5	0,5*	0,6*	0,3-0,9	1461	9,9	1,3		
Smokes daily										
Yes	121	16,1	1			865	18,2			
No	176	7,9	0,5*	0,5*	0,4-0,7	944	7,1	0,4*	0,6*	0,5-0,7
Consumption of cannabis, cocaine, amphetamines, ecstasy or similar[α]										
No	249	9,1	1			1360	8,1	1		
Yes	45	26,2	2,9*	2*	1,4-2,7	432	42,6	5,1*	2,4*	2,1-2,7

Note. cPR: Crude Prevalence Ratio; aPR: Adjusted Prevalence Ratio; * p<0,05; α In the last 12 months; β Students or persons in training with unpaid internship, pensioners or retired, unfit for work, homemakers and others. I Andalucia, Murcia, Canarias, Ceuta-Melilla; II Valencia, Baleares, Cataluña; III Aragón, Rioja, Navarra, País Vasco, Cantabria, Asturias, Galicia, Castilla-León; IV Madrid, Castilla-La Mancha, Extremadura.

Immigrants have different behavior patterns, values and perceptions regarding the consumption of drugs which are related to those prevailing in their countries of origin (Daniel Ulloa et al., 2014). The migratory process brings up new situations and opportunities (Alaniz, 2002). The consumption of substances is not extraneous to the process of acculturation or adaptation to the culture of the host country (Zemore, 2007). And in this process both the culture of the country of origin and that of the host country, in this case, Spain, play a role. In this sense, it would be useful to make, as has been done in other countries (Delva et al., 2005; Susmann, 2005) interventions that find a balance between the positive reinforcement of safety measures "of origin" and the identification of those processes and situations that may increase the risk of excessive alcohol consumption. As well as this, alcohol consumption cannot be analyzed in isolation. It bears a close relationship with the general processes of integration. So much so that some authors analyze it in a wider context and as a symptom or indicator of integration processes. (Conde and Harranz, 2004). Research into this population must stay up to date. The massive arrival of immigrants to Spain has slowed down in recent years, but the majority of those who came, did so with the intention of staying (INE, 2013).

One limitation of this study is that its cross-sectional design does not allow for the direction of association to be known nor to establish causality. Regarding the variable of origin, we do not know how long it has been since they arrived in Spain. There have been descriptions of how the patterns of alcohol consumption among the immigrant po-

pulation approach those of the autochthonous population as the years pass living in the host country (De La Rosa et al., 2012). This is a variable that is not contemplated in the survey and which should be borne in mind for any future studies. Nevertheless, the great majority of the immigrants who were in Spain in 2010, the end date of this survey, had arrived in the country in the years immediately preceding this date (INE, 2013), which may mean that the results were not so different. In this sense, some studies similar to this one carried out in other environments found no differences according to the length of time spent in the host country (Szaflarski, Cubbins, and Ying, 2011). Another limitation was the impossibility of giving the results according to the countries of origin and not just the areas. Despite the large sample, this is insufficient for a "country-by-country" analysis. It would be recommendable for the areas highlighted as those of greater alcohol consumption (Northern and Western Europe, and Latin America in terms of excessive episodic consumption) to be subject to more detailed research so as not to fall into the trap of dealing with these populations as "collectives". Even employing this variable according to areas and not countries, some contribute such a small sample that the relative results have to be interpreted with great caution.

Another shortfall is in the gathering of other variables regarding substance use. They are not profound and did not allow for more thorough analyses than those presented to determine their relationship with alcohol consumption (though this was well collected, and detailed). This is one of the problems derived from this type of wide population surveys which, on the other hand, give us an enormous sample size. Finally, homeless people were not included owing to the data collection strategy. This is a population that, where alcohol consumption is concerned, could be especially relevant.

Beyond the limitations, the current study provides a first approximation to the epidemiology of alcohol abuse among the immigrant population living in Spain, at the same time as identifying subgroups among which it might be advisable to carry out specific interventions. In order to plan possible preventive strategies in the present and the future. The increase in immigrant population in Spain demands an integral approach to their health problems and, in this context, alcohol abuse is a priority.

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Conflict of interests

The authors declare that no potential conflict of interests exists with the publication of this article.

References

Adrian, M. (1996). Substance use and multiculturalism. *Substance Use & Misuse, 31, 1459-1501.*

Alaniz, M. L. (2002). Migration, acculturation, displacement: migratory workers and "substance abuse". *Substance Use & Misuse, 37, 1253-1257.*

Anderson P, M. (2012). Alcohol in the European Union. Consumption, harm and policy approaches. *World Health Organization. Regional Office for Europe.*

Babor, T. F., McRee, B. G., Kassebaum, P. A., Grimaldi, P. L., Ahmed, K. & Bray, J. (2007). Screening, Brief Intervention, and Referral to Treatment (SBIRT): toward a public health approach to the management of substance abuse. *Substance Abuse, 28, 7-30.*

Carrasco-Garrido, P., de Miguel, A. G., Barrera, V. H. & Jimenez-Garcia, R. (2007). Health profiles, lifestyles and use of health resources by the immigrant population resident in Spain. *European Journal of Public Health, 17, 503-507.*

Conde, F. & Herranz, D. (2004). Los procesos de integración de los inmigrantes. Pautas de consumo de alcohol y modelos culturales de referencia. Madrid: *Fundación CREFAT.*

Daniel-Ulloa, J., Reboussin, B. A., Gilbert, P. A., Mann, L., Alonzo, J., Downs, M. & Rhodes, S.D. (2014). Predictors of heavy episodic drinking and weekly drunkenness among immigrant latinos in North Carolina. *American Journal of Men´s Health, 8, 339-348.*

De La Rosa, M., Sanchez, M., Dillon, F. R., Ruffin, B. A., Blackson, T. & Schwartz, S. (2012). Alcohol use among Latinos: a comparison of pre-immigration, post-immigration, and US born Latinos. *Journal of Immigrant and Minority Health, 14,* 371-378.

De Maio, F. G. (2010). Immigration as pathogenic: a systematic review of the health of immigrants to Canada. *International Journal for Equity in Health, 9,* 27.

Delva, J., Wallace, J. M., Jr., O'Malley, P. M., Bachman, J. G., Johnston, L. D. & Schulenberg, J. E. (2005). The epidemiology of alcohol, marijuana, and cocaine use among Mexican American, Puerto Rican, Cuban American, and other Latin American eighth-grade students in the United States: 1991-2002. *American Journal of Public Health, 95, 696-702.*

Donath, C., Grassel, E., Baier, D., Pfeiffer, C., Karagulle, D., Bleich, S. & Hillemacher, T. (2011). Alcohol consump-

tion and binge drinking in adolescents: comparison of different migration backgrounds and rural vs. urban residence: a representative study. *BMC Public Health, 11, 84.*

Gutmann, M. C. (1999). Ethnicity, alcohol, and acculturation. *Social Science & Medicine, 48, 173-184.*

Instituto Nacional de Estadística (INE). (2009). Encuesta Europea de Salud en España EES-2009. Metodología.

Madrid: *Ministerio de Sanidad, Política Social e Igualdad.*

Instituto Nacional de Estadística (INE). (2013). *Cifras de Población y Estadística de Migraciones.* Madrid: Ministerio de Sanidad, Política Social e Igualdad.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H. … Ezzati, M. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380, 2224-2260.*

MacPherson, D. W. & Gushulak, B. D. (2001). Human mobility and population health. New approaches in a globalizing world. *Perspectives in Biology and Medicine, 44,390-401.*

Marsiglia, F. F., Kulis, S., Luengo, M. A., Nieri, T. & Villar, P. (2008). Immigrant advantage? Substance use among Latin American immigrant and native-born youth in Spain. *Ethnicity and Health, 13, 149-170.*

Martinez-Hernaez, A., Mari-Klose, M., Julia, A., Escapa, S. & Mari-Klose, P. (2012). Heavy episodic drinking among adolescents: the association with negative mood states and family factors. *Revista Española de Salud Pública, 86,101-114.*

Mills, B. A. & Caetano, R. (2012). Decomposing associations between acculturation and drinking in Mexican

Americans. *Alcoholism Clinical and Experimental Research,36,1205-1211.*

Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI) (2013). *Serie Informes monográficos nº 1. Consumo de alcohol.* Madrid: MSSSI. Observatorio permanente de la inmigración. (2006). *Extranjeros con tarjeta o autorización de residencia en vigor a 31de marzo de 2006.* Madrid: Ministerio de trabajo y asuntos sociales.

Rehm, J., Rehm, M. X., Shield, K. D., Gmel, G. & Gual, A. (2013). *Consumo de alcohol, dependencia alcohólica, trastornos relacionados con el alcohol en España. Impacto de los tratamientos de la dependencia alcohólica. Adicciones, 25, 11-18.*

Skarlund, M., Ahs, A. & Westerling, R. (2012). Health-related and social factors predicting non-reemployment

amongst newly unemployed. *BMC Public Health, 12, 893.*

Schmidt, L.A, Mäkelä, P, Rehm, J, Room, R. Alcohol: equity and social determinants. In: Blass E, Kurup, A.S,

editors. Equity, social determinants and public health programmes. (2010). Geneva: *World Health Organization.*

So, D. W. & Wong, F. Y. (2006). Alcohol, drugs, and substance use among Asian-American college students. *Journal of Psychoactive Drugs, 38, 35-42.*

Spiegelman, D. & Hertzmark, E. (2005). Easy SAS calculations for risk or prevalence ratios and differences. *American Journal of Epidemiology, 162, 199-200.*

Sussman, S. (2005).Prevention of adolescent alcohol problems in special populations. *Recent Developments in Alcoholism, 17, 225-253.*

Szaflarski, M., Cubbins, L. A. & Ying, J. (2011). Epidemiology of alcohol abuse among US immigrant populations. *Journal of Immigrant and Minority Health, 13,* 647-658.

Valencia-Martin, J. L., Galan, I. y Rodriguez-Artalejo, F. (2007). Binge drinking in Madrid, Spain. *Alcoholism Clinical and Experimental Research, 31, 1723-1730.*

World Health Organization (WHO). (2000). *International Guide for Monitoring Alcohol Consumption and Related Harm.* Geneva: WHO.

World Health Organization (WHO). (2006). International Standard ISO 3166-1, Codes for the representation of

names of countries and their subdivisions–Part 1: Country codes, ISO 3166-1: 2006. International Organization

on Standardization. Geneva: WHO.

World Health Organization (WHO). (2014). *The global status report on alcohol and health 2014.* Geneva: WHO.

Zamboanga, B. L., Schwartz, S. J., Jarvis, L. H., & Van, T. K. (2009). Acculturation and substance use among Hispanic early adolescents: investigating the mediating roles of acculturative stress and self-esteem. *The Journal of Primary Prevention, 30,315-333.*

Zemore, S. E. (2007). Acculturation and alcohol among Latino adults in the United States: a comprehensive

review. *Alcoholism Clinical and Experimental Research, 31,* 1968-1990.

Hepatitis C associated with substance abuse: ever closer to a treatment without Interferon

Hepatitis C asociada al abuso de sustancias: nunca tan cerca de un tratamiento sin Interferón

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Abstract

With 3-4 million of new infections occurring annually, hepatitis C virus (HCV) infection is a global Public Health problem. In fact, hepatitis C virus infection is one of the leading causes of liver disease in the world; in Western countries, two thirds of the new HCV infections are associated with injection drug use.

The treatment of hepatitis C will change in the coming years with the irruption of new anti-HCV drugs, the so called Direct Antiviral Agents (DAA) that attack key proteins of the HCV life cycle. The new antiviral drugs are effective, safer and better tolerated. The 2014 WHO HCV treatment guidelines include some of them. The new DAA are used in combination and it is expected that Interferon will be not necessary in future treatment regimens against HCV infection.

The irruption of new and potent antivirals mandate the review of the current standards of care in the HCV infected population. More inclusive and proactive treatment policies will be necessary in those individuals with substance use disorders.

Key words: substance abuse; hepatitis C; treatment; direct antiviral action.

