

Adicciones

■ **SOCIDROGALCOHOL** Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías

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Alcoholism and mutual help. From necessity to evidence

Alcoholismo y ayuda mutua. De la necesidad a la evidencia

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Alcohol consumption is one of the most important public health risk factors worldwide, with a high proportion of the toxic effects of drinking associated with deterioration, which may have a permanent impact at the level of the central nervous system (Soler et al., 2014).

Despite the passing of time, mutual help or self-help movements (sometimes used synonymously) continue to be a reality in the treatment of addictions, in general, and of alcoholism, in particular.

With historical roots dating back to 19th century temperance movements (Pascual Pastor & Castellano Gómez, 2006), in some cases of a religious or military nature, their ultimate aim is to achieve and obtain complete abstinence from alcohol. The progress of these movements has enabled creating programmes such as Alcoholics Anonymous (AA) (Pascual Pastor, 2009) based on 12 steps, or Recovered Alcoholics (RA), with a more multidisciplinary approach including recovered alcoholics, professionals (physicians, psychologists, social workers, etc.) and family support in accordance with the so-called Minnesota method (Carreras Alabau, 2011).

Though the terms “self-help” and “mutual help” are used interchangeably, far from being synonyms both are complementary, while the first refers to assuming personal responsibility for taking care of oneself, and the second refers to support given by someone to another.

In 1978, the Mental Health Commission of the U.S. Government proposed self-help as the main pillar of community mental health interventions (Villalba Quesada, 1996). Rather than weakening the model, the passing of time has consolidated it, and regional and national organizations exist across different points worldwide. Even in Europe, one of these groups has established the European Mutual Help Network for Alcohol Related Problems (EMNA), for the purpose of standardizing support, offering help and fostering advocacy.

In Spain, the Confederation of Alcoholic Addicts in Recovery and Family Members (CAARFE), founded in early 2015 on the basis of the experience of the extinct Federation of Recovered Alcoholics of Spain (FARE), has completed the structure with the participation of three pillars: the ill undergoing rehabilitation, family members and professionals. Addictions other than alcohol have also been included, given

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that types of substance use have changed the profile of the user, presenting a pattern of polydrug use or several addictions, normally of alcohol together with cocaine, cannabis, tobacco or even behavioural addictions, especially gambling.

Now then, our objective is to define these groups or movements, listing their goals and evaluating their efficiency based on scientific evidence.

Self-help Groups (SHGs) are a health model, especially relevant as a “peer” model, comprised of individuals sharing the same pathology or conflict. These arose in response to the lack of professional services, quickly revealed their efficiency and the World Health Organization itself recommended it for certain community health needs (WHO, 1987).

Its strengths are founded on learning, emotional support, participation and self-esteem, the ability to request social changes and the capacity for organization.

Its main principles are its meetings, knowledge and personal experience and support among its participants, originally without the presence of professionals, but their development revealed an increase of their validity for the community through the participation of professionals for completing the treatment (Roca Soriano, 1998), using the reciprocity inherent to this therapeutic approach based on Giving, Receiving and Contributing (Módena, 2009).

The basic essence of the structure is its democratic nature, adapted to the place, surroundings and culture where experiences are shared without generalizing, without offering advice, without making value judgments and without stances of speaking from the perspective of knowing or being (Montaño Fraire, 2010).

Its fundamental objectives are to satisfy a shared need, to overcome an obstacle that seriously hinders one’s life and to achieve desired social or personal changes (Villalba Quesada, 1996). As concerns addictions, this entails attaining and maintaining abstinence, improving one’s personal weaknesses, and modifying one’s way of being, acting and relating.

According to García Roldán et al. (1997), interaction within self-help groups enables patients to acquire knowledge about their illness, debunk myths about drugs, learn coping strategies and, especially, share experiences on how to confront and overcome conflicts that have generated their addiction, alcohol consumption, and change their lifestyle and remain abstinent, achieving integration within family, employment and social circles (Martínez Leiva et al, 2010).

However, are these actually effective?

Apparently, different studies claim they are. In 2004 a study was carried out with 279 alcohol-dependent patients (Zemore et al, 2004), obtaining positive results, analysing the progress of patients participating in the 12-step programme, likewise corroborated by the Match project (Paganó et al, 2004), even asserting that participants in SHGs remained abstinent longer than those who participated in conventional treatment, wherefore physicians were encouraged to refer alcoholic patients to these groups.

These results led the American Psychiatric Association in 2006 to position SHGs as a primary recommendation for treating alcoholism (APA, 2006)

However, a review of Cochrane Library literature mostly using the work carried out by AA is inconclusive, and highlights the lack of more complete studies to establish scientific evidence (Ferri et al., 2006).

Though the AA model is the longest-standing programme with the widest dissemination to date, paradoxically its only requirement is for participants to desire to quit drinking and, despite the group’s heterogeneity, the sole target is to attain abstinence, though a minimum participation of once per week is necessary to obtain good results (Martínez Ortiz, 2013). Other studies claim that participating twice weekly results in at least 3 more days per month of abstinence from alcohol (Humphreys et al., 2014).

In Spain, results are currently being evaluated. In 2013, a study was published based on the integration of SHGs for family members in a public alcohol treatment programme (Rubio et al., 2013) that concluded that interventions with family members of patients dependent on alcohol proved efficient for improving the prognosis of dependency on alcohol, which improves when said family members participate in the SHGs, resulting in lower rates of abandonment and fewer days of drinking during treatment for the patients themselves.

Coordination with the public health system and membership in these groups increases abstinence and decreases the number of relapses, confirming that the longer the participation in these groups the lower the probability of relapsing as to substance abuse (Pascual, 2015), making the SHGs a good therapeutic strategy together with public assistance for alcohol-related problems.

According to the Socidrogalcohol Clinical Guide, evidence for these interventions attains a level of 2B and a recommendation level of B (Tomás, 2013).

Clearly, these are useful therapeutic strategies, but a more exhaustive, homogeneous evaluation of resources and methods is required to assert their suitability as a therapeutic option. For now, there is no doubt that it is a useful, complementary therapy to reduce relapses, increase adherence to treatment and maintain longer abstinence. Even better results are obtained when family members and patients participate together, with the corresponding professional support and guidance.

Therefore, we are in the presence of an assistance model for problems related with the consumption of alcohol and other addictions, which may be assumed to be an ideal complement that brings treatment closer to patients and their family members, due to geographical nearness, flexible time schedules and the empathy of the structure itself, comprised of individuals who have experienced the same addiction. However, we insist on the participation of professionals and of coordination with community health services specialized in this type of pathology.

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Hepatitis C and HIV in injecting drug users in Armenia, Colombia

Hepatitis C y VIH en usuarios de drogas inyectables en Armenia-Colombia

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Abstract

A constant and progressive increase in the availability of heroin in Colombia in recent decades and the intravenous use of this drug have established the need to prevent a possible epidemic of HIV and hepatitis C. This research determined the sero-prevalence of hepatitis C and HIV according to sociodemographic characteristics and risk behaviors in people who inject drugs in Armenia, Colombia. This is a cross-sectional study on 265 users captured through respondent-driven sampling after informed consent. Sero-prevalence of hepatitis C was 22.3 % [95% CI 12.3 % -23.5 %]; for HIV infection, it was 2.6 % [95% CI 0.4 to 6.0]; 67.5% reported injecting for more than two years, 35 % shared needles and syringes, and 12.4 % had used a condom during their last sexual intercourse. Users who did not purchase syringes in drugstores in the last six months are 2.7 times [95% CI 1.32 to 5.48] more likely to contract hepatitis C; daily injection frequency was higher in HIV- positive cases [OR 2.87; 95% CI 0.55 to 15.9] but nonsignificant. One fourth of respondents are infected with HIV or hepatitis C, either as a single infection or co-infection. This study identified risk practices such as sharing needles and low condom use in the last six months, worldwide documented and discussed risk factors. This research is a first step in the search for strategies to prevent the spread of HIV infection and hepatitis C in networks of injecting drug users.

Key words: hepatitis C, HIV, heroin, epidemiology.

Resumen

Un aumento constante y progresivo en la disponibilidad de heroína en Colombia en las últimas décadas, y el uso de esta droga vía intravenosa, ha establecido la necesidad de prevenir una posible epidemia de VIH y hepatitis C. Esta investigación determinó la seroprevalencia de hepatitis C y VIH según características sociodemográficas y comportamientos de riesgo en población que se inyecta drogas en Armenia-Colombia. Estudio transversal en 265 usuarios captados a través de muestreo guiado por el encuestado previo consentimiento informado. La seroprevalencia de hepatitis C fue 22,3% [IC95% 12,3%-23,5%]; la infección por VIH fue 2,6% [IC95% 0,4-6,0]. El 67,5% reportó inyección por más de dos años, el 35% compartió jeringas y agujas y el 12,4% utilizó condón en su última relación sexual. Los usuarios que no adquirían jeringas en droguerías en los últimos seis meses tienen 2,7 [IC95% 1,32-5,48] veces el riesgo de hepatitis C; la frecuencia diaria de inyección fue mayor en los casos positivos con VIH [OR 2,87; IC95% 0,55-15,9] pero no significativa. La cuarta parte de los encuestados, están infectados por VIH o hepatitis C, en forma de infección única o coinfección. Este estudio identificó prácticas de riesgo, como compartir jeringas y baja utilización del condón en los últimos seis meses, factores de riesgo documentados y discutidos mundialmente. Esta investigación constituye un primer paso en la búsqueda de estrategias para prevenir la propagación de infecciones por VIH y hepatitis C en redes de usuarios de drogas inyectables.

Palabras clave: hepatitis C, VIH, heroína, epidemiología.

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The World Health Organization (WHO, 2012) calculates that each year, between three and four million people worldwide are infected with hepatitis C virus (HCV), 150 million people suffer from chronic infection, and 350,000 people die from HCV-related diseases.

Hepatitis C is distributed worldwide. It is estimated that each injecting drug user (IDU) who acquires HCV can transmit the virus approximately to 20 people, and half of these transmissions occur in the first two years of infection (Magiorkinis et al., 2013).

According to UNAIDS (2012), transmission of HIV by injecting drug use continues to be one of the most important challenges. It is estimated that in 49 countries, the prevalence of HIV in IDUs is 22 times higher than in the rest of the population; and in 11 countries, the level of infection is 50 times higher. To this challenge are added stigma and lack of access to health services.

Worldwide HIV seropositivity in population aged 15-49 years is 0.8% but morbidity from this infection still varies considerably between countries and regions (UNAIDS, 2012).

HIV and HCV epidemics associated with injected drug use have been widely documented and the search for appropriate and timely intervention is currently one of the priority actions in countries where this type of consumption is observed (WHO, 2012).

Latin American countries are characterized by a mainly concentrated HIV epidemic, affecting people who use drugs, sex workers, transgender people, and people who have sex with men. Among these people who use drugs, the group that has been identified as the most vulnerable is that of IDUs (Bravo & Barrio, 2008).

In 2010, a study of HIV prevalence and risk behaviors in IDUs was carried out in two cities of Colombia (Medellín and Pereira), the results of which reported prevalences of 3.8% and 1.9%, respectively. This study concluded that there is a risk of extending HIV to other cities of Colombia among the networks of IDUs (Berbesi et al., 2012). As can be expected, in Colombia, infection by HIV also has been defined as a concentrated epidemic that fulfills the conditions established by the WHO (UNAIDS, 2000).

During the last decades, a steady and progressive increase in the availability of heroin in Colombia has revealed the need to prevent a possible epidemic of infections such as HIV and HCV due to the intravenous consumption of drugs (Berbesi et al., 2013). Although drug use is decriminalized in the country since 1994, the health system has not been adequately developed, and there are no clear policies against mitigation, reduction, or needle exchange programs (Gómez, 2013).

Therefore, this study sought to estimate the prevalence of HIV and HCV and to identify risk behaviors for their transmission among IDUs in Armenia-Colombia.

Method

A cross-sectional study was conducted using respondent-driven sampling. The target population was IDUs living in the city of Armenia¹-Colombia. Inclusion criteria were being an active IDU (in the past six months); being between 18 and 65 years of age, signing the informed consent, and having an effective of Respondent Driven Sampling (RDS) coupon.

Recruitment began with a group of "seeds" or participants selected nonrandomly from the target population through key informants. These people received two types of economic incentives: primary, for participating in the study and secondary, linked to the successful recruitment of three new participants. The incentive values ranged between US \$5 and \$4, respectively.

To calculate sample size, the Fleiss formula was used to estimate a proportion, the confidence level was 95%, absolute accuracy was 4%, design effect was 4, with an expected ratio of 3%, taking into account the HIV prevalence among the IDU population in 2010 (Berbesi et al., 2012). The size of the sample was of 250 IDUs; RDS sampling estimates sampling errors through measures such as homophilia, heterophilia, and proportional population estimates. The sample size was reached within a period of six weeks.

We used the same instrument as was applied to the IDU population in Medellín and Pereira in 2010 (Berbesi et al., 2012), which was based on that designed by the WHO in Bogotá in 2000 by Mejía and Gómez (2005). This form included questions about the demographic characteristics and risk behaviors and was applied by a group of previously trained and standardized interviewers; blood samples were also taken in filter paper for laboratory tests to detect HCV and HIV; cases were confirmed by RNA Viral load tests and Western Blot, respectively.

The statistical analysis of the data and tables of results were generated with RDSAT® and SPSS® 21.0. We described the socio-demographic characteristics of the IDUs and the determination of HCV and HIV prevalence with 95% confidence intervals (CI 95%). The association between injection frequency, sharing syringes and needles, purchasing syringes at the drugstore, and the use of a condom in the last six months and prevalence of HCV and HIV was established through Chi-square, and the strength of association was calculated by means of the odds ratio (OR) and CI 95%.

The raw measures of association for HCV were adjusted through binary logistic regression, in which we included associated factors or *p*-values less than .25 (Hosmer-Lemeshow criterion). This analysis was not performed for HIV due to the low number of cases.

1 Armenia is considered a medium-sized city, which carries out functions of intermediation between smaller nuclei and the large metropolitan areas of the country; its population projected for 2014 is approximately 400,000 according to figures from the National Administrative Department of Statistics (DANE).

This project was endorsed by the institutional Committee of Ethics of the CES University. Confidentiality was ensured, and informed consent was obtained.

Results

With regard to the 265 participating IDUs' socio-demographic characteristics, it was found that 87% (214) were male, 76% were single, and 48% (136) were in the age range of 25 to 34. The mean age was 26.8 years ($SD = 5.68$); age range was 18 to 50 years. By sex, the men's mean age was 27 years, and the women's was 25.7 years. In terms of socio-economic status, 83.3% were low level, 14.4% medium level, and 2.3% had a high level. Of the IDUs, 75.8% had complete secondary studies, 27.9% were autonomous workers, 25.3% had temporary jobs, and 20.8% were street vendors.

There was a 2.6% prevalence of HIV (95% CI [1.40, 6.0]), 1.1% presented indeterminate results, perhaps due to the stage of seroconversion. For men, the prevalence of HIV was 2.7%, and for women, it was 2.9%. No statistically significant association between sex and prevalence of HIV was identified.

Likewise, 31.0% of the IDUs presented reactivity for HCV antibodies, and 22.3% (95% CI [12.3%, 23.5%]) presented active infection of HCV. By sex, the prevalence of hepatitis in men was 22.4%, and in women, it was 22.9%, finding no statistically significant differences.

Regarding the consumption practices investigated, 67.5% of users reported having injected for more than two years, and 35% had shared syringes and needles. In relation to sexual practices, 87.6% of IDUs admitted not using condoms

Table 1
Proportional Estimate of the Sociodemographic Characteristics of Injecting Drug Users. Armenia-Colombia

Age group	Proportional estimate of the population (%)	95% CI
Age		
18 to 24 years	42.0	34.0-49.4
25 to 34 years	48.0	40.7-56.1
35 to 44 years	7.1	3.8-10.7
45 years or older	2.9	0.7-5.8
Sex		
Male	87.3	82.9-92.8
Female	12.7	7.2-17.1
Level of schooling		
Primary	11.4	6.7-16.3
Secondary	75.8	68.7-82.1
Higher	12.4	7.7-18.5
Civil status		
Single	76.2	70.6-81.8
Married/common-law marriage	17.2	12.0-22.8
Divorced/separated	5.6	2.8-8.7
Widowed	1.0	0.0-2.8

Note. *CI = Confidence interval.

Table 2
Demographic Characteristics and Risk Behaviors in Injecting Drug Users related to Hepatitis C and HIV. Armenia 2014

Variable	Hepatitis C					VIH				
	n	%	ORc	IC	Valor de p	n	%	ORc	IC	Valor de p
Sex										
Females	8	22.9	1.03	0.44-2.40	0.95	1	2.9	1.06	0.12-9.11	0.96
Males	50	22.4	1.00			6	2.7	1.00		
Schooling										
Primary	7	23.3	1.07	0.44-2.64	0.88	2	6.7	3.29	0.61-17.7	0.17
Secondary	52	22.1	1.00			5	2.1	1.00		
Injection frequency (last 6 months)										
Daily	30	24.0	1.2	0.68-2.16	0.52	5	4.0	2.87	0.55-15.9	0.21
Weekly	29	20.7	1.00			2	1.4	1.00		
Shared syringes (last six months)										
Yes	22	24.2	1.18	0.64-2.16	0.6	7	3.3	1.4	0.30-6.42	0.66
No	36	21.3	1.00			4	2.4	1.00		

Note. *OR: Razón de disparidad

when having sex with stable partners in the last six months; 54.3% did not use condoms with casual partners, and 22.5% did not use condoms with prostitutes.

Regarding the socio-demographic characteristics of the positive cases of HCV infection, 85.7% were men, and 71.4% had started secondary school, their mean age was 27.69 years, and 75% of the IDUs with hepatitis C were 32 years old or younger. Regarding consumption practices, as with HIV, having injected drugs for more than two years and sharing injection equipment were more frequently reported in the positive cases, like previously documented risk behaviors but which were not statistically significant in this study.

An important finding is that people who had not bought their syringes in drugstores in the last six months were 2.7 times more likely ([95% CI [1.32, 5.48]]) to acquire hepatitis C than users who reported that they had bought their syringes in drugstores.

Regarding other injection risk practices, such as sharing cotton, spoons, and water, we found no statistically significant differences in performing these practices and having hepatitis C.

Table 3

Risk Factors Associated with Hepatitis C in People who inject Drugs. Raw and Adjusted OR

Variable	%	ORr	95% CI	P-value	ORa	95% CI	P-value
Time-interval injections							
> 4 Years	26.8	1,71	1,13-2,57	0,01	1,68	0,94-3,00	0,08
< 4 Years	18.1						
Condom use							
No	27	7,01	0,91-54,18	0,06	6,63	0,83-52,80	0,07
Yes	5						
HIV-positive							
Yes	42.9	2,71	0,59-12,44	0,20	10,22	0,84-124,22	0,07
No	21.7						
Buys syringes in drug stores (last six months)							
No	39	2,69	1,32-5,48	0,01	2,96	1,09-8,01	0,03
Yes	19.2						
Sex							
Females	22.9	1,03	0,44-2,40	0,95	1,43	0,52-3,97	0,48
Males	22.4						
Age M(SD)							
HCV	26.6 (5.5)	1,03	0,98-1,08	0,19	0,98	0,91-1,05	0,65
No HCV	27.6 (6.0)						

Note. *ORr = raw odds ratio. ORa = adjusted odds ratio. CI = Confidence interval.

Table 4. *Injecting Characteristics in Injection Drug Users and HCV. Armenia 2014*

In the last six months...	Yes	95% CI
Has injected with syringes containing the mixture ready for use	12.7%	8.5-16.9
Has shared the mixture with others	21.3%	16.0-26.6
Has shared cotton, spoons, or water with others	21.7%	16.5-26.9
Has taken doses of a mixture of drugs that others were also sharing	19.3%	14.3-24.3
Has injected in an outdoor consumption place	79.9%	74.9-85.0
Has been injected by a person who is paid for injecting	21.6%	16.4-26.8
Has injected with a "homemade" syringe"	7.4%	4.0-10.7

Discussion

According to UNAIDS (2012), there is sufficient evidence showing that harm reduction programs can significantly reduce the transmission of infections such as HIV and HCV among IDUs. However, this is not yet apparent in Colombia. Official drug policies continue to pay more attention to the reduction of supply and drug trafficking (USAID, 2012), and this is one of the few studies on the practices of IDUs in an intermediate city of the country (Berbesi et al., 2013), and the only work that includes the detection of hepatitis C in IDUs with the RDS methodology (Ramírez et al., 2005). This study identified a significant number of IDUs who perform risk practices, such as sharing syringes and a low use of condoms, risk factors which have been documented and widely discussed in other countries for several decades (Ball, et al., 1998; Des Jarlais & Friedman, 1987; Des Jarlais et al., 2013).

In relation to the sociodemographic characteristics, the IDUs in this study, as in the rest of the world, are predominantly male, with a mean age of 26 years, younger than those reported in other investigations (Clatts et al., 2010; Platt et al., 2009). Of the IDUs, 50% had begun injecting four years ago; the available evidence suggests that HCV is acquired relatively quickly after starting to inject (Garten et al., 2004). This is a fundamental aspect in the prevention and control of infection in users who have initiated this risk practice.

In Mexico, the individual, social, and environmental factors were independently associated with HIV infection among IDUs in Tijuana. These findings suggest the need to intervene not only in individual risk behaviors, but in the social processes that drive these behaviors (Strathdee et al., 2008).

One fourth of the IDUs in this study are infected by HIV or HCV, in the form of single infection or co-infection, very low numbers compared to those found in other countries (Platt et al., 2008; Ruan et al., 2007). However, this group has a high prevalence in comparison with the general population of the country (Ministry of Health and Social Protection, 2012), linked not only to the injection of drugs, but also other to characteristics and risk behaviors (Hagan et al., 2007).

Transmission through shared needles and syringes, having injected drugs for more than four years, and having sex without using condoms are classical risk factors for the acquisition of HCV and HIV (Shapatava et al., 2006). This research identified that the risk of hepatitis C was six times higher in people who had not used condoms in the past six months.

In this study, being female was not a significant risk factor for infections, unlike the findings in other investigations (Oliveira & Paiva, 2007). Women have been identified as likely to work in prostitution, have sex under the influence of substances, and they are in a situation of submission that does not allow them to negotiate safe sex, thereby increasing transmission of HIV and becoming an even more complex public health problem (Mendez et al., 2009).

However, in this work, the fact of not purchasing syringes in drug stores was identified as a risk factor for hepatitis C, which possibly suggests that users acquire syringes in other places (drug shops, crack houses², among others), which may be contaminated, as there are no needle exchange programs in Colombia. In this research, we also found a directly proportional tendency between infection positivity and increased injection frequency, similar to the observations of a research conducted in Uruguay (Osimani et al., 2005).

Successful efforts to prevent the transmission of infections among IDUs have been related to the implementation of harm reduction programs; however, no intervention has led to the elimination of risk behaviors. To reduce HIV transmission, harm reduction strategies may be sufficient, whereas HCV control may require the use of injection practices that ensure the elimination of exposure to contaminated equipment.

Important differences in the epidemiology of HIV and HCV in different populations of IDUs have been recognized. The prevalence of HIV varies from 5 to 80%, with HCV prevalence showing a lower range (50-90 %). The factors that favor the rapid spread of HCV among IDUs suggest that HCV infection in a population of IDUs may become endemic in a relatively short time, as HIV transmission is slower (Hagan & Jarlais, 2000; Platt et al., 2009).

Prompt actions are required to prevent an epidemic in Colombia. It is very important for the country to prioritize policies of harm reduction and prevention strategies of hepatitis C and HIV for IDUs, with the implementation of needle exchange programs, as well as the safe disposal of contaminated syringes and needles, among other public health measures.

As the limitations of this study, we note that respondent-driven sampling is considered nonrandom sampling that must comply with a series of assumptions to be considered as an independent and representative sample of the social network. Due to the type of design (cross-sectional study), it is not possible to conclude cause-effect relations between HCV infection and the risk factors found. The population with the highest socioeconomic level was not included in this study, possibly due to the lack of interest in receiving an incentive for participating. Finally, as the data was obtained from reports of risk practices, inaccurate responses may have affected the results.

In conclusion, an IDU profile was identified: male, under 34 years of age, with secondary education, single, with high injection frequency, and low condom use in the past six months; one fourth of them are infected with HIV or HCV in the form of single infection or co-infection; moreover, one out of three also shared syringes. For Colombia, this research is a first step in the search for prevention strategies.

2 Meeting place used for micro-traffic and drug consumption

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Conflicts of interest

There are no conflicts of interest.

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Implementation and adaptation in Colombia of the Communities That Care

Implementación y adaptación en Colombia del sistema preventivo Communities That Care

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Abstract

For more than two years, Corporación Nuevos Rumbos (Colombia) has been carrying out, in eight Colombian communities, a preventive system called *Comunidades Que se Cuidan (CQC)*, an adaptation of *Communities That Care (CTC)*, created at the University of Washington (Seattle), developed for more than 25 years in the United States of America and implemented in eight countries of America, Oceania, and Europe. The system is based on the public health approach, and the social development strategy for community empowerment. The core idea is to teach communities how to make decisions based on data regarding drugs and alcohol consumption and the identification of protective and risk factors, on the basis of the original survey validated in Colombia: these will allow communities to choose the best preventive interventions, tailored for each of them according to their needs. This paper describes the process of implementation of CQC in Colombia, its differences with CTC, the creation of Colombian cut-points, the main difficulties and how these were solved. CQC seems to be a preventive system with a wide potential applicability in other Latin American countries.

