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Why is it (also) so difficult to legislate gambling in Spain? '*Déjà vu*' of what occurred with alcohol

¿Por qué (también) es tan difícil legislar sobre juego en España? Un 'déjà vu' de lo ocurrido con el alcohol

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Some years ago, the journal Adicciones entitled one of its editorials "*Why is it so difficult to legislate alcohol in Spain?*" (Rodríguez-Martos, 2007), denouncing how incomprehensible it is not to adequately legislate to prevent alcoholism in our country, especially after observing the positive effects that legislation of tobacco had for public health. Today, with regard to gambling addiction, we find ourselves in a very similar situation to the former one of alcohol, although perhaps more severe because the recent regulatory measures for gambling imply the promotion of an activity that is the main cause of compulsive gambling, considered as a mental disorder both by the World Health Organization (WHO) and by the American Psychiatric Association (APA). In scientific and clinical fields, it is considered an addictive disorder and was reflected as such in *DSM-5,* the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (APA, 2013).

In spite of the severity of the problem and the positive correlation between the availability and accessibility with gambling, the successive regulations on this subject in our country have been exponentially increasing the offer of gaming and the gambling access as well as the attractiveness of such games and their publicity. At the present time, we are in a situation of absolute permissiveness regarding gambling, and it seems that the authorities are not aware of the risks of excessive promotion of gambling for citizens' health and well-being, and that regulatory measures are the best way to prevent gambling addiction.

The history of the legislation on gambling in Spain is really remarkable. We have one of the oldest regulations in the world on gambling, such as "*El Ordenamiento de Tafurerías"* [*The Tafurerias Ordering]* of Alfonso X el Sabio, which was actually a code containing a series of measures to punish dishonest behaviors in gambling, with penalties corresponding to Castilla of the Low Middle Ages. Six centuries later, in 1812, in the midst of the War against Napoleon, the National Lottery was established as a form of revenue, as Carlos III had done several decades before with the Neapolitan Lottery, which can be considered the predecessor of the current Primitive Lottery. This coincides with a turning point in the regulation of gambling because, as of the 19th century, gambling ceases to be essentially private (that is, between players) to become an economic activity of the first degree in two relevant dimensions: on the one hand, as a form of tax collection for the State, by means of lotteries and other minor drawings; and on the other hand, as a lucrative activity through which some companies promote business whose benefits are based on what players bet (and lose). The casinos and gambling lounges are born, mainly linked to economically favored social environments, where the ruling classes gamble. From then on, and to the degree to which it is an activity whose economic regulation depends on the State, all gambling that was not expressly allowed was considered forbidden. This restriction reached the height of prohibition during the dictatorship of general Franco – according to some, due to the dictator's

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rejection of gambling because his father had been a gambler – a period in which gambling was considered a vice.

In our recent history as a democratic society, there have been two very relevant milestones in the legislation of gambling and the implications of these regulations on problem gambling. We refer to the Royal Decree 16/1977 and the more recent Law 13/2011 of Gambling Regulation, to which we will refer later on.

Gambling was fully legalized in Spain in 1977. As mentioned, during the Franco regime, most gambling was forbidden, and only the National Lottery, the ONCE sweepstakes, the sports pools, and some minority bets (mainly, greyhounds and horses) were permitted. After the death of Franco, gambling was legalized as a form of attraction of foreign tourist capital and catchment of Spaniards who went to bet in neighboring countries, mainly the casinos of France. Bingos, casinos and 'recreational betting machines with prizes' (known as "tragaperras" [slot machines]) were legalized, and the sector was liberalized, allowing gambling to become a business activity. Bingo halls and casinos opened, and, very particularly, slot machines were installed in bars and restaurants. From then on, with regard to addiction, slot machines became responsible for more than 80% of the cases of problem gambling in Spain.

Regardless of the structural features of the machines, which make them potentially more addictive than any other type of gambling due to the immediacy of the reward, which is based on variable reinforcement programs, or to the fact that they induce cognitive bias that encourages continuing to play in spite of recurrent losses, two particularities, unrelated to the machines but directly related to the regulatory aspects, have fostered their most addictive effects. These are their tremendous availability and easy accessibility.