Resumen

La infección por el virus de la hepatitis C (VHC) es un problema de Salud Pública de primera magnitud; cada año ocurren entre 3 y 4 millones de nuevas infecciones y de hecho, la hepatitis crónica C es una de las principales causas de enfermedad hepática en el mundo. Usar drogas por vía parenteral está en el origen de dos de cada tres nuevas infecciones por VHC en el mundo occidental.

El tratamiento de la hepatitis C va a cambiar en los próximos años. El cambio es debido a la aparición de los llamados Antivirales de Acción Directa (AAD), unos fármacos que actúan contra proteínas clave del ciclo vital del VHC y que serán más eficaces, mejor tolerados y se administrarán durante menos tiempo. En este sentido, la nueva guía de tratamiento de la OMS en 2014 ya incluye alguno de ellos en sus recomendaciones; los nuevos fármacos se utilizarán en combinación y probablemente se podrá prescindir del Interferón.

Con la aparición de más y mejores antivirales contra el VHC es probable que debamos revisar el modelo asistencial vigente y orientarlo hacia uno más ágil e integrador, que trate al mayor número posible de pacientes, incluyendo a aquellos con abuso de sustancias.

Palabras clave: abuso de sustancias; hepatitis C; tratamiento; antivirales acción directa.

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Treatment of chronic hepatitis C will change in the coming years. This change will occur due to the introduction of medication that is more efficacious, better tolerated, that scarcely generates any pharmacological resistance, and that is administered during shorter periods of time. Studies published since 2012 have revealed the efficacy of some of these drugs, and if this is indeed the case, it indicates the need to expand such treatment to a larger numbers of patients; detection of the infection and assessment of liver disease will be relevant if it is confirmed that infection cure can reach levels greater than 90%, regardless of viral genotype or of previous treatment failure. When the efficacy of the new therapies is confirmed in clinical trials, treatment of the illness will be generalized, and subsequently the population effectiveness of those therapies will be demonstrated. But clinical efficacy and population effectiveness are not the same thing; the latter is necessary to reduce the enormous burden of hepatitis C virus (HCV) on society. What has all this got to do with substance users? A great deal. In Western countries, two out of three new HCV infections occur in individuals who have injected or are injecting drugs, but this population – not by coincidence – receives the least treatment for HCV. The reasons why people with a history of substance abuse do not receive HCV treatment are quite diverse, and are described in this review, but one of the most widely cited is their poor tolerance to Interferon, an immunomodulatory drug that has formed part of the core of HCV treatment for some two decades. But if the advantages of the new medications are confirmed, patients with substance-use-related HCV will be more likely to seek treatment, as occurred after the irruption of the highly effective antiretroviral drugs for the treatment of human immunodeficiency virus (HIV).

Epidemiology of hepatitis C

HCV infection is one of the principal causes of liver disease worldwide (Shepard, Finelli, & Alter, 2005). Prevalence of the infection in the world population, disregarding marked regional differences, is close to 3% – equivalent to some 185 million people. It is estimated that 10 million individuals infected by HCV are, or have been, injection drug users (IDUs) (Nelson et al., 2011; Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013).

Globally, prevalence of the infection is higher in men, in people aged 30 to 49, and in those with low socio-economic status (Alter, 2007). Risk factors for infection vary, but transfusions (blood and/or blood derivatives) carried out before 1992, the use of re-usable healthcare materials and injection drug use are still the most important ones (Des Jarlais et al., 2003; Memon & Memon, 2002). In the USA there are over 2 million injection drug users, and the incidence of HCV infection is estimated at between 8% and 25% annually among the youngest of these. Data from the US also indicate that 30,000 new cases of infection are diagnosed each year, and that the incidence of infection is greater in new drug users and during the first year of drug use (Nelson et al., 2011; Page et al., 2009). It has been demonstrated that the transmission of HCV is 10 to 15 times higher than that of HIV (Page et al., 2009; Page, Morris, Hahn, Maher, & Prins, 2013), which reveals just how easily it can be transmitted in this population.

Also, people with alcohol use disorder present higher prevalence of HCV infection than the general population. Up to 20% of a series of 700 patients who sought treatment for alcoholism in the Barcelona were infected with HCV, according to a recent study (Rivas et al., 2013).

HCV is the principal cause of liver transplant and of hepatocellular carcinoma (HCC) in Western countries (Freeman et al., 2008; Yang et al., 2011). In fact, HCC and cirrhosis of the liver have increased in recent years among people infected with HCV, and it is forecasted that incidence of the two diseases will increase significantly in the coming decades (Mehta et al., 2010; Rein et al., 2011). A study in the US highlighted the growing number of deaths among those infected with HCV, which is now higher than that for deaths attributed to HIV/AIDS (Ly et al., 2012); the same study indicated that deaths related to HCV occur mainly in the age group 45 to 64 (Ly et al., 2012), and this has led health authorities in the US to recommend that the general population in this age group should be screened for HCV. It has been estimated, moreover, that a million people with HCV infection in the US will die as a result of complications related to the illness if they go untreated (Rein et al., 2011, 2012).

In Spain, estimates reveal that the number of people with HCV infection is around 430,000, with people older than 50 showing the highest prevalence of infection. The explanation for this can probably be found in the explosion of intravenous heroin use that occurred among young people in this country from the early 1980s onwards (Cornberg et al., 2011).

Natural history of hepatitis C

HCV causes an acute infection that remains asymptomatic in the majority of cases. Around 20-25% of substance-abusing patients will eliminate the viremia spontaneously in the 6 months following infection (Grebely et al., 2012; Page et al., 2009). Among the factors associated with spontaneous cure of the infection are being a woman, infection through genotype 1 (the most common in our context), and being a homozygote for the Interleukin-28 (IL-28B) gene, a gene that codes the Interleukin-23 protein, involved in the replication of HCV (Liu, Fisher, Thomas, Cox, & Ray, 2012; Page et al., 2009). On the other hand, 75-80% of those infected will develop a chronic infection, and the risk of developing cirrhosis, HCC, or other extra-hepatic complications may be

relatively high in the medium and long term (Grebely, de-Vlaming, Duncan, Viljoen, & Conway, 2008), especially if we take into account that the majority of patients with a history of substance abuse become infected at a very early age.

In chronic HCV infection, hepatic histological alteration is characterized by portal and lobular necro-inflammation. In a third of patients, the infection will follow an indolent course, but in the rest there will be a progressive increase of hepatic fibrosis, which will manifest clinically on the long term (Afdhal, 2004). The progression of hepatic fibrosis is not a linear process, since factors such as HIV infection, HBV, alcohol use and others can accelerate it (Muga et al., 2012; Cartón et al., 2011); age at the time of infection, male sex, obesity, diabetes mellitus and hepatic steatosis have also been associated with greater risk of fibrosis progression (Afdhal, 2004; Poynard, Bedossa, & Opolon, 1997). Once established the final phase of the disease, or liver cirrhosis, the probability of presenting a decompensation is 5% the first year and 30% ten years after diagnosis, whilst the risk of occurrence of HCC is 1-4% per year (Dore, Freeman, Law, & Kaldor, 2003; Raimondi, Bruno, Mondelli, & Maisonneuve, 2009). In general, it is accepted that median survival of patients presenting a first decompensation of liver cirrhosis is 5 years (Dore et al., 2003).

Diagnosis and assessment

Hepatic fibrosis is the principal marker of the course of liver disease (Thomas & Seeff, 2005). Liver biopsy has been considered the most reliable method for assessing the presence of fibrosis, and hence the most suitable tool for selecting candidates for treatment. However, recent years have seen the introduction of new methods for assessing fibrosis levels without the need for an invasive procedure, with elastography and biochemical markers playing an increasingly important role (de Ledinghen et al., 2006; Sanvisens et al., 2009; Sterling et al., 2006; Wai et al., 2003).

Among the biochemical markers, the APRI (AST-to-Platelet Ratio Index) or the FIB-4 (age, platelets, AST, ALT) are easy to use, since their calculation requires parameters that are employed in the routine clinical assessment of patients with liver disease. These two indexes are recommended by the World Health Organization (WHO) in the recently-published Guidelines for the screening, care and treatment of persons with HCV (World Health Organization, 2014); moreover, they have been validated in patients with HCV infection (Mallet et al., 2009; Vallet-Pichard et al., 2007; Wong et al., 2010), though their validity in chronic alcohol users might be limited.

Knowing the magnitude of hepatic damage in this group of patients with chronic hepatitis C is of crucial importance with the advent of new therapeutic regimens. In our experience, the prevalence of moderate and severe hepatic fibrosis is 40% and 17%, respectively, in this population (Sanvisens et al., 2011).

Current situation of hepatitis C treatment in substance-abusing patients

The prevalence of HCV infection in injection drug users is very high (50%-80%), and the most common genotypes are 1a, 1b and 3 (Robaeys et al., 2013). Despite the fact of being the population at greatest risk of infection, these patients tend not to receive treatment for chronic hepatitis C. According to European Union figures, the number of patients treated for hepatitis C does not reach 0.5% of the 700,000 people currently receiving methadone treatment (European Monitoring Centre for Drugs and Drug Addiction 2011).

In general, current standard treatment for hepatitis C is received over a period of 24 to 48 weeks, and the drugs employed are pegylated Interferon (PEG-IFN), Ribavirin (RBV) and Boceprevir or Telaprevir, these last two as first-generation protease inhibitors (World Health Organization, 2014). Treatment with PEG-IFN consists in the administration of weekly subcutaneous injections, and the side-effects are well-known and include flu-like symptoms, anxiety, depression, asthenia and cytopenias which, if they affect the erythrocyte series, may require treatment with erythropoietin (Chung, 2012). The ultimate goal of hepatitis C treatment is the eradication of the virus; the so-called sustained viral response (SVR) defined as undetectable HCV RNA 6 months after the end of treatment. Given its adverse effects, mainly on the Central Nervous System, a portion of patients receiving PEG-IFN should add antidepressants to their hepatitis C treatment.

In patients with a history of substance abuse, the healthcare reality of hepatitis C treatment is that only a minority are treated (Grebely et al., 2008; Mehta et al., 2008); the reasons for not receiving treatment are many, but three of them stand out: risk of poor therapeutic compliance, risk of reinfection and risk of exacerbation of psychiatric comorbidity (Edlin, 2002; Kramer et al., 2011).

At the care level there are still other barriers to access treatment for chronic hepatitis C, such as the lack of care contexts for the treatment of this population or the insufficient clinical training in the management of liver disease and substance abuse (Grebely & Tyndall, 2011; Litwin et al., 2007; Reimer & Haasen, 2009). Here in Spain, although the rate of diagnostic screening is high, the assessment of substance abuse and of medical and psychiatric comorbidity is somewhat heterogeneous, and involves various specialities; moreover, the care protocols for the assessment of drug dependence, psychopathology and liver disease are long-winded, and certainly do not favour the retention of these patients in the health system. Lack of knowledge about the illness by patients themselves and lack of social support have also been cited as barriers to acceding to treatment (Alavi et al., 2013). Table 1 includes a summary of the principal barriers to access to HCV treatment.

Various studies indicate that alcohol or substance use does not usually affect adherence to hepatitis C treatment,

Table 1.
Major difficulties in access to treatment of chronic hepatitis C in patients with substance abuse

In the health system	In patients
Insufficient knowledge of hepatitis C: – Limited training – Inexperience in the evaluation of liver damage – Low awareness of the need for treatment: • asymptomatic disease • Ignorance of the stage of fibrosis • Other priority co-morbidities	Inadequate knowledge of hepatitis C: – Limited Education in relation to HCV
Misperceptions about treatment: – High risk / benefit – Patients with substance abuse are poor candidates: • Addiction / psychiatric illness • Poor adherence	Low perceived need for treatment: – Asymptomatic disease – Ignorance of the stage of fibrosis – Other priority co-morbidities
Lost entries or delayed entries in the care circuit for hepatitis C	Misperceptions about treatment: – High risk / benefit – Fear of the complexity of treatment and side effects
	Poor retention in care circuits: – Addiction / psychiatric illness – Inadequate access to care circuits – Stigma / poorer social conditions

and nor does such abuse imply poorer response rates, even if more difficulties for treatment completion have been observed (Anand et al., 2006; Grebely & Tyndall, 2011; Hellard, Sacks-Davis, & Gold, 2009). A recent systematic review on drug users eligible for HCV treatment with PEG-IFN and RBV yielded a global SVR of 56% (37% for genotypes 1/4 and 67% for 2/3) (Aspinall et al., 2013); these figures are somewhat lower than those reported in most clinical trials for these drugs, but are similar to those described in two studies on the effectiveness of the treatment (39%-46% for genotype 1 and 70%-84% for genotype 2/3) (Borroni et al., 2008; Innes et al., 2012). In that same systematic review (Aspinall et al., 2013) a high level of treatment adherence was observed, 83%, somewhat higher than that shown in patients not abusing substances (McHutchison et al., 2002; Ravi, Nasiri Toosi, Karimzadeh, Ahadi-Barzoki, & Khalili, 2013) – though it should be borne in mind that the differences observed would be explained by the way adherence is defined. Moreover, the HCV reinfection rate was moderate (2.4 per 100 person-years), suggesting that this has little effect on long-term treatment effectiveness (Aspinall et al., 2013).