Key Words: Communities That Care (CTC), prevention, drug use, risk factor, protective factors.

Resumen

La Corporación Nuevos Rumbos (Colombia) viene implementando hace más de dos años en ocho comunidades de Colombia, el sistema preventivo *Comunidades Que se Cuidan (CQC)*, adaptación de *Communities That Care (CTC)*, creado en la Universidad de Washington en Seattle, que ha sido desarrollado por más de 25 años en los Estados Unidos y en ocho países de América, Oceanía y Europa. El sistema busca que, a través del empoderamiento comunitario y empleando el enfoque de la Salud Pública y en la estrategia de desarrollo social, las comunidades tomen las mejores decisiones basadas en los datos de prevalencias de consumo y en la identificación de los factores protectores y de riesgo (basada en la utilización de la encuesta original validada en Colombia) y puedan escoger las estrategias de intervención probadas que más se ajusten a sus necesidades. Este documento describe el proceso de implementación en Colombia, sus diferencias con CTC, la creación de *puntos de corte propios* para el país, las principales limitaciones en el proceso de adaptación y cómo se abordaron. CQC aparece como un sistema preventivo que puede tener amplia aplicabilidad en otros países de América Latina.

Palabras clave: Comunidades Que se Cuidan, prevención, consumo de drogas, factores de riesgo, factores protectores.

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Emergence of Communities That Care (CTC)

At the end of the 1980's, J. David Hawkins and Richard Catalano, professors at the University of Washington in Seattle, created a preventive system known as *Communities That Care (CTC)*. This system, based on the social development strategy and on the approach to public health, is also supported by the integration of three major elements: work aimed towards community empowerment, the regular application of the "Youth Survey", and a "Menu" of proven and effective programs available to communities (Catalano, Arthur, Hawkins, Berglund & Olson, 1998; Hawkins, Catalano & Arthur, 2002).

CTC has enjoyed nearly 25 years of permanent implementation and evaluation, which support its development conceptually and theoretically with high quality empirical data collection, which has generated its recognition as being one of the best preventive systems in the western world (Brown, Hawkins, Arthur, Briney & Abbot, 2007; Brown, Hawkins, Arthur, Briney & Fagan, 2011; Feinberg, Greenberg, Osgood, Sartorius & Bontempo, 2007; Hawkins, Catalano & Miller, 1992; Rhew, Brown, Hawkins, & Briney, 2013; Social Development Research Group, 2014). Likewise, CTC is being implemented in the United States (more than 400 communities), Canada, Australia, Netherlands, Germany, United Kingdom, Croatia, and Cyprus. In Spain, one of its main instruments, the survey to measure the prevalence of drug consumption and risk and protective factors, has been used (López & Rodríguez, 2010) and it is being validated in Chile and Brazil, India, Sweden, and countries of Central America (Guatemala, Honduras, and El Salvador) have shown interest or are using certain elements of the system.

CTC as a preventive system

This system is based on the concept of *Community Coalitions*, leading to the reduction of social disorganization, the promotion of effective community rules against the consumption of psychoactive substances, delinquency, and other adolescent problem behaviors (violence, academic failure, and pregnancy), and the appropriation by the community of preventive activities (France & Crow, 2005). Having the community as its main axis, a number of objectives are focused on its organization and the training of members of the Community Boards; other goals are related to the implementation of effective programs and the permanent evaluation of protective and risk factors of problem behaviors. It has the following main objectives:

- To provide training to communities about concepts related to the science of prevention and data-based planning exercise;
- To identify, prioritize, assess, and monitor protective and risk factors in each community, through the ap-

plication of an instrument and the use of local file data, for a focused planning;

- To create inter-institutional networks and a common language of prevention;
- To implement tested and effective *programs* focused on priority protective and risk factors in the communities, to reduce problem behaviors in adolescents;
- To assess the existing community resources and the interventions carried out from the viewpoint of the action plan.

The reason why CTC is a *system* and not a program refers to the articulation of the processes of community empowerment, the development of community profiles, and the construction of a menu of proven and effective programs. These elements are explained below:

- A *process of community empowerment* in which, throughout the first four phases, the notions related to the science of prevention, and also the individual and institutional relationships necessary to support the implementation and monitoring of an action plan, are strengthened among community members;
- The development of a *community profile* based on community file data and a diagnostic tool called the "Youth Survey", which was tested in seven states of the United States, with a sufficient sample of students ($n = 172.628$; Briney, Brown, Hawkins & Arthur, 2012; Brown, Graham, Hawkins, Arthur, Baldwin, Oesterle, Briney, Catalano & Abbott, 2009; Glaser, van Horn, Hawkins, Arthur & Catalano, 2005). The original CTC questionnaire is aimed at evaluating 25 risk factors (RF) and 13 protective factors (PF) in the four domains proposed by CTC (family, community, school and peers, and individual; Arthur, Hawkins, Brown, Briney, Oesterle & Abbott, 2010; Arthur, Hawkins, Pollard, Catalano & Baglioni, 2002; Hawkins, 2006), and it places students at high and low risk or protection by means of cut-points. In the United States, the psychometric characteristics of the questionnaire have been widely studied; the results have shown that this instrument has high reliability, as well as good construct and predictive validity both for men and for women, as well as in different ethnic groups, including Latinos (Arthur et al, 2002; Briney, Brown, Hawkins & Arthur, 2012; Glaser, Van Horn, Arthur, Hawkins & Catalano, 2005). In the Colombian case, the Youth Survey assesses with 103 items psychoactive substance consumption behaviors and the risk and protective profile, divided into 11 of the 23 risk factors of the original survey, and three protective factors (see Table 1);
- Construction of a "*menu*" of *preventive programs* that have been assessed, and are used by each Community Board in order to deal with priority risk factors, the result of the development of the community's profile.

Goal

To describe the process of implementation and adaptation of the CTC to the sociocultural conditions of Colombia, indicating why it is not possible to use the system in the same way as it was used in the country where it was created.

CTC Phases

The system is divided into five cyclical phases:

1. *Beginning*: the community's disposition toward change is assessed, actors are identified, leaders are recruited, and the support of the schools to apply the survey of protective and risk factors is obtained.
2. *Organize, introduce, and involve*: A coalition is formed that will extend over the five phases, and the main adult actors are trained. A vision of the future is developed for the children of the community, and a structure is organized to be able to move in that direction. Two trainings are carried out: leaders' orientation on prevention, and how to organize a Community Committee, which will be the highest authority when making decisions.
3. *Development of a community profile*: A phase in which the Youth Survey is administered to the young people; the chosen leaders receive training on how to interpret the protective and risk factors, and on that basis, they suggest which ones are the priorities. The community programs, policies, and resources concerning the existing risk and protective factors are also evaluated.
4. *Action plan*: The Community Board reviews the results of Phase 3 and develops an action plan, based on a training in community planning. Programs, practices, and policies that can change the risk factors and problem behaviors are chosen. Goals and measurable objectives are proposed.
5. *Implementation*: Training for the implementation of the community plan is offered, considering the importance of sticking to the guidelines of the system, of the financial aspects of the implementation, and of the elements that will allow the adequate assessment of the results.

The implementation of CTC in Colombia 2011-2014

Colombia is a country in which the problem of drug abuse has had a major impact, which has increased due to phenomena such as drug trafficking and guerrillas (Pérez Gómez, 2013). Also, as demonstrated by the Pan American Health Organization (PAHO) (Monteiro, 2013), and national studies (Ministry of Justice and the Law, Ministry of National Education, and Ministry of Health and Social Protection, 2011), the country presents a high consumption of alcohol, which particularly affects very young populations.

Although there have been no major developments in the field of prevention in the country, significant changes

in this area that grant great importance to community and neuropsychological dimensions (Sloboda, 2014) have attracted the attention of the national authorities and institutions dealing with prevention.

In 2007, Nuevos Rumbos (hereafter, New Directions) established contact with the Social Development Research Group (SDRG) of the University of Washington, in order to learn more about the preventive system and to determine the conditions to carry it out in Colombia. This contact led to creating a version in Spanish of the Youth Survey and to the translation of all the material available from CTC by the team of New Directions, with the permanent support of the creators of the system. The efforts were rewarded in the year 2011, when the PAHO and the Ministry of Health and Social Protection (MSPS) invited the Corporation to pilot the system in two communities in the country, under the name "Comunidades Que se Cuidan" (CQC; Communities That Care). One of the communities was made up of a group of neighborhoods from the city of Bogota, and another was a municipality 25 km away. Eight months later, a third community from the department of Cundinamarca was added to the pilot experience, and this time, the system was included in the Committee of psychoactive substances of the municipality. One and one half years after the first experience, with the support of the Colombian Institute of Family Welfare, the implementation of the first four phases of the CQC was initiated in five municipalities of the coffee region, where high levels of consumption of alcohol and drugs among adolescents are observed, as well as other social problems.

In general, we attempted to maintain high fidelity to the CTC, but given the sociocultural differences of communities in comparison with the United States, we introduced some changes that are described below:

1. In Phase 1, to ensure the adequate implementation of the system, New Directions decided to personally coordinate, train, and accompany the communities, whereas in CTC, the trainer is hired by an entity, usually an NGO, and fulfills the functions of coordinator and person in charge of the process in that community (Brooke-Weiss, Haggerty, Fagan, Hawkins, & Cady, 2008). Although the Municipal Administrations, as a local contribution, appointed some of its officials as coordinators, their functions were far from those expected by the system, as New Directions was in charge of the convocation, the meetings with the key leaders, the meetings of the Community Board, and the definition of strategies to attract new members to the group, among other aspects. When the first cycle of the system was implemented, the coordinators began to assume functions that were much more committed and responsible, this time with the accompaniment, but not the leadership, of New Directions.

Another important element in the development of Phase 1 was the construction of a flexible and effective measurement instrument of *readiness to change*, as, in the initial meetings, much interest in participating is always expressed by the Community Board, but its members may not represent all the sectors of the community, they may not be true leaders who support the process in the future, or the community's present moment may not be optimal to start a CQC in its municipality. This instrument mainly measures the disposition of the leaders, of the community in general, and the strength of the community ties, and it is based on a simpler instrument designed by the University of Washington (Arthur, Hawkins, Catalano & Olson, 2002)

2. The second part of Phase 2 (Orientation of the Community Board - OCB) was performed a few weeks after introducing the system to the key leaders, whereas in CTC, this is done between one and three months later. The goal is to give the leaders, together with the contracted coordinator and the contracting agency, enough time to invite and enhance the process of convocation of the people who will become members of the Community Board (Brooke-Weiss et al., 2008; SDRG, 2014).

Additionally, during its pilot study, the CQC did not divide the general group into subgroups because the small number of people (12-15) permanently attending the meetings was insufficient for the development of the six working groups proposed by CTC (data, funding, evaluation, public relations, maintenance of the coalition, and youth involvement: SDRG, 2014). Once Phase 4 had ended, due to the even closer knowledge of the experience and to our contact with the Masters of Trainers of the United States, three of the eight community boards constituted to date formed working subgroups in order to ensure the continuation of the system when New Directions leaves the communities; the working groups were Maintenance, Financing, and Evaluation. The first group is concerned with attracting new members and training in the basics of CQC; the second group, with permanent funding for the implementation of the action plans; and the third group is in charge of designing and implementing the evaluation plans of the programs and practices selected in Phase 4 and of the system in general.

3. The construction of community profile in Phase 3 began from the moment in which we contacted the local authorities, so that we had all the data when the communities, between 2 and 3 months after the process started, were developing the community map, in terms of consumption of psychoactive drugs and of protective and risk factors in the four prevention ar-

eas. This training phase included the entire group of the Community Board and not subgroups, as foreseen in CTC, which, in most cases, prompted a delay in its development because not all the members could or were interested in taking over the data collection and analysis on an ongoing basis. The division into subgroups would ensure that these tasks would remain in the hands of epidemiologists or those responsible for the follow-up of the social phenomena of each community, and would be adequately handled and used.

4. A menu of programs should be developed to carry out the process of planning in Phase 4 (Fagan, van Horn, Hawkins & Arthur, 2007; Ringwalt, Vincus, Hanley, Ennett, Bowling & Haws, 2010). The construction of our menu did not include experimental assessments because neither in Colombia nor in Latin America are this type of evaluations common. In contrast, we performed quasi-experimental assessments and with these, we constructed the menu of programs used by the communities to select the programs to be implemented in Phase 5, with the following result: there are 15 programs used nationwide, but only one (Anímate [Cheer up!]) has conducted systematic assessments for 13 years with nine measurements (Aja Eslava & Gómez Avila, 2013); seven programs have some sort of monitoring (perception of risk, information about assessment tools, systematizations or baselines and closure lines; these programs are: Consentidos, Sanamente, Familias Fuertes, Leones Educando, Habilidades para la Vida, CEMA-PEMA/NEF-PIP, Zonas de Orientación Escolar [Spoiled, Healthily, Strong Families, Educating Lions, Life Skills, CEMA-PEMA/NEF-PIP, School Orientation Areas]), and seven perform no evaluation (Colombia Joven, Experiencias para Vivir y Convivir, ACJ-YMCA, Fundación CreSer, Caminos, Retomemos [Young Colombia, Experiences to Live and Coexist, ACJ-YMCA, CreSer Foundation, Pathways, Retake, and DARE])¹. At the time of formulating the action plan, the communities chose to implement the two programs with the most developed assessment (Anímate and Consentidos [Cheer up! and Spoiled/With meanings]). To overcome this difficulty, the Boards also identified other practices that could respond to the priority factors identified in Phase 3, and some strategies were considered to change the methodology and facilitate the implementation of the selected programs and practices. Likewise, New Directions offered a set of strategies to

1 At the end of 2014, New Directions received training in a program of proven effectiveness with Hispanic population in the United States, Familias que se cuidan: encaminándolos hacia buenas decisiones" [Families that care: Guiding Good Choices]. There are contacts with the GIZ in Germany, whose program, Thousands of Hands, is being used in Central America.

support those that were already available in the community:

- Training sessions for community leaders, parents, and teachers, in order to clarify and unify concepts related to prevention; in these sessions, they described protective and risk factors, the importance of coalitions to solve social problems, and of addressing the use of alcohol and drugs among adolescents from a public health perspective.
- Strategies for adequate use of leisure time: the community develops options for adolescents to occupy their time productively, in moments in which they are more prone to consume alcohol and other psychoactive drugs, for instance, sports and cultural activities created by the communities in accordance with the inhabitants' interests.
- Brief interventions:
 - BIMI (Brief Intervention with Motivational Interviewing): this is implemented with adolescents at school, mostly in the eighth and ninth grades. The program consists of a first intervention, two follow-ups, and two interventions with the parents, inspired by motivational interviewing, and accompanied by a screening instrument (CRAFT/CARLOS) (Harris et al., 2012; Knight, Sherritt, Harrys, Gates & Chang, 2003; Pérez-Gómez & Scoppetta, 2011; Substance Abuse and Mental Health Services Administration, 1999). This latter instrument places the student at a level of risk so that each one of the participants will consider a goal of decreased consumption or delay in their age of onset. Follow-ups are carried out on the basis of this self-imposed goal, and interventions with parents are conducted based on the risk factors that were most predominant in each school.
 - "Capsules of humor": are short videos (3 minutes), in which a known actor ridicules situations related to the consumption of alcohol or other substances. The videos stimulate reflection based on identification with the character and also serve to demystify consumption-related issues and to clarify doubts.
- *Profession: being a parent*: This book is designed for parents, with information about alcohol and drugs, sexuality, eating disorders, bullying, and other problems of adolescence, as well as tips for handling specific situations and small questionnaires that help parents identify and respond to these situations.
- Basic training of the community in assessment processes, so they will be able to carry out or monitor the assessment of their programs and practices, as one of the pillars of CQC.

- The use of 'the Mystery Shopper' practice in order to prevent the sale of alcohol to minors and as a form of social control.

In CTC guidelines, each phase lasts between one and three days, with an approximate intensity of eight hours per day; in CQC, the trainings are performed according to the specific agreements reached in each community, and are usually scheduled weekly or biweekly, with a duration of each meeting of two and four hours, respectively. This is proposed because a large number of the Community Board members are not volunteers, and they must comply with public functions that do not allow them several free days each month to attend the training sessions.

Throughout the implementation of CQC in eight communities, it was observed that the communities whose Phase 5 could be financed immediately, with their own or with external resources, were more successful. Ideally, during the first four CQC phases, the communities restructure and optimize the budget allocated to prevention, but this time, focusing on the priority factors identified by the instrument used to construct the community profile.

The lack of file data in the small municipalities of Colombia, the potential communities to implement CQC, is one of the greatest difficulties. Therefore, the data about juvenile delinquency, drugs, or incidents associated with the consumption of alcohol in these municipalities have been replaced with unofficial information or indirect indicators.

Instrument

Currently, the reliability and construct validity of the CQC questionnaire (available at www.nuevosrumbos.org) has been analyzed with data from 33,790 students. The results showed a high and moderate internal consistency in the risk factors and high in the three protective factors (see Table 1). Construct validity analysis is currently being conducted through confirmatory factor analysis for ordinal data. This process is carried out in the framework of a project with the University of Washington and NIDA, and the results will be revealed in future publications. So far, the fit of the measurement models of each risk and protective factor has been adequate, with values less than or equal to .08 for the *root mean square error of approximation* (RMSEA) and equal to or greater than .95 for the *comparative fit index* (CFI) and the *Tucker Lewis index* (TLI).

Cut-points

As mentioned above, the CTC Youth Survey has cut-points that place students at a high or low level of risk and protection. These cut-points, developed by the Social Development Research Group of the University of Washington (Arthur, Briney, Hawkins, Abbott, Brooke-Weiss & Catalano, 2007), were found to have high sensitivity and specificity in U.S. population and ethnic minorities.

Table 1
Reliability Coefficients of the Risk and Protection Factors
assessed in the CQC Youth Survey

Risk factors	Cronbach's alpha
Perception of drug availability	0.81
Rules and regulations favoring drug use	0.69
Parents' attitudes towards drug use	0.57
Poor family management	0.83
Low commitment to school	0.70
Youth perceived risks of drug use	0.70
Favorable attitudes of youth towards drug use	0.79
Favorable attitudes of youth toward anti-social behavior	0.86
Drug use in friends	0.76
Antisocial behaviors in friends	0.76
Parents' favorable attitudes towards antisocial behavior	0.67
Protective factors	
School rewards for prosocial involvement	0.76
Family opportunities for prosocial involvement	0.92
Family rewards for prosocial involvement	0.89

Note. We could not perform factor analysis of the risk factors that have no values in the fit indices because of the low number of items in these two factors (three items each).

Initially, the cut-points of the United States were used to establish the profiles in Colombian communities; however, in some cases, the data seemed counter-intuitive: risk decreased with age, and lower grade students (sixth grade) seemed to be at higher risk in some factors. For this reason, we decided to calculate the cut-points for the Colombian population using the 33.790 surveys.

We calculated the cut-points for these communities using the methodology of Arthur et al. (2007). The procedure was performed for each risk and protective factor on an individual basis, as well as for each grade level.

In comparison with the cut-points of the United States, their calculation for the CQC communities revealed: (a) differences in the profiles of nine risk factors; (b) the cut-points of CTC and CQC tend to become more similar as the school grade increases for the community risk factor, "Rules and regulations favoring drug use"; and, (c) a community risk factor that was not very different, "Perception of drug availability", was found. Figure 1 shows an example of three community risk factors, using the preliminary cut-points calculated by the New Directions Corporation for CQC and those of CTC.

It is important to highlight that these cut-points have been used only to submit the data to the CQC communities because these data are adapted to the distribution of the data, and they do not correspond to a representative sample of the country. The New Directions Corporation is gathering new data to calculate cut-points that can be standardized for the Colombian population.

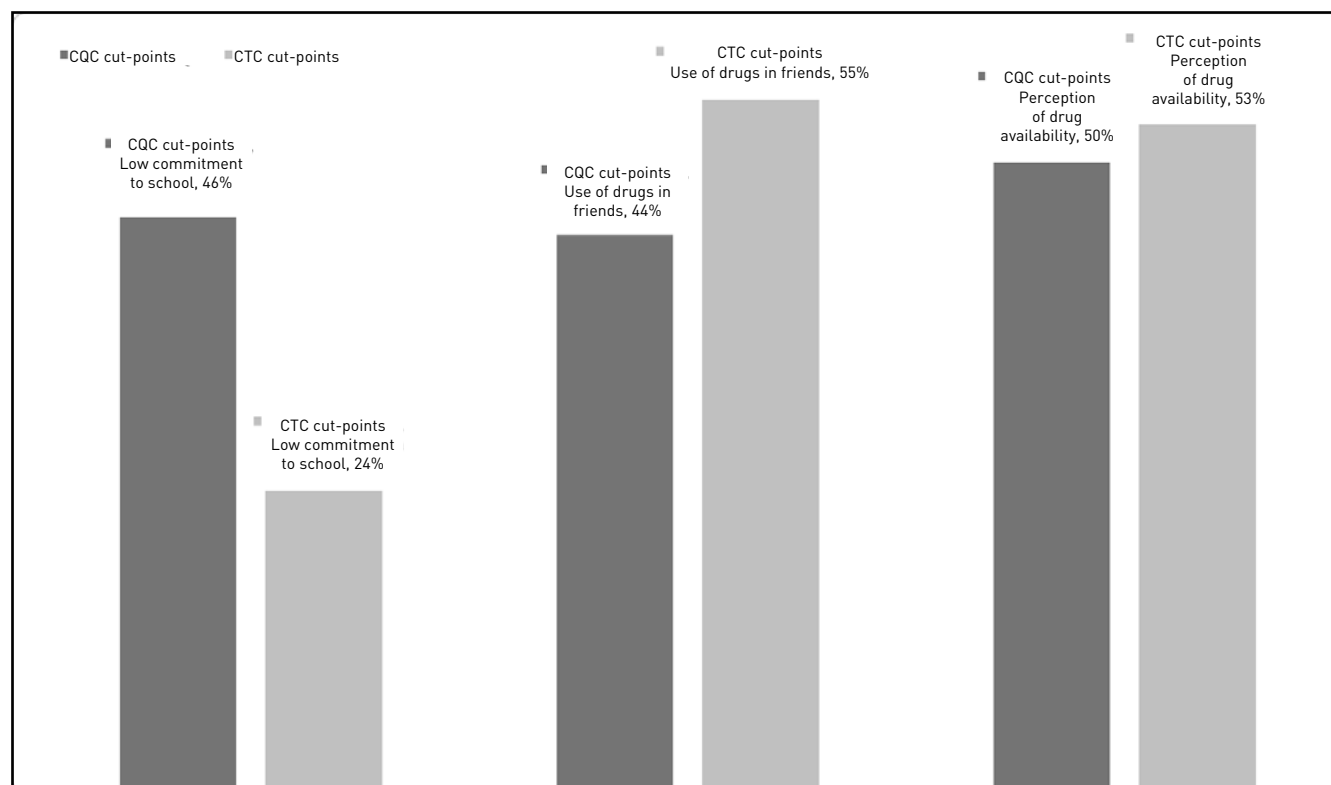


Figure 1

Table 2

Comparison of lifetime, yearly, and monthly prevalence rates of consumption of psychoactive drugs from the data of the CQC Youth Survey and from the national prevalence of drug consumption among students

Psychoactive substances	Prevalence rates					
	Lifetime		Yearly		Monthly	
	EJCQC ^a	National	EJCQC	National	EJCQC	National
Alcohol	76,9%	63,4%	72,9%	56,7%	40,0%	39,8%
Tobacco	31,0%	24,3%	24,9%	16,1%	11,3%	9,8%
Marihuana	14,2%	7,0%	12,1%	5,2%	5,7%	2,8%
Cocaine	1,7%	2,4%	1,2%	1,9%	0,3%	1,0%
Basuco	0,6%	0,7%	0,4%	0,5%	0,1%	0,2%
Inhalants	5,1%	3,1%	3,5%	1,8%	0,9%	0,9%
Ecstasy	1,4%	1,2%	0,9%	0,8%	0,1%	0,4%
Mushrooms	2,2%	N/a	1,5%	N/a	0,3%	N/a
Acids	1,9%	1,5%	1,3%	1,0%	0,3%	0,4%
Tranquilizers	1,2%	1,1%	0,9%	0,8%	0,2%	0,4%
Poppers	1,9%	2,5%	1,2%	1,4%	0,3%	0,6%
Amphetamines	0,2%	N/a	0,1%	N/a	0,0%	N/a
Heroin	0,3%	0,5%	0,1%	0,4%	0,0%	0,2%
Dick	5,8%	4,1%	3,7%	2,7%	0,7%	1,3%

Note. ^a Youth Survey for CQC.

Risk and Protection Profiles of the CQC Communities

Information about almost 37,000 high school students, aged between 11 and 18 years, from six municipalities of Quindío and three of Cundinamarca, were collected in a total of 31 schools, of which 28 were public and 3 were private. Fifty-two percent of the students were female and 48% were male. After refining the sample, 33.790 surveys were retained. The survey was applied in grades sixth to eleventh, to all of the students who attended class on the day of the application.