With regard to their availability, since gambling was legalized, slot machines were implemented in all the restaurants and bars throughout Spain and although in fact, this is not exclusive of Spain, it is not the norm in most countries, with the aggravating circumstance that bars are a sociologically central element in our society. The proliferation of slot machines in many catering establishments is explained by the serious deficiencies in the regulation of gambling by the Ministry of Home Affairs of the Unión de Centro Democrático [UCD - Central Democratic Union], as well as by the uncontrolled grant of licenses during the early governments of the Partido Socialista Obrero Español [PSOE - Spanish Socialist Worker's Party], a situation that was exploited – and even prompted – by some companies to become in the real owners of the sector of slot machines, practically in a regime of oligopoly. Currently, there are more than two hundred thousand slot machines, many more than in Las Vegas, distributed throughout the entire Spanish geography in most of the bars. We should also take into account that in bars, people are usually drinking alcohol, and this hinders the necessary behavioral control the gambler needs to avoid being immersed in a maelstrom of gambling, and the consequential loss that every game of chance provokes when people bet with excessive frequency.

With regard to accessibility, in contrast to bingos and casinos, in which one must identify oneself to enter the lounges, bar access is free, without the need to register or perform any other special requirement in order to gamble. Moreover, the mechanism of gambling is simple, as the greatest complication required by these machines is to insert a coin into a slot and press a button or lever: as simple as it is cheap because you can even play with twenty cents.

That is, in Spain, any person finds in their near environment many slot machines – which are the most addictive games – in places where people normally drink alcohol, – which hinders control and favors risk behaviors, – and there is no need for any type of accreditation which might limit excessive gambling. As a consequence of this, until the arrival of online gambling, 40% of the money spent in all the legal games of chance was spent on these machines; in 2015, it was nearly ten billion euros, coin by coin.

As in the case of alcohol and other drugs, the crux of the matter is that both the availability and the accessibility are two of the main factors involved in the development of addiction, can be controlled with appropriate regulatory systems; that is, with appropriate laws and regulations that would set as one of their main goals the prevention of addictive disorders. Like with alcohol, that is currently one of the main challenges of the Spanish legislation in the issue of gambling.

Regulation Initiatives

The development of the information and communication technologies (ICT) has also led to a revolution in gambling. Currently, games are much more accessible thanks to electronic devices, and the connection to Internet has led to the development of new gambling modalities and an increase of the offers, that is, higher availability. In this field, the legislator arrived late, to the extent that when it proposed to legalize online gaming through Law 13/2011 of gambling regulation, online gambling businesses had been operating for a long time in Spain illegally, or alegally (because they had none authorization), although not clandestinely, because for years, they had been visible, with the sponsorship of teams from the Professional Soccer League. The paradox is that gambling advertising was banned for casinos, bingo halls, and slot machines, whose activity was regulated and legal, whereas sports pools or online poker companies not only performed this activity abnormally, but they also had a huge media presence.

One of the motivations of Law 13/2011 of Gambling Regulation was the prevention of problem gambling and, to this effect, the Advisory Council of Responsible Gambling was created, a consultative body whose decisions were not binding for the Government and whose main goals were to propose a Responsible Gambling Strategy and to advise on issues concerning the implementation of the law that involved the promotion healthy gambling habits.

With regard to the Strategy, the members of the Advisory Council who subscribe to these lines proposed a regulation model that was presented both in the Congress of Representatives and in the "Dirección General de Ordenación del Juego" [Directorate General for the Regulation of Gambling] (DGOJ), but these recommendations were ignored by the Government and were rejected by the companies of the sector that are part of the Advisory Council. Some of the substantial aspects of this proposal appear in the article of this same journal: "Regular el juego para prevenir la adicción: hoy más necesario que nunca" [Regulate gambling to prevent addiction: More necessary today than ever] (Chóliz & Sáiz, 2016).