Paradigm shift: new treatments for hepatitis C without IFN

The growing numbers of patients that will need hepatitis C treatment, the contraindications and side effects of current treatment with IFN, and improved knowledge of the HCV life cycle have led to the development of new drugs. The advent of treatment regimens without IFN will represent a fundamental step forward in increasing treatment access. Everything points to the fact that patients with a history of substance abuse and hepatitis C will be no exception.

This paradigm shift in the treatment of hepatitis C begins to become a reality after the approval in the USA of the second-generation protease inhibitors and of the first HCV polymerase inhibitor in 2013. The first step in the direction of new treatment came after 2011, with the introduction of first-generation HCV protease inhibitors (Telaprevir and Boceprevir).

Second-generation protease inhibitors provide a better barrier with regard to pharmacological resistance, have fewer adverse effects, and show enhanced pharmacological activity against other HCV genotypes (Wendt et al., 2014). Protease and polymerase are key proteins in the HCV life cycle, only understood in detail in the last few years. Various pharmaceutical companies have analyzed therapeutic targets in key areas of the virus. The identification of these new therapeutic targets, based on attacking non-structural proteins of the virus, has led to the recognition of more than 10 Direct Antiviral Agents (DAAs). These agents include inhibitors of the protease NS3/4A, inhibitors of the polymerase NS5B, inhibitors of the NS5A complex, inhibitors of cyclophilin and direct inhibitors of RNA viral polymerase. Antivirals against HCV and Sofosbuvir (Lawitz & Gane, 2013) or Simeprevir (Asselah & Marcellin, 2014) approved by the FDA at the end of 2013, and others such as Daclatasvir (Gentile et al., 2013), Asunaprevir (Suzuki et al., 2013), Faldaprevir, Deleobuvir (Zeuzem et al., 2013) or Ledipasvir (Link et al., 2014), are highly efficacious, and set out to eradicate the virus through oral therapeutic regimens of 12 weeks in some genotypes, and with few adverse effects (Gane et al., 2014; Sulkowski et al., 2014). In this regard, the recent Guide published by the WHO in April 2014 already includes in its recommendations the two drugs approved by the FDA (sofosbuvir, simeprevir) and recently incorporated into the Spanish National Health System, and anticipates regular updates as new licences are granted (World Health Organization, 2014). Even though clinical trials on the new drugs have not been carried out on substance-injecting patients, the WHO Guide recommends not excluding this population from treatment (priority recommendation); likewise, the WHO recommends detecting heavy drinkers and offering such patients interventions for reducing their intake.

We should point out the need for studies that analyze potential pharmacological interactions between DAAs and

the drugs most widely used in the treatment of substance abuse. Simeprevir and faldaprevir are metabolized by the cytochrome P450 system, and it is possible that they show pharmacokinetic interactions with drugs such as methadone and buprenorphine (Mauss & Klinker, 2013).

In any case, improvements in the pharmacological treatment of hepatitis C should perhaps be accompanied by changes in the clinical care model applied to substance-abusing patients; diagnosis of the infection and clinical assessment are of great importance in the prioritization of treatment for the most in need. Health care professionals involved in the treatment of substance abuse should play a key role in ensuring that these patients are clinically evaluated, are treated for their illness, and obtain therapeutic results similar to those we would expect to obtain in patients without substance abuse. Establishing a more inclusive care model for patients with substance-use-related hepatitis C will become necessary in the face of all the imminent changes.

Conclusion

The substantial burden of liver disease and the high incidence of HCV infection in substance-abusing patients make it necessary to improve diagnosis and treatment in this population. New, innovative drugs are appearing that directly attack proteins responsible for forming the viral replication complex of HCV; the combination of two or more of these drugs can be highly efficacious against the majority of HCV genotypes and in the majority of clinical situations, including liver cirrhosis. With the introduction of such efficacious and well-tolerated drugs, there is a need to review the current care model and replace it with a more flexible and integrated one that attempts to treat the highest possible number of HCV-infected patients. Figure 1 shows a first approach to a multidisciplinary care model. Likewise, optimizing the prevention, diagnosis, assessment and treatment access of chronic hepatitis C is high-priority. The approaches that can be proposed are diverse, and would include:

- Identifying perceived barriers and needs in primary care and drug-dependence clinics and developing educational activities for improving knowledge about chronic hepatitis C,
- Reviewing the process of clinical assessment of patients with hepatitis C associated with substance abuse,
- Categorizing patients' clinical situation: new diagnosis, previously treated, stage of liver disease, etc.
- Identifying patients at risk of HCV infection and preventing infection through a brief intervention and screening for viral hepatitis.
- Offering treatment for alcohol or drug abuse to patients with chronic hepatitis C.

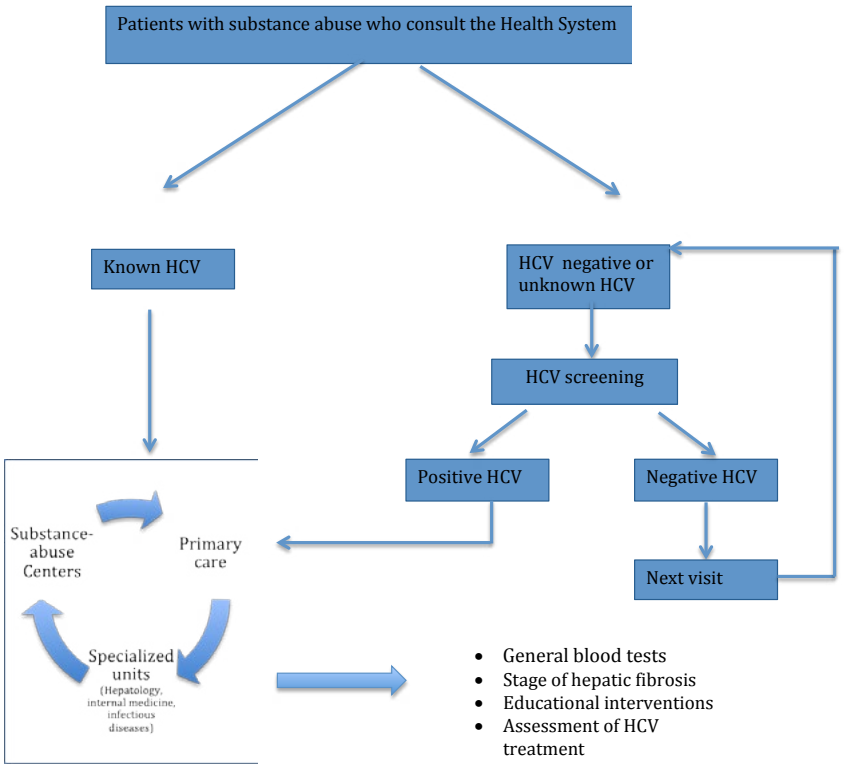

Figure 1. Model for increasing the participation of substance-abusing patients in access to treatment for chronic hepatitis C

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Conflicts of interests

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References

Afdhal, N. H. (2004). The natural history of hepatitis C. *Seminars in Liver Disease*, *24*, 3–8. doi:10.1055/s-2004-832922

Alavi, M., Grebely, J., Micallef, M., Dunlop, A. J., Balcomb, A. C., Day, C. A., … Dore, G. J. (2013). Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: ETHOS study. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *57*, S62–9. doi:10.1093/cid/cit305

Alter, M. J. (2007). Epidemiology of hepatitis C virus infection. *World Journal of Gastroenterology : WJG*, *13*, 2436–41.

Anand, B. S., Currie, S., Dieperink, E., Bini, E. J., Shen, H., Ho, S. B., & Wright, T. (2006). Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. *Gastroenterology*, *130*, 1607–1616. doi:10.1053/j.gastro.2006.02.023

Aspinall, E. J., Corson, S., Doyle, J. S., Grebely, J., Hutchinson, S. J., Dore, G. J., … Hellard, M. E. (2013). Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *57*, S80–89. doi:10.1093/cid/cit306

Asselah, T., & Marcellin, P. (2014). Second-wave IFN-based triple therapy for HCV genotype 1 infection: simeprevir, faldaprevir and sofosbuvir. *Liver International : Official Journal of the International Association for the Study of the Liver*, *34*, 60–68. doi:10.1111/liv.12424

Borroni, G., Andreoletti, M., Casiraghi, M. A., Ceriani, R., Guerzoni, P., Omazzi, B., … Salerno, F. (2008). Effectiveness of pegylated interferon/ribavirin combination in "real world" patients with chronic hepatitis C virus infection. *Alimentary Pharmacology & Therapeutics*, *27*, 790–797. doi:10.1111/j.1365-2036.2008.03657.x

Cartón, J. A., Collazos, J., de la Fuente, B., García-Alcalde, M. L., Suarez-Zarracina, T., Rodríguez-Guardado, A., & Asensi, V. (2011). Factors associated with liver fibrosis in intravenous drug users coinfected with HIV and HCV. *Antiviral Therapy*, *16*, 27–35. doi:10.3851/IMP1708

Chung, R. T. (2012). A watershed moment in the treatment of hepatitis C. *The New England Journal of Medicine*, *366*, 273–275. doi:10.1056/NEJMe1113272

Cornberg, M., Razavi, H. A., Alberti, A., Bernasconi, E., Buti, M., Cooper, C., … Zeuzem, S. (2011). A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. *Liver International : Official Journal of the International Association for the Study of the Liver*, *31*, 30–60. doi:10.1111/j.1478-3231.2011.02539.x

De Ledinghen, V., Douvin, C., Kettaneh, A., Ziol, M., Roulot, D., Marcellin, P., … Beaugrand, M. (2006). Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *41*, 175–179.

Des Jarlais, D. C., Diaz, T., Perlis, T., Vlahov, D., Maslow, C., Latka, M., … Garfein, R. S. (2003). Variability in the incidence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection among young injecting drug users in New York City. *American Journal of Epidemiology*, *157*, 467–471.

Dore, G. J., Freeman, A. J., Law, M., & Kaldor, J. M. (2003). Natural history models for hepatitis C-related liver disease: different disease progression parameters for different settings. *Antiviral Therapy*, *8*, 365–372.

Edlin, B. R. (2002). Prevention and treatment of hepatitis C in injection drug users. *Hepatology (Baltimore, Md.)*, *36*, S210–219. doi:10.1053/jhep.2002.36809

Freeman, R. B., Steffick, D. E., Guidinger, M. K., Farmer, D. G., Berg, C. L., & Merion, R. M. (2008). Liver and intestine transplantation in the United States, 1997-2006. *American Journal of Transplantation : Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, *8*, 958–976. doi:10.1111/j.1600-6143.2008.02174.x

Gane, E. J., Stedman, C. A., Hyland, R. H., Ding, X., Svarovskaia, E., Subramanian, G. M., … Pang, P. S. (2014). Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A Inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. *Gastroenterology*, *146*, 736–743.e1. doi:10.1053/j.gastro.2013.11.007

Gentile, I., Borgia, F., Coppola, N., Buonomo, A. R., Castaldo, G., & Borgia, G. (2013). Daclatasvir: The First of a New Class of Drugs Targeted Against Hepatitis C Virus NS5A. *Current Medicinal Chemistry,* 21, 1391-1404.