As shown in Table 2, the population studied with the CQC Youth Survey presented a lifetime and yearly prevalence greater than the one shown by the national study (Ministry of Justice and Law, Ministry of Education and Ministry of Health and Social Protection, 2011) in alcohol, tobacco, marijuana, and inhalants. It is important to highlight that the consumption of marijuana in the population studied by CQC presents a lifetime, yearly, and monthly prevalence that is twice that of the national data.

The students' risk and protection profiles of the communities studied as a function of grade level can be observed in Table 3. In general, it was found that the parents' attitudes towards drug use was the lowest risk factor, that community risk factors seem to be homogeneous, especial-

ly as the school grade increases. On the other hand, the youngest people appear to be at increased risk compared with the participants of higher school grades in the risk factors of poor family management, low commitment to school, anti-social behaviors in friends, and in the two community risk factors.

Regarding protective factors, 40 to 50% of the participants were found to be at a high level of protection. Another finding was that the protective factors are relatively homogeneous in all grades and tend to decrease as the grade increases, with the exception of the family protective factor acknowledgment of prosocial involvement.

Discussion

The prevention of the use of psychoactive substances has come a long way in its 45 years of existence. The complexity of the problem has led a growing number of researchers to explore a large number of variables and relationships among them, generating a greater understanding of the phenomenon, the factors that determine it, and ways to influence them through proven and effective prevention programs (Bukowski, 2003; Hawkins et al, 2002; O'Connell, Boat & Warner, 2010; Sloboda, 2014).

CTC/CQC seems to be a highly promising preventive system for the countries of Latin America. Even though

Table 3
Risk and Protection Profile per Grade

CQC Domain	Risk factors	Percentage of students at risk by grade					
		6	7	8	9	10	11
Community	Perception of drug availability	47%	49%	45%	44%	41%	44%
	Rules and regulations favoring drug use	47%	47%	45%	39%	43%	46%
Family	Parents' favorable attitudes towards antisocial behavior	42%	36%	43%	42%	40%	40%
	Parents' attitudes towards drug use	31%	39%	31%	36%	40%	44%
	Poor family management	49%	45%	42%	43%	43%	45%
School	Low commitment to school	47%	50%	49%	40%	43%	49%
Peers and individual	Youth perceived risks of drug use	41%	47%	40%	38%	48%	48%
	Favorable attitudes towards youth drug use	39%	41%	37%	45%	49%	37%
	Favorable attitudes toward youth anti-social behavior	41%	42%	48%	49%	47%	47%
	Drug use in friends	42%	49%	44%	42%	48%	47%
	Antisocial behaviors in friends	48%	44%	38%	48%	45%	41%
Protective factors		Percentage of protected students by school grade					
		6	7	8	9	10	11
School	School rewards for prosocial involvement	46%	39%	45%	43%	41%	40%
Family	Family opportunities for prosocial involvement	51%	49%	45%	45%	41%	44%
	Family rewards for prosocial involvement	36%	49%	44%	37%	34%	35%

the authors (David Hawkins & Richard Catalano) have always considered that the key to success is the correct selection of the prevention programs in Phase 5 (Haggerty & Shapiro, 2013; Haggerty, McGlynn-Wright & Klima, 2013; Hawkins et al., 2002; Shapiro, Hawkins, Oesterle, Monahan, Brown & Arthur, 2013; Steketee, Oesterle, Jonkman, Hawkins, Haggerty & Aussems, 2013), the experience in Colombia shows that the first four phases consolidate processes in the community that no other preventive strategy has achieved: solidarity, awareness of responsibility for the future of our youth, the need to identify risk and protective factors and to change them whenever possible and necessary, and to systematically evaluate problem behaviors and ways to deal with them. This is the necessary condition for the successful implementation of the action plans.

Even when fidelity is undoubtedly an essential element to ensure the smooth functioning of the system and the

programs (Fagan, Hanson, Hawkins & Arthur, 2008; Fagan, Arthur, Hanson, Briney & Hawkins, 2011; Quinby, Hanson, Brooke-Weiss, Arthur, Hawkins & Fagan, 2008), the Colombian experience, like that of some other countries (Jonkman, Junger-Tas & van Dijk, 2005; Jonkman, Haggerty, Steketee, Fagan, Hanson, & Hawkins, 2009; Steketee et al., 2013), shows that there are a series of adaptations that must be implemented due to cultural reasons, to the communities' functioning, or to unforeseeable conditions and special circumstances. In the case of Colombia, although the elements introducing variations in the system structure were not changed, numerous changes were carried out in training routines, in some contents (elements were removed or added according to the needs), the timing was modified (for example, the profiles were presented at the beginning of the process to awaken the communities' interest), and public employees were involved as members of the Community Boards. The only point that

can be considered a structural change was the beginning of Phase 5, with very few tested and effective programs, and our helping the communities to grant more importance (temporarily) to the activities that they defined as suitable. New Directions also offered a set of practices which are being assessed at the present time and that are based on principles that are currently considered universal (NIDA, 2003; OPS, 2010).

The results showed that the psychometric analysis of the instrument and of the cut-points is essential to ensure an accurate diagnosis. This process contributes to the generation of measurement technologies in the area of prevention in the Latin American context.

The prevalence of use of drugs such as alcohol, tobacco, marihuana, and inhalants was much higher than the national averages in populations in which the implementation of CQC has been requested. The rest of the substances have very similar consumptions; the exception is cocaine, which presents lower consumption rates than the national average (MJD, MEN & MSPS, 2011).

Most communities consider community risk factors—the availability of drugs, and rules and regulations favoring substance use—to be a priority. In this case, a confounding factor is the very high prevalence of alcohol and the marked tolerance in most of the country with regard to its consumption in minors. This should lead to an analysis in which legal and illegal psychoactive drugs are separated.

A final reflection emerges from having been immersed for more than two years in the study of CTC: although CTC/CQC is a highly flexible *system*, in general, the preventive *programs* are not. The best proof of this may be what happened with the most famous of all, Life Skills Training (LST). A recent study (Luna-Adame, Carrasco-Giménez & Rueda-García, 2013), carried out with extreme rigor to avoid the criticism of lack of fidelity, showed null results in Spain in the prevention of the onset of smoking in adolescents, which supposedly is the area in which LST is more effective. This fact is not surprising: LST was created 30 years ago, and has not suffered any kind of modifications, whereas the world has changed enormously during this period, especially for adolescents. Its authors, Gilbert Botvin, and Kenneth Griffin (2004), have maintained that their program is very efficient, and they have rejected criticism, refusing to introduce changes. Other authors have reported similarly poor results (Gorman, 2011; Johnson, Shamblen, Ogilvie, Collins, & Saylor, 2009; Vicary et al., 2004, 2006). This same outcome is probably occurring with many other prevention programs.

However, logic leads to thinking that this way of proceeding means that all prevention programs will be very outdated with regard to reality within a few years, which would jeopardize the entire functioning of CTC. This means, in short, that:

1. Preventive programs must be updated constantly, which creates some difficulties with regard to assessments;
2. We need to develop preventive programs that are easily modifiable without altering their core structure, which is responsible for the achievements. They should also contain flexible and reliable evaluation processes.

Limitations

The following can be considered the main limitations of this study:

The collected surveys do not constitute a representative sample of the country, so we require new calculations in other regions. Also, new adaptations may be needed in different communities, such as the Pacific region, the Eastern Plains, or the Caribbean coast.

The very limited availability of tested and effective prevention programs advises taking the results obtained in Phase 5 with caution. There are currently five programs, and we will very likely soon have Miles de Manos (Thousands of hands), GIZ -Deutsche Gesellschaft für Internationale Zusammenarbeit) and United Families (University of Miami).

There are no reliable data outside of the big cities.

This work should be considered an invitation to try out one of the best existing systems of prevention in Latin America and the Caribbean. In addition to all the benefits mentioned above, implementation costs are modest, and it has its own assessment strategy, which will facilitate the adjustments and allow making comparisons and accurately identifying what may or may not be modifiable.

Conflicts of interest

There are no conflicts of interest.

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Problematic Internet Use in University Students: associated factors and differences of gender

Uso problemático de internet en estudiantes universitarios: factores asociados y diferencias de género

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Abstract

The aim of this paper is to make a descriptive analysis of Problematic Internet Use in college students, evaluating the possible association with health problems and addictive behaviors, as well as gender differences in user types. A total of 2,780 students participated in the study between 2011 and 2014, 29% of them being males (age 20.8 ± 5.1 years) and 71% females (age 20.3 ± 4.4 years). The prevalence of Problematic Internet Use (PIU) assessed by the Internet Addiction Test was 6.08%. Being under 21 years of age and studying for degrees in subjects other than the health sciences were associated factors with a higher frequency of this problem, no differences by gender or type of address were found. The results show a significant association with some health problems (migraines, back pain, excess weight or obesity, insufficient rest), psychological aspects (risk of eating disorders, risk of mental disorder, depression), family problems and discrimination; with no associations with substance use (alcohol, cannabis or tobacco) being found. Concerning the time of Internet use, weekly hours were significantly higher in women than in men, both the total time as for leisure. The analysis of the profile use in problematic users revealed that males are related to aspects of entertainment such as games or shopping online and females are related to aspects of socialization, such as chats and social networks.

Keywords: Problematic Internet Use, Epidemiology, Prevalence, University Students

Resumen

El objetivo del presente trabajo es realizar un análisis descriptivo del uso problemático de Internet en estudiantes universitarios, evaluando la posible asociación con problemas de salud y conductas adictivas, así como diferencias de género en los tipos utilización. Un total de 2780 alumnos participaron en el estudio entre los años 2011 – 2014, siendo un 29% varones (edad 20.8 ± 5.1 años) y un 71% mujeres (edad de 20.3 ± 4.4 años). La prevalencia de uso problemático de Internet evaluada mediante el Internet Addiction Test fue del 6.08%. Ser menor de 21 años y cursar titulaciones diferentes a ciencias de la salud fueron factores asociados a una mayor frecuencia de este problema, no existiendo diferencias en función del sexo o tipo de domicilio. Los resultados muestran una asociación significativa con algunos problemas de salud (migrañas, dolor lumbar, sobrepeso u obesidad, descanso insuficiente), aspectos psicológicos (riesgo de trastornos de la conducta alimentaria, riesgo de trastorno mental, depresión), problemas familiares y discriminación; no encontrándose asociaciones con consumo de sustancias adictivas (alcohol, tabaco o cannabis). Respecto al tiempo de uso de Internet, las horas de conexión semanales fueron significativamente mayores en las mujeres que en los hombres, tanto en el tiempo total como por motivos de ocio. El análisis del perfil de utilización en usuarios problemáticos reveló que los varones se relacionan más con aspectos de ocio como los juegos o las compras online y las mujeres con aspectos de socialización, como el chat o las redes sociales.

Palabras clave: Uso problemático de Internet, Epidemiología, prevalencia, Estudiantes universitarios.

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According to the latest data from the Internet World Stats, more than 2,405 million people worldwide, and 518 million people in Europe, are users of Internet. Spain is among the top 20 user countries in the world, occupying the seventh position in the European Union with more than 31 million users (Internet World Stats, 2014).

This tool, which came into being at the end of the 1960s in the United States in response to the need for a communications network between government agencies as part of a defense system, began to spread to academic and scientific areas during the 1980s and over the last 20 years we have witnessed its exponential growth (Glowniag, 1998). In our country, this growth has been observed especially over the last decade, from 27% of the population being users of Internet in 1993, to 64.5% in 2013, according to data reported by the Encuesta General de Medios (General Media Survey) (AIMC, 2013).

This explosive growth is closely related to the numerous advantages that the net provides, such as the immediacy of information and communication, socialization and its use as a medium of leisure and entertainment, especially among younger people; allowing for, in addition, anonymity to be maintained, virtual socialization or the construction of identities, which makes communication easier for shy or introverted people (Muñoz-Rivas, Navarro and Ortega, 2003).

But this medium, which has become a feature of our daily lives, is not free of problems. Its use requires time, and a lack of self-control can lead to an escape from real life and even to states of dependence or addiction (Diddia, Dorphinghaus, Maggi & Haro, 2009; Echeburúa & Corral, 2010; Gracia, Vigo, Fernández & Marco, 2002; Young, 1998).

On many occasions, what is attractive about the net could well be compared with the boosting properties of addictive substances, a reason for which some authors have described psychological symptoms or profiles derived from the excessive use of the net, similar to those that are produced in people who are addicted to substances (such as stress, anxiety or restlessness when no connection is available) (Lam-Figueroa et al., 2011; Young, 1998).

Terms such as "Internet Addiction", "Pathological Internet Use", "Compulsive Internet Use", "Net Addiction" or "Cyber Addiction" have been used widely in the scientific literature to refer to this problem (Douglas et al., 2008; Luengo, 2004; Young, 1998; Young, 2010). However, addiction to Internet, which comes within the framework of the addictions denominated as behavioral or psychological, is not registered as such in any diagnostic manual (American Psychiatric Association, 2003; World Health Organization, 1992), with only pathological online gaming having been considered as a disorder related to the use of Internet in the recent publication of the DSM-V (American Psychiatric Association, 2014; Carbonell, 2014).

In a descriptive study carried out among the adolescent population in eleven European countries, a direct association with Pathological Internet Use (PIU) was found, in those who presented symptoms of depression, anxiety and distress in maintaining personal relationships in real life, especially males (Kaess et al., 2014). As well as this, some authors have found an association with other health problems, such as sleep deprivation, eating disorders, migraines or back pains (Didia et al., 2009; Pezoa-Jares, Espinoza-Luna & Vasquez-Medina, 2012; Spada, 2014).

On another note, around 12% of adults who are addicted to Internet also have problems of dependence, or addiction to, alcohol and 5% to drugs in general, as the revision carried out by Sussman, Lisha and Griffiths (2011) shows. This aspect has been evidenced in the recent study by Secades-Villa et al. (2014), carried out among the European adolescent population, in which they found a statistically significant relationship between the number of hours of connection to Internet and the frequency of consumption of alcohol, tobacco, cannabis and other illegal drugs.

The highest PIU risk profile is that of a male, under the age of 21, with low self-esteem and who lives away from home, making him more vulnerable to the problems described above (Sánchez-Carbonell, Beranuy, Castellana, Chamarro & Oberst, 2008; Frangos, Frangos & Kiohos, 2010; Muñoz-Rivas et al., 2003).

Regarding the types of use, gender differences have been described in the scientific literature, with males being the ones who spend most hours per week on e-mail, playing online games and browsing in web pages (Muñoz-Rivas et al., 2003), while females are the ones who most use chats or social networks (Andreassen, Torsheim, Brunborg & Pallesen, 2012).

The analysis of the behaviors related to Internet use is of great interest, especially among the young population, given that adolescents and university students are the groups that are most susceptible to losing their self-control (Hicks & Heastie, 2008; Kandell, 1998; Ledo-Varela et al., 2011).

The university stage is a period of transition that in many cases implies becoming independent from the family nucleus, stress brought on by the new situation or the search for new friendships, all motives that can interfere in net use as well as lifestyle changes that may have future health repercussions. The prevalence of PIU in this population is between 6 and 40%, there being controversy owing to methodological differences between the studies published (Pezoa-Jares et al., 2012; Sussman et al., 2011).

For that reason, the University of León decided to set up the uniHcos project in 2011 with the aim of analyzing the influence of the university stage on different lifestyles, and now has the collaboration of another eight Spanish universities (Fernández-Villa et al., 2013).

This paper, which comes within the framework of the project, is a descriptive epidemiological study that has as a novelty a proposed wide-ranging analysis of possible fac-

tors or behaviors that may be associated with PIU, with three principal hypotheses being advanced: (a) that there is a stronger association in young people, under the age of 21, who live away from the family home and who have low self-esteem or states of depression or anxiety, with the masculine sex being the most vulnerable; (b) that there is also an association not only with health problems, both physical and psychological, but with the use of addictive substances such as alcohol, tobacco and other illegal drugs and; (c) that there are gender differences in Internet user profiles.

With the aim of checking these hypotheses, three principal objectives are established: (a) to evaluate the relationship between PIU and sociodemographic aspects; (b) to analyze the possible association with health problems, both physical and psychological, as well as with the consumption of addictive substances (alcohol, tobacco and cannabis) and, (c) to describe Internet user profiles in the search for gender differences.

Method

Design

Observational, descriptive, cross-sectional epidemiological study.

Participants

The target population were all first-year and first-enrolment university degree students, from any of the subjects offered at the universities collaborating in the uniHcos project (Fernández-Villa et al., 2013), from October 2011 until April 2014. Students were recruited by means of an invitation sent to their university email addresses, and took part totally voluntary without receiving any form of compensation for the survey that was carried out involving some 2,780 students (3.5%). Of them, 28.8% were males (with an average age of 20.8 ± 5.1) and 71.2% were females (with an average age of 20.3 ± 4.4), with all the participating universities being represented (2% from Alicante, 2% from Cantabria, 37% from Granada, 4% from Huelva, 8% from Jaén, 17% from León, 14% from Salamanca, 3% from Valladolid and 14% from Vigo). It was not necessary to delete any survey from the analysis, as it was obligatory to respond to all the items on the questionnaire for which reason there were no errors and no absent data.

Tools

By means of a self-administered online questionnaire of 373 items, information was gathered concerning: sociodemographic questions (age, sex, degree course, type of accommodation, university attended) consumption of substances (alcohol, tobacco, cannabis), physical and psychological characteristics, as well as questions related to Internet use (the number of hours connected daily and weekly, and the type of use made). The tools used to this end were:

The APGAR Test (Adaptability, Partnership, Growth, Affection, Resolve). This is a brief, unidimensional questionnaire, consisting of five questions with a Likert scale (0-2 points) which is used to evaluate family functionality or dysfunctionality (Cronbach alpha coefficient of .84). A score above six points indicates good family functionality, while a score of six or below indicates moderate-to-grave family dysfunction (Bellón, Delgado, Del Castillo & Lardelli, 1996; Smilkstein, Ashworth & Montano, 1982).

The SCOFF questionnaire (Sick, Control, One stone, Fat and Food). This questionnaire consists of five dichotomous questions, for which each question is worth one point. A total of two or more points determines a greater probability of risky eating behavior, with a sensitivity level of .98 and a specificity level of .94 (García-Campayo et al., 2005; Morgan, Reid & Lacey, 1999).

GHQ-12 Test (General Health Questionnaire). This test consists of twelve items, six of a positive and six of a negative orientation. It shows good reliability in different studies carried out with Cronbach alpha coefficients of between .82 and .86 (Goldberg et al., 1997). It is evaluated according to a Likert scale with dichotomous scoring (0-0-1-1). A final result of three or more points corresponds to a greater risk of psychological problems (Rocha, Pérez, Rodríguez, Borrell & Obiols, 2011).

AUDIT Test (Alcohol Use Disorders Identification Test). A questionnaire comprising 10 items which are evaluated by means of a five-possibility Likert scale (0-4 points) with the exception of items numbers 9 and 10, whose scale is of three options (0-2-4 points). A score of eight or more points indicates problematic alcohol consumption, with a level of sensitivity of .90 and a specificity of .80 (Saunders, Aasland, Babor, de la Fuente & Grant, 1993).

IAT Survey (Internet Addiction Test). This was drawn up by Kimberly Young in 1998 in order to measure the extent to which Internet affected people's daily life, social life, productivity, sleep and feelings (Young 1998). In the different validations that have been published of this questionnaire, between one and six different dimensions have been found, with a Cronbach alpha correlation that is close to .90. It comprises 20 items that are evaluated by means of a five-point Likert scale (0 = Never; 1 = Almost never; 2 = Occasionally; 3 = Frequently; 4 = Often; 5 = Always). Given the controversy on the number of factors involved, for this study we have decided to analyze the PIU in accordance with a cut-off point of 40, considering as problematic users all those who scored 40 points or more (Jelenchick, Becker & Moreno, 2012).

Procedure

This present study comes within the framework of the uniHcos Project, whose design is multi-centric and with a prospective cohort. All university students who fit the inclusion criteria are invited to take part via their university email address, all being monitored afterwards on a two-year basis.

In the descriptive study presented here, data from the first survey carried out on the students from the first three waves (from 2011 to 2014) have been used.

All those who wished to participate filled in an informed consent form online before completing the questionnaire. Once they accepted this, they were directed to the aforementioned questionnaire, run by the SphinxOnline® platform, which allows for participants' anonymity, in compliance with the Ley Orgánica de Protección de Datos de Carácter Personal (Organic Law on Protection of Personal Data, published in the Official State Bulletin in 1999). As well as this, the project has the approval of the Ethics Committees of all the collaborating universities regarding the use of the students' personal data.

Statistical Analysis

The dichotomous categorization of Internet use was used as a dependent variable and the rest of the information collected (health problems, physical and psychological aspects, substance use and other aspects related to Internet use) as independent variables. In the descriptive analysis, the prevalences with their respective confidence intervals at 95% were calculated to categorical variables, while the numerical variables were analyzed by means of the calculation of means and standard deviations. The relationship between problematic Internet use and other variables was established by means of bi-variant and multi-variant logistical regression models, with the Odds Ratio and its respective confidence intervals being calculated at 95%, adjusting for gender, age and degree course. The STATA 13 statistics package was used for all the analyses (Stata Corp, 2013).

Results

General Aspects

The prevalence of PIU in the sample was of 6.04%, there being no statistically significant differences by age or type of residence. Regarding the age and the subjects studied, Table 1 shows how the under-21s and those studying subjects other than health sciences present Odds Ratios (OR) close to 1.5 both in the raw and in the adjusted analyses.

Association with Health Problems and Psychosocial Aspects

In Table 2 we can observe that there is a greater problem of PIU in persons who present back pains in the lumbar region and migraines, while no association was found with cervical pain.

The evaluation of physical constitution by means of the body mass index shows an association of PIU with persons who are overweight or obese, with this problem being almost 2.5 times more frequent in persons with an index of body mass higher than 30Kg/m² ($p = .009$).

On another note, aspects such as a perceived poor state of health, the risk of eating disorders as analyzed by means of the SCOFF survey, or depression, were also associated positively with PIU in both analyses, with a prevalence of PIU among those surveyed who were at risk of mental health problems that was almost four times higher, evaluated by means of the GHQ-12 ($aOR = 3.58$; $p = .000$), standing out.

Our results show as well that social and family relationships are also relevant in the problems related to Internet use, given that the students who show family dysfunction, be it moderate or serious (positive AGPAR), or some form of

Table 1
Sociodemographic Characteristics of Problematic Users.

	Problematic Internet Use										
	N	n	%	cOR ¹	95%CI	B	p	aOR ²	95%CI	B	p
Gender											
Female	1979	118	6.0	1				1			
Male	801	50	6.3	1.05	.75 - 1.48	.049	.779	1.03	.74 - 1.47	.039	.823
Age											
≥ 21	2001	37	4.5	1				1			
< 21	816	168	6.7	1.50	1.03 - 2.19	.409	.032	1.52	1.05 - 2.22	.421	.028
Degree course											
Health Sciences	726	33	4.6	1				1			
Other degree courses	2054	135	6.6	1.48	.99 - 2.18	.390	.050	1.49	1.01 - 2.21	.399	.046
Accommodation type											
Family Home	1190	79	6.6	1				1			
Student Residence Hall	300	16	5.3	.79	.45 - 1.37	-.236	.402	.72	.41 - 1.25	-.330	.246
Other	1384	168	6.0	.84	.61 - 1.17	-.169	.312	.87	.62 - 1.21	-.131	.402

Note. ¹cOR= crude Odds Ratio; ²aOR= adjusted Odds Ratio by Gender, Age and Degree course.

discrimination, double or even triple the prevalence of PIU respectively.

The role of good sleep is also highlighted, given that those persons who refer insufficient rest double the fre-

quency of problems derived from Internet use ($p = .000$), with statistically significant differences regarding the daily number of hours of sleep (normal users: 7.6 ± 1.2 h/day; problematic users: 7.3 ± 1.5 h/day ; $p = .003$).

Table 2

Relation of Problematic Internet Use to health problems and psychological aspects.