Other recommendations that we proposed in the field of gambling regulation, such as the prohibition of marketing strategies that induce excessive gambling (for example, welcome bonus) or the legalization of online slot machines, were not taken into account. In fact, bonus tokens, which were initially only used in online poker, have been extended to other types of betting, whereas online slot machines are the kind of online gambling that is expanding the most with regard to spending. According to the DGOJ data, only in the first quarter of 2016, Spaniards spent more than 247 million euros on this type of gambling machines (DGOJ, 2016a). We have gone from having two slot machines in each bar to having them on every one of our mobiles.

The responsible gambling strategies applied by the companies only are generic recommendations, presented as if they were the legal conditions of the small print of a contract, to which one has access by tracking through the web, after dodging all sorts of banners, ads, or advertising pop-ups and marketing strategies that incite to gamble and that are irresistible for the pathological player. Among the seals of quality, granted by private associations that are not necessarily related to the promotion of health, is that of Ministry itself, called "Safe Gambling". It is an equivocal logo, because it gives the gambler a false sense of security, as it is backed by the Administration itself, but all it means is that the company is authorized to operate. That is, rather than "Safe Gambling," it means "Legal Gambling."

By last, the DGOJ's webpage of responsible gambling, called "JugarBien.es" [Playwell.es], is also at issue. While it agrees that information about prevention is necessary, the Administration cannot just remain fixed at this point and not take the necessary preventive measures based on regulation, especially when the information about gambling is presented in a naive fashion, minimizing the risks of gambling and the consequences of problem gambling. Nevertheless, the most questionable aspect of this initiative is that it attributes the responsibility of the disorder to the gambler for not playing adequately, when the fact is that the environmental conditions incite excessive gambling, and the pathological player, by definition, is unable to stop playing. And the environmental conditions, as we are observing, are regulated by means of the corresponding legislation.

But when it comes to the legislation of gambling, not everything can be attributed to the State government. The Autonomous Communities are competent in matters of private gambling (casinos, bingo halls, and slot machines) and also in betting with machines. These betting machines are located in gambling halls – whose number has grown spectacularly in the last two years – , as well as in bars, depending on the regulations established by each autonomous community, so that currently, we find betting machines beside the slot machines in catering establishments. The story of 1981, when the sector caught the UCD Government by surprise, is repeated. The difference is that now we know the negative effects of placing these machines in bars, and for a long time, the necessary regulatory measures of limited access to them have been demanded, as a measure of prevention of gambling addiction.

The situation is so serious that, in less than three years since legalization of online gambling, it is the second cause of gambling addiction for patients seeking help for their problem gambling – only followed by the slot machines – and now, the online gambling is the main cause of addiction in young people (Chóliz, 2015).

Is it possible to prevent it without controlling environmental exposure?

No doubt, there are personal vulnerability factors for gambling addiction but, as with alcohol, the environmental factors encourage and trigger the onset and development of this pathology to a greater extent. Gambling is socially acceptable, it coincides with many of the prevalent values of our society about obtaining easy money and it is even an example of speculative activity, which is how the market economy obtains its greatest monetary benefits. Moreover, since the legalization of online gambling, its presence in the mass media through advertising and commercial strategies has grown exponentially. According to data from the Ministry of Finance, in 2015, the online gambling companies spent 164 million euros on advertising and promotion (DGOJ, 2016b), which is more than twice the amount that they contribute in gambling taxes to the Ministry. This leads to the fact that online gambling is currently pervasive in the mass media because, to make matters worse, there is no law specifically governing the publicity and commercial

strategies of gambling. Thus, the problem is not that there are no preventive campaigns against gambling addiction, or that there is a benevolent conception of this activity, but that it is being promoted and encouraged irresponsibly.