Grebely, J., deVlaming, S., Duncan, F., Viljoen, M., & Conway, B. (2008). Current approaches to HCV infection in current and former injection drug users. *Journal of Addictive Diseases*, *27*, 25–35. doi:10.1300/J069v27n02_04

Grebely, J., Prins, M., Hellard, M., Cox, A. L., Osburn, W. O., Lauer, G., … Dore, G. J. (2012). Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *The Lancet Infectious Diseases*, *12*, 408–414. doi:10.1016/S1473-3099(12)70010-5

Grebely, J., Raffa, J. D., Lai, C., Krajden, M., Kerr, T., Fischer, B., & Tyndall, M. W. (2009). Low uptake of treatment for

hepatitis C virus infection in a large community-based study of inner city residents. *Journal of Viral Hepatitis*, *16*, 352–358. doi:10.1111/j.1365-2893.2009.01080.x

Grebely, J., & Tyndall, M. W. (2011). Management of HCV and HIV infections among people who inject drugs. *Current Opinion in HIV and AIDS*, *6*, 501–507. doi:10.1097/COH.0b013e32834bcb36

Hellard, M., Sacks-Davis, R., & Gold, J. (2009). Hepatitis C treatment for injection drug users: a review of the available evidence. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *49*, 561–573. doi:10.1086/600304

Innes, H. A., Hutchinson, S. J., Allen, S., Bhattacharyya, D., Bramley, P., Carman, B., … Hayes, P. (2012). Ranking predictors of a sustained viral response for patients with chronic hepatitis C treated with pegylated interferon and ribavirin in Scotland. *European Journal of Gastroenterology & Hepatology*, *24*, 646–655. doi:10.1097/MEG.0b013e32835201a4

Kramer, J. R., Kanwal, F., Richardson, P., Giordano, T. P., Petersen, L. A., & El-Serag, H. B. (2011). Importance of patient, provider, and facility predictors of hepatitis C virus treatment in veterans: a national study. *The American Journal of Gastroenterology*, *106*, 483–491. doi:10.1038/ajg.2010.430

Lawitz, E., & Gane, E. J. (2013). Sofosbuvir for previously untreated chronic hepatitis C infection. *The New England Journal of Medicine*, *369*, 678–679. doi:10.1056/NEJMc1307641

Link, J. O., Taylor, J. G., Xu, L., Mitchell, M., Guo, H., Liu, H., … Desai, M. C. (2014). Discovery of Ledipasvir (GS-5885): A Potent, Once-Daily Oral NS5A Inhibitor for the Treatment of Hepatitis C Virus Infection. *Journal of Medicinal Chemistry, 57*, 2033–2046. doi:10.1021/jm401499g

Litwin, A. H., Kunins, H. V, Berg, K. M., Federman, A. D., Heavner, K. K., Gourevitch, M. N., & Arnsten, J. H. (2007). Hepatitis C management by addiction medicine physicians: results from a national survey. *Journal of Substance Abuse Treatment*, *33*, 99–105. doi:10.1016/j.jsat.2006.12.001

Liu, L., Fisher, B. E., Thomas, D. L., Cox, A. L., & Ray, S. C. (2012). Spontaneous clearance of primary acute hepatitis C virus infection correlated with high initial viral RNA level and rapid HVR1 evolution. *Hepatology (Baltimore, Md.)*, *55*, 1684–1691. doi:10.1002/hep.25575

Ly, K. N., Xing, J., Klevens, R. M., Jiles, R. B., Ward, J. W., & Holmberg, S. D. (2012). The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Annals of Internal Medicine*, *156*, 271–278. doi:10.7326/0003-4819-156-4-201202210-00004

Mallet, V., Dhalluin-Venier, V., Roussin, C., Bourliere, M., Pettinelli, M. E., Giry, C., … Pol, S. (2009). The accuracy of the FIB-4 index for the diagnosis of mild fibrosis in chronic hepatitis B. *Alimentary Pharmacology & Therapeutics*, *29*, 409–415. doi:10.1111/j.1365-2036.2008.03895.x

Mauss, S., & Klinker, H. (2013). Drug-drug interactions in the treatment of HCV among people who inject drugs. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *57*, S125–128. doi:10.1093/cid/cit299

McHutchison, J. G., Manns, M., Patel, K., Poynard, T., Lindsay, K. L., Trepo, C., … Albrecht, J. K. (2002). Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology*, *123*, 1061–1069.

Mehta, S. H., Genberg, B. L., Astemborski, J., Kavasery, R., Kirk, G. D., Vlahov, D., … Thomas, D. L. (2008). Limited uptake of hepatitis C treatment among injection drug users. *Journal of Community Health*, *33*, 126–133. doi:10.1007/s10900-007-9083-3

Mehta, S. H., Vogt, S. L., Srikrishnan, A. K., Vasudevan, C. K., Murugavel, K. G., Saravanan, S., … Solomon, S. S. (2010). Epidemiology of hepatitis C virus infection & liver disease among injection drug users (IDUs) in Chennai, India. *The Indian Journal of Medical Research*, *132*, 706–714.

Memon, M. I., & Memon, M. A. (2002). Hepatitis C: an epidemiological review. *Journal of Viral Hepatitis*, *9*, 84–100.

Mohd Hanafiah, K., Groeger, J., Flaxman, A. D., & Wiersma, S. T. (2013). Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology (Baltimore, Md.)*, *57*, 1333–1342. doi:10.1002/hep.26141

Muga, R., Sanvisens, A., Fuster, D., Tor, J., Martinez, E., Perez-Hoyos, S., & Munoz, A. (2012). Unhealthy Alcohol Use, HIV Infection and Risk of Liver Fibrosis in Drug Users with Hepatitis C. *Plos One*, *7*. doi:10.1371/journal.pone.0046810

Nelson, P. K., Mathers, B. M., Cowie, B., Hagan, H., Des Jarlais, D., Horyniak, D., & Degenhardt, L. (2011). Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*, *378*, 571–583. doi:10.1016/S0140-6736(11)61097-0

Observatorio Europeo de las Drogas y las Toxicomanías. (2011) *Informe anual 2011: el problema de la drogodependencia en Europa*. Retrieved from http://www.emcdda.europa.eu/attachements.cfm/att_143743_ES_EMCDDA_AR2011_ES.pdf

Page, K., Hahn, J. A., Evans, J., Shiboski, S., Lum, P., Delwart, E., … Busch, M. P. (2009). Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *The Journal of Infectious Diseases*, *200*, 1216–1226. doi:10.1086/605947

Page, K., Morris, M. D., Hahn, J. A., Maher, L., & Prins, M. (2013). Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clinical Infectious Diseases :*

An Official Publication of the Infectious Diseases Society of America, *57*, S32–38. doi:10.1093/cid/cit300

Poynard, T., Bedossa, P., & Opolon, P. (1997). Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*, *349*, 825–832.

Raimondi, S., Bruno, S., Mondelli, M. U., & Maisonneuve, P. (2009). Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *Journal of Hepatology*, *50*, 1142–1154. doi:10.1016/j.jhep.2009.01.019

Ravi, S., Nasiri Toosi, M., Karimzadeh, I., Ahadi-Barzoki, M., & Khalili, H. (2013). Adherence to chronic hepatitis C treatment regimen: first report from a referral center in Iran. *Hepatitis Monthly*, *13*, e11038. doi:10.5812/hepatmon.11038

Reimer, J., & Haasen, C. (2009). Need-adapted HCV-treatment setting for injection drug users. *Lancet*, *373*, 2090–2091. doi:10.1016/S0140-6736(09)60347-0

Rein, D. B., Smith, B. D., Wittenborn, J. S., Lesesne, S. B., Wagner, L. D., Roblin, D. W., … Weinbaum, C. M. (2012). The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Annals of Internal Medicine*, *156*, 263–270. doi:10.7326/0003-4819-156-4-201202210-00378

Rein, D. B., Wittenborn, J. S., Weinbaum, C. M., Sabin, M., Smith, B. D., & Lesesne, S. B. (2011). Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*, *43*, 66–72. doi:10.1016/j.dld.2010.05.006

Rivas, I., Sanvisens, A., Bolao, F., Fuster, D., Tor, J., Pujol, R., … Muga, R. (2013). Impact of medical comorbidity and risk of death in 680 patients with alcohol use disorders. *Alcoholism, Clinical and Experimental Research*, *37*, E221–227. doi:10.1111/j.1530-0277.2012.01861.x

Robaeys, G., Grebely, J., Mauss, S., Bruggmann, P., Moussalli, J., De Gottardi, A., … Dore, G. J. (2013). Recommendations for the management of hepatitis C virus infection among people who inject drugs. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *57*, S129–137. doi:10.1093/cid/cit302

Sanvisens, A., Fuster, D., Serra, I., Tor, J., Tural, C., Rey-Joly, C., & Muga, R. (2011). Estimated liver fibrosis and its impact on all-cause mortality of HCV-monoinfected and HCV/HIV-coinfected drug users. *Current HIV Research*, *9*, 256–262. doi:10.2174/157016211796320298

Sanvisens, A., Serra, I., Tural, C., Tor, J., Ojanguren, I., Barluenga, E., … Muga, R. (2009). Hyaluronic acid, transforming growth factor-beta1 and hepatic fibrosis in patients with chronic hepatitis C virus and human immunodeficiency virus co-infection. *Journal of Viral Hepatitis*, *16*, 513–518.

Shepard, C. W., Finelli, L., & Alter, M. J. (2005). Global epidemiology of hepatitis C virus infection. *The Lancet Infectious Diseases*, *5*, 558–567. doi:10.1016/S1473-3099(05)70216-4

Sterling, R. K., Lissen, E., Clumeck, N., Sola, R., Correa, M. C., Montaner, J., … Investigators, A. C. (2006). Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology (Baltimore, Md.)*, *43*, 1317–1325. doi:10.1002/hep.21178

Sulkowski, M. S., Gardiner, D. F., Rodriguez-Torres, M., Reddy, K. R., Hassanein, T., Jacobson, I., … Grasela, D. M. (2014). Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection. *New England Journal of Medicine*, *370*, 211–221. doi:10.1056/NEJMoa1306218

Suzuki, Y., Ikeda, K., Suzuki, F., Toyota, J., Karino, Y., Chayama, K., … Kumada, H. (2013). Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options. *Journal of Hepatology*, *58*, 655–662. doi:10.1016/j.jhep.2012.09.037

Thomas, D. L., & Seeff, L. B. (2005). Natural history of hepatitis C. *Clinics in Liver Disease*, *9*, 383–398, vi. doi:10.1016/j.cld.2005.05.003

Vallet-Pichard, A., Mallet, V., Nalpas, B., Verkarre, V., Nalpas, A., Dhalluin-Venier, V., … Pol, S. (2007). FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology (Baltimore, Md.)*, *46*, 32–36. doi:10.1002/hep.21669

Wai, C. T., Greenson, J. K., Fontana, R. J., Kalbfleisch, J. D., Marrero, J. A., Conjeevaram, H. S., & Lok, A. S. (2003). A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology (Baltimore, Md.)*, *38*, 518–526. doi:10.1053/jhep.2003.50346

Wendt, A., Adhoute, X., Castellani, P., Oules, V., Ansaldi, C., Benali, S., & Bourlière, M. (2014). Chronic hepatitis C: future treatment. *Clinical Pharmacology : Advances and Applications*, *6*, 1–17. doi:10.2147/CPAA.S30338

Wong, V. W.-S., Vergniol, J., Wong, G. L.-H., Foucher, J., Chan, H. L.-Y., Le Bail, B., … de Lédinghen, V. (2010). Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology (Baltimore, Md.)*, *51*, 454–462. doi:10.1002/hep.23312

World Health Organization. (2014). Guidelines for the screening, care and treatment of persons with hepatitis c infection. Retrieved from http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1

Yang, J. D., Kim, W. R., Coelho, R., Mettler, T. A., Benson, J. T., Sanderson, S. O., … Roberts, L. R. (2011). Cirrhosis

is present in most patients with hepatitis B and hepatocellular carcinoma. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *9*, 64–70. doi:10.1016/j.cgh.2010.08.019

Zeuzem, S., Asselah, T., Angus, P., Zarski, J.-P., Larrey, D., Müllhaupt, B., … Mensa, F. J. (2013). Faldaprevir (BI 201335), deleobuvir (BI 207127) and ribavirin oral therapy for treatment-naive HCV genotype 1: SOUND-C1 final results. *Antiviral Therapy,* 18,1015-1019. doi:10.3851/IMP2567

Would Adding an Anesthesic to Nicotine Mouth Spray Increase Smoking Cessation Rates? Would this Justify Starting a Research Project?