	Problematic Internet Use										
	N	n	%	cOR ¹	95%CI	B	p	aOR ²	95%CI	B	p
Cervical pain											
No	2493	150	6.0	1				1			
Yes	287	18	6.3	1.04	.63 - 1.73	.044	.864	1.09	.66 - 1.82	.090	.727
Back pain											
No	2427	138	5.7	1				1			
Yes	353	30	8.5	1.54	1.02 - 2.33	.432	.040	1.60	1.06 - 2.43	.472	.026
Migraines											
No	2284	129	5.7	1				1			
Yes	496	39	7.9	1.43	.98 - 2.07	.355	.062	1.48	1.01 - 2.17	.394	.042
BMI ³											
Normal weight	2005	112	5.6	1				1			
Underweight	267	16	6.0	1.08	.63 - 1.85	.746	.787	1.05	.61 - 1.82	.055	.854
Overweight / Obesity	508	40	7.9	1.44	.99 - 2.10	.368	.054	1.53	1.04 - 2.24	.425	.029
Perceived health											
Good/Very good	2206	115	5.2	1				1			
Regular or Worse	574	53	9.2	1.85	1.32 - 2.60	.615	.000	1.90	1.35 - 2.68	.643	.000
Scoff											
No risk	2239	116	5.2	1				1			
At risk	541	52	9.6	1.95	1.38 - 2.74	.666	.000	1.94	1.37 - 2.74	.660	.000
Ghq_12											
No risk	1266	34	2.7	1				1			
At risk	1514	134	8.9	3.52	2.40 - 5.17	1.258	.000	3.58	2.44 - 5.27	1.276	.000
Depression											
No	2432	131	5.4	1				1			
Yes	348	37	10.6	2.09	1.42 - 3.07	.737	.000	2.22	1.50 - 3.28	.799	.000
Apgar											
Normal functioning	2067	103	5.0	1				1			
Dysfunctional	713	65	9.1	1.91	1.38 - 2.64	.649	.000	1.87	1.35 - 2.59	.627	.000
Discrimination											
No	2354	115	4.9	1				1			
Yes	426	53	12.4	2.77	1.96 - 3.90	1.018	.000	2.78	1.97 - 3.93	1.023	.000
Sleep											
Yes	1584	66	4.2	1				1			
No	1196	102	8.5	2.14	1.56 - 2.95	.763	.000	2.17	1.58 - 3.00	.777	.000

Note. ¹cOR= crude Odds Ratio; ²aOR= adjusted Odds Ratio by Gender, Age and Degree course; BMI = Body Mass Index in Kg/m2 considering Underweight as ≤ 18.5 Kg/m2 and Overweight/Obesity as ≥ 25 Kg/m2, the other remaining values being evaluated as Normal weight.

Association with the Consumption of Legal and Illegal Drugs

Concerning the consumption of addictive substances (alcohol, tobacco and cannabis), no statistically significant association has been found, either in the raw or the adjusted analyses, as shown in Table 3. However, if we evaluate the risk of problems related to the consumption of alcohol by means of the AUDIT test, we find that there is a two-fold prevalence of PIU among the students with a positive AUDIT result.

Types of Internet Use and Gender Differences

In the global analysis of the different types of use made of Internet, we found that the use of chats or social networks behaves as a risk factor for PIU, while the use of email was associated with a lesser prevalence of this problem, and no significant association being shown with the remaining uses (Table 4).

If we analyze the profile of persons with PIU criteria, we observe statistically significant gender differences, as

is shown in Table 5. The females who use chats and social networks show this problem with greater frequency, while among the males, the greater prevalence of PIU is seen in those who play online games or purchase online. The frequency of problems derived from Internet related to online shopping among males needs to be analyzed with caution given the small sample size.

Regarding the time spent using Internet, we have found a weekly mean of 32.2 ± 24.3 h connection time among normal users, and one of 52.7 ± 31.7 h among problematic users, with the time spent on leisure activities being especially relevant. Our results reveal that females spend more time connected to the net (Figure 1), with significant differences being observed both in the overall time connected and that spent connected for leisure activities among those users who did not show problematic use and those who did, with there being no such difference in the time used for activities related to studying or working.

Table 3

Relation of Problematic Internet Use to consumption of addictive substances in the last month.

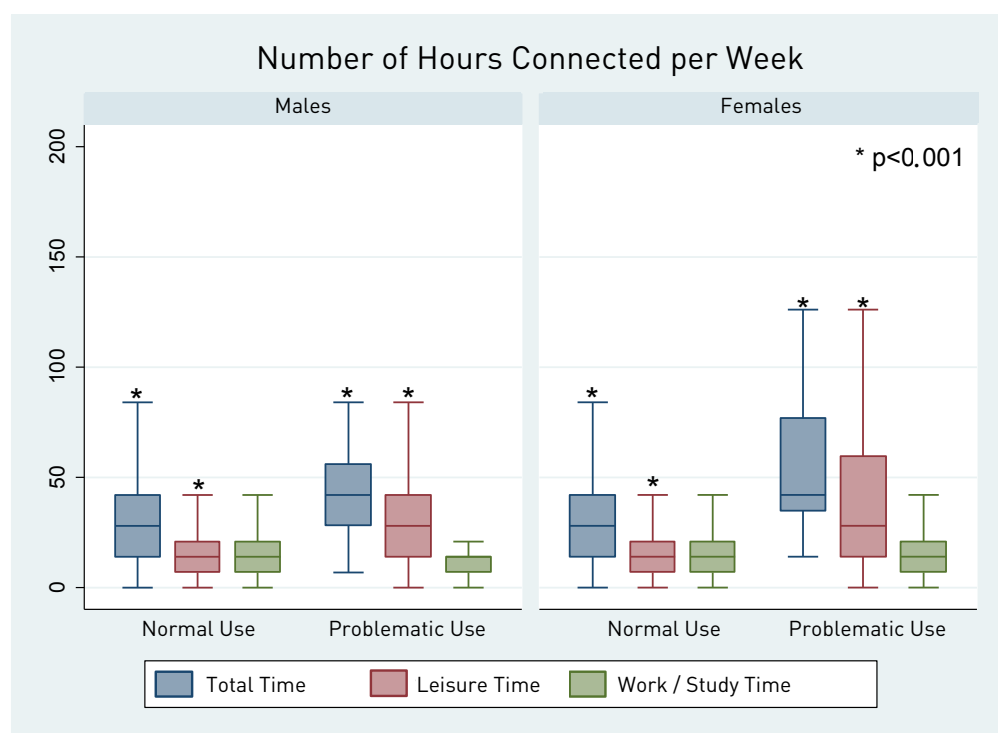
	Problematic Internet Use										
	N	n	%	cOR ¹	95%CI	B	p	aOR ²	95%CI	B	p
Cannabis											
No	1638	101	6.2	1				1			
Yes	1142	67	5.9	.95	.69 - 1.30	-.053	.745	.98	.71 - 1.35	-.020	.902
Tobacco											
No	2121	126	5.9	1				1			
Yes	659	42	6.3	1.08	.75 - 1.55	.785	.689	1.12	.78 - 1.62	.117	.530
Alcohol											
No	576	36	6.3	1				1			
Yes	132	132	6.0	.96	.65 - 1.39	-.045	.815	.96	.66 - 1.41	-.037	.851
Binge Drinking ³											
No	1395	77	5.5	1				1			
Yes	1385	91	6.6	1.20	.88 - 1.65	.185	.246	1.21	.88 - 1.65	.189	.237
Audit											
Negative	2279	115	5.1	1				1			
Positive	501	53	10.6	2.23	1.58 - 3.13	.800	.000	2.20	1.56 - 3.11	.789	.000

Note. ¹ cOR=crude Odds Ratio; ² aOR= adjusted Odds Ratio by Gender, Age and Degree course; ³ Binge Drinking = drinking five or more drinks for men and four or more drinks for women in a single occasion (approximately in two hours).

Table 4
Types of use made of Internet among problematic users.

Problematic Internet Use											
	N	n	%	cOR ¹	95%CI	B	p	aOR ²	95%CI	B	p
Chats											
No	1375	64	4.7	1				1			
Yes	1286	95	7.4	1.63	1.18 - 2.26	.491	.003	1.60	1.14 - 2.23	.469	.006
Email											
No	1908	126	6.6	1				1			
Yes	753	33	4.4	.65	.44 - .96	-.434	.031	.67	.45 - .99	-.401	.047
Games											
No	2454	141	5.8	1				1			
Yes	207	18	8.7	1.56	.94 - 2.61	.446	.088	1.50	.89 - 2.54	.407	.130
Social Networks											
No	885	37	4.2	1				1			
Yes	1776	122	6.9	1.69	1.16 - 2.46	.525	.006	1.70	1.16 - 2.49	.532	.006
Shopping											
No	2578	151	5.9	1				1			
Yes	83	8	9.6	1.71	.81 - 3.62	.539	.157	1.81	.85 - 3.83	.591	.123
Press											
No	2250	142	6.3	1				1			
Yes	411	17	4.1	.64	.38 - 1.07	-.445	.090	.64	.38 - 1.08	-.444	.097
Series											
No	1517	87	5.7	1				1			
Yes	1144	72	6.3	1.10	.80 - 1.52	.099	.547	1.08	.78 - 1.50	.080	.628

Note. ¹ cOR= crude Odds Ratio; ² aOR= adjusted Odds Ratio by Gender, Age and Degree course.



Note. In the graphic representation, the line in the middle of the boxes corresponds to the percentile 50 or the median, its height is established by the interquartile range and the external lines explain the deviation of the data by 1.5 times the interquartile range.

Figure 1. Total hours connected to Internet per week for leisure, work or studies.

Table 5
Gender differences by types of Internet use among Problematic Users

		Males										
		N	n	%	cOR ¹	95%CI	B	p	aOR ²	95%CI	B	p
Chats	No	463	33	7.1	1				1			
	Yes	327	16	4.9	.67	.36 - 1.24	-.400	.202	.67	.36 - 1.25	-.401	.208
Email	No	574	39	6.8	1				1			
	Yes	216	10	4.6	.67	.33 - 1.36	-.407	.264	.66	.32 - 1.35	-.414	.258
Games	No	670	36	5.4	1				1			
	Yes	120	13	10.8	2.14	1.10 - 4.17	.761	.025	2.11	1.08 - 4.14	.747	.029
Social Networks	No	312	16	5.1	1				1			
	Yes	478	33	6.9	1.37	.74 - 2.54	.316	.314	1.40	.75 - 2.59	.334	.289
Shopping	No	775	46	5.9	1				1			
	Yes	15	3	20.0	3.96	1.08 - 14.53	1.377	.038	3.98	1.08 - 14.62	1.381	.038
Press	No	583	40	6.9	1				1			
	Yes	207	9	4.4	.62	.29 - 1.29	-.483	.202	.61	.29 - 1.29	-.492	.195
Series	No	438	25	5.7	1				1			
	Yes	352	24	6.8	1.21	.68 - 2.16	.190	.521	1.20	.67 - 2.14	.184	.532
		Females										
		N	n	%	cOR ¹	95%CI	B	p	aOR ²	95%CI	B	p
Chats	No	912	31	3.4	1				1			
	Yes	959	79	8.2	2.55	1.67 - 3.90	.937	.000	2.42	1.57 - 3.72	.882	.000
Email	No	1334	87	6.5	1				1			
	Yes	537	23	4.3	.64	.40 - 1.03	-.444	.065	.67	.42 - 1.08	-.393	.104
Games	No	1784	10	5.9	1				1			
	Yes	87	5	5.8	.98	.39 - 2.46	-.025	.957	.98	.39 - 2.48	-.018	.970
Social networks	No	573	21	3.7	1				1			
	Yes	1298	89	6.9	1.93	1.19 - 3.14	.660	.008	1.90	1.16 - 3.09	.640	.010
Shopping	No	1803	105	5.8	1				1			
	Yes	68	5	7.4	1.28	.51 - 3.26	.250	.600	1.36	.53 - 3.47	.307	.520
Press	No	1667	102	6.1	1				1			
	Yes	204	8	3.9	.63	.30 - 1.31	-.468	.212	.66	.32 - 1.39	-.410	.276
Series	No	1079	62	5.8	1				1			
	Yes	792	48	6.1	1.06	.72 - 1.56	.057	.775	1.03	.70 - 1.53	.033	.866

Note. ¹ cOR= crude Odds Ratio; ² aOR= adjusted Odds Ratio by Gender, Age and Degree course.

Discussion

The use of Internet has grown in recent years (AIMC, 2013; Internet World Stats, 2014), with several authors relating this tool to possible states of dependency or addiction (Brenner, 1997; Echeburúa and Corral, 2010; Young, 1998). The scanty knowledge of the health problems that may be derived from the overuse of this medium, as well as the disparity of tools and diagnostic criteria, justify the need for studies such as this one in which not only the situation of the university population in relation to Internet use, given their vulnerability, has been studied (Echeburúa & Corral, 2010; Muñoz-Rivas et al., 2003), but also some of the possi-

ble health problems related to its use, and some of the gender differences that exist, have been identified.

Our results reflect that six out of every hundred university students have occasional or frequent problems with Internet use, which may have repercussions on their daily or social life. This is in line with data provided by other authors both for the adolescent population and for university students. In the SEYLE study that was carried out in eleven European countries a prevalence of problematic Internet use was found in 4.4% of adolescents (Durkee et al., 2012). In general European population the figures vary between 1% and 9%. (Kaltiala-Heino, Lintonen and Rimpela, 2004; Siomos,

Dafouli, Braimiotis, Mouzas and Angelopoulos, 2008). If we refer to the university population, the figures vary between 6% and 40%, making it difficult to establish a comparison given the geographical and, fundamentally, methodological differences found (Pezoa-Jares et al., 2012; Sussman et al., 2011).

Remarkable risk factors that are associated to a PIU are: male gender, under the age of 21 years, living outside the family home, having low self-esteem and a dependence on other addictive behaviors such as drug consumption (Sánchez-Carbonell et al., 2008; Frangos et al., 2010; Muñoz-Rivas et al., 2003; Secades-Villa, 2014). Despite the fact that our results concur in that it is the under-21 age group that show the highest PIU rates, as well as those who are studying for degrees in subjects other than the health sciences, we have not found any statistically significant differences regarding gender.

In relation to possible health problems associated with PIU, Didia et al. (2009) established links with back pains, migraines, sleeping disorders, irregular eating habits and family problems. These findings are in line with the results of this study, where there is a slightly higher prevalence of PIU in persons with migraines and pains in the lumbar region, but no significant association being found with cervical pains. Our data also reveal a positive association with eating disorders and with excess weight and obesity.

On the other hand, it is important to highlight the role of the family and of society in PIU, given that those students who expressed that they had suffered some form of discrimination, or had a positive result in the APGAR test, presented greater prevalences.

Some authors also describe symptoms of depression, sadness or loneliness as risk factors for behavioral addictions, among which is Internet addiction (Alavi et al., 2012; Kaess et al., 2014). In this sense, our data reveal that students at risk of mental disorders evaluated by means of the GHQ-12 survey present four times more PIU (aOR= 3.58 IC95%: 2.44 – 5.27), which highlights at the same time that those who say they have suffered at some time a depressive disorder double the frequency of this problem (aOR=2.22 IC95%: 1.50 – 3.28).

On another note, previous studies have established a connection between the consumption of addictive substances and PIU (Pezoa-Jares et al., 2012; Secades-Villa, 2014; Sussman et al., 2011), which is in line with our data on the relationship between PIU and the problematic use of alcohol as measured by the AUDIT test. However, no association was observed between PIU and the consumption of these substances (tobacco, alcohol, illegal drugs) which may be explained by the use of a classification criterion that does not distinguish whether it is a case of occasional use or of problematic use, which means that the group of problematic users is included within the much larger group of non-problematic users, thus generating a regression towards

a null association. Our results, therefore, point to the idea that there is an association between PIU and other problematic behaviors, even if it is not possible to establish a directionality in the relationship given the cross-sectional nature of the study.

Regarding the disturbance of sleeping patterns, it is important to highlight not so much the difference regarding the number of hours of sleep per day (normal users: 7.6±1.2 h/day; problematic users: 7.3±1.5 h/day; $p=.003$), but rather their quality, given that those persons who say they do not get sufficient rest are doubly at risk of suffering from PIU (aOR=2.17 95%CI: 1.58 – 3.00), compared to those with sufficient amounts of sleep.

As for the time spent using Internet, some studies establish differences between problematic users with a weekly average of 28 hours of connection and those who do not show any problems, whose average is of 12 hours (Yang & Tung, 2007). Our study reflects times that are relatively higher, with an average of 32 hours a week of connection for users without problems and of 53 hours a week for problematic users, with the time spent on leisure activities (19 and 32 hours respectively) being highlighted and it being females who use the net for the most hours a week.

Regarding other possible gender differences, we found that the males use the Internet principally for activities related to leisure, such as online games, or for making purchases, while the females are more associated with activities related to socialization, such as chats and social networks, which is in line with what has been published in the scientific literature (Andreassen et al., 2012; Muñoz-Rivas et al., 2003). What most stands out is that it is females who spend most time connected to Internet, whether for reasons of leisure, work or study, which differs from the findings of other studies, in which being male behaves as a risk factor (Tsai et al., 2009; Leung & Lee, 2012).

This study contributes relevant information concerning the use made of Internet by the university population, given the scarce number of publications on this matter. However, the data must be analyzed with caution, given that our study does have its limitations. The voluntary nature of the study and the tendency of students to downplay those behaviors that society disapproves of in their responses, possibly skew both the selection and the differential classification. On another note, the methodological differences regarding the diagnostic tools or criteria used (IAT, GHQ-12, APGAR, SCOFF) may make it difficult to compare this with other studies and, at the same time, the descriptive design of this paper impedes us from establishing causal relationships.

For that reason, it is proposed, as a future line of research, not only to analyze the momentary situation of Internet with descriptive studies, but also to monitor it over time, as was proposed in the design of the cohort for the uniHcos project, with the aim of determining causal associations with health problems, drug consumption, behavioral

changes related to Internet use and even changes in academic or professional performance that may be associated with the amount of connection time.

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Conflict of Interests

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

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Evidence of validity of an inhalant-craving questionnaire

Evidencias de validez de un cuestionario de craving a inhalables

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Abstract

Inhalants are substances widely used as recreational drugs: their addictive potential has been demonstrated by many studies. There is no reported measurable evidence of craving in inhalant users. The main goal of this study was to design and obtain evidence of validity of the score of a questionnaire for the evaluation of inhalant craving (ICQ) in a Mexican population sample. The ICQ is a type of visual analog scale with ten items. Face validity was evaluated by a group of experts in the addiction field. Reviewers considered the completeness, semantics, and sentence structure to guarantee a conceptual representation of the items. The final ICQ was applied to a sample of 520 Mexican high school students, 46% women and 54% men, between 12-19 years of age ($M=15.18$; $SD=1.48$), from 7th to 12th grades. The internal consistency of the ICQ showed a Cronbach's Alpha of 0.947. The 10 items were grouped into one single factor, with a factor loading above 0.74 for each of them. ROC analysis breakpoint was located at 18.5 mm with a sensitivity of 0.855 and specificity of 0.753. Thirty-three per cent ($n=172$) of the student population evaluated reported the use of inhalants at some point in their lifetimes, with an average of misuse beginning at 13.6 years of age. The ICQ showed adequate psychometric properties, suggesting that the instrument may be considered a useful tool for screening for craving in young inhalant users.

Keywords: Inhalants, craving, addiction, adolescent, clinical assessment.

Resumen

Los inhalables son sustancias ampliamente utilizadas como drogas recreativas: su potencial adictivo ha sido demostrado por numerosos estudios. No hay reportada evidencia medible del *craving* en usuarios de inhalables. El objetivo principal de este trabajo fue diseñar y obtener las evidencias de validez de las puntuaciones en un cuestionario para la evaluación del *craving* a sustancias inhalables (ICQ) en una muestra de población mexicana. El ICQ es un tipo de escala análoga visual de diez ítems. La validación de apariencia fue evaluada por un grupo de expertos en el campo de las adicciones. Los revisores consideraron la integridad, la semántica y la estructura de los enunciados, para garantizar una representación conceptual de los ítems. La versión final del ICQ fue aplicada a una muestra de 520 estudiantes mexicanos, 46% mujeres y 54% hombres, con edad comprendidas entre 12-19 años ($M=15.18$; $SD=1.48$), con años de escolaridad entre 7-12 años. La consistencia interna del ICQ mostró un Alfa de Cronbach de 0.947. Los 10 ítems se agruparon en un solo factor, con una carga factorial por encima de 0.74 para cada uno de ellos. El análisis ROC mostró que el punto de corte se localizó a 18.5 mm con una sensibilidad de 0.855 y especificidad de 0.753. El 33% ($n=172$) de la población de estudiantes evaluados reportó el uso de inhalables en algún momento de su vida, con un promedio de edad de inicio de 13.6 años. El ICQ mostró propiedades psicométricas adecuadas, lo que sugiere que el instrumento puede ser una herramienta útil para el tamizaje de *craving* en jóvenes usuarios de inhalables.

Palabras clave: Inhalables, *craving*, adicción, adolescentes, evaluación clínica.

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Abused inhalants contain volatile substances that are self-administered as gases or vapors to induce a psychoactive or mind-altering effect (Balster, Cruz, Dell & Cottler, 2009). These substances are available in legal, relatively inexpensive and common household products (National Institute on Drug Abuse [NIDA], 2012). Among the products most commonly abused by young people are: paint thinner, school supplies (markers, felt pens, correction fluid), spray paints and glues (Lubman, Yücel & Lawrence, 2008; Substance Abuse and Mental Health Services Administration [SAMHSA], 2008). Solvents constitute the most abundant class of volatile substances; they evaporate rapidly at room temperature and are usually inhaled through the nose and mouth. They have different chemical structures, and different names are used for a single compound. However, among them, toluene has been the most studied, and is likely the most commonly abused volatile solvent globally (Cruz, 2011).

In inhalation of volatile substances, a marked variability is seen in the type of substances abused and the pattern of consumption in each country (Elkoussi & Bakheet, 2011; Hynes-Dowell, Mateu-Gelabert, Taunhauser & Delva, 2011; Vazan, Khan, Poduska, Stastná and Miovský, 2011). For example, the National Addiction Surveys conducted studies in schools in Australia and North America that indicated high rates of experimental inhalant use during early adolescence, as high as 26% of 12 year old students (Johnston, O'Malley & Bachman, 2003; White & Hayman, 2004). It is estimated that in the United States, up to two million teenagers, between 12 and 17 years of age, have at some time used an inhalant (Howard, Bowen, Garland, Perron & Vaughn, 2011; Wu, Pilowsky & Schlenger, 2004). In Mexico, it has been estimated that 77% of inhalant users are younger than 18 years of age (Encuesta Nacional de Adicciones [ENA], 2011); they usually start between the ages of 12 and 14 years. Global prevalence of inhalant misuse used to be higher among marginal groups, the mentally ill or young people in conflict with the law, but nowadays it is a widespread practice in the general population (Gigengack, 2013; Villatoro, Cruz, Ortiz & Medina-Mora, 2011). More recently, a survey conducted in Mexican high school students indicated that volatile substance misuse has increased to become the second drug of choice in this particular population, with a prevalence of 9.7% in males and 10.3% in females (Villatoro, Medina-Mora, Hernandez, Fleiz, Amador, & Bermúdez, 2005; Villatoro, Medina-Mora, Fleiz-Bautista, Téllez-Rojo, Mendoza-Alvarado & Romero-Martínez, 2012; Villatoro et al., 2013). Volatile substances are the third choice of drugs in the general population (ENA, 2011). In addition, in this country there are significant regional variations in the rates of treatment demand. In the central region, inhalants represent 11.6% of cases in treatment. In the south, only 4.8% of inhalant users seek medical help (Medina-Mora & Real, 2013).

The immediate effects of inhaling solvents are similar to the early stages of alcohol intoxication in low concentrations: initial euphoria and excitation are caused by the suppression of inhibitory brain functions. At higher concentrations, inhibition occurs in the nervous system in general. Both solvents and alcohol exert depressive effects (Cruz, 2011).

Chronic inhalant use is associated with numerous medical consequences; however, the most commonly reported are neurotoxicity and psychiatric issues (Bowen, Batis, Paez-Martinez & Cruz, 2006; Kurtzman, Otsuka & Wahlet, 2001; Lubman et al., 2008; Ridenour, Bray & Cottler, 2007). Patients show peripheral neuropathy, cerebellar dysfunction, cranial nerve damage, cortical atrophy and encephalopathy (Anderson & Loomis, 2003; Finch & Lobo, 2005; Gautschi, Cadosch & Zellweger, 2007; Lubman et al., 2008; Morrow, Steinhauer & Condry, 1998;). Furthermore, cognitive dysfunction (e.g. attention problems, learning and memory, psychomotor function, executive abilities, and speed of information processing) and comorbidity with mental health disorders (e.g. antisocial behavior, anxiety, major depression, suicide ideation and suicide attempts, and polydrug use) have been reported with regular, long-term exposure (Howard, Perron, Vaughn, Bender & Garland, 2010; Howard et al., 2011; Yücel, Takagi, Walterfang & Lubman, 2008). This long-term use is linked to social destructive effects, and poor academic performance. Both consequences have an impact on the budgets of health and welfare systems (Dell, Gust & MacLean, 2011).

Like any other addictive substances, prolonged inhalant abuse requires the support of medical professionals (NIDA, 2012). Addiction is a chronically relapsing disease, characterized by drug intoxication, craving, bingeing, and withdrawal, with loss of control over drug-related behaviors (Parvaz, Alia-Klein, Woicik, Volkow & Goldstein, 2011). Specifically, craving is included as one of the diagnostic criteria for addiction; it is defined as a strong desire or compulsion to take drugs, immediately after withdrawal (Drummond, 2001; O'Brien, Childress, Ehrman & Robbins, 1998). The craving phenomenon has been described as the result of neuroadaptive changes in cortical and subcortical structures such as the dorsolateral prefrontal cortex and amygdala, and has been considered a key element to take into account when developing and testing the efficacy of treatments for substance abuse disorders (Goldstein, Craig, Bechara, Garavan, Childress, Paulus & Volkow, 2009; Koob & Volkow, 2010; Grant et al., 1996).