It is surprising that, nearly four years after the concession of licenses to operate, there is still no specific regulation of the publicity and the commercial techniques of gambling. The Administration has left the regulation of advertising in the very hands of the sector, by means of a self-control code, instead of establishing concrete measures such as those taken in the case of tobacco and alcohol. This code of behavior about commercial communications, called *Self-control*, is patently insufficient, as it does not take into account the special characteristics of gambling advertising, nor does it distinguish between commercial communication and incitement to dysfunctional consumption. Moreover, not even all the companies of the sector have signed it.

We cannot forget that the State, in its dual function of regulator of gambling and guarantor of citizens' security and well-being, must fulfill its obligation to clearly define the advertising limits and accurately specify the rules under which one can advertise an activity that, as has been scientifically demonstrated, is potentially addictive and the cause of a severe psychological pathology that frequently has very serious consequences. Meanwhile, not only are the addictive effects of gambling not prevented, but this activity is promoted and encouraged, seeking new market niches in the youth.

Can we prevent pathological gambling without legislation?

In one of the most comprehensive and rigorous reports about the prevention of excessive gambling carried out by investigators of the *Alberta Gambling Research Institute* (Williams, West, & Simpson, 2012), it is concluded that the only really efficacious way to prevent pathological gambling is through gambling policies, that is, by means of regulation. This same report states that other types of measures, even educational ones, although somewhat useful, are not efficacious unless there is an adequate rule that legislates the availability and accessibility of games of chance.

In this sense, the fact that the regulation of gambling has gone from depending on the Ministry of Home Affairs to the Ministry of Finances is no less relevant. Irrelevant as it may seem, in our view, this fact is essential to understand the shortsightedness that is sometimes observed in the authorities about the risks of an economic activity they are obliged not only to monitor, but also to regulate. Regulation doesn't end with the legalization of gambling; that is only the beginning, at least with regard to the prevention of gambling addiction.

Lastly, this need to properly legislate for the prevention of gambling addiction is not only noted and defended from the clinical and social spheres, but also demanded in the Report of the European Parliament on online gambling in the internal market (Fox, 2013). This report clearly shows that gambling "*is not a conventional economic activity because of its possible negative social effects, in particular problem gambling, with consequences and costs that are difficult to estimate…*", that "*due to the special nature of online gambling, the protection of human health and of the consumers must be the essential guiding principle when developing recommendations at the EU level and legislation at the national level*" "*… the Court of Justice has confirmed that the offer of gambling games is an economic activity of a special nature in which constraints are justified for compelling reasons of general interest … such as the public health…*". With regard to advertising, a subject that we discussed in the former section, "*… it reiterates its position that, in a matter as delicate as gambling, self-regulation of the sector can complement the national regulations, but never replace them.*"

To conclude, we must remember that gambling is not a conventional economic activity, but rather the business profits of the gambling companies come directly from what players lose when they bet. If we take into account that those who bet the most – and lose the most – are pathological gamblers, people suffering from a mental disorder, the regulation of this activity must be subject to special measures to prevent, as much as possible, the onset of one of the mental diseases that causes so much unhappiness in patients and their families. Therefore, once and for all, it is necessary to legislate gambling from the different State administrations (State and Autonomous), considering that gambling is not a conventional economic activity, but instead that it has serious health risks that should be prevented by means of adequate gambling policies that are based on the evidence provided by science.

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Validation of the Alcohol Use Disorders Identification Test in university students: AUDIT and AUDIT-C

Validación del test para la identificación de trastornos por uso de alcohol en población universitaria: AUDIT y AUDIT-C