¿Añadir un anestésico al spray bucal de nicotina aumentaría las tasas de abstinencia tabáquica? ¿Se justifica por ello iniciar un proyecto de investigación?

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Dear Sir: Although the addictive properties of tobacco depend on nicotine, this addictive power reflects complex interactions between the drug and the context in which it is released. It is known that there are sensory components that contribute towards the satisfaction felt by the smoker, there being a sensory cue associated with the drug that makes it a conditioned replenisher associated with tobacco. There are nicotine-associated cues with each puff such as, for example, visual, olfactory and gustatory stimuli, that provoke subjective states that can in turn trigger off the search for the drug and thus lead to relapse (Dani and Balfour, 2011). Recently, Liu (2014) has shown the role of cholinergic neurotransmission, via the activation of the acetylcholine receptor alpha7, in the mediation of the conditioned incentive properties of external nicotine cues, for which reason manipulating the activity of the acetylcholine receptor alpha7 could be a target in the development of drugs to prevent relapse brought on by outward cues.

Until such time as neuroscientific research clears up the matter, it has to be said that when cigarette smoke enters the smoker's mouth and passes the pharynx, the larynx and the lower respiratory tract a series of sensations are provoked, it having been hypothesized that these chemosensory signals become powerful conditioned reinforcement stimuli owing to their being associated with the replenishing effect of the nicotine on the central nervous system (Smolka et al., 2006). Indeed, it has even been shown that sensory factors may be as important in the sensation of satisfaction after smoking, the acceptance of the product and on the desire to smoke as the pharmacological factors of nicotine on a cerebral level (Pritchard, Robinson, Guy, Davis y Stiles, 1996). Rose, Zinser, Tashkin, Newcomb y Ertle (1984) showed that anesthetizing the upper and lower respiratory tracts reduced the craving for nicotine and the number of puffs desired. The satisfaction experienced by smokers who inhale diminishes if the upper and lower areas are anesthetized (Rose, Tashkin, Ertle, Zinser y Lafer, 1985). As far as we know, this line of research was not continued afterwards.

We currently have available the nicotine mouth spray to help smokers stop and it has shown its efficacy in increasing the smoker's chances of remaining abstinent (Tønnesen, Lauri, Perfekt, Mann, and Batra, 2012). There is evidence that fast-acting nicotine replacement therapy prescriptions work quickly to alleviate craving and thus calm the discomfort caused by abstinence (Hansson, Hajek, Perfekt and Kraiczi, 2012). Reducing the temptation to smoke, by alleviating the craving, will diminish the number of relapses. Nicotine mouth spray has shown that it alleviates craving rapidly (Hansson et al., 2012).

However, as far as we know, there are no studies that have measured smoking abstinence after adding an anesthetic to the nicotine replacement therapy habitually employed and the question at this point would be: would adding an anes-

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thetic to nicotine mouth spray increase smoking abstinence rates? With this we would add two effects at the same time as maintaining abstinence; on the one hand the proven rapid absorption of nicotine via the mouth spray (Hansson et al., 2012) which quickly alleviates craving and, on the other, the anesthetic would equally diminish the craving and the satisfaction that the smoker experiences when inhaling tobacco smoke thus lessening the sensory effects of the nicotine and, therefore, diminishing the conditioned reinforcement stimulus that it leads to. Logically, the key is in the duration of the anesthetic effect. Although we have no answer to the above, possibly what we have expounded in this letter would justify a research project to find such a response.

References

Dani, J. A. & Balfour, D. J. K. (2011). Historical and current perspective on tobacco use and nicotine addiction. *Trends in Neuroscience, 34*, 383–392. doi: 10.1016/j.tins.2011.05.001

Hansson, A., Hajek, P., Perfekt, R., & Kraiczi, H. (2012). Effects of nicotine mouth spray on urges to smoke, a randomised clinical trial. BMJ Open, *2*, pii: e001618. doi: 10.1136/bmjopen-2012-001618.

Liu, X. (2014). Effects of blockade of α4β2 and α7 nicotinic acetylcholine receptors on cue-induced reinstatement of nicotine-seeking behaviour in rats. *International Journal of Neuropsychopharmacology*, *17*, 105–116. doi: 10.1017/S1461145713000874

Pritchard, W. S., Robinson, J. H., Guy, T. D., Davis, R. A., & Stiles, M. F. (1996). Assessing the sensory role of nicotine cigarette smoking. *Phychopharmacology(Berl)*, *127*, 55–62.

Rose J. E., Tashkin, D. P., Ertle, A., Zinser, M. C., & Lafer, R. (1985). Sensory blockade of smoking satisfaction. *Pharmacology Biochemistry and Behavior*, *23*, 289-293.

Rose, J. E., Zinser, M. D., Tashkin, D. P., Newcomb, R., & Ertle, A. (1984). Subjetive response to cigarette smoking following airway anesthetization. *Addictive Behaviors*, *9*, 211-215.

Smolka, M. N., Bühler, M., Klein, S., Zimmermann, U., Mann, K., Heinz, A.,... Braus, D. F. (2006). Severity of nicotine dependence modulates cue-induced brain activity in regions involved in motor preparation and imagery. *Psychopharmacology (Berl)*, *184*, 577–588.

Tønnesen, P., Lauri, H., Perfekt, R., Mann, K., & Batra, A. (2012). Efficacy of a nicotine mouth spray in smoking cessation: a randomised, double-blind trial. *European Respiratory Journal*, *40*, 548 - 554. doi: 10.1183/09031936.00155811.

MENSUAL suspensión inyectable de liberación prolongada

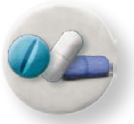
XEPLION®

palmitato de paliperidona

EFICACIA PARA SENTIRSE EFICACIA

FARMACOCINÉTICA[1, 2]

EFICACIA[1]



SIN SUPLEMENTACIÓN ORAL[3]

MONOTERAPIA[1, 4, 5]

TOLERABILIDAD CONTRASTADA[3, 6-9] *

SIN METABOLISMO HEPÁTICO[3]

CLARIDAD DE PENSAMIENTO[10-13]

FLEXIBILIDAD DE PAUTA POSOLÓGICA[3]

En España no se comercializa la presentación de 25 mg.

*Para más información sobre efectos adversos consultar apartado 4.8 de la Ficha Técnica

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PHES/XEP/0315/0010 Marzo 2015

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

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

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

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

de divalproex sódico de liberación prolongada y la inyección intramuscular de XEPLION. Esta interacción no se ha estudiado con XEPLION. Uso concomitante de XEPLION y risperidona. Risperidona administrada por vía oral o intramuscular se metaboliza en un grado variable a paliperidona. Se debe proceder con cautela en caso de administración concomitante de risperidona o paliperidona oral con XEPLION. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a antipsicóticos (como paliperidona) durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. XEPLION no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. XEPLION no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a XEPLION. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estas, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con XEPLION. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1000 a <1/100), *raras* (≥1/10.000 a <1/1000), *muy raras* (<1/10.000), y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

Clasificación por órganos y sistemas	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, cistitis, infección de oídos, infección de ojos, amigdalitis, celulitis, acarodermatitis, absceso subcutáneo	onicomicosis	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, anemia, disminución del hematocrito, aumento del recuento de eosinófilos	agranulocitosis[e] neutropenia, trombocitopenia	
Trastornos del sistema inmunológico			hipersensibilidad	reacción anafiláctica[e]	
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, aumento de los triglicéridos en sangre	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, disminución del apetito, aumento del colesterol en sangre	intoxicación por agua[e], cetoacidosis diabética[e], hipoglucemia, polidipsia	
Trastornos psiquiátricos	insomnio[d]	agitación, depresión, ansiedad	trastorno del sueño, manía, estado de confusión, disminución de la líbido, nerviosismo, pesadillas	embotamiento afectivo[e], anorgasmia	
Trastornos del sistema nervioso	cefalea	parkinsonismo[b], acatisia[b], sedación/somnolencia, distonia[b], mareos, discinesia[b], temblor	discinesia tardía, convulsión[e], síncope, hiperactividad psicomotora, mareo postural, alteración de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, sin respuesta a estímulos, pérdida de la consciencia, disminución del nivel de consciencia, coma diabético[e], trastorno del equilibrio, coordinación anormal[e], titubeo de la cabeza[e]	
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma[e], trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		
Trastornos cardiacos		bradicardia, taquicardia	fibrilación auricular, bloqueo auriculoventricular, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, anomalías del electrocardiograma, palpitaciones	arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	embolismo pulmonar[e], trombosis venosa, isquemia[e], rubor	
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión pulmonar, sibilancias, dolor faringeolaríngeo, epistaxis	síndrome de apnea del sueño[e], hiperventilación[e], neumonía por aspiración[e], congestión del tracto respiratorio disfonía[e]	
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, sequedad de boca, flatulencia	pancreatitis, obstrucción del intestino[e], íleo, hinchazón de la lengua, incontinencia fecal, fecaloma, disfagia, queilitis[e]	
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas	ictericia[e]	
Trastornos de la piel y del tejido subcutáneo		erupción cutánea	urticaria, prurito, alopecia, eccema, sequedad de la piel, eritema, acné	angioedema[e], erupción debida al medicamento, hiperqueratosis, decoloración de la piel[e], dermatitis seborreica[e], caspa	
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda	espasmos musculares, rigidez en las articulaciones, dolor de cuello, artralgia	rabdomiólisis[e], aumento de la creatina fosfoquinasa en sangre, anomalía postural[e], inflamación de las articulaciones, debilidad muscular	
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales				síndrome de abstinencia neonatal (ver sección 4.6)[e]	
Trastornos del aparato reproductor y de la mama			disfunción eréctil, trastorno de la eyaculación, amenorrea, retraso en la menstruación, trastornos menstruales[d], ginecomastia, galactorrea, disfunción sexual, secreción vaginal	priapismo[e], dolor de las mamas, malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción mamaria	
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[e], alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, disminución de la temperatura corporal[e], escalofríos, aumento de la temperatura corporal, sed, síndrome de abstinencia a medicamentos[e], absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección[e], hematoma en el lugar de la inyección	
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

[a]Referido a "Hiperprolactinemia" a continuación. [b]Referido a "Síntomas extrapiramidales" a continuación. [c]En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con XEPLION comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,47% en todos los pacientes tratados con XEPLION. [d]**Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** menstruación irregular, oligomenorrea. [e]No se observaron en estudios clínicos de XEPLION pero sí en la experiencia tras la comercialización con paliperidona.