Several tests for craving assessment have been developed for commonly abused drugs such as cannabis (Heishman, Evans, Singleton, Levin, Copersino, & Gorelick, 2009), cocaine (Tiffany, Singleton, Heartzen & Hennigfield, 1993), alcohol (Guardia-Serecigni, Segura, Gonzalvo, Trujols, Tejero, Suárez, & Martí, 2004), nicotine

(May et al., 2014), and even food, for instance, chocolate (Cartwright & Stritzke, 2007; Pelchat, 1997; Rodgers, Stritzke, Bui, Franko & Chabrol, 2011). The cognitive process model of conceptualization is the one that best fits the craving phenomenon. This model suggests that among the different techniques and instruments one can possibly use, self-report is the one that often provides better information about a patient's craving, and plays a major role in its measurement (Tiffany & Wray, 2012; Tiffany, Niaura, Martin & Shadel, 2000; Sayette, Shiffman). One such self-report is the Cocaine Craving Questionnaire Now (CCQ). The CCQ is a ten item Likert scale instrument that measures craving at the moment in which the evaluation is taking place and it is one of the most commonly used tests (Tiffany et al., 1993; Marín-Navarrete et al., 2011). Another commonly used test is the Multidimensional Alcohol Craving Scale (MACS), which uses twelve items to evaluate two factors: craving for a drink and behavioral disinhibition. MACS discriminate among intensity levels of dependence (severe, moderate, and mild). Both CCQ and MACS have been translated and adapted to Spanish-speaking populations and also possess adequate psychometric properties and internal consistency (Guardia-Serecigni et al., 2004; Marín-Navarrete et al., 2011).

Despite the fact that current data demonstrate that dependence on inhalants is a real phenomenon (Perron, Howard, Vaughn & Jarman, 2009; Ögel & Coskun, 2011) and clinical behavioral evidence shows that craving is a key component in this process (Volkow et al., 2006), so far there has been no measurable evidence of craving in inhalant users. This has been because to our knowledge there are no clinical tools to assess this phenomenon. A questionnaire with reliable scores from which to make valid inferences to measure craving in the dependent population would be a useful research and clinical tool to improve medical diagnosis and to make better treatment decisions. Thus, the main goal of this study was to design and obtain evidence of the validity of the score of a questionnaire for evaluation of inhalant craving in a Mexican population sample. We hypothesized that in an asymptomatic young population, non-users would obtain lower scores (and closer to zero) than those obtained by inhalant users.

Methods

Participants

All participants were recruited from schools in the metropolitan area of the city of Puebla, which is located in the central part of Mexico. 555 students participated, but only 520 Mexican high school students with ages between 12-19 years, ($M=15.18$; $SD=1.48$), who were studying from 7th to 12th grades, met the inclusion criteria (full questionnaire replies). All participants spoke Spanish as their native language; they were 54% males and 46% females.

Instrument

The Inhalant Craving Questionnaire (ICQ) is a self-administered instrument that has two sections. The first part asks participants for information about drug-use history, such as age of onset, attempts to stop use, frequency of inhalant use, average level of use per occasion and number of years using inhalants. The second section has ten statements indicating different conditions, as shown in the next example: *Señala qué tan fuerte es tu deseo de consumir ____ en este momento que casi puedes sentir su olor.* (Please indicate how strong is your desire to use ____ at this moment, in which you can almost feel its scent). Each one has to be answered in a visual analog scale (VAS). Response options of type VAS consisted of a 100 millimeter line, without divisions. At each end of the printed line there are phrases indicating opposite statements related to each condition, for instance "No deseo" (no desire) at one end and "Más que nunca" (more than ever) at the other. The participant marks the point on the line that best describes the intensity of his desire. The length of the line to the point marked by the students is measured and recorded in millimeters (mm).

Procedure

The study consisted of five stages.

- Stage I. Theoretical and conceptual approach to craving. A review of the literature on this population was made to provide a precise approach, which contributed significantly to development of the instrument.
- Stage II. Instrument design. The literature describes one-dimensional scales for craving assessment. An example of such a scale is the Visual Analog Scale for Heroin. In this kind of evaluation the participant is asked to rank his/her desire to consume on a printed line. The phrase "not at all" is written at one end of the line and "extremely high" at the other end (Eaton, Comer, Revicki, Tredeau, Van Inwege, Stauffer & Katz, 2011).

The construction of the items was performed based on previously validated scales in Spanish. We first choose two instruments validated in Spanish and commonly used in Mexico to assess craving for other substances: the Cocaine Craving Questionnaire (CCQ) (Marín-Navarrete et al., 2011) and the Multidimensional Alcohol Craving Scale (MACS) (Guardia-Serecigni et al., 2004). Ten items from both scales were selected and adapted for inhalant craving, according to the items in the design guidelines (Moreno, Martínez & Muñoz, 2004).

- Stage III. Judges review. This first version was evaluated by a group of 22 expert researchers and/or clinicians on addictions. In this review the experts evaluated every item, considering comprehensiveness, semantics, phrase structure and face validity. They gave a score to each item in the questionnaire and

commented on it. The score parameters were a maximum of five points and a minimum of one point. The maximum average score of the items was 4.09 and the minimum was 3.41. After this expert review, the questionnaire was modified based on comments from the experts and a second version of the ICQ underwent further evaluation by the authors in order to obtain the final version. Table 1 shows the items in Spanish with the English translation in order to make it easier to read. It should be considered that adaptation in another language must be adjusted to specific populations.

- Stage IV. Application of the questionnaire. It was used as a convenient sampling for this study. Some schools were selected to match the socio-demographic characteristics of inhalant users that commonly go to the Mental Health Center in the city of Puebla. These schools are located in low income, high-risk areas, far away from the city center and supported with public funds. Four schools were contacted and asked for their cooperation in recruiting students. Only three of them agreed to participate in the study. Each of

these schools organized a meeting with parents or legal guardians in which the researchers provided information about the study. An informed consent form was given to all those attending the meeting, including students interested in participating in the study. Participation was voluntary; confidentiality and anonymity of responses were guaranteed. The students did not receive any kind of incentive for their participation. To ensure anonymity, the ICQ was applied in groups where participants were seated with enough space between them. Evaluators read the instructions and each of the items to participants. Once they were completed, the questionnaires were placed in a secured box.

The study was approved by the Research Ethics Committee of the Medical School of the National Polytechnic Institute (ESM-IPN). A written informed consent was obtained from all volunteers and guardians prior to study enrollment, in accordance with the Declaration of Helsinki.

- Stage V. Data analysis was performed to assess the evidence of validity.

Table 1
Items in the ICQ instrument in Spanish with translations into English.

Items	
1	<i>Señala qué tan fuerte es tu deseo de consumir ____ en este momento (tan fuerte que casi puedes sentir su olor).</i> Indicate how strong is your desire to consume ____ at this moment (so strong that you can almost feel its scent).
2	<i>Señala qué tan intenso ha sido tu deseo de inhalar ____ en el último mes.</i> Indicate how intense your desire to inhale ____ in the last month was.
3	<i>Señala la frecuencia con la que has deseado inhalar ____ en el último mes.</i> Indicate how often did you feel the desire to inhale ____ in the last month.
4	<i>Durante el último mes, señala que tanta urgencia has tenido de inhalar ____ cuando has estado frente a cosas que te lo recordaban (bolsa con pegamento, estopa, lata de PVC, olores, entre otras cosas).</i> During the last month, indicate the urgency you felt to inhale ____ when you were exposed to things that reminded you of inhaling (bag of glue, PVC, odors, among other things).
5	<i>Imagina que estás en una situación que te recuerda tu consumo de ____.</i> Si estuvieras en esa situación en este momento, ¿Cuál sería la posibilidad de que inhalaras ____? Imagine that you are in a situation that reminds you of the consumption of _____. If you were in that situation right now, what would be the possibility that you inhaled _____?
6	<i>¿Inhalarías ____ tan pronto como se te presentará la ocasión?</i> Would you inhale ____ as soon as you had the opportunity?
7	<i>Si en el último mes hubiera inhalado ____, no hubiese sido capaz de parar.</i> If in the last month I had inhaled _____, I would not have been able to stop.
8	<i>Si en el último mes hubiera tenido delante de mí ____, me hubiera sido muy difícil no inhalarlo.</i> If in the last month I had had in front of me _____ it would have been very difficult for me not to inhale it.
9	<i>Inhalar ____ en el último mes me hubiera hecho sentir menos irritable o inquieto.</i> To inhale _____ in the last month would have made me feel less irritable or restless.
10	<i>Inhalar ____ en el último mes habría hecho que todo pareciese mejor.</i> To inhale _____ in the last month would have made everything seemed better.

Data analysis

Descriptive analysis was applied to the demographic data, taking frequencies as categorical variables and central tendency measures as continuous variables.

The internal structure was determined by exploratory factor analysis (EFA). This exploratory analysis was performed on the individual items of the questionnaire, to evaluate which ones were grouped consistently in accordance with the construct theoretical basis. The reliability of the scores of the items was obtained with Cronbach's coefficients.

Student's T analysis was applied to contrast "users" from "non-users" as sub-populations within the sample and in age groups. These categories were assigned based upon the answers to the items about drug use history.

Receiver Operating Characteristic (ROC) analysis was used to determine ICQ sensitivity and specificity, as well as the ideal cutoff point to differentiate the groups.

Data processing and data analysis were performed using the Statistical Package for the Social Sciences (SPSS), Version 17.0 for Windows.

Results

Each of the item responses was obtained by measuring the distance from the start line to the point marked by the participants. The results are:

Descriptive analysis of ICQ

Average values of the items were ranged in millimeters, where 6.11mm was the minimum (item 7) and 7.39mm the maximum (item 5), with a mean (*M*) summary index of 6.69mm and a standard deviation (*SD*) of 16.14 mm and significance level of $p=0.000$, as shown in Table 2. The distribution curve of the ICQ scores gave higher values; the curve showed a symmetry index = 3.48-3.87 and kurtosis = 12.26-16.12.

Internal consistency

The ICQ gave a Cronbach's Alpha = 0.947, which represents a high internal consistency. In addition, all item-total correlations were higher than 0.688, indicating that the scale is composed of homogeneous items, as shown in Table 2.

Table 2

Descriptive data, exploratory factorial analysis and internal consistency of score of the ICQ instrument in Spanish

Descriptive			Reliability		Exploratory factorial analysis	t	gl	Sig.
Item	Mean	SD	Correlation Element-Total	Alpha if the item is removed	Factor loadings			
1	7.29	15.99	0.770	0.942	0.820	10.39	519	.000
2	6.55	15.35	0.790	0.941	0.837	9.73	519	.000
3	6.38	15.91	0.755	0.943	0.806	9.14	519	.000
4	6.31	15.03	0.827	0.940	0.866	9.57	519	.000
5	7.39	17.30	0.833	0.939	0.869	9.74	519	.000
6	6.92	16.61	0.780	0.941	0.822	9.49	519	.000
7	6.11	15.77	0.741	0.943	0.791	8.83	519	.000
8	6.65	16.45	0.688	0.946	0.742	9.22	519	.000
9	6.55	16.21	0.795	0.941	0.837	9.21	519	.000
10	6.77	16.78	0.803	0.940	0.846	9.2	519	.000
Total	6.69 mm	16.14 mm	Cronbach's Alpha	0.947	Explained variation 67.95 %	11.47	519	.000

Exploratory factorial analysis

Bartlett's sphericity test gave a chi-squared value of 4343.73 ($p = 0.000$, $df = 45$) and a satisfactory index of sampling adequacy (Kaiser-Meyer-Olkin) of 0.93. On the other hand, the results of the factor analysis indicated a percentage of total explained variation of 67.95%. The 10 items were grouped into one single factor, which means that all components showed coefficients above 0.74, as shown in Table 2.

Descriptive analysis of the sample

Of the students evaluated, 33% ($n = 172$) reported the use of inhalants in their lifetimes, with an average onset of misuse at the age 13.6 years. The substances most used were thinner and nail polish, as shown in Table 3. Among users, 40% chose only one substance consumption and 60% used two or more; 72% mentioned a usage time of less than 6 months and 60% reported a frequency of use of once a month. 35 % of the participant had made attempts to stop the use of inhalants.

In the population analyzed, we decided to divide the sample into these two groups: users and non-users. We conducted a Student's T test for the means of each item in the ICQ test. All items showed a significant difference, as shown in Table 4.

Table 3
Percentage of mentions of volatile substances used by students

Substance	Percentage
Thinner	19
Nail polish	13
Polyvinyl chloride	11
Markers	10
Spray paints	7
Cleaning liquids	7
Paints	7
Nail polish remover	7

Table 4
Descriptive data of the two groups (Non-use of inhalants vs Inhalant use)

Ítem	Groups	Mean	SD	<i>t</i>	<i>gl</i>	<i>F</i>	<i>Sig.</i>
1	Non-use of inhalants	2.04	5.86	-12.02	518	247.10	.000
	Inhalant use	17.9	23.17	-8.84	181		
2	Non-use of inhalants	1.77	6.07	-11.24	518	241.71	.000
	Inhalant use	16.22	22.36	-8.32	183		
3	Non-use of inhalants	1.37	3.13	-11.40	518	267.74	.000
	Inhalant use	16.51	24.38	-8.11	173		
4	Non-use of inhalants	1.56	5.59	-11.47	518	276.67	.000
	Inhalant use	15.92	22.00	-8.43	182		
5	Non-use of inhalants	1.68	5.42	-12.12	518	350.21	.000
	Inhalant use	18.95	25.46	-8.80	178		
6	Non-use of inhalants	1.77	5.56	-11.16	518	292.27	.000
	Inhalant use	17.3	24.75	-8.13	179		
7	Non-use of inhalants	1.48	4.91	-10.45	518	246.72	.000
	Inhalant use	15.45	23.97	-7.57	178		
8	Non-use of inhalants	1.54	5.19	-11.21	518	312.97	.000
	Inhalant use	16.98	24.62	-8.13	178		
9	Non-use of inhalants	1.48	4.28	-11.31	518	348.72	.000
	Inhalant use	16.8	24.55	-8.12	176		
10	Non-use of inhalants	1.55	4.59	-11.24	518	338.11	.000
	Inhalant use	17.33	25.38	-8.09	176		

Table 5
Descriptive data of different age and gender groups in the population

Item	Groups	Mean	SD	t	gl	F	Sig.
1	12-14 years	7.76	16.71	0.594	518	.703	.400
	15-19 years	6.92	15.43	0.588	465		
	Men	8.4	16.78	-1.730	517	5.27	.022
	Women	5.99	14.94	-1.715	518		
2	12-14 years	7.4	16.9	1.119	518	2.12	.146
	15-19 years	5.89	14.02	1.093	435		
	Men	6.15	13.17	0.639	437	3.7	.055
	Women	7.03	17.57	0.653	518		
3	12-14 years	6.33	15.24	-0.057	518	.343	.558
	15-19 years	6.41	16.43	-0.058	501		
	Men	6.66	15.31	-0.418	490	.097	.755
	Women	6.07	16.61	-0.421	518		
4	12-14 years	7.07	16.6	1.025	518	2.37	.124
	15-19 years	5.71	13.69	1.000	433		
	Men	7.18	15.43	-1.422	518	2.54	.111
	Women	5.3	14.51	-1.415	513		
5	12-14 years	7.68	18.09	0.334	518	.195	.658
	15-19 years	7.17	16.68	0.331	465		
	Men	6.91	15.31	0.670	452	3.49	.062
	Women	7.95	19.38	0.682	518		
6	12-14 years	6.42	14.38	-0.595	518	2.84	.092
	15-19 years	7.29	18.16	-0.612	517		
	Men	7.75	17.86	-1.254	518	3.38	.066
	Women	5.94	15	-1.238	517		
7	12-14 years	7.28	18.11	1.499	518	6.87	.009
	15-19 years	5.19	13.64	1.448	407		
	Men	6.23	15.45	-0.179	498	.039	.844
	Women	5.98	16.16	-0.180	518		
8	12-14 years	7.81	18.67	1.420	518	6.34	.012
	15-19 years	5.75	14.46	1.376	415		
	Men	7.73	17.76	-1.637	518	7.33	.007
	Women	5.4	14.71	-1.614	517		
9	12-14 years	8.36	19.32	2.254	518	16.25	.000
	15-19 years	5.14	13.16	2.152	379		
	Men	6.16	14.45	0.589	455	2.94	.087
	Women	7.01	18.06	0.599	518		
10	12-14 years	8.05	18.55	1.533	518	7.75	.006
	15-19 years	5.78	15.21	1.495	432		
	Men	6.61	15.86	0.241	483	.784	.376
	Women	6.97	17.81	0.243	518		

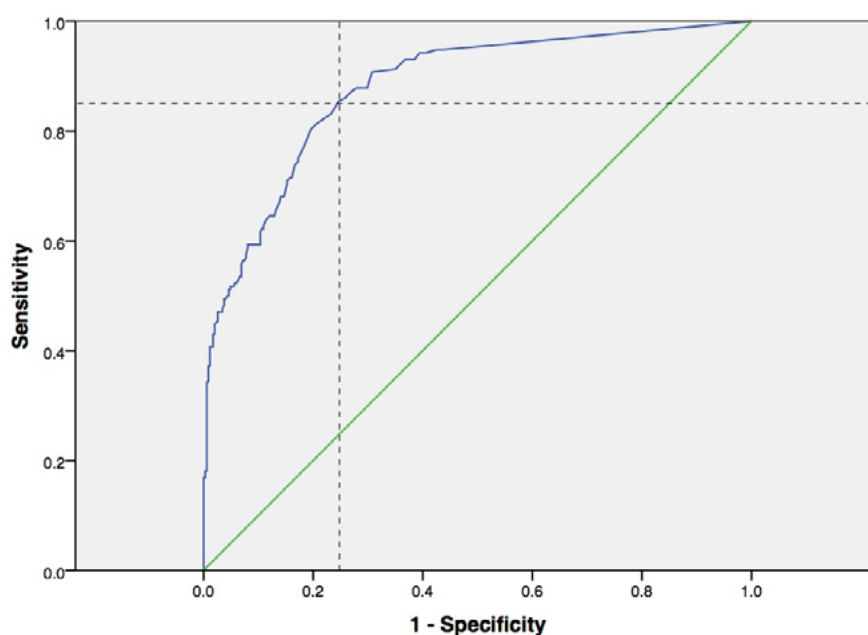


Figura 1. ROC Curve of ICQ, proposed cutoff point to differentiate the two groups (users and non-users)

A Student's T test was carried out for the means of each item. Table 5 shows the results of age groups and sex. For the age group, the sample was divided in two: one group aged 12-14 years (227) and the other group aged 15-19 (293). It is observed that only items 7, 8, 9 and 10 show a significant difference of ($p < 0.05$). The results of the gender group (men / women), indicate that only items 1 and 8 show a significant difference ($p < 0.05$).

ROC analysis

To assess the capability of the ICQ to discriminate users ($n = 172$, $M = 169.40$, $SD = 186.48$) from non-users ($n = 348$, $M = 16.29$, $SD = 39.08$), a ROC curve was employed, with this analysis technique, we determined ICQ sensitivity and specificity, as well as the ideal cutoff point to differentiate the two groups. The analysis showed that the breakpoint was located at 18.5 mm, with a sensitivity of 0.855 and specificity of 0.753 (1 - Specificity of 0.247), as seen in Figure 1.

Discussion

Recent studies have revealed that the abuse of inhalants has increased in recent decades and it has become a widespread public health problem in the population. Inhalants are within the first three psychoactive substances chosen by the general population (ENA, 2011). However, there is a lack of screening instruments for the detection of craving. These instruments could be key tools in decision-making for the diagnosis and treatment of addictions (Sayette et al., 2000).

Early detection of inhalants addiction may provide relevant information for prevention and treatment campaigns.

ICQ data indicated that one-third of the study population had been in contact with inhalants, and that the first use was usually at an early age (13 years old on average). These data are consistent with the literature indicating that the age of onset is between 12 and 14 years of age. Also, inhalants rank as the third preference within this population (ENA, 2011; Villatoro et al., 2012).

It is noteworthy that some studies report that misuse of inhalants is not restricted to high-risk groups (Gigengack, 2013; Villatoro et al., 2011); however, our study confirmed that misuse of inhalants is relatively common in the Mexican student population. Consumption data from our sample indicate that 46.2% of users were females and 53.8% males. Preferred substances were: paint thinners, nail polish and polyvinyl chloride (PVC). Analogous findings have been reported in previous studies in similar populations (Villatoro et al., 2005, 2012, 2013).

The distribution curve of ICQ total scores showed a shifting to higher values with an asymmetry index of 2.85 and a kurtosis of 8.69. ICQ range of total scores included values from 0 to 833 mm. Results of the ROC curve analysis indicated that the questionnaire is suitable for assessment of craving severity. This instrument not only has the ability to discriminate, but it also shows good specificity and sensitivity, starting from a general average of the ten items of 18.5 mm. In the questionnaire, zero value means the absence of craving and a value of 18.5 mm marks the starting point for the presence of this phenomenon.

ICQ data were consistent with those shown by other instruments commonly used in the clinical setting for assessing the presence or absence of psychiatric disorders. For example, in the Beck Depression Inventory, zero represents the absence of significant clinical symptoms whereas a total larger than eighteen in adults and ten in adolescents suggests the presence of depression, and even larger scores represent more severe levels (Sanz, Perdigón & Vázquez, 2003; Beck, Steer & Garbin, 1988).

The reliability analysis showed that the scores had a Cronbach's alpha of 0.947, which means that the ICQ has high internal consistency, a desirable feature for clinical purposes (Cicchetti, 1994). Moreover, this result is also consistent with other scales in Spanish that measure craving for psychoactive substances such as cocaine and alcohol. For instance, the CCQ-G, which has an alpha of 0.87 (Marín-Navarrete et al., 2011), the CCQ-N-10, which has an alpha value of 0.95 (Castillo, Albet, Jimenez-Lerma & Landabaso, 2009), and the Desire to Drink Alcohol Scale (DDS) with an alpha of 0.91 (Gan, Sanz, Valladolid & Calvo, 2006).

With regard to evidence of internal structure, factor analysis revealed that ICQ scores had a one-factor structure, which explains 67.9% of the variance. This means that this questionnaire measures the craving construct as a single phenomenon. This result is consistent with other studies, such as the one on cocaine craving (Durán & Becona, 2006). On the other hand, this outcome contravenes other instruments that show a multidimensional measure of the theoretical components of craving (Tiffany, Carter & Singleton, 2000; Tiffany & Conklin, 2000).

ICQ also showed face validity as evaluated by a group of experts in the addiction field. Experts were asked to consider whether completeness, semantics, and sentence structure of the items guaranteed ICQ conceptual representation. The evaluation gave an average score of 3.8, which meant that the experts agreed with the items.

Other evidence supporting the validity of the ICQ instruments is the difference in total scores between groups; age and sex did not show differences, but consumption is a significant indicator, as shown by the groups (non-users and users). In this analysis, differences in scores for each item and totals were observed. The results suggest that the non-users reported significantly lower values of craving intensity as compared with those who had used inhalants. Thus, ICQ appears to provide quick and reliable information for the presence of craving for inhalants in different populations.

Implementation of the ICQ is simple and quick. Furthermore, since it is a self-report instrument, it may be used in different care centers. It also avoids the subjective perception of the clinician.

Visual analog scales such as the ICQ are common instruments for measuring craving (Sánchez-Hervás, Molina, Del Olmo, Tomás & Morales, 2001; Marín-Navarrete et al.,

2011; Serecigni Guardia et al., 2004), because given their characteristics, they are useful in evaluating specific populations, such as the poorly educated and those with some cognitive impairment, as is the case of inhalant users (Castillo & Bilbao, 2008). These characteristics suggest that the ICQ may become an attractive tool in the clinical setting for the assessment of craving in inhalant users.

Our results suggest that the ten items of the ICQ instrument provide a valid global measure of the intensity of craving for inhalants. The ICQ has adequate psychometric properties and may be used in assessing craving in clinical and epidemiological settings (Iraurgi & Corcuera, 2008).

This study, although useful, is not without limitations. First, it is a cross-sectional study, which means that we cannot conclude causality or evaluate predictive validity. It is necessary to continue doing longitudinal research to compare the results and better understand the issues involved in them. On the other hand, the self-administered questionnaires may have some limitations. Further research should incorporate other diagnostic instruments, preferably objective measures, in order to evaluate concurrent validity.

Among the issues that remain to be assessed is application of the instrument in addicted populations, for the purpose of calculating the sensitivity and estimated cutoff of the intensity of craving and also to define the score to be considered clinically significant for the presence of craving. Additionally, it would be interesting to make evaluations comparing addicted populations with other tests for evaluating craving for the same and other substances. It will also be interesting to get the performance in different age groups and with comorbid personality disorders.

In conclusion, it should be noted that this research certainly opens the possibility of conducting future studies to analyze craving for inhalants. As is well known, inhalant misuse is a growing problem with an increasing proportion of persons at risk that require improved and more sustainable prevention efforts (Medina-Mora & Real, 2013).

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Conflict of interest

All authors declare no conflict of interests.