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Abstract

The aim of this study was to determine the psychometric properties of the Alcohol Use Disorders Identification Test (AUDIT and AUDIT-C) in order to detect problems related to the consumption of alcohol in the university population. The sample consisted of 1309 students. A Weekly Alcohol Consumption Diary was used as a gold standard; Cronbach's Alpha, the Kappa index, Spearman's correlation coefficient and exploratory factor analysis were applied for diagnostic reliability and validity, with ROC curves used to establish the different cut-off points. Binge Drinking (BD) episodes were found in 3.9% of men and 4.0% of women with otherwise low-risk drinking patterns. AUDIT identified 20.1% as high-risk drinkers and 6.4% as drinkers with physical-psychological problems and probable alcohol dependence. Cronbach's alpha of 0.75 demonstrates good internal consistency. The best cut-off points for high-risk drinking students were 8 for males and 6 for females. As for problem drinkers and probable ADS, 13 was the best cut-off point for both sexes. In relation to AUDIT-C, 5 and 4 were the best cut-off points for males and females with high-risk patterns, respectively. The criterion validity of AUDIT and AUDIT-C to detect binge drinking episodes was found to have a moderate K value. The results obtained show that AUDIT has good psychometric properties to detect early alcohol abuse disorders in university students; however, it is recommended that the cut-off point be reduced to 8 in men. AUDIT-C improves its predictive value by raising the cut-off point by one unit. Items 2 and 3 should be reviewed to increase its predictive value for BD.

Keywords: Alcohol-Related Disorders/diagnosis*, Psychometrics/methods*, University students, AUDIT, AUDIT-C.

Resumen

El objetivo de este trabajo fue determinar las propiedades psicométricas de los cuestionarios Alcohol Use Disorders Identification Test (AUDIT y AUDIT-C) para la detección de problemas por consumo de alcohol en universitarios. Participaron 1309 estudiantes, utilizando el Diario de consumo semanal como patrón de referencia y para el análisis de fiabilidad y validez el alfa de Cronbach, análisis exploratorio, índice kappa, coeficiente de correlación de Spearman y curvas ROC para los diferentes puntos de corte. Un 3,9% de hombres y un 4% de mujeres con consumo de riesgo bajo presentaba consumo intensivo de alcohol (BD). AUDIT identificó un 20,1% de Bebedor de riesgo y un 6,4% de Bebedor con problemas físico-psíquicos y probable dependencia alcohólica. El instrumento presentó un alfa-Cronbach de 0,75 demostrando buena consistencia interna. Los puntos de corte óptimos fueron ocho para Bebedor de riesgo en hombres y seis para mujeres; trece puntos para Bebedor con problemas físico-psíquicos y probable dependencia alcohólica en ambos sexos; con AUDIT-C, fueron para Consumo de riesgo cinco para hombres y cuatro para mujeres. La validez de criterio para detectar consumo intensivo de alcohol (BD) con ambas versiones presentó un valor K moderado. Los resultados indican que AUDIT cuenta con adecuadas propiedades psicométricas para detectar precozmente problemas de consumo de alcohol en universitarios, recomendándose reducir su punto de corte a ocho en varones. El AUDIT-C mejora su poder predictivo aumentando en una unidad el punto de corte. Se recomienda revisar los ítems 2 y 3 para aumentar el valor predictivo del BD.

Palabras clave: Trastornos relacionados con el alcohol, Psicometría, Universitarios, AUDIT, AUDIT-C.

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AUDIT (Alcohol Use Disorders Identification Test) is a self-administered questionnaire which is short, easy to use and flexible. It is consistent with CIE-10 definitions of alcohol consumption and dependence and assesses consumption over the previous year, thereby generating information which can be useful in providing feedback for those taking the questionnaire. As one of the most extensively used screening tests worldwide, the WHO recommends its systematic use in health care and other settings (Rosón, 2008).

The Spanish version has been validated in health care settings (Martínez 1996; Rubio, Bermejo, Caballero, & Santo-Domingo, 1998) and even in a university student population (Adewuya, 2005; Kokotailo et al., 2004), but as this was in different cultural contexts and with different terminology it is difficult to know whether its psychometric properties make it a suitable instrument for the Spanish university population.

AUDIT consists of ten questions, the first three of which refer to high-risk consumption, with the following three exploring potential dependence symptoms, and the final four focusing on hazardous consumption. Depending on the cut-off points, the total score enables the identification of risky consumption patterns and possible alcohol dependence. In the Spanish validation, (Rubio et al., 1998), the cut-off point for high-risk consumption was set at 9 or above for men and 6 or above for women. A short version, AUDIT-C, which uses the first three questions, is sensitive and specific enough to be a valid tool for identifying high-risk consumption.