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

ción de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de XEPLION en el día 8. Los resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de XEPLION, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

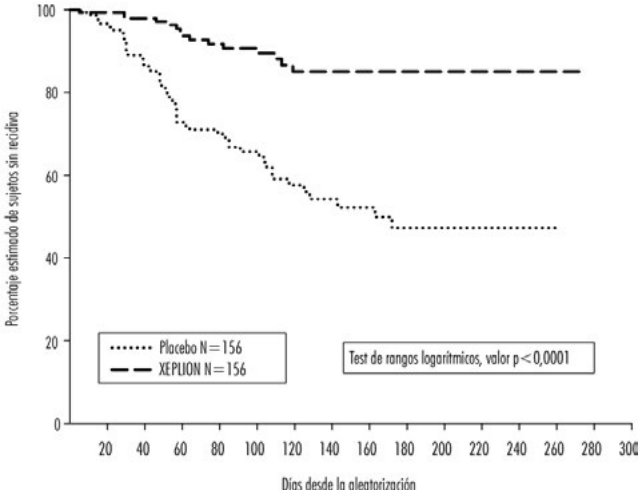
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con XEPLION en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de XEPLION se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de XEPLION fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de XEPLION fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de XEPLION a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de XEPLION es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. XEPLION está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de XEPLION (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con XEPLION se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de XEPLION permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (días 8 y 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque XEPLION no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a los de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{inf}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con XEPLION en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. No se recomienda ajustar la dosis únicamente en función de la edad. Sin embargo, puede ser necesario realizar el ajuste de la dosis debido a las disminuciones en el aclaramiento de creatinina relacionadas con la edad (ver Insuficiencia renal más arriba y la sección 4.2). Peso. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de XEPLION. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. 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. No se evaluó el tabaquismo con XEPLION. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte masivamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** XEPLION 50 mg suspensión inyectable de liberación prolongada: PVL: 197,72 €; PVP: 243,63 €; PVP (IVA): 253,38 €. XEPLION 75 mg suspensión inyectable de liberación prolongada: PVL: 287,86 €; PVP: 338,77 €; PVP (IVA): 352,32 €. XEPLION 100 mg suspensión inyectable de liberación prolongada: PVL: 345,43 €; PVP: 396,34 €; PVP (IVA): 412,19 €. XEPLION 150 mg suspensión inyectable de liberación prolongada: PVL: 449,06 €; PVP: 499,97 €; PVP (IVA): 519,97 €. **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-Glag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** XEPLION 50 mg: EU/1/11/672/002. XEPLION 75 mg: EU/1/11/672/003. XEPLION 100 mg: EU/1/11/672/004. XEPLION 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** 04 de marzo de 2011. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 10/2014. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

Bibliografía:

1. Pandina GJ, et al., A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. J Clin Psychopharmacol. 2010;30: 235-244.
2. Samtani MN et al. Population Pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia. Clin Pharmacacokinet. 2009; 48 (9): 585-600.
3. Ficha Técnica de Xeplion®.
4. Mesones Peral JE et al. Comparative analysis of the prevention of relapse in psycotic patients following the introduction of Paliperidone Palmitate. XVI Congreso Mundial de Psiquiatría. Madrid, España, 14-18 de septiembre de 2014. Póster 309.
5. Benito A et al. Outcomes económicos del tratamiento con palmitato de paliperidona: Dos años de seguimiento. XVI Congreso Mundial de Psiquiatría. Madrid, España, 14-18 de septiembre de 2014. Póster 393.
6. Jones MP et al. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia.International Journal of Clinical Pharmacology and Therapeutics. 2010; 48 (6): 383-399.
7. Manzano Callejo JM et al. Antipsicóticos atípicos, esquizofrenia y síndrome metabólico. Póster presentado en el XVII Congreso Nacional de Psiquiatría. Sevilla, 2013.
8. Bergmans P, et al. Flexibly dosed paliperidone palmitate in non-acute but symptomatic patients with schizophrenia previously unsuccessfully treated with long-acting injectable risperidone. Póster presentado en el Congreso DGPPN, 27-30 de noviembre de 2013, Berlín, Alemania, Póster P003 (sesión P-06).
9. Montalvo I et al. Changes in prolactin levels and sexual function in young psychotic patients after switching from long-acting injectable risperidone to paliperidone palmitate. Int Clin Psychophacol. 2012; 28: 46.49.
10. Schreiner A. Paliperidone palmitate in acute patients with schizophrenia - Treatment response, safety and tolerability: a prospective flexible dose study in patients previously unsuccessfully treated with oral antipsychotics. Póster presentado en congreso internacional del Royal College of Psychiastrists, 2-5 de julio de 2013, Edimburgo, Reino Unido.
11. Vázquez JM, et al. Evolución de la Brief Psychiatric Rating Scale (BPRS) y la UdvalgfürKliniskeUndersogelser (UKU) en pacientes con trastorno por uso de sustancias y diagnóstico adicional en el espectro psicótico: "Palmitato de Paliperidona versus antipsicóticos orales / R.I.L.". Póster presentado en el XVII Congreso Nacional de Psiquiatría. Sevilla, 2013.
12. Schreiner A, et al. Paliperidone palmitate - Impact on negative, disorganized and depressive symptoms, subjective well-being and patient satisfaction in non-acute patients with schizophrenia previously unsuccessfully treated with oral antipsychotics. Póster presentado en el congreso DGPPN, 27-30 de noviembre de 2013, Berlín, Alemania, póster P006 (sesión P-08).
13. Hargarter L, et al. Functional outcomes with once monthly paliperidone palmitate in acute and non-acute patients with schizophrenia: data from a prospective fexible dose study in patients with schizophrenia previously unsuccessfully treated with oral antipsychotics. Póster presentado en el congreso del Royal College of Psychiastrists's International, 2-5 de julio de 2013, Edimburgo, Reino Unido.

Desde el año 2012 sólo se admite la normativa APA.

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

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

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

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

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

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

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

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

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

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

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

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

PRESENTACIÓN DE LOS TRABAJOS

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

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

- Una copia del manuscrito revisado.
- 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.