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Enforcing regulations on alcohol sales and use as universal environmental prevention

Hacer cumplir las regulaciones sobre venta y consumo del alcohol como prevención ambiental universal

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Abstract

The informal social control over alcohol consumption that was traditional in Southern European countries has weakened. At the same time there is an increase in binge drinking and drunkenness among young people in Spain. To mitigate this problem, regulations on alcohol and driving and restrictions on the sale and consumption of alcohol have been adopted. This paper documents the current regulations in the city of Barcelona and describes efforts to enforce them and their outcomes. Data from the municipal information systems on infringements reported for the period 2008-13 are provided.

There is an increasing pressure of municipal services to enforce the rules in two areas: a) alcohol sales at night (retailers); and b) consumption in the public space (citizens). An increase in the controls of drink-driving has also taken place, and the proportion above legal limits has decreased. The largest relative increase occurred in the control of retailers.

In Barcelona interventions are made to limit the supply and consumption of alcohol at low cost and during the night, and of driving under the influence of alcohol. There have been no documented episodes of massive drinking in public spaces (known as 'botellón') in the city. These actions, which complement other preventive efforts based on health education, can change the social perceptions of alcohol by minors in a direction less favorable to consumption, promoting environmental prevention.

Key words: alcohol, prevention, regulation, authority.

Resumen

El control social informal sobre el consumo de alcohol, tradicional en los países del Sur de Europa, se ha debilitado. Este cambio ha ido acompañado de un incremento de los episodios de consumo intensivo y borracheras en jóvenes en España. Para mitigar este problema, se han adoptado regulaciones sobre alcohol y conducción, y otras que restringen la venta y el consumo de alcohol. Este trabajo documenta las regulaciones vigentes y describe los esfuerzos realizados en la ciudad de Barcelona en este campo y sus resultados. Asimismo, se recopilan datos de infracciones denunciadas en los sistemas de información municipal para el período 2008-13.

Se observa un incremento de la presión de los servicios municipales para hacer cumplir las normas en dos aspectos: a) la venta en horario nocturno (establecimientos); y b) el consumo en la vía pública (ciudadanía). Por otra parte, también se aprecia un aumento en la actividad de control de la alcoholemia de los conductores, mientras que la proporción que superan los límites legales descendió. El mayor incremento relativo se ha producido en las acciones sobre establecimientos.

En Barcelona se realizan intervenciones para limitar la oferta y consumo de alcohol a bajo coste y en horario nocturno, así como la conducción bajo la influencia del alcohol. En la ciudad no se han documentado episodios de botellón masivo en espacios públicos. Estas acciones, que complementan otros esfuerzos preventivos basados en la educación para la salud, pueden modificar la percepción social del alcohol por los menores en un sentido menos favorable al consumo, contribuyendo a crear un entorno de prevención ambiental.

Palabras clave: alcohol, prevención, regulación, autoridad.

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For many years it was considered that in the countries of southern Europe the consumption of alcohol was integrated within the cultural structure, with no restrictive mechanisms of formal control, and with problematic consumption being barely visible (Room & Mäkelä, 2000). With the social changes that have come in recent decades, however, this profile has been challenged (Anderson & Baumberg, 2006). On the one hand, average consumption is lower as is daily consumption, but on the other, an increase in episodes of binge drinking and drunkenness on the part of young people in this country can be appreciated, with health and social consequences (Villalbí & Brugal, 2012). This reflects that among some segments of young people there is a perception of intensive consumption as being the norm among their peers (Calafat Far, 2007; Pascual Pastor, 2002; Salamó, Gras, & Font-Mayolas, 2010) as well as easier access to alcohol. Progressively, various formal regulations have been adopted as a response to this problem (Villalbí, Bosque-Prous, Gili-Miner, Espelt, & Brugal, 2014). The most visible and best known of these are those relating to alcohol and driving, which have achieved an important reduction in traffic accident injuries in Spain (Pulido et al., 2014). Other relevant regulations are those affecting the availability of alcohol, by means of restrictions on its sale and consumption (Valencia-Martín, Galán, & Rodríguez-Artalejo, 2007), that several local and regional governments have adopted and have then applied in different ways, according to the context. The value of regulatory policies aimed at reducing the problematic consumption of alcohol has been exhaustively reviewed recently (Babor et al., 2010).

The city of Barcelona has, since 1989, approved action plans to combat drug dependency, including both illicit and licit drugs, with a special emphasis on alcohol. These plans were approved in plenary sessions of the city council with political consensus (Manzanera et al., 2000). They are intersectoral and incorporate objectives related to various municipal and health services (Brugal, Guitart & Espelt, 2013). From the beginning, the public health services now concentrated in the Agència de Salut Pública de Barcelona (Barcelona Public Health Agency, ASPB in its Catalan initials) coordinated and evaluated them. This agency is a consortium-style body run jointly by the local government and that of the autonomous region (Catalonia) which groups together all the public health services of the city and, in the field of the Drug Plans, acts in coordination with other municipal services and also with the Departamento de Salud and the Servicio Catalán de la Salud (Health Department and the Catalan Health Service) (Guix et al., 2008). As part of this work, it fosters the effective enforcement of the regulations on the promotion, sale and consumption of alcohol in the city and collects data on the enforcement actions of the various municipal services in this area.

The objective of this paper is to document the efforts made to apply some regulations about alcohol in the city.

Information that reflects actions taken in this field and its evolution over time is compiled and analyzed, and its contribution is discussed from a comprehensive preventive perspective.

Method

This is a descriptive study that is focused on the city of Barcelona over a six-year period, from 2008 to 2013. Data was collected on the main categories of reports of infringements of the alcohol regulations dealt with by the Guardia Urbana de Barcelona (Barcelona Local Police), registered in the municipal database of infringements, reports and sanctions. Its evolution over this period is described, and the data from the first three-year period (2008-10) are compared with those of the second, from 2011-13. The changes are measured by means of the chi-squared test for the comparison of proportions or the calculation of the confidence interval at 95%, using the Epidat program. The information systems from which violation reports are extracted are centralized in municipal computer applications. The aggregated and anonymized data regarding reported infringements related to alcohol were obtained by the central services of the Local Police who make them available to the public health services as part of the monitoring of the objectives of the Action Plan on Drug Dependency.

The regulations regarding alcohol that the Local Police enforce are basically three, and they are shown in Table 1. All of them were in force before 2008, which is the beginning of the period under study. State-wide traffic regulations are brought together in the Ley sobre Tráfico, Circulación de Vehículos a Motor y Seguridad Vial (Law on Traffic, Circulation of Motor Vehicles and Road Safety) and its successive modifications (*Real Decreto Legislativo 339/1990, de 2 de marzo, por el que se aprueba el Texto Articulado de la Ley sobre Tráfico, Circulación de Vehículos a Motor y Seguridad Vial, 1990; Royal Legislative Decree 339/1990, of March 2nd, by which the Articulated Text of the Law on Traffic, Circulation of Motor Vehicles and Road Safety, 1990, is approved.*). This law prohibits driving if the level of alcohol in the blood is above certain limits. Above these are the corresponding administrative sanctions, such as the withdrawal of points from the driving license and fines, habitually of €500.

The regulations governing the sale and consumption of alcohol are included in the Catalan law covering prevention and assistance in the matter of substances which may cause dependence, and its successive modifications (*Llei 20/1985, de 25 de juliol, de prevenció i assistència en matèria de substàncies que poden generar dependència, 1985; Law 20/1985, of July 25th, for the prevention and assistance in the matter of substances which may cause dependence, 1985*). This law prohibits the sale of alcohol in retail establishments in which consumption is not permitted (food stores) from 23:00 until 08:00 the following morning and since 1998 shopkeepers must

Table 1. *Some aspects of the regulations in force governing the sale of alcohol, driving of vehicles and drinking in the public thoroughfare. Barcelona, 2008-13*

Purpose of the regulation	Territorial scope of the regulation	Form of the regulation	Specific aspects regulated	Date of the regulation	Principal agents to ensure their compliance	Infringements and sanctions
Driving of vehicles while under the influence of alcohol	Spain	Law on Traffic, Circulation of Motor Vehicles and Road Safety (RDL 339/1990)	Quantities of alcohol in exhaled air when driving greater than 0.25 mg/L (0.15 for novice and professional drivers).	1990, amended in 2006	Local Police and Catalan Police	Very serious offence (€500) and loss of license points
			Quantities of alcohol greater than 0,6 mg/L in exhaled air.	2007 (amendments to the Law)	Local Police and Catalan Police	Crime against traffic safety with criminal penalty
Sale of alcohol	Catalonia	Law for the prevention and assistance in the matter of substances which may cause dependence, 1985 (Law 20/1985)	Sale prohibited in establishments where consumption is not permitted between 23:00 and 08:00.	1998 (amendments to the Law)	Local Police and Catalan Police	Serious offence (3,000 €)
			Sale to minors under the age of 18 prohibited.	2002 (amendments to the Law)	Local Police and Catalan Police	Serious offence (3,000 €)
Consumption of alcohol in the public thoroughfare	City of Barcelona	Ordinance of measures to foster and guarantee the coexistence of citizenry in public spaces	Consumption of alcohol in the public thoroughfare when it may inconvenience neighbors and passers-by and in bottles or cans (outside of pavement cafés) prohibited.	2006	Local police	Minor offence (30€)

display a sign that states this in a visible place. Also, the sale of alcoholic beverages to persons under the age of 18 has been prohibited since 2002. Infringements for selling to the under-18s and for selling at night are considered serious, violation reports are sanctioned with fines of a minimum of €3,000 and require administrative procedures.

The Municipal Ordinance of measures designed to foster and guarantee the coexistence of the citizenry in public spaces (*Ordenanza de medidas para fomentar y garantizar la convivencia ciudadana en el espacio público de Barcelona*, 2005; Ordinance of measures to foster and guarantee the coexistence of citizenry in public spaces of Barcelona, 2005), popularly known as the civic ordinance, came into force in 2006. It includes two relevant prohibitions: the consumption of alcohol in the public thoroughfare when it may inconvenience neighbors and passers-by, and the consumption of alcohol in bottles or cans, except at café and restaurant terraces. Infringements of this type are considered minor, and therefore, when reported, carry a minimum fine of €30, which may be substituted by alternative measures.

Results

In Figure 1, the number of breath alcohol tests (BAT) carried out by the Local Police on drivers from 2008 to 2013 are shown, as well as the proportion of tests that were over the established limit. The number of BAT appears to be stable, although there are variations: the mean is of 129,000 a year, and the values show a range of between 115,023 and

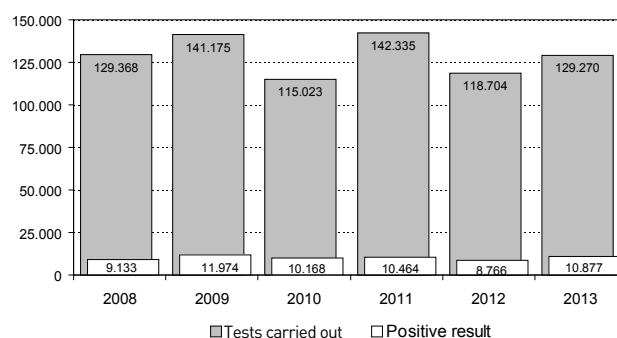


Figure 1. Breath alcohol tests carried out by the Local Police on drivers of vehicles and number over the limit. Barcelona, 2008-13.

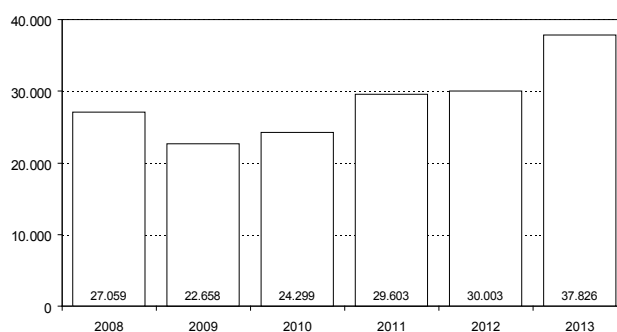


Figure 2. Violation reports issued by the Local Police for the consumption of alcohol in the public thoroughfare against the municipal ordinances. Barcelona, 2008-13.

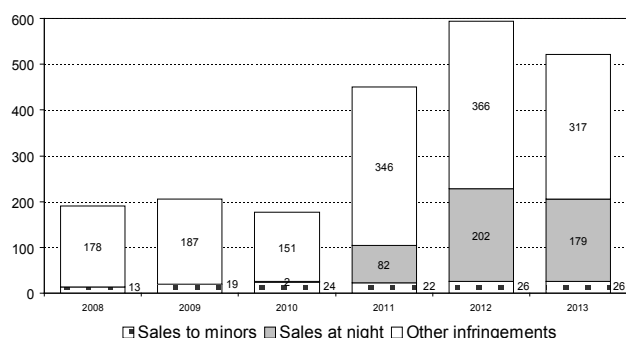


Figure 3. Violation reports issued by the Local Police to commercial establishments for infringements of the regulations governing the sale of alcohol, by type of infringement. Barcelona, 2008-13.

142,336. During the period from 2011 to 2013, 1.2% more BAT were carried out than between 2008 and 2010. These BAT generated between 9,000 and 11,000 fines a year for driving over the limit, shown by means of a breath test. In the period from 2008 to 2011, 8.11% of the BAT (CI 95%: 8,03-8,20) gave positive, while from 2011 to 2013, the figure was 7.71% (CI 95%: 7,63-7,80), a lower proportion.

Figure 2 shows the fines issued by the Local Police for consumption of alcohol in the public thoroughfare. After the municipal ordinance came into force, the annual figure increased from 27,000 in 2008 to approximately 38,000 in 2013. In terms of three-year periods, they go from 74,016 to 97,432 tickets handed out, which in yearly figures would be 1,759.77 (CI 95%: 1.747,12-1.772,50) and 2,316.50 (CI 95%: 2.301,98-2.331,09) fines per 100,000 inhabitants over the age of 14.

Figure 3 illustrates the number of violation reports issued by the Local Police to establishments frequented by the public (principally food stores, bars and cafeterias) for alcohol-related infringements between 2008 and 2013. The graph shows those due to the sale of alcohol to minors, to the sale of alcohol after hours, and to other infringements, (mostly for lack of signage). As can be seen, the number of reports increased notably after 2011, with the emergence of those due to selling alcohol after hours. These go from being merely token and limited to gas stations within the city limits to around 200 fines a year, and from 0.35% of fines in the first three-year period to 29.57% in the second ($p < 0.0001$). Fines handed out for selling alcohol to minors doubled from 13 to 26 a year, but represent a lower percentage of the total, going down from 9.76% to 4.73% ($p < 0.0001$).

Discussion

Although news stories about fines to shops or individuals for selling or consuming alcohol frequently appear in the media and on Internet, we have not found any data from other cities or communities on their absolute or relative frequency; only the data related to road safety are system-

atically gathered together in the reports of the Dirección General de Tráfico (Directorate General of Traffic, DGT) or those of the regional or autonomous police forces. Data from Barcelona indicate that, in the city, the changes in the law in recent years are translating into an organized and ever more coherent effort aimed at reducing the supply and consumption of low cost alcohol available to young people, its sale at night, and drink-driving. In accordance with the scheme proposed by Foxcroft (2014), these actions, which complement other preventive efforts based on health education, should change the social perception that minors have of alcohol consumption in a sense less favorable to consumption, contributing to the creation of a preventive environment. Maybe in the future this will mean differences in patterns of adolescent consumption in the city with regard to other areas. In any case, there are no documented cases in the city of large groups of young people having open-air binge drinking sessions (botellón), which have taken place in other cities in Spain (Rodríguez-Martos, 2007).

We can attempt to estimate the relative magnitude of these efforts, which will be key for the public's perception. It is estimated that in Barcelona there are 968,000 registered vehicles, as well as those that circulate in the city coming from the metropolitan area (Departament d'estadística, Ajuntament de Barcelona, Department of Statistics, City Council of Barcelona, 2013). This means that there are 13 alcohol checks carried out every year per 100 registered vehicles. Checks are carried out with greater frequency at night and at weekends, and in areas where there are more leisure spots, and one infringement is detected for every 13 checks made. The actions of the Local police are added to those of the *Mossos d'Esquadra* (the police force of Catalonia): between 400,000 and 600,000 checks are carried out per year in Catalonia, especially on interurban roads. Together, this makes for a sizable pressure regarding the control of drink-driving, which has meant a favorable impact on the indicators of breathalyzer tests based on representative samples and on injuries from traffic accidents (Alcañiz et al., 2014; Pulido et al., 2014; Sarasa-Renedo et al., 2014). Regarding small retail outlets selling food, it is estimated that there are 4,200 of them in the city, most of which close before 21:00. If we use as a denominator the fines issued for nighttime sales of alcohol in this sector, it would be around five out of every hundred establishments over the last year studied. We cannot estimate it for those that open at night as we have no reference figures, but it would supposedly be much higher. These estimations of relative frequency, such as those made for fines handed out for drinking in the street, are not real rates (as they would require assumptions to be made on numerators and denominators that are not fulfilled), but they are indicative.

This dynamic must be put in the context of the changes that have come about in the market for the sale of alcohol-

lic beverages and in the leisure available in the city. On one hand, the increasing deregulation of shopping hours has meant that the sale of alcohol in food stores (traditional in our context, and not subject to alcohol license) has extended to the night and the weekends. The limitation on sales at night is precisely an attempt to reduce the problems that come with easy access to cheap alcoholic beverages (Villabí et al., 2014). On the other hand, the hospitality sector has expanded notably in a city in which tourism has an ever greater weight in the economy (Barcelona Tourist Office, 2014; Department of Statistics, City Hall of Barcelona, 2014). Finally, the changes in family dynamics and the patterns of adolescent and youth leisure time lead to a growth in the proportion of young people (including minors) who stay out until late, and this is associated with risky consumption (Llorens, Barrio, Sánchez, Suelves, & ESTUDES Working Group, 2011). Therefore, the efforts made in terms of regulations and enforcement go against other social changes that favor greater consumption. Another force to take into account is the marketing of the alcohol industry, of which there are signs of its impact on consumption (Montes-Santiago, Alvarez Muñoz, & Baz Lomba, 2007).

Evidently, other actions on the part of the public health services to reduce the consumption of alcohol among adolescents and young people have to be taken into account. Important in the city are the educational programs aimed at universal prevention (Foxcroft & Tsertsvadze, 2012) offered in secondary education, and which are very extensive (Juárez, Pasarín & Arcas, 2014), as well as the selective prevention actions based on unspecific prevention interventions in neighborhoods deemed to be high-risk (Bartoli et al., 2012; Bartoli, Espelt, Castellano, & Brugal, 2012), as well as the indicated prevention programs (Guitart et al., 2012). But as the reviews of the literature show, population-based prevention actions have the greatest preventive potential (Martineau, Tyner, Lorenc, Petticrew, & Lock, 2013). We should contemplate the actions of exercising authority to enforce the formal regulations governing the sale and consumption of alcohol in our milieu as universal prevention actions, which modify the environment (Burkhart, 2011; Foxcroft, 2014). The sequence that goes from the approval of regulations on the consumption of alcohol until their effective enforcement is the key to reducing the social perceptions that have led to the banalization of alcohol consumption among some population groups. This influences the balance between costs and benefits of consumption perceived by young people, as well as the perceived social norm (Vries, Backbier, Kok, & Dijkstra, 1995), which are key determinants of behavior.

Conflict of interests

The authors declare that they have no conflict of interests.

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Spinal cord injury and substance use: a systematic review

Lesión medular y uso de sustancias: una revisión sistemática

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Abstract

The objective of this study was to review recent findings about the prevalence of substance use (SU) and substance use disorders (SUD), and to discuss the related impact on health in spinal cord injury (SCI) population. For this purpose, computer-aided searches of MEDLINE (PubMed) and the Cochrane Library were conducted. From an initial pool of 59 articles, 52 met the inclusion criteria. Most of the studies referred to alcohol and tobacco and only a few studies reported on other substances. Study designs were mainly cross-sectional and descriptive, with scarce intervention and longitudinal studies. Although a high prevalence of post-injury SU has been documented among SCI patients, limited research exists on pre-injury SU and on longitudinal studies. Moreover, when exploring SUD, it has not been systematically studied in accordance with CIE or DSM criteria. Alcohol appears to be the most consumed substance among this population. Additionally, those patients with SU have shown poorer outcomes in different health indicators. Therefore, more insight is required to increase scientific knowledge in this field and to recommend tailored preventive interventions and research priorities in relation to this population.

Key Words: Spinal cord injury, substance use, substance use disorders, addictive behaviours, health outcomes.

Abbreviations: SCI: Spinal Cord Injury(ies); SU: Substance Use; SUD: Substance Use Disorder(s).

Resumen

El objetivo de este estudio fue el de revisar los hallazgos recientes sobre la prevalencia de uso de sustancias (US) y trastornos por uso de sustancias (TUS) y discutir su impacto en la salud en población con lesiones medulares (LM). Para este propósito, se realizaron búsquedas asistidas por ordenador en MEDLINE (PubMed) y en la Biblioteca Cochrane. A partir de un conjunto inicial de 59 artículos, 52 cumplieron los criterios de inclusión. La mayoría de trabajos se centraban en el consumo de alcohol y tabaco, y sólo unos pocos informaron acerca del uso de otras sustancias. El tipo de diseño de investigación fue mayoritariamente transversal y descriptivo, siendo escasos los estudios de intervención y longitudinales. A pesar de la alta prevalencia de US documentada en pacientes con LM, apenas existen trabajos sobre el consumo previo a la LM y de diseño longitudinal. Además, cuando se ha evaluado el TUS, éste no se ha estudiado de forma sistemática siguiendo criterios diagnósticos CIE o DSM. El alcohol ha resultado ser la sustancia más consumida entre esta población. Además, los pacientes con US han mostrado peores puntuaciones en distintos indicadores de salud. Por ello, se necesita más investigación para seguir avanzando en este ámbito de estudio, así como para poder diseñar intervenciones preventivas más efectivas adaptadas a las necesidades específicas de esta población, y para sugerir prioridades de investigación.

Palabras clave: Lesión medular, uso de sustancias, trastorno por uso de sustancias, comportamiento adictivo, salud.

Abreviaturas: LM: Lesión Medular(es); TUS: Trastorno por Uso de Sustancias; US: Uso de Sustancias.

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The impact of a Spinal Cord Injury (onwards SCI) after a major trauma can lead to negative emotional responses (i.e. depression, anxiety), disengagement-type coping (i.e. injury-related factors denial, avoidance) and altered psychosocial functioning (i.e. family roles, identity); (Antonak & Livneh, 1991; Hammell, 1992; Vash & Crewe, 2004; Wright, 1960). Sometimes, post-injury psychological distress could be so intense and unbearable that patients might seek relief in substance consumption (Smedema & Ebener, 2010; Treischmann, 1988). On the one hand, people with pre-injury substance use (onwards SU) could exacerbate their consumption and increase their odds for developing a substance use disorder (SUD) or, in the best case scenario, they can decide to give up or reduce their SU behaviours (Bombardier, Stroud, Esselman & Rimmele, 2004; Burns & Ditunno, 2001; Krause, 2004; Saunders & Krause, 2011; Smedema & Ebener, 2010).

Scientific research agrees to point out that SU and especially SUDs have a negative impact on a person's vocation, academic performance, family and social life, as well as on physical and psychological health status; if SUDs occur in population with severe chronic health conditions, such a SCI, disability and negative consequences increase considerably (Burns & Ditunno, 2001; de Groot, Post, Snoek, Schuitemaker, van der Woude, 2013; Hammell, 1992; Smedema & Ebener, 2010; Vash & Crewe, 2004).

To date, existing research on SU and SCI is mainly descriptive and designed as cross-sectional (Smedema & Ebener, 2010; Wegener, Adams & Rohe, 2012). To our knowledge, only one literature review on this topic exists, but it dates from 2010 and it is not exclusively focused on SCI population (Smedema & Ebener, 2010).

Given the potential risks that SU and SUDs could entail in SCI patients mid-long term adjustment and health status (Smedema & Ebener, 2010; Wegener et al., 2012; Wright, 1960), it is important to acknowledge the magnitude of the problem and to consider it as a key element in rehabilitation programs (Bozzacco, 1990; Krause, 1992; Smedema & Ebener, 2010; Wegener et al., 2012). Only by doing this, it will be feasible to design accurate screenings and assessments that allow diagnosing and to plan specific interventions to address such issues (Hammell, 1992; Treischmann, 1988; Wright, 1960).

Therefore, this paper is aimed to systematically review scientific literature on SU and SUDs in SCI patients (considering pre- and/or post-injury period) and to discuss their impact on different general health indicators. It is expected that this knowledge will serve to encourage further research in this field and to recommend clinical priorities with this population.

Methods

Search strategy

The primary data source for this review was the electronic database MEDLINE (PubMed). The Cochrane library was also accessed and searched via the Health Information Resources website, www.library.nhs.uk/default.aspx (formerly the National Library for Health). Reference lists of reviewed articles were also searched to identify potentially relevant missing studies. The search terms (in English only) were *spinal cord injury* in combination with: *substance use, substance use disorder, substance dependence, substance disorder, addiction, alcohol, tobacco, cocaine, stimulants, opioids/opiates, marijuana/marijuana, and cannabis/cannabinoid*. Duplicated results were removed. Hyphens and abbreviations were not used in case they limited the search. The remaining citations were displayed and examined in depth. The PRISMA guidelines were followed to conduct this systematic review.