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

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Este medicamento está sujeto a seguimiento adicional, lo que agilizará la detección de nueva información sobre su seguridad. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas. Ver la sección 4.8, en la que se incluye información sobre cómo notificarlas. **1. NOMBRE DEL MEDICAMENTO** Selincro 18 mg comprimidos recubiertos con película. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA** Cada comprimido recubierto con película contiene 18,06 mg de nalmefeno (como dihidrato de hidrocloruro). Excipiente con efecto conocido: cada comprimido recubierto con película contiene 60,68 mg de lactosa. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA** Comprimido recubierto con película (comprimido). Comprimido recubierto con película de color blanco, ovalado, biconvexo, de 6,0 x 8,75 mm y grabado con "S" en una cara. **4. DATOS CLÍNICOS 4.1 Indicaciones terapéuticas** Selincro está indicado para la reducción del consumo de alcohol en pacientes adultos con dependencia del alcohol que presentan un nivel de consumo de alcohol de alto riesgo (NCR) [ver sección 5.1], sin síntomas de abstinencia físicos y que no requieran una desintoxicación inmediata. Selincro solo se debe prescribir junto con apoyo psicosocial mantenido dirigido a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. El tratamiento con Selincro se debe iniciar únicamente en los pacientes que mantienen un NCR alto dos semanas después de la evaluación inicial. **4.2 Posología y forma de administración** Posología En la visita inicial, se deben evaluar el estado clínico, la dependencia del alcohol y el nivel de consumo de alcohol del paciente (según el paciente). Por lo tanto, se debe solicitar al paciente que registre su consumo de alcohol durante aproximadamente dos semanas. En la siguiente visita, se puede iniciar el tratamiento con Selincro en los pacientes que mantienen un NCR alto, (ver sección 5.1) durante este periodo de dos semanas, junto con una intervención psicosocial dirigida a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. Durante los ensayos clínicos pivotales la principal mejoría se observó durante las 4 primeras semanas. Se debe evaluar la respuesta del paciente al tratamiento y la necesidad de mantener farmacoterapia con regularidad (p. ej., mensualmente) (ver sección 5.1). El médico debe seguir evaluando la evolución del paciente en cuanto a la reducción del consumo de alcohol, el funcionamiento general, la adherencia al tratamiento y los posibles efectos adversos. Se dispone de datos clínicos para el uso de Selincro en condiciones controladas y aleatorizadas para un periodo de 6 a 12 meses. Se recomienda precaución al prescribir Selincro durante más de 1 año. Selincro se toma a demanda: cada día que el paciente perciba un riesgo anticipado de consumo de alcohol debe tomar un comprimido, preferiblemente 1-2 horas antes del momento de consumo. Si el paciente ha empezado a beber alcohol sin haber tomado Selincro, el paciente debería tomar un comprimido lo antes posible. La dosis máxima de Selincro es un comprimido al día. Selincro se puede tomar con o sin alimentos (ver sección 5.2). *Poblaciones especiales Población de edad avanzada (≥ 65 años de edad)* No se recomienda el ajuste de la dosis para este grupo de pacientes (ver secciones 4.4 y 5.2). *Insuficiencia renal* No se recomienda el ajuste de la dosis para los pacientes con insuficiencia renal leve o moderada (ver secciones 4.4 y 5.2). *Insuficiencia hepática* No se recomienda el ajuste de la dosis para los pacientes con insuficiencia hepática leve o moderada (ver secciones 4.4 y 5.2). *Población pediátrica* No se ha establecido la seguridad y eficacia de Selincro en niños y adolescentes de < 18 años. No se dispone de datos (ver sección 5.1). Forma de administración Selincro es un medicamento que se administra por vía oral. El comprimido recubierto con película se debe tragar entero. El comprimido recubierto con película no se debe dividir ni aplastar porque el nalmefeno puede provocar sensibilización cutánea en contacto directo con la piel (ver sección 5.3). **4.3 Contraindicaciones** Hipersensibilidad al principio activo o a alguno de los excipientes incluidos en la sección 6.1. Pacientes en tratamiento con agonistas opioides (como analgésicos opioides, opioides para terapia de sustitución con agonistas opioides (por ejemplo metadona) o agonistas parciales (por ejemplo buprenorfina)) (ver sección 4.4). Pacientes con una actual o reciente adicción a opiáceos. Pacientes con síntomas agudos de abstinencia de opiáceos. Pacientes con sospecha de uso reciente de opiáceos. Pacientes con insuficiencia hepática grave (clasificación de Child-Pugh). Pacientes con insuficiencia renal grave (eGFR < 30 ml/min por 1,73 m2). Pacientes con historia reciente de síndrome de abstinencia del alcohol agudo (incluyendo alucinaciones, convulsiones y delirium tremens). **4.4 Advertencias y precauciones especiales de empleo** Selincro no está indicado en pacientes cuyo objetivo terapéutico sea la abstinencia inmediata. La reducción del consumo de alcohol es un objetivo intermedio en el camino hacia la abstinencia. Administración de opiáceos En una situación de urgencia en la que se deban administrar opiáceos a un paciente que toma Selincro, la cantidad de opiáceo requerida para lograr el efecto deseado puede ser superior a la habitual. El paciente se debe someter a un estricto control para detectar síntomas de depresión respiratoria como consecuencia de la administración de opiáceos, así como otras reacciones adversas. Si se precisan opiáceos en una urgencia, la dosis siempre se debe ajustar de forma individual. Si se requieren dosis excepcionalmente altas, será necesaria una estrecha observación. El tratamiento con Selincro se debe interrumpir temporalmente 1 semana antes del uso previsto de opiáceos (p. ej., cuando se vayan a utilizar analgésicos opioides en una intervención quirúrgica programada). El médico prescriptor deberá advertir a los pacientes de la importancia de informar a su médico de la última toma de Selincro en caso de que sea necesario el uso de opiáceos. Se debe tener precaución cuando se utilicen medicamentos que contengan opiáceos (p. ej., antitusígenos, analgésicos opioides (ver sección 4.5)). Comorbilidad *Trastornos psiquiátricos* Se han registrado efectos psiquiátricos en estudios clínicos (ver sección 4.8). Si los pacientes presentan síntomas psiquiátricos no asociados al inicio del tratamiento con Selincro, y/o que no son transitorios, el médico prescriptor deberá considerar otras causas de los síntomas y valorar la necesidad de continuar el tratamiento con Selincro. Selincro no se ha investigado en pacientes con enfermedad psiquiátrica inestable. Se debe proceder con precaución al prescribir Selincro a pacientes con comorbilidad psiquiátrica presente como el trastorno depresivo mayor. *Trastornos convulsivos* Se dispone de experiencia limitada en pacientes con antecedentes de trastornos convulsivos, incluidas las convulsiones por abstinencia de alcohol. Se recomienda precaución si se inicia un tratamiento para reducir el consumo de alcohol en estos pacientes. *Insuficiencia renal o hepática* Selincro se metaboliza principalmente en el hígado y se elimina predominantemente por la orina. Por lo tanto, se debe tener precaución cuando se prescriba Selincro a pacientes con insuficiencia renal o hepática leve o moderada, por ejemplo, realizando controles más frecuentes. Se debe proceder con precaución al prescribir Selincro a pacientes con valores altos de ALAT o ASAT (> 3 veces el LSN), ya que estos pacientes fueron excluidos del programa de desarrollo clínico. Pacientes de edad avanzada (≥ 65 años de edad) Se dispone de datos clínicos limitados sobre el uso de Selincro en pacientes ≥ 65 años de edad con dependencia del alcohol. Se debe tener precaución al prescribir Selincro a pacientes ≥ 65 años de edad (ver secciones 4.2 y 5.2). Otras Se recomienda precaución si Selincro se administra conjuntamente con un inhibidor potente de la enzima UGT2B7 (ver sección 4.5). Lactosa Los pacientes con intolerancia hereditaria a galactosa, insuficiencia de lactasa de Lapp o problemas de malabsorción de glucosa o galactosa no deben tomar este medicamento. **4.5 Interacción con otros medicamentos y otras formas de interacción** No se han llevado a cabo estudios de interacción farmacológica *in vivo*. Según estudios *in vitro*, no se prevén interacciones clínicamente relevantes entre el nalmefeno, o sus metabolitos, y medicamentos administrados simultáneamente metabolizados por las enzimas más comunes CYP450 y UGT o transportadores de membrana. La administración conjunta con medicamentos que sean inhibidores potentes de la enzima UGT2B7 (p. ej., diclofenaco, fluconazol, acetato de medroxiprogesterona, ácido meclofenámico) puede aumentar significativamente la exposición a nalmefeno. Es improbable que esto suponga un problema con el uso ocasional, pero si se inicia un tratamiento a largo plazo simultáneo con un inhibidor potente de la UGT2B7, no se puede descartar la posibilidad de un aumento en la exposición a nalmefeno (ver sección 4.4). Por el contrario, la administración conjunta con un inductor de la UGT (p. ej., dexametasona, fenobarbital, rifampicina, omeprazol) puede dar lugar a concentraciones plasmáticas subterapéuticas de nalmefeno. Si se toma Selincro de manera simultánea con agonistas opioides (p. ej., algunos tipos de antitusígenos y antigripales, determinados antidiarreicos, y analgésicos opioides), puede que el paciente no se beneficie del agonista opioide. No existe ninguna interacción farmacocinética clínicamente relevante entre el nalmefeno y el alcohol. Se produce un pequeño deterioro en la función cognitiva y psicomotora tras la administración de nalmefeno. No obstante, el efecto de la combinación de nalmefeno y alcohol no superó la suma de los efectos de cada uno de ellos por separado. El consumo simultáneo de alcohol y Selincro no previene los efectos de la intoxicación del alcohol. **4.6 Fertilidad, embarazo y lactancia** Embarazo No hay datos o estos son limitados (menos de 300 resultados en embarazos) relativos al uso de nalmefeno en mujeres embarazadas. Los estudios en animales han mostrado toxicidad en la reproducción (ver sección 5.3). No se recomienda Selincro durante el embarazo. Lactancia Los datos farmacodinámicos/toxicológicos disponibles en animales muestran que nalmefeno/metabolitos se excretan en la leche (ver sección 5.3). Se desconoce si nalmefeno se excreta en la leche materna. No se puede excluir el riesgo en recién nacidos/lactantes. Se debe decidir si es necesario interrumpir la lactancia o interrumpir/abstenerse de iniciar el tratamiento con Selincro tras considerar el beneficio de la lactancia para el niño y el beneficio del tratamiento para la madre. Fertilidad En estudios de fertilidad en ratas, no se observaron efectos de nalmefeno sobre la fertilidad, el apareamiento, el embarazo o los parámetros espermáticos. **4.7 Efectos sobre la capacidad para conducir y utilizar máquinas** No se ha estudiado la influencia de nalmefeno sobre la capacidad para conducir y utilizar máquinas. Selincro puede provocar reacciones adversas como náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, relacionadas con el inicio del tratamiento y tuvieron una corta duración. La influencia de Selincro sobre la capacidad para conducir y utilizar máquinas es nula o insignificante. **4.8 Reacciones adversas** Resumen del perfil de seguridad Más de 3.000 pacientes han sido expuestos a nalmefeno en estudios clínicos. En general, el perfil de seguridad concuerda en todos los estudios clínicos realizados. Las frecuencias de las reacciones adversas en la Tabla 1 se calcularon basándose en tres estudios aleatorizados, a doble ciego y controlados con placebo en pacientes con dependencia del alcohol (1.144 pacientes expuestos a Selincro a demanda y 797 expuestos a placebo a demanda). Las reacciones adversas más frecuentes fueron náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración. En los estudios clínicos se comunicaron estados confusionales y, en raras ocasiones, alucinaciones y disociación. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración (de unas pocas horas a unos pocos días). La mayoría de estas reacciones adversas se resolvieron con el tratamiento continuo y no recurrieron con la administración repetida. Si bien estos acontecimientos tuvieron generalmente una corta duración, podrían tratarse de psicosis alcohólica, síndrome de abstinencia alcohólica o enfermedad psiquiátrica comórbida. Tabla de reacciones adversas Las frecuencias se definen como: muy frecuentes (≥1/10), frecuentes (≥1/100 a <1/10), poco frecuentes (≥1/1.000 a <1/100), raras (≥1/10.000 a <1/1.000), muy raras (<1/10.000) o frecuencia no conocida (no puede estimarse a partir de los datos disponibles). Notificación de sospechas de reacciones adversas Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del sistema Español de Farmacovigilancia de medicamentos de Uso Humano: https://www.notificaram.es. **4.9 Sobredosis** En un estudio en pacientes diagnosticados de ludopatía, se investigaron dosis de nalmefeno de hasta 90 mg/día durante 16 semanas. En un estudio en pacientes con cistitis intersticial, 20 pacientes recibieron 108 mg/día de nalmefeno durante más de 2 años. Se ha registrado la toma de una dosis única de 450 mg de nalmefeno sin cambios en la tensión arterial, la frecuencia cardiaca y respiratoria o la temperatura corporal. No se ha observado un patrón atípico de reacciones adversas en estos contextos, si bien la experiencia es limitada. En caso de sobredosis, se recomienda realizar un tratamiento sintomático y someter al paciente a observación. **5. PROPIEDADES FARMACOLÓGICAS 5.1 Propiedades farmacodinámicas** Grupo farmacoterapéutico: Otros fármacos del sistema nervioso utilizados en la dependencia del alcohol. Código ATC: N07BB05 Mecanismo de acción El nalmefeno es un modulador del sistema opioide con un perfil definido de receptores μ, δ y κ. - Estudios *in vitro* han demostrado que el nalmefeno es un ligando selectivo de los receptores opioides con actividad antagonista en los receptores μ y δ y actividad agonista parcial en el receptor κ. - Estudios *in vivo* han demostrado que el nalmefeno reduce el consumo de alcohol, posiblemente como resultado de la modulación de las funciones corticomesolímbicas. Los datos de estudios no clínicos, estudios clínicos y literatura médica no indican ninguna forma de posible dependencia o abuso de Selincro. Eficacia clínica y seguridad En dos estudios de eficacia se evaluó la eficacia de Selincro en la reducción del consumo de alcohol en pacientes con dependencia del alcohol (DSM-IV). Se excluyó a los pacientes con antecedentes de delirium tremens, alucinaciones, convulsiones, comorbilidad psiquiátrica significativa, o alteraciones significativas de la función hepática así como a aquellos que presentaban síntomas de abstinencia físicos apreciables en la selección o la aleatorización. La mayoría (80%) de los pacientes incluidos tenían un NCR alto o muy alto (consumo de alcohol > 60 g/día en hombres y > 40 g/día en mujeres según los NCR de alcohol de la OMS) en la selección, y de estos el 65% mantuvieron un NCR alto o muy alto entre la selección y la aleatorización. Ambos estudios fueron aleatorizados, a doble ciego, con grupos paralelos y controlados con placebo, y al cabo de 6 meses de tratamiento, los pacientes que recibieron Selincro se volvieron a aleatorizar para recibir placebo o Selincro durante un periodo de lavado final de 1 mes. La eficacia de Selincro también se evaluó en un estudio aleatorizado, a doble ciego, con grupos paralelos, controlado con placebo y de 1 año de duración. En conjunto, en los estudios participaron 1.941 pacientes, de los cuales 1.144 fueron tratados con Selincro 18 mg a demanda. En la visita inicial se evaluaron el estado clínico, la situación social y el patrón de consumo de alcohol de los pacientes (según la información del paciente). En la visita de aleatorización, que tuvo lugar al cabo de 1 a 2 semanas se reevaluó el NCR, y se inició el tratamiento con Selincro junto con una intervención psicosocial (BRENDA) dirigida a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. Selincro se prescribió a demanda, y los pacientes lo tomaron, de promedio, aproximadamente la mitad de los días. La eficacia de Selincro se evaluó utilizando dos criterios de valoración principales: el cambio desde la visita basal al mes 6 en el número de días de consumo excesivo de alcohol (DCE) al mes y el cambio desde la visita basal al mes 6 en el consumo de alcohol total diario (CAT). Un DCE se definió como un día con un consumo ≥ 60 g de alcohol puro en hombres y ≥ 40 g en mujeres. Se produjo una reducción significativa del número de DCE y CAT en algunos pacientes en el periodo entre la visita inicial (selección) y la aleatorización debido a efectos no farmacológicos. En los estudios 1 (n = 579) y (n = 655) 2, el 18% y el 33% de la población total, respectivamente, redujeron considerablemente su consumo de alcohol en el periodo comprendido entre la selección y la aleatorización. Con respecto a los pacientes con un NCR alto o muy alto en la visita basal, el 35% de los pacientes experimentaron mejorías debido a los efectos no farmacológicos en el período entre la visita inicial (selección) y la aleatorización. En la aleatorización, estos pacientes consumían una cantidad tan baja de alcohol que era poco el margen para seguir mejorando (efecto suelo). Por lo tanto, los pacientes que mantuvieron un NCR alto o muy alto en la aleatorización se definieron a posteriori como la población objetivo. En esta población post hoc, el efecto terapéutico fue mayor en comparación con el de la población total. La eficacia y relevancia clínicas de Selincro se analizaron en pacientes con un NCR alto o muy alto en la selección y la aleatorización. En la visita basal, los pacientes tenían, de promedio, 23 DCE al mes (11% de los pacientes tenían menos de 14 DCE al mes) y consumían 106 g/día. La mayoría de los pacientes tenían una dependencia del alcohol baja (55% con una puntuación de 0 a 13) o intermedia (36% con una puntuación de 14 a 21) según la Escala de Dependencia de Alcohol. *Análisis post-hoc de la eficacia en pacientes que mantuvieron un NCR alto o muy alto en la*

Tabla 1: Frecuencias de las reacciones adversas

Sistema de clasificación de órganos	*Frecuencia*	*Reacción adversa*
Trastornos del metabolismo y de la nutrición	Frecuente	Apetito disminuido
Trastornos psiquiátricos	Muy frecuente	Insomnio
	Frecuente	Trastorno del sueño
		Estado confusional
		Inquietud
		Libido disminuida (incluida la pérdida de líbido)
	No conocida	Alucinación (incluidas alucinaciones auditivas, alucinaciones táctiles, alucinaciones visuales y alucinaciones somáticas)
		Disociación
Trastornos del sistema nervioso	Muy frecuente	Mareo
		Cefalea
	Frecuente	Somnolencia
		Temblor
		Alteración de la atención
		Parestesia
		Hipoestesia
Trastornos cardiacos	Frecuente	Taquicardia
		Palpitaciones
Trastornos gastrointestinales	Muy frecuente	Náuseas
	Frecuente	Vómitos
		Boca seca
Trastornos de la piel y del tejido subcutáneo	Frecuente	Hiperhidrosis
Trastornos musculoesqueléticos y del tejido conjuntivo	Frecuente	Espasmos musculares
Trastornos generales y alteraciones en el lugar de administración	Frecuente	Fatiga
		Astenia
		Malestar general
		Sensación anormal
Exploraciones complementarias	Frecuente	Peso disminuido

Tabla 2: Resultados de los análisis de respondedores con datos agrupados de pacientes con un NCR alto o muy alto en la selección y la aleatorización

Respuesta[a]	Placebo	Nalmefeno	Odds ratio (IC del 95%)	Valor p
CAT R70[b]	19,9%	25,4%	1,44 (0,97; 2,13)	0,067
0-4 DCE[c]	16,8%	22,3%	1,54 (1,02; 2,35)	0,040

a En el análisis se trata a los pacientes que abandonaron como no respondedores
b Reducción del CAT ≥ 70% respecto al valor basal en el mes 6 (periodo de 28 días)
c De 0 a 4 DCE/mes en el mes 6 (periodo de 28 días)

aleatorización En el estudio 1, el porcentaje de abandonos fue más elevado en el grupo de Selincro que en el grupo de placebo (50% frente a 32%, respectivamente). En cuanto a los DCE, se registraron 23 días/mes en la visita basal en el grupo de Selincro (n = 171) y 23 días/mes en la visita basal en el grupo de placebo (n = 167). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el número de DCE fue de 9 días/mes en el grupo de Selincro (n = 85) y 14 días/mes en el grupo de placebo (n = 114). El CAT fue de 102 g/día en la visita basal en el grupo de Selincro (n = 171) y 99 g/día en la visita basal en el grupo de placebo (n = 167). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el CAT fue de 40 g/día en el grupo de Selincro (n = 85) y 57 g/día en el grupo de placebo (n = 114). En el estudio 2, el porcentaje de abandonos fue superior en el grupo de Selincro que en el grupo de placebo (30% frente a 28%, respectivamente). En cuanto a los DCE, se registraron 23 días/mes en la visita basal en el grupo de Selincro (n = 148) y 22 días/mes en la visita basal en el grupo de placebo (n = 155). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el número de DCE fue de 10 días/mes en el grupo de Selincro (n = 103) y 12 días/mes en el grupo de placebo (n = 111). El CAT fue de 113 g/día en la visita basal en el grupo de Selincro (n = 148) y 108 g/día en la visita basal en el grupo de placebo (n = 155). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia en el mes 6, el CAT fue de 44 g/día en el grupo de Selincro (n = 103) y 52 g/día en el grupo de placebo (n = 111). Los análisis de respondedores con los datos agrupados de los dos estudios se incluyen en la Tabla 2. Se dispone de datos limitados sobre Selincro en el periodo de lavado final de 1 mes. *Estudio de 1 año* En este estudio participaron un total de 665 pacientes: 52% de ellos tenían un NCR alto o muy alto en la visita basal, y de estos el 52% (que representan el 27% de la población total) siguieron teniendo un NCR alto o muy alto en la aleatorización. En esta población objetivo post-hoc, abandonaron más pacientes que recibían nalmefeno (45%) que aquellos que recibían placebo (31%). En cuanto a los DCE, se registraron 19 días/mes en la visita basal en el grupo de Selincro (n = 141) y 19 días/mes en la visita basal en el grupo de placebo (n = 42). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia al cabo de 1 año, el número de DCE fue de 5 días/mes en el grupo de Selincro (n = 78) y 10 días/mes en el grupo de placebo (n = 29) E l CAT fue de 100 g/día en la visita basal en el grupo de Selincro (n = 141) y 101 g/día en la visita basal en el grupo de placebo (n = 42). Respecto a los pacientes que continuaron en el estudio y proporcionaron datos de eficacia al cabo de un año, el CAT fue de 24 g/día en el grupo de Selincro (n = 78) y 47 g/día en el grupo de placebo (n = 29). Población pediátrica La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Selincro en los diferentes grupos de la población pediátrica en el tratamiento de la dependencia del alcohol (ver sección 4.2 para consultar la información sobre el uso en la población pediátrica). **5.2 Propiedades farmacocinéticas** Absorción El nalmefeno se absorbe rápidamente tras una única administración oral de 18,06 mg, con una concentración máxima (C_{max}) de 16,5 ng/ml al cabo de aproximadamente 1,5 horas, y una exposición (AUC) de 131 ng*h/ml. La biodisponibilidad oral absoluta de nalmefeno es del 41%. La administración de alimentos ricos en grasas aumenta la exposición total (AUC) en un 30% y la concentración máxima (C_{max}) en un 50%; el tiempo hasta la concentración máxima (t_{max}) se retrasa 30 minutos (t_{max} es de 1,5 horas). Se considera poco probable que este cambio tenga relevancia clínica. Distribución La fracción media de nalmefeno unida a proteínas en plasma es de aproximadamente el 30%. El volumen de distribución (Vd/F) estimado es de aproximadamente 3200 l. Los datos de ocupación obtenidos en un estudio PET tras la administración diaria única y repetida de 18,06 mg de nalmefeno muestran un 94-100% de ocupación de los receptores 3 horas después de la administración, lo que indica que el nalmefeno atraviesa fácilmente la barrera hematoencefálica. Biotransformación Tras la administración oral, el nalmefeno sufre un extenso y rápido metabolismo para formar su principal metabolito, el nalmefeno-3-O-glucurónido, siendo la enzima UGT2B7 la principal responsable de la conversión, y con las enzimas UGT1A3 y UGT1A8 como factores contribuyentes secundarios. Un pequeño porcentaje de nalmefeno se convierte en nalmefeno-3-O-sulfato por sulfatación y en nornalmefeno por CYP3A4/5. El nornalmefeno se convierte posteriormente en nornalmefeno 3 O glucurónido y nornalmefeno-3-O-sulfato. Se considera que los metabolitos no contribuyen con un efecto farmacológico significativo sobre los receptores opioides en humanos, salvo en el caso de nalmefeno-3-O-sulfato, que posee una potencia comparable a la de nalmefeno. No obstante, el nalmefeno-3-O-sulfato está presente a concentraciones inferiores al 10% de la de nalmefeno, por lo que es muy poco probable que constituya un factor contribuyente principal en el efecto farmacológico de nalmefeno. Eliminación El metabolismo por conjugación del glucurónido es el principal mecanismo de aclaramiento de nalmefeno, y la excreción renal es la principal vía de eliminación de nalmefeno y sus metabolitos. El 54% de la dosis total se elimina por la orina en forma de nalmefeno-3-O-glucurónido, mientras que el nalmefeno y sus otros metabolitos están presentes en la orina en cantidades inferiores al 3% cada uno. Se calcula que el aclaramiento oral de nalmefeno (CL/F) es de 169 l/h y la semivida de eliminación de 12,5 horas. De los datos de distribución, metabolismo y eliminación se desprende que el nalmefeno tiene un coeficiente de extracción hepática elevado. Linealidad/No linealidad El nalmefeno muestra un perfil farmacocinético lineal independiente de la dosis en el intervalo de dosis de 18,06 mg a 72,24 mg, con un aumento de 4,4 veces en la C_{max} y un aumento de 4,3 veces en el AUC_{0-tau} (en estado estacionario o casi). El nalmefeno no muestra diferencias farmacocinéticas importantes entre sexos, entre jóvenes y ancianos, o entre diferentes grupos étnicos. Sin embargo, el tamaño corporal parece afectar mínimamente al aclaramiento de nalmefeno (el aclaramiento aumenta cuanto mayor es el tamaño corporal), si bien se considera poco probable que tenga relevancia clínica. Insuficiencia renal No se dispone de datos tras la administración oral en pacientes con insuficiencia renal. La administración IV de 1 mg de nalmefeno en pacientes con insuficiencia renal grave produjo una exposición 1,6 veces mayor (AUC_{inf} ajustada por dosis), y una menor C_{max} (en un factor de aproximadamente 2,1 a 4,6) que en voluntarios sanos. La semivida de eliminación (26 horas) fue más larga que la de los voluntarios sanos (10 horas) (ver secciones 4.3 y 4.4). Insuficiencia hepática La administración de una dosis única de 18,06 mg de nalmefeno a los pacientes con insuficiencia hepática leve o moderada aumentó la exposición respecto a la de los voluntarios sanos. En pacientes con insuficiencia hepática leve, la exposición aumentó 1,5 veces y el aclaramiento oral se redujo en aproximadamente un 35%. En pacientes con insuficiencia hepática moderada, la exposición aumentó 2,9 veces para el AUC y 1,7 veces para la C_{max}, mientras que el aclaramiento oral se redujo en cerca del 60%. No se observaron cambios clínicamente relevantes en el t_{max} o la semivida de eliminación en ninguno de los grupos. No se dispone de datos farmacocinéticos tras la administración oral de nalmefeno a pacientes con insuficiencia hepática grave (ver secciones 4.3 y 4.4). Pacientes de edad avanzada No se ha realizado ningún estudio específico con administración oral en pacientes de ≥ 65 años. Un estudio con administración IV indicó que no existen cambios relevantes en la farmacocinética en pacientes de edad avanzada en comparación con adultos más jóvenes (ver secciones 4.2 y 4.4). **5.3 Datos preclínicos sobre seguridad** El nalmefeno ha mostrado potencial de sensibilización cutánea en el ensayo de ganglio linfático local en ratones tras la aplicación tópica. Los estudios en animales no sugieren efectos perjudiciales directos con respecto a la fertilidad, el embarazo, el desarrollo embrionario o fetal, el parto o el desarrollo posnatal. En un estudio de toxicidad para el desarrollo realizado en conejos, se observaron efectos en los fetos en términos de reducción de peso fetal y retraso en la osificación, pero no anomalías graves. La AUC a dosis máximas sin efecto adverso observado (NOAEL), para estos efectos fue inferior a la exposición en humanos a la dosis clínica recomendada. Se observó un aumento de la viabilidad natal y una disminución de la viabilidad posnatal de las crías en estudios de toxicidad prenatal y posnatal en ratas. Este efecto se consideró un efecto indirecto relacionado con la toxicidad materna. Los estudios en ratas han mostrado excreción de nalmefeno o sus metabolitos en leche. Los datos no clínicos no muestran riesgos especiales para los seres humanos según los estudios convencionales de farmacología de seguridad, toxicidad a dosis repetidas, genotoxicidad o potencial carcinogénico. **6. DATOS FARMACÉUTICOS 6.1 Lista de excipientes** Núcleo del comprimido Celulosa microcristalina Lactosa anhidra Crospovidona, tipo A Estearato de magnesio Recubrimiento del comprimido Hipromelosa Macrogol 400 Dióxido de titanio (E171) **6.2 Incompatibilidades** No procede. **6.3 Periodo de validez** 3 años. **6.4 Precauciones especiales de conservación** Este medicamento no requiere condiciones especiales de conservación. **6.5 Naturaleza y contenido del envase** Blísters transparentes de PVC/PVdC/aluminio en cajas de cartón. Tamaños de envases de 7, 14, 28, 42, 49 y 98 comprimidos recubiertos con película. Puede que solamente estén comercializados algunos tamaños de envases. **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** H. Lundbeck A/S Ottiliavej 9 DK-2500 Valby Dinamarca **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN** EU/1/12/815/001 7 comprimidos EU/1/12/815/002 14 comprimidos EU/1/12/815/003 28 comprimidos EU/1/12/815/004 42 comprimidos EU/1/12/815/005 98 comprimidos EU/1/12/815/006 49 comprimidos EU/1/12/815/007 14 comprimidos, tarjeta EU/1/12/815/008 28 comprimidos, tarjeta **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN** Fecha de la primera autorización: 25 de Febrero de 2013 **10. PRESENTACIÓN Y PRECIO PVP (IVA)** Selincro 18 mg, envase con 14 comprimidos. P.V.P 63,04 € P.V.P iva 65,57 € **11. CONDICIONES DE DISPENSACIÓN POR LA SEGURIDAD SOCIAL** Con receta médica. Especialidad reembolsable por el Sistema Nacional de Salud. Con visado de inspección. Cícero de aportación reducida. **12. FECHA DE LA REVISIÓN DEL TEXTO:** Mayo 2015 La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu/.

Reducir para ganar

Único fármaco indicado para la reducción del consumo de alcohol[2]

(2) Ficha técnica Selincro 2013

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