Inclusion and exclusion criteria

Eligibility criteria were made by a single author (CC), with consensus from the other author (PL) on the basis of information found in the article's title, abstract, key words or full text if necessary. Studies were included in the review if they met the following criteria: (1) any study with humans attempting to evaluate substance abuse (such as: alcohol, tobacco and/or other drugs) in SCI before, during or after the rehabilitation. Studies with SCI samples plus other samples were also included. Studies were excluded if they were in any other language than English or else if substance use was referred to only in the introduction or the discussion of the article. That is, neither its assessment was an objective of the study nor specific measures for it were taken. Studies on prescribed drugs such as medication with psychotropic effects (e.g. to treat neuropathic pain) were not included in this review. Commentaries, proceedings and letter to the editor were also excluded. No publication date limits were set (search updated until May 2014).

Data extraction

Data extraction was conducted in three stages. At stage 1, one reviewer conducted the preliminary search and selection of studies applying inclusion criteria. At stage 2, two reviewers performed data extraction independently. At stage 3, synthesis of literature was put in common and discussed. Data from eligible articles were summarized into a form with the following column headings: author(s), year of publication, study design, sample, assessment tool(s) and measures for substance use, other measures, target substances, assessment period (pre/post injury), prevalence of substance use (when specified in the article) and main findings. This procedure was performed by both authors independently (CC & PL), with disagreements being resolved through discussion.

Results

Search results

The literature search of MEDLINE resulted in 224 potentially relevant articles related to the review topics. Excluded on duplicate, title and abstract were 165 articles, leaving 59 relevant articles. These retrieved articles were evaluated in depth according to the inclusion criteria. Fifty-two out of 59 previously selected articles met inclusion criteria. Cochrane database retrieved only 2 relevant articles already included in the MEDLINE search. As a result, 52 studies were finally reviewed.

General findings

A summary of reviewed articles is displayed in Tables 1 & 2.

Our review highlights that SU/SUDs are very common among SCI patients. Most of the studies have indicated higher rates of SU compared to general population. However, there are also several studies that do not compare prevalence found to general population or other clinical samples, which is clearly a limitation to yield conclusions. Additionally, prevalence of SU/SUDs varies widely across studies. Therefore, our results point out the need to improve research methodologies when addressing these questions.

As some theoretical studies have indicated (Smedema & Ebener, 2010), we have found that the most studied substances have been alcohol ($n = 45$, 86.5% of included articles) and tobacco ($n = 15$, 28.8% of included articles) being stimulants or sedative drugs less explored (Heinemann, Doll, Armstrong, Schnoll & Yarkony, 1991; McKinley et al., 1999). In this sense, studies on cannabis use/abuse ($n = 6$, 11.5% of included articles; Heinemann et al., 1988; 1991; Hwang et al., 2012; Stroud et al., 2011; Turner, Bombardier & Rimmele, 2003; Young, Rintala, Rossi, Hart & Fuhrer, 1995) and illicit drugs ($n = 6$, 11.5% of included articles; Heinemann et al., 1991; Kolakowsky-Hayner et al., 1999; 2002; McKinley et al., 1999; Rish, Dilustro, Salazar, Schwab & Brown, 1997; Turner et al., 2003) are scant.

With regard to alcohol, although consumption patterns have been found to be similar to general population in terms of gender and age (higher consumption in young males); (Banerjee et al., 2009; Saunders & Krause, 2011; Krause et al., 2009), rates of "risk consumption" are higher in SCI population (Tate et al., 2004; Turner et al., 2003). More than 50% injured patients show alcohol consumption patterns ranging from moderate-to-heavy drinking according to screening procedures and, in some studies, DSM or CIE criteria (Heinemann et al., 1991). Even though evidences are still scarce and not conclusive enough, risk consumption seems to be associated with family history of alcoholism and pre-injury "at risk" alcohol consumption (Schandler et al., 1995; Tate, 1993).

Overall, results seem to indicate higher rates of SU (especially, alcohol) prior to the injury and an exacerbation of this behaviour after the injury (de Groot et al., 2013; Wegener et al., 2012). In this sense, some studies have identified high rates of positive blood alcohol concentration at the time of the injury, and have associated these outcomes to the onset of the SCI (Forchheimer et al., 2005; Levy et al., 2004). Interestingly, there is also one study (Stroud et al., 2011) that points out that up to 71% of the sample described the onset of the injury as a "teachable moment" for quitting. However, it is a cross-sectional design and no further evidences are provided regarding final rates of alcohol consumption abandonment and specific motivations.

Tobacco is the second most consumed substance by this clinical population (Weaver et al., 2011). As in the case of alcohol, the prevalence/percentage of tobacco consumption varies greatly depending on the study (Levy et al., 2004; Weaver et al., 2001). Also noteworthy is that many studies do not provide specific rates of tobacco use/consumption and compare these values to general population. Additionally, in some studies cannabis smoking and tobacco smoking are not clearly differentiated and we cannot conclude if indicated prevalence is explained by tobacco, cannabis, or else a combination of both substances. Overall, where it is specified, prevalence ranges between 19-40% of the injured patients. Although being non-constant, tobacco use is frequently related to harmful alcohol consumption in this population. Logically, this negatively impacts on the health of individuals and increases their likelihood of suffering from other medical complications, as some studies have demonstrated (De Groot et al., 2013; Hwang et al., 2012; Krause & Saunders, 2009).

Regarding consumption of illegal substances, this has been studied by only few authors and less systematically. In this sense, results are based on screening procedures in the acute moment at hospital admission and no follow-up assessments are scheduled. Thus, very few studies have been carried out using procedures to collect such measures pre/post injury in a longitudinal design. Consequently, the prevalence found may reflect occasional rather than regular illegal substances consumption. As it can be observed in our study (see Table 2), only seven studies assessed SU/SUD based on clear diagnostic criteria.

With the exception of cannabis, the prevalence of illegal drugs consumption varies widely between 8 and 70% of patients. Cocaine and psycho-stimulants prevalence ranges from 0 to 14.4% and opiate use is around 4%. These percentages are clearly lower to those related to alcohol and tobacco. It is important to highlight that this prevalence may not be entirely accurate because several works included the consumption of substances as varied as sedatives, narcotic analgesics and barbiturates under the heading "psychotropic substances".

Measures to explore the possible relationship between SU/SUDs and health outcomes are many and varied. Consequently, comparison between studies is difficult and no conclusive results can be yielded. However, evidences seem to suggest poorer health-related outcomes (both physical and psychological) among those patients considered as risk substance consumers (Tate, 2004). In this sense, it has been indicated that moderate to severe SU has been related to higher risk of life-time substance-related problems and impaired health (Stroud et al., 2011). There are few studies addressing one substance at a time ($n = 16$, 30.8% of included articles, see Tables 1 and 2 for more details). Most of them evaluate a broad range of substances. Consequently, the individual effects of each of them on the health of the injured patients are not always specifically described (Banerjea et al., 2009; Smedema & Ebener, 2010; Tate et al., 2004). Moreover, prevalence of SUs has not always been provided (Bozzacco, 1990; Krause, 1992; Njoki, Frantz & Mpofu, 2007; Perez & Pilsecker, 1994; Sweeney & Foote, 1982).

Finally, it is worthwhile mentioning that most of the studies were descriptive and designed as cross-sectional (see Tables 1 & 2). In addition to this, assessment period of SU/SUD (and specific timing pre/post injury) varies widely among studies. While some studies assess and report data regarding both pre- and post injury period time, the majority of them are focused on a single period, either pre or post-injury. Moreover, there are only a few empirical studies assessing SUD following DSM or CIE criteria (See Table 2); (Banerjea et al., 2009; Findley et al., 2011; Heinemann et al., 1991; Tate et al., 2004; Turner et al., 2003). The majority of the included articles in this review only provide a concise description of SU patterns and/or prevalence in relation to diverse health outcomes employing screening tools (see Table 1); (Davies & McColl, 2002; Furlan & Fehlings, 2013; Hwang et al., 2012; Krause, 1992; 2004; Krause, Coker, Charlifue & Whiteneck, 2000; Tate et al., 2004). As a consequence, the exact prevalence of SUD among SCI population remains unclear. Additionally, it is noteworthy mentioning that the DSM and CIE criteria have changed in the updated versions and no studies have used these new criteria. Similarly, only two studies have reported prevalence of dual diagnosis according to DSM criteria (co-existence of both SUD and mental disorders); (Banerjea et al., 2009; Findley et al., 2011).

In brief, as previous theoretical reviews have stressed, all these characteristics make it difficult to examine thoroughly long-term relationships between SU/SUDs and health outcomes (Smedema & Ebener, 2010; Wegener et al., 2012).

Table 1
Articles on SU in SCI population

Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
Pre-SCI	Saunders & Krause	2011	Cross-sectional survey	N=1435 - BRFSS	- ZKPQ - Annual household & education	Alcohol	Moderate (29.4% of the sample) and heavy drinking (19.3% of the sample) was related to gender (male), age (younger), higher income and education, impulsivity and sensation seeking traits and less severe SCI.
	Krause et al	2009	Cross-sectional survey	N=1388 - BRFSS - CAGE - SCIHs	None	Alcohol, tobacco, psychotropic prescribed medication	Severe SCI exhibits less alcohol/tobacco use but more psychotropic prescription medications. More alcohol/tobacco use in younger.
	Garrison et al	2004	Cross-sectional survey	N=448 - Self-report	None	Alcohol	Participants with cervical SCI had increased relative odds (2.06) of having used alcohol at injury compared with participants without cervical SCI; 12% of them used alcohol at the time of the injury.
	Kolakowsky-Hayner et al	1999	Case-control	N=26 SCI, matched with N=26 TBI - GHIHQ	None	Alcohol and other illicit drugs (cocaine, heroin, marijuana, speed)	96% SCI patients reported pre-injury alcohol use and 57% were heavy drinkers. The rate of pre-injury heavy drinking for both groups was alarmingly high.
	De Groot et al	2013	Prospective cohort	N=130 - Health behavior scale (2 items on SU)	- Blood lipid levels - BMI - PASIPD	Alcohol, tobacco	More than 70% of the sample drinks alcohol regularly and more than 40% smokes. Lifestyle factors are related to cardiovascular risks.
Post-SCI	Furlan & Fehlings	2013	RCT-prospective cohort	N=499 - BAC	- NASCIS pain score - FIM - Mortality (1 year post injury)	Alcohol	9.4% illegal BAC 94.4% survival at year 1 post injury No relationship between BAC and FIM/mortality
	Hwang et al	2012	Cross-sectional survey	N=215 - Medical chart review for frequency of use and type of substance	- FIM - SF-12 - SWLS - PHQ-9 - CHART	Alcohol, cocaine, marijuana, tobacco, other illicit drugs (not specified)	Rates of regular use: 55.4% alcohol, 27.9% tobacco, 10.7% marijuana, 0% cocaine/other drugs. Depression was related to tobacco use, alcohol and independent living. Regular use of alcohol was not associated with chronic medical conditions.
	Krause & Saunders	2009	Cross-sectional survey	N=1386 - BRFSS - CAGE - SCIHs	None	Alcohol, tobacco, psychotropic prescribed medication	Use of prescribed medication (OR 2.58) and smoking behaviour (1.43) more predicts hospitalizations.
	Krause et al	2009	Prospective cohort	N=1386 - CAGE - SCIHs - Self-rated questionnaire	None	Alcohol, tobacco, psychotropic prescribed medication	Smoking, binge drinking, use of prescribed medication and hours in bed were the best set of behavioural predictors of mortality.
	Forchheimer et al	2005	Cross-sectional survey	N=119 - BAC	None	Alcohol	42% had a (+) BAC at the time of their injury; among (+) BAC, 87% had BACs > 0.08 (+) BAC related to severe SCI impairments (60% tetraplegia)

Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
Krause	2004	Cross-sectional survey	N=13280	- BRFSS - CAGE - Ad hoc brief index of prescribed medication usage	- General health survey - ZKPQ - Multidimensional Health Locus of Control Scale	Alcohol, psychotropic prescribed medication	Heavy drinking and prescription medication use for pain, spasticity, depression, and sleep were associated with a greater likelihood of subsequent injuries, and certain personality traits (sensation seekers)
Rothstein et al	1992	Cross-sectional survey	N=153	- Urine toxicology screening	None	Amphetamines, barbiturates, BZD, cocaine, methadone, opiates	29% of the sample used BZD, ≤ 13% other illicit substances and use of barbiturates was not found.
Post-SCI							
Cushman et al	1991	Cross-sectional survey (with matched control group)	N=60 (n ₁ =30, n ₂ =30)	- Alcohol use: police and medical report	- Medical records - Scene investigation from police - Mortality, rollover crashes, human factors, night-time accidents, weather or road conditions	Alcohol	SCI patients were not different from controls in terms of mortality, number of rollover crashes, alcohol use or other conditions referred in the police accident report. However, none of the SCI drivers had used restraints compared to the control group.
Heinemann et al	1988	Cross-sectional survey	N=88	- Serum ethanol - Urine toxicology screening - Self-report	None	Alcohol, BZD cannabinoids, cocaine, opiates	35% urine tests (+) for substances: 40% serum ethanol, 14% cocaine, 8% cannabinoids, 5% BZD and 4% opiates. Self-report of intoxication and urine analyses were discordant in 34% of the cases.
Stroud et al	2011	Cross-sectional survey	N=118	- Urine toxicology screening & BAC - Self-report - consume Brief Drinker Profile - Readiness to change questionnaire to change - SMAST	- Ad-hoc questionnaire for attributions about cause of injury	Amphetamines, BZD, cocaine, marijuana, opiates	Alcohol caused the injury in 50% of at-risk drinkers. 51% "at risk" drinkers with 38% reporting life-time alcohol-related problems. 71% were willing to change alcohol use (SCI as a "teachable moment" for quitting) 33% illicit drugs (28% marijuana, 9% amphetamines and 6% cocaine)
Pre/post-SCI							
Weaver et al	2011	Cross-sectional survey (multisite)	N=1210	- Self-reported measures (lifespan tobacco use) - Semi-structured interview for key informants about tobacco	None	Tobacco	22% current smokers, 57% past smokers & 27% never smoked. Current smokers reported more respiratory illnesses, alcohol use, overweight, pain and depression than past or never smokers. Smokers received referral to counseling and 23% prescription for medication/nicotine replacement. Key informants identify the following barriers: difficulty of providing follow-up, patients' unwillingness to give up tobacco

Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
Krause	2010	Longitudinal	N=1386	- BRFSS - Ad hoc brief index of prescribed medication use	- ZKPQ	Alcohol, prescribed medication	Binge drinking, psychotropic medication use & some personality characteristics (sensation seekers, impulsivity) were related to injury-related hospitalizations.
Hitzig et al	2008	Cross-sectional survey	N=781	- A.T. Jousse LTF questionnaire: - A.T. Jousse LTF questionnaire: drug addiction	- A.T. Jousse LTF questionnaire: impairment, health status, self-reported secondary health complications	Substance use/abuse (not specified)	Drug addiction [OR=0.966 (95% CI, 0.935–0.997, $p<0.05$)] decreased per year with age.
Njoki et al	2007	Cross-sectional survey	N=10	- Ad hoc interview: alcohol, tobacco and other drugs	- Ad hoc interview: physical activity & lifestyle	Alcohol, tobacco, other substances (not specified)	The focus group participants were involved in diverse health risk behaviors.
Bombardier et al	2004	Cross-sectional cohort	N=76	- SMAST	- FIM - Length of stay	Alcohol	39% had a history of problem drinking related to lower years of education, tetraplegia and longer length of stay, with lower functional recovery.
Levy et al	2004	Cross-sectional survey	N=11376 (SCI=967)	- Retrospective data from a statewide, population-based injury surveillance system	None	Alcohol, tobacco, other drugs	Alcohol involved in 34% of SCIs Large differences also existed in victim alcohol involvement between fatal and nonfatal cases of intentional SCIs (0% vs. 48%) Those who imbibed were 3 times as likely to suffer SCI. These excess risks persisted for all age groups between 15–64 years, with the excess risk especially high for drinkers aged 15 to 20. In contrast, people aged >65 did not appear to be at excess risk on days that they imbibed.
Seltz et al	2004	Case-control	N=14 ($n_1=7$ SCI, $n_2=7$ no-SCI; monozygotic twins)	- AUDIT	- SCID-P	Alcohol	No significant differences between SCI and non-SCI co-twins' SU patterns, suggesting that drinking patterns might not be significantly affected by SCI and substance misuse might precede the injury.
Kolakowsky-Hayner et al	2002	Case-control	N=30 SCI & matched TBI group	- Medical history about quantity & frequency of alcohol intake	- GHQ	Alcohol, other illicit drugs	41% SCI & 43% TBI patients were moderate or heavy drinkers. Illicit drugs' use was higher among post-injury SCI patients.
Davies & McColl	2002	Cross-sectional survey	N=97	- Sections of the LCHRA	- LSH-QCPC - ATS-DLD	Alcohol, tobacco	The interaction between cigarettes smoked per day and excessive alcohol consumption was related to respiratory morbidity. Urinary tract morbidity was (+) related to smoking and (-) related to alcohol consumption.
Krause et al	2000	Cross-sectional survey	N=97	- Ad hoc semi-structured interview including items from the BRFSS	- RSS - OAHMQ - CHART - Pressure ulcers	Alcohol, tobacco	49% consume alcohol on a regular basis and it was significantly related to greater risk for post-SCI injuries.

Pre/post-SCI

Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
McKinley et al	1999	Longitudinal	N=87	- Urine toxicology screening & BAC	- FIM - Length of stay	Alcohol, cocaine, BZD, opiates, amphetamines, phencyclidine, barbiturates	53% (+) admission toxicology screens with 37% (+) for alcohol and 30% (+) illicit drug screens. No differences between (+) and (-) screens for toxics at admission in rehabilitation outcomes.
Bombardier & Rimmele	1998	Cross-sectional survey	N=58	- SMAST - RTC - Ph Scale from Brief Drinkers Profile	None	Alcohol	35% "alcoholic" range in the SMAST and 50% at risk (21% pre-contemplation, 45% contemplation, 10% action) Multivariate analyses indicated that a positive history of alcoholism and higher daily consumption were associated with greater readiness to change.
Wineman et al	1999	Cross-sectional survey	N=78	- Ad hoc records for SU	- Medical records: injury-related variables, comorbid health conditions, healthcare utilization (last 5 years)	Substance use (not specified)	Results indicated that high users, compared to non-users and low-users, had a higher SU rate, a higher unemployment rate at the time of the most recent health care visit, and more violent causes of their SCI.
Krause et al	1999	Cross-sectional survey	N=76	- BRFSS	None	Alcohol, tobacco	28% American Indians smoke regularly and 43% reported to drink in the last month. Among them, 60% drank heavily. However, health screens were better or comparable to GP.
Rish et al	1997	Cross-sectional survey	N=230	- Medical records (including cause of death if appropriate)	- Medical records regarding SU: alcohol, drugs (illicit & prescribed)	Alcohol and other drugs (illicit & prescribed)	Psychosocial maladjustment and substance abuse were prevalent and created heavy health care demand. Psychiatric problems and substance abuse were strong determinants for morbidity and mortality.
Schandler et al	1996	Cross-sectional survey	N=90	- Family history of alcoholism (CAST & The Family Tree) - SMAST	- WOC - Questionnaire	Alcohol	Compared to subjects with no family alcoholism history, those with antecedents reported significantly higher use of constructive coping, but their use of alcohol and anti-social behaviors indicated that they were less effective in actual coping
Schandler et al	1995	Cross-sectional survey	N=100	- Ad hoc interview and questionnaire about past and present use of alcohol - SMAST - CAST	None	Alcohol	The incidence of SCI patients with family history of alcoholism was over 4 times than found in GP. Possible relationship between predisposition to alcoholism and accidents/SCI.

Pre/post-SCI

Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
Young et al	1995	Cross-sectional survey	N=123	- Ad hoc interview and questionnaire about past and present use SU - SMAST	- Health ratings - FIM - CHART - CES-D - LSJA - PSS-10 - Social Support scale - Health maintenance behaviors	Alcohol, marijuana	Prevalence of alcohol use was lower than GP (40-60% women and men with SCI vs. 59%-79% women and men from GP). However, alcohol abuse was higher (13%-23% women and men with SCI vs. 5%-16% women and men GP). Marihuana use was also lower than GP (16% vs. 12%). However, more SCI-women used marihuana (15%) compared to women from the GP (12%). The reverse was true for men (16% SCI vs. 24% GP)
Perez & Pilsecker	1994	Longitudinal / intervention study	N=10	- Program for substance abusers SCI patients	Not applicable	Several substances (not stated)	Group psychotherapy for SCI substance abusers has demonstrated the usefulness as a part of a comprehensive therapeutic package. The importance of denial, physical associated problems and kindness norm and challenging among this population is discussed.
Tate	1993	Cross-sectional survey	No stated	- CAGE - Alcohol history	- Injury-related variables	Alcohol	Age did not correlate significantly with patient's CAGE scores; however, SCI subjects with higher mean' scores [CAGE] had higher incidence of medical complications. CAGE scores were significantly correlated with previous history of alcohol and drug abuse, and with the average weekly number of drinks pre-injury.
Krause	1992	Review	Not applicable	Not applicable	Not applicable	Several substances (not specified)	Research is paying more attention to substance use/abuse and its impact on SCI patients' rehabilitation. Alcohol is the most consumed substance (pre/post-injury) and could have detrimental effects on rehabilitation. However, fewer patients receive specific treatment for it and abuse of substances as well as drug prescriptions continues to be a source of problems.
Radwanski	1992	Cross-sectional survey	N=16	- DUI - Self-medication practices - Drug Use for Chronic Pain Management Survey	- VAS for pain - MCPQ - Chronic Pain Modifier Questionnaire	Alcohol	45% experienced chronic pain and reported that SUD relieved pain (from 50-100%). Over-the-counter, prescription, illicit drugs or alcohol are the most agents employed in self-medication.
Kiwinski & Krasuski	1992	Cross-sectional survey	N=1193	- State at the time of the injury (sober vs. under the influence of alcohol)	- Ad hoc medical and demographic records	Alcohol	Functional results were better in the sober group. Intoxication also affects the general state of health and the course of recovery in the early post-traumatic period.
Sliwa et al	1992	Case study	N=1	- Ad hoc records related to alcohol use	Ad hoc records for risk factors	Alcohol	Risk factors for the second SCI: wheelchair use, previous spinal fusion, alcohol use and sensation-seeking behaviour.

Pre/post-SCI

Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
Charliffe & Gerhart	1991	Cross-sectional survey (with matched control group)	N=5200	- Ad hoc records related to alcohol abuse	- Medical records related to physical & psychological health status	Alcohol	Alcohol abuse was identified as an important risk factor (among others) related to higher probability to commit suicide.
Bozzacco	1990	Theoretical	Not applicable	Not applicable	Not applicable	Alcohol and other substances (not specified)	Pre/post-injury reported SU is varied and probably underreported. In the absence of severe physiological symptoms, the SUD disorder is not made due to the stigma of disability.
Heinemann et al	1988	Cross-sectional survey	N=103	- Drinking histories: prevalence of alcohol abuse, consequences of alcohol use - SMAST	None	Alcohol	A significant number of individuals with recent SCI have heavy drinking histories and experience behavioural problems resulting from alcohol use. Enjoyment was cited by 92% of the sample as a reason for drinking.
Meyers et al	1985	Cross-sectional survey	N=96	- Ad hoc records for substance use	- Medical, injury-related variables	Alcohol, cannabis and tobacco	There were no significant relationships between either numbers of hospitalizations or total days hospitalized and SU (alcohol, cannabis or tobacco) as well as other medical or demographical variables.
Frisbie & Tun	1984	Cross-sectional survey	N=137	- The course of alcohol consumption and causes of remission	None	Alcohol	A high percentage had high pre-injury alcohol consumption. Reasons given for remissions were general health considerations and possible complications, compounding of the disabilities and loss of taste for liquor.
Sweeney & Foote	1982	Longitudinal / intervention study	N=36	- Program for drug and alcohol dependent SCI patients.	- Ad hoc 26-item questionnaire to assess achievements in environmental adaptation.	Alcohol, other substances (not specified)	The Drug Dependence Treatment Program was proved useful to reduce alcohol and drugs use among SCI patients.

Pre/post-SCI

Note. ATS-DLD: American Thoracic Society-Division of Lung Diseases; BAC: blood alcohol concentration; BMI: Body Mass Index; BRFSS: The Behavioral Risk Factor Surveillance System; BZD: Benzodiazepines; CAGE: Screening for alcohol; CAST: The Children of Alcoholics Screening Test; CES-D: The Center for Epidemiologic Studies Depression Scale; CHART: Craig Handicap Assessment and Recording Technique; DUI: The Drug Use Inventory; FIM: Functional Independence Measure; GHQ: The General Health History Questionnaire; GP: General Population; LCHRA: Lyndhurst Computerized Health Risk Assessment; LSH-QCPC: London school of Hygiene Questionnaire on Chest Pain and Intermittent Claudication; LSIA: Life Satisfaction Index-A; MCPQ: McGill Comprehensive Pain Questionnaire; NASCIS: National Acute Spinal Cord Injury Study; OAHMQ: The Older Adult Health and Mood Questionnaire; PASIPD: The Physical Activity Scale for Individuals with Physical Disabilities; PHQ-9: Patient Health Questionnaire-9 items; PSS-10: Perceived Stress Scale-10 items; RSS: The Reciprocal Social Support Scale; RTC: Readiness to change questionnaire; SCI: Spinal Cord Injury; SCIHS: The Spinal Cord Injury Health Survey; SF-12: Short-Form Health Survey-12 items; SMAST: The Short Michigan Alcoholism Screening; SU: Substance Use; SWLS: The Satisfaction with Life Scale; TBI: Traumatic brain injury; WOC: Ways of Coping Questionnaire.

Table 2
Articles on SUD in SCI population

	Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
Post-SCI	Findley et al	2011	Longitudinal	N=8344	- ICD-9 criteria	- ICD-9 criteria for mental illness	Alcohol, tobacco, other drugs (not specified)	62% no mental illness or SUD, 26% only mental illness, 12% alcohol and/or drug use, 8% mental illness and SUD. Tobacco use was the most prevalent abused substance 19%. Patients with SUD had significantly higher rates of mortality (OR 1.30) and 8% of the sample had dual diagnosis.
	Banerjee et al	2009	Longitudinal	N=8338	- ICD-9 criteria	- ICD-9 criteria for mental illness - Medical Chart	Alcohol, tobacco, other drugs (not specified)	26% SUD (19% tobacco, 9% alcohol, 8% other drugs) & 14% dual diagnosis SUD more common in male, younger, shorter time of SCI duration and those diagnosed with depression, anxiety and/or PTSD.
	Wegener et al	2012	Theoretical article/Book chapter	Not applicable	Not applicable	Not applicable	Alcohol and other drugs (illicit and prescribed)	An overview of core clinical issues (emotional responses, substance use, pain, cognitive deficits, sexuality and vocational rehabilitation) providing guidance on incorporation of rehabilitation psychology into SCI rehabilitation. SUD are identified as risk pre/post-injury factors.
Pre/post-SCI	Smedema & Ebener	2010	Literature review	Not applicable	Not applicable	Not applicable	Alcohol, tobacco and other illicit drugs	Pre-injury substance abuse appears unrelated to acceptance of disability in persons with SCI. Recent substance abuse tends to have a detrimental effect on psychosocial outcomes across all disability groups.
	Tate et al	2004	Cross-sectional survey	N=3041	- DSM-IV criteria for alcohol - Recommended questions (5 items) by the National Institute on Alcohol Abuse and Alcoholism - CAGE - Self-reported (prescribed medication)	- Ad hoc questionnaire for pain - CHART - SWLS - SF-36	Alcohol, psychotropic prescribed medication	60% consume alcohol regularly, among them, 15% at risk consumers. 11% use illegal drugs or prescribed medication for non-medical reasons (73.3% marijuana, 14.4% crack or cocaine and 12.3% others) At-risk drinkers and substance users tended to be younger, single, male, less educated and paraplegic CAGE (+) and substance users reported more pain, more pressure ulcers and lower life satisfaction.

Author(s)	Year	Study design	Sample	Assessment tool(s) for SU	Other measures	Target substance(s)	Main findings
Pre/post-SCI	Turner et al	2003	Cross-sectional cohort	N=218	- DSM-IV criteria for alcohol - SMAST - PDS - Total drinks/week - Total illicit drugs used 3 months prior - injury admission toxicology - The readiness to change questionnaire - Treatment intention questionnaire	None	Alcohol, cocaine, heroin, LSD, methadone, marijuana, speed, heroin, other illicit drugs Four typologies: (I) 17.9% abuse alcohol; (II) 21.1% alcohol dependence; (III) 14.7% in partial remission or relapse & (IV) 46.3% no alcohol problems Group I (high-use, high-consequences) was more likely to report an alcohol-related injury. Groups high in alcohol use-related consequences, type I and type III, were more likely to express a desire to participate in alcohol treatment
	Heinemann et al	1991	Longitudinal	N=86	- Ad hoc semi-structured interview based on DSM criteria	- Ad hoc semi-structured interview for perceived need of treatment for SUD	Alcohol, analgesics, barbiturates, BZD, cocaine, codeine, marijuana, narcotic, stimulants 52% SUD post-injury with 16% reporting need for treatment. Only 7% received treatment for SUD. 69% consumed alcohol pre-injury and 71% post. First 6 months post-injury more risky for SUD.

Discussion

People with acute injuries such as SCI are at disproportionately greater risk for SU and/or SUDs than the general population (Kolakowsky-Hayner et al., 1999; Schandler et al., 1996; Schandler, Cohen, Vulpe & Frank, 1995; Smedema & Ebener, 2010; Wegener et al., 2012). Additionally, as some research has pointed out, SU could be also a major contributor to SCI (Bombardier et al., 2004; Forchheimer et al., 2005; Garrison et al., 2004; Heinemann et al., 1988; Kolakowsky-Hayner et al., 1999; Krause et al., 2000; Krause, 2004; Levy et al., 2004; McKinley et al., 1999; Tate et al., 2004). Therefore, this is a topic of great interest for health providers and scientists due to its potential relationship with patients' mental health, collaboration during rehabilitation process and subsequent functioning, as well as lifestyle choices when discharge (Bombardier & Rimmele, 1998; Frisbie & Tun, 1984; Njoki, Frantz & Mpofu, 2007; Post & van Leeuwen, 2012; Stroud et al., 2011).

Our review highlights that the most prevalent substances consumed by SCI population are alcohol, tobacco and sedative drugs (with and without prescription); as well as the fact that these results are very commonly linked to significantly poorer outcomes regarding health (e.g. higher rates of secondary falls or medical complications) and mental health (e.g. higher rates of mood disorders) (Post & van Leeuwen, 2012; Smedema & Ebener, 2010; Wegener et al., 2012). In this sense, the prevalence of mental disorders and illicit drugs use/abuse remains unknown; although it may be a cause of concern among health providers and it usually adds an increased difficulty in dealing with these patients (Smedema & Ebener, 2010).

Additionally, we have found that most of the research done in this field has been designed as cross-sectional and little research has been done on longitudinal or intervention studies to prevent or treat SU and SUDs (Bombardier et al., 2004; Levy et al., 2004; Perez & Pilsecker, 1994; Smedema & Ebener, 2010; Sweeney & Foote, 1982; Wegener et al., 2012).

In general, methodologies and measured variables differ widely among studies. Most of the literature focused on assessing alcohol intake or screen blood alcohol concentration (Furlan & Fehlings, 2013; McKinley et al., 1999; Rotheinstein et al., 1992; Stroud et al., 2011; Turner et al., 2003). There are several studies that assessed tobacco and other additional legal substances (e.g. prescribed medication). However, there are only few studies on illegal substances. Moreover, assessment periods are very divergent; some authors have only measured pre-injury substance abuse, others have only measured recent substance abuse and some studies were focused on assessing pre- and recent substance abuse. Besides, SU was measured and diagnosed in many different ways in every study. Most of the studies used screening tools and did not check DSM or CIE criteria for SUD (Banerjee et al., 2009; Findley et al., 2011; Smedema & Ebener, 2010; Tate, Forchheimer, Krause, Meade & Bombardier,

2004). In this sense, it is worthwhile mentioning that any of the included articles based their outcomes on the updated criteria of DSM-IV-TR or CIE-10 for substance use disorders. Moreover, among those studies using DSM-IV criteria, it is not stated whether they have employed the substance use disorders section of the Structured Clinical Interview for the DSM (SCID), which is very useful to diagnostic interviews/assessments. Taking all this into account, a recommendation for future research is to use the updated version of the DSM, the DSM-5 (American Psychiatric Association, 2013).

This variability among studies regarding the operationalization of main variables of substance use/abuse vs. disorder makes comparisons difficult and hampers to yield conclusions regarding the precise prevalence of SU and SUD among this population, as well as its potential relationship with physical and mental health.

In spite of the aforementioned, some important trends can be identified. First, a high use of substances such as alcohol, tobacco and/or marijuana has been described among injured patients. It has been hypothesized that substance abuse could be used as a coping resource to decrease distress and facilitate disengagement of the injury or its consequences (Bracken & Shepard, 1980; Krause, McArdle, Pickelsimer & Reed, 2009; Post & van Leeuwen, 2012). Nevertheless, it is well known that substance abuse and dependence imposes a great risk on the health status of SCI patients because of existing medical complications and medication prescriptions (Hitzig et al., 2008; Krause et al., 1999; 2000; 2009; Smedema & Ebener, 2010; Wegener et al., 2012). Thus, it must be properly addressed with rehabilitative therapies by a multidisciplinary professional team (Antonak & Livneh, 1991; Hammell, 1992; Vash & Crewe, 2004; Wegener et al., 2012; Wright, 1960). As the study of Stroud et al. (Stroud et al. 2011) has demonstrated, the onset of the injury could be a very appropriate moment to start this type of psychoeducative interventions. Addictive behaviours among this population add a special difficulty and an additional cost to their treatment, implying recurrent hospitalizations and higher follow-up and medical appointments after the injury (Levy et al., 2004; Krause, 2004; 2010; Schandler et al., 1995). Therefore, it is crucial to screen for these patterns and to intervene by psycho-education, group therapies or appropriate psychological interventions to reduce comorbidity and facilitate post-injury adjustment (Antonak & Livneh, 1991; Hammell, 1992; Smedema & Ebener, 2010; Perez & Pilsecker, 1994; Vash & Crewe, 2004; Wegener et al., 2012; Wright, 1960). Follow-up assessments after discharge from the rehabilitation programme are equally important to prevent the recurrence of dependency problems (Antonak & Livneh, 1991; Hammell, 1992; Smedema & Ebener, 2010; Perez & Pilsecker, 1994; Vash & Crewe, 2004; Wegener et al., 2012; Wright, 1960). In addition to this, efforts to try to involve the family of the injured when possible could add an important value to preventive and rehabilitative practices

and ensure higher rates of success (Hammell, 1992; Smedema & Ebener, 2010; Vash & Crewe, 2004; Wegener et al., 2012; Wright, 1960).

Secondly, the link between the use of illicit substances or even alcohol and occurrence of SCIs has often been reported in scientific literature. In most cases, alcohol abuse post-injury is a continuation of an earlier pattern of problem drinking or other substance abuse (Forchheimer et al., 2005; Frisbie & Tun, 1984; Kolakowsky-Hayner et al., 1999; McKinley et al., 1999; Schandler et al., 1996; Smedema & Ebener, 2010; Stroud et al., 2011; Wegener et al., 2012). Therefore, pre-injury substance abuse seems to be an important predictor of post-injury substance abuse. However determining the extent of these substance abuse patterns on injured patients' mental health and final adjustment is a field that deserves further exploration since most of the studies are not designed as longitudinal and pre/post injury period has not been properly studied for SU/SUDs (Smedema & Ebener, 2010; Wegener et al., 2012).

Conclusion

Scientific literature has pointed out that many people with physical disabilities or chronic health conditions have a hidden additional disability very often, which is substance use or abuse (SUD) involving alcohol and/or other psychotropic drugs. Patterns of SU behaviour vary according to the use before disability, following the onset of disability, or both before and following the onset of disability.

Even though some studies suggest that many people living with SCI manage the consequences of their disability without significant levels of psychopathology, there are evidences pointing out to a high risk of psychopathology and SU/SUD among these patients several years after the injury. Thus, SU is a very common health issue experienced by people sustaining a SCI. For that reason, health providers should pay special attention to unhealthy lifestyles and mood disturbances at both, short term and mid-term follow-up appointments since a high risk of maladjustment and SU among this population has been described.

To our knowledge, this is the first systematic review on this topic. One analysis of the literature exists but it dates from 2010. Besides it is not systematic and it is not exclusively focused on SCI population (Smedema & Ebener, 2010). Therefore, this review adds to the knowledge and it is expected to serve as a starting point to design future research in this field, overcoming current limitations. In this sense, our results have highlighted the need for more longitudinal studies assessing pre- and post-injury patterns of SU, as well as studies assessing the effectiveness of interventions aimed to address such issues among SCI patients. Ideally, such approach will be led by multidisciplinary teams that include SU as pathology and as a central issue in the rehabilitative program rather than as a secondary problem.

Limitations of this review

The main limitation of this review was that only articles written in English were included, excluding therefore several suitable studies written in other languages. There are also some issues that must be taken into consideration when reading our results. Most of the studies were designed with male sample populations and a specific differentiation of paraplegic and patients with tetraplegia was not established. Thus, generalization of results must be cautious. Additionally, not all the studies control the possible confounding effect of prescribed drugs on SU behaviours (such as opiates or other sedatives for neuropathic pain) and some authors have pointed out that a high risk for SUD exists among patients who are already on treatment with such substances.

Recommendations for further studies

The information provided in this study will give a clearer picture on SU among SCI patients. Besides it will enable clinicians to acknowledge potential risks in this sense and to better target individuals at risk for SU and/or SUD. Future research should be undertaken using longitudinal designs to include long-term outcomes, as well as the nature of the risk for secondary health complication in relation to specific substances. Moreover, specific SU/SUD diagnosis for both illicit and legal drugs (and not only screenings) should be carried out to allow comparisons across studies. Only by doing this, it will be possible to advance in the field of follow-up studies after interventions on SU/SUD.

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Conflicts of interest

Nothing to declare.

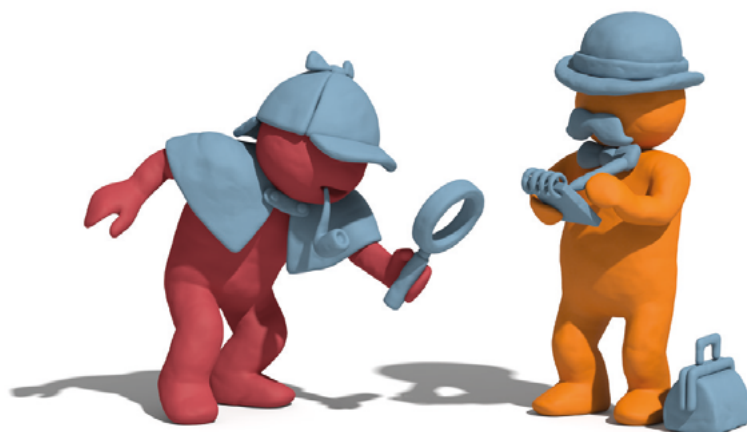
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1. **NOMBRE DEL MEDICAMENTO.** XEPLION 50 mg suspensión inyectable de liberación prolongada. XEPLION 75 mg suspensión inyectable de liberación prolongada. XEPLION 100 mg suspensión inyectable de liberación prolongada. XEPLION 150 mg suspensión inyectable 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 FARMACEÚTICA.** 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 los 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 ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (>7 semanas desde la primera inyección).* Si han transcurrido más de 7 semanas desde la primera inyección de XEPLION, inicie la administración según las pautas recomendadas para la iniciación de XEPLION recogidas anteriormente. *Omisión de la dosis de mantenimiento mensual (1 mes a 6 semanas).* Tras la iniciación, el ciclo de inyección recomendado de XEPLION es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones o 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. Las 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 neuroleptico maligno.* Se han notificado casos del Síndrome Neuroleptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la conciencia y elevación de los niveles séricos de creatina fosfoquinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiolisis) 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 post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con XEPLION si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos <1x10⁹/L) se debe discontinuar el tratamiento con XEPLION y controlar los niveles de GB hasta la recuperación. *Hiper glucemia 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 cetoadicosis 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. *Hiperproliferación.* Los estudios de cultivo de tejidos sugieren que prolactina puede estimular el crecimiento de células en los tumores de mama humanas. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona 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 (dase 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 (DL), ya que ambos grupos pueden tener mayor riesgo de padecer Síndrome Neuroleptico Maligno, así como tener una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, abnucilación, 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 preclínicos con paliperidona. Este efecto, si se produce en humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de enfermedades como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. *Administración.* Se debe tener cuidado para evitar la inyección involuntaria de XEPLION en un vaso sanguíneo. *Síndrome del Iris Flácido Intraoperatorio.* Se ha observado síndrome del iris flácido intraoperatorio (IFS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1-adrenérgico, como XEPLION (ver sección 4.8). El IFS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloquantes 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. *Possibilidad de que XEPLION afecte a otros medicamentos.* No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos que sean metabolizados por los 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, seducidos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenitoínas o butirofenonas, tizídicos o LRS, 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. *Possibilidad 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, hipertonia, hipotonia, 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, otidialitis, celulitis, acrodermatitis, absceso subcutáneo	oncomicosis	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, anemia, disminución del hematocrito, aumento del recuento de eosinófilos	agranulocitosis ^a neutropenia, trombocitopenia	
Trastornos del sistema inmunológico			hipersensibilidad	reacción anafiláctica ^a	
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 ^a , hiperinsulinemia, aumento del apetito, anorexia, disminución del apetito, aumento del colesterol en sangre	intoxicación por agua ^a , cetoadicosis diabética ^a , hipoglucemia, polidipsia	
Trastornos psiquiátricos	insomnio ^a	agitación, depresión, ansiedad	trastorno del sueño, manía, estado de confusión, disminución de la libido, nerviosismo, pesadillas	embotamiento afectivo ^a , anorgasmia	
Trastornos del sistema nervioso	cefalea	parkinsonismo ^a , acatisia ^a , sedación/somnolencia, distonía ^a , mareos, discinesia ^a , temblor	discinesia tardía, convulsión ^a , 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 conciencia, disminución del nivel de conciencia, coma diabético ^a , trastorno del equilibrio, coordinación anormal ^a , titubeo de la cabeza ^a	
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma ^a , 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 cardíacos		bradicardia, taquicardia	fibrilación auricular, bloqueo aurículoventricular, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, anomalías del electrocardiograma, palpitaciones	arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	embolismo pulmonar ^a , trombo-sis venosa, isquemia ^a , rubor	
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión pulmonar, sibilancias, dolor faringolaringeo, epistaxis	síndrome de apnea del sueño ^a , hiperventilación ^a , neumonía por aspiración ^a , congestión del tracto respiratorio distal ^a	
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, sequedad de boca, flatulencia	pancreatitis, obstrucción del intestino ^a , íleo, hinchazón de la lengua, incontinencia fecal, fecloema, dislagia, queilitis ^a	
Trastornos hepato-biliares		umento de las transaminasas	aumento de la gamma-glutamyltransferasa, aumento de las enzimas hepáticas	ictericia ^a	
Trastornos de la piel y del tejido subcutáneo		erupción cutánea	urticaria, prurito, alopecia, ecema, sequedad de la piel, eritema, acné	angioedema ^a , erupción debida al medicamento, hiperqueratosis, decoloración de la piel ^a , dermatitis seborreica ^a , caspa	
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda	espasmos musculares, rigidez en las articulaciones, dolor de cuello, artralgia	rabdomiólisis ^a , aumento de la creatinina fosfoquinasa en sangre, anomalía postural ^a , inflamación de las articulaciones, debilidad muscular	
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, parto y enfermedades perinatales				síndrome de abstinencia neonatal (ver sección 4.6) ^a	

Trastornos del aparato reproductivo y de la mama			disfunción eréctil, trastorno de la eyaculación, amenorrea, retraso en la menstruación, trastornos menstruales ^a , ginecomastia, galactorrea, disfunción sexual, secreción vaginal	priapismo ^a , dolor de las mamas, molestia 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 ^a , alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, disminución de la temperatura corporal ^a , escalofríos, aumento de la temperatura corporal, sed, síndrome de abstinencia a medicamentos ^a , absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección ^a , hematoma en el lugar de la inyección	
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

^aReferido a "Hiperprolactinemia" a continuación. ^bReferido a "Síntomas extrapiramidales" a continuación. ^cEn 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 fovea. **Trastornos menstruales incluyen:** menstruación irregular, oligomenorrea. ^eNo 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, basadas en una escala analógica visual, indican que el dolor tiende a disminuir en frecuencia e intensidad con el tiempo en todos los estudios de fase 2 y 3. 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, hiperkinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreoatetosis, atetosis y mioclonía), distonía (incluye distonía, hipertonia, tortícolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo orofaríngeo, pleurotónos, espasmo lingual y trismo) y temblor. Hay que destacar que se incluye un espectro más amplio de síntomas que no tienen forzadamente su origen en el trastorno extrapiramidal. **Aumento de peso.** En el estudio de 13 semanas de duración que incluyó un régimen de dosificación inicial de 150 mg, la proporción de sujetos con un aumento anormal de peso ≥7% mostró una tendencia relacionada con la dosis, con una tasa de incidencia del 5% en el grupo placebo, en comparación con tasas del 6%, 8%, y 13% en los grupos tratados con 25 mg, 100 mg y 150 mg de XEPLION, respectivamente. Durante el periodo abierto de transición/mantenimiento de 33 semanas de duración del ensayo de prevención de recaídas a largo plazo, el 12% de los pacientes tratados con XEPLION cumplieron este criterio (aumento de peso de ≥7% desde la fase doble ciego hasta el final del estudio); la media (DE) del cambio de peso desde el nivel basal del periodo abierto fue de +0,7 (4,79) 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 seguir 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.notificar.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 empeorar inmediatamente e induir 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: psicofarmacológicos, otros antipsicóticos. Código ATC: N05AX13. XEPLION contiene una mezcla racémica de paliperidona (+) y (-). **Mecanismo de acción.** Paliperidona es un agente bloqueante selectivo de los efectos de los monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT₂ y dopaminérgicos D₂. Paliperidona también bloquea los receptores adrenérgicos α₁ y β₁ y bloquea, en menor medida, los receptores histaminérgicos H₁ y los adrenérgicos α₂. 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 cataplexia 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 (individuos 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 mejora de la puntuación total de la PANSS. En este estudio, tanto los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntuación

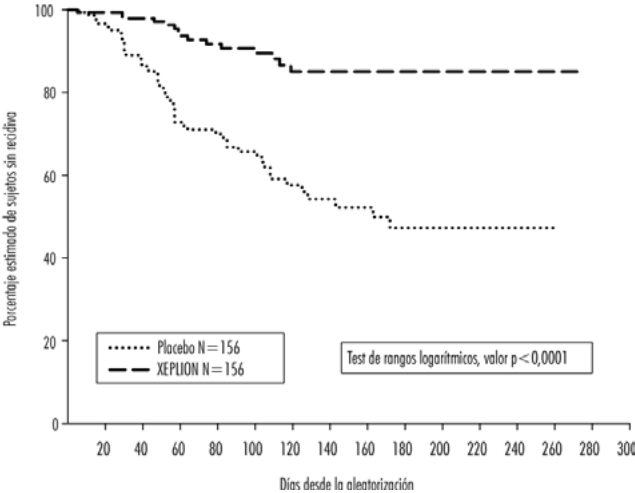
ción de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de XEPLION en el día 8. Los resultados de los otros 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 periodo 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 periodo de transición de 9 semanas de duración, seguido de un periodo de mantenimiento de 24 semanas, en el que los sujetos debían tener una puntuación PANSS ≤ 75 . Los ajustes de la dosis sólo se permitieron en las primeras 12 semanas del periodo de mantenimiento. Se realizó la asignación aleatoria de un total de 410 pacientes estabilizados a XEPLION (mediana de la duración de 171 días [intervalo de 1 día a 407 días]) o a placebo (mediana de la duración de 105 días [intervalo de 8 días a 441 días]) hasta que 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: Gráfica de Kaplan-Meier del tiempo hasta la recidiva. Análisis intermedio (arreglo 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 radioactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y oxidación de benzisoxazol. Aunque en estudios *in vitro* se señaló que los 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 periodo mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de XEPLION (150 mg/100 mg en el músculo deltoides en el día 1/día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con XEPLION se encontraron

dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de XEPLION permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (días 8 y 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. **Insuficiencia hepática.** Paliperidona no se metaboliza ampliamente en el hígado. Aunque XEPLION no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar los 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_{0-24}) 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 unos 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 ratas preñadas. 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 carcinógeno 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 clórico monohidratado. 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 (ácido-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 visita 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. NUMERO(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>.

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Desde el año 2012 sólo se admite la normativa APA.

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

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- 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 resume sólo las observaciones más importantes. Adicciones adopta el sistema convencional del 5% como valor para la significación estadística y no acepta tener en cuenta las tendencias para valores menores.

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

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

limitaciones (estas preferiblemente formarán un párrafo al final del artículo).

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

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

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 hidrocloreto). **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 pivotaes 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., antitúisígenos, 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 antitúisígenos y antigrúales, 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 ($\geq 1/10$), frecuentes ($\geq 1/100$ a <1/10), poco frecuentes ($\geq 1/1.000$ a <1/100), raras ($\geq 1/10.000$ a <1/1.000), muy raras (<1/10.000) 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 cardíaca 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 2 (n = 655) 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 periodo 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 libido)
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

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 nalmefeno por CYP3A4/5. El nalmefeno se convierte posteriormente en nalmefeno 3 O glucurónido y nalmefeno-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

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*	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 (período de 28 días)
c De 0 a 4 DCE/mes en el mes 6 (período de 28 días)

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-∞} (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_{0-∞} 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 anhídrica Crospovidona, tipo A Estearato de magnesio **Recubrimiento del comprimido** Hipromelosa Macrogol 400 Dióxido de titanio (E171) **6.2 Incompatibilidades** No procede. **6.3 Período 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** Blisters 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. Círculo 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 alcohol²

(2) Ficha técnica Selincro 2013