Given the changes in alcohol consumption patterns among university students, there is great interest in developing an instrument to detect these; indeed, various studies have confirmed differences in drinking patterns among young people depending on educational background, so for example while non-university students drink more often (Dawson, Grant, Stinson, & Chou, 2004; Kypri, & McAnally, 2005), university students tend to binge-drink more (O'Malley & Johnston, 2002). *Binge drinking (BD)* is one of the major high-risk behaviors among university students (Cortés, Espejo, & Giménez, 2008; Kypri et al., 2009; Wicki, Kuntsche, & Gmel, 2010), which can provoke short- and long-term problems. Recent research among young binge drinkers shows physiological changes in parameters such as blood pressure and state anxiety immediately on consumption (Vinader-Caerols, Monleón, & Parra, 2014), and structural changes in white and gray matter, neuronal hyper/hypoactivation, and cognitive impairment in memory, attention and execution associated with a pattern of binge drinking over time (López-Caneda et al., 2014). While some international controversy surrounds the definition of binge drinking, the last report in 2001 by the Spanish Observatory on Drugs and Drug Addiction defines it as drinking which takes place in short sittings of a few hours, mainly at the weekend, in peer groups and with a low perception of risk. The prevalence of BD among young people aged 20 to 29 is 15.2%, according to the EDADES study of 2011/12.

For these reasons, it is important to be able to rely on instruments which allow early detection and point towards preventive measures, hence the interest in discovering the sensitivity, specificity and predictive power of AUDIT and AUDIT-C among the university population, and in determining the utility and validity of these tests.

The hypotheses considered in this study are firstly that the AUDIT questionnaire is a good tool for the early detection of drinking problems and discrimination between low-, moderate- and high-risk alcohol use, and secondly that the short version (AUDIT-C) is of sufficient reliability and diagnostic validity among the population of university students with high-risk consumption.

The aim of the study is to determine the psychometric properties of AUDIT and AUDIT-C for the detection of problems linked to alcohol consumption at university.

Method

Participants

The questionnaire was completed by a total of 1352 students selected by proportional sampling, of which 43 were rejected for not meeting basic quality criteria. This left a sample of 1309 (59.1% women) with an average age of 21.78 (SD ± 4,45) and an age range of 18 to 65. The expected frequency of consumption in the previous month was considered to be 63%, with an absolute margin of error of 2.5% (Committee for Equality and Social Welfare, Government of Andalusia, 2009)

Instruments

All participants completed an anonymous self-report with socio-demographic variables, the AUDIT questionnaire, and the weekly alcohol consumption diary.

AUDIT is a self-administered questionnaire with a scoring range of 0-40 points. The first eight questions are scored from 0 to 4, and questions nine and ten with 0, 2 and 4 points. The cut-off points proposed by Rosón (2008) identify three population subtypes: *low-risk drinker* (with cut-offs of 0-7 for men, 0-5 for women), *high-risk drinker* (cut-offs 8-12 and 6-12), and *drinker with physical-psychological problems and probable alcohol dependence (ADS)* (cut-off 13 for both). The first three questions of this test make up AUDIT-C, in which scores of 4 or higher in men (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998) and 3 or higher in women (Bradley et al., 2003) are considered to represent high-risk drinking.

The weekly alcohol consumption diary is a record of Standard Drink Units (SDU) consumed at different times or occasions throughout the day (morning, aperitif, lunchtime, afternoon, evening meal, night). Following Rodríguez-Martos (2007a), three categories were considered: *low-risk consumption* (SDUs ≤ 21 and ≤ 14 for men and wo-

men respectively), *moderate-risk consumption* (22-27 and 15-16 SDUs) and *high-risk consumption* (≥ 28 and 17 SDUs). Special attention was paid to BD as a separate category, considered to be the consumption of five or more SDUs in a single sitting, which could represent problematic drinking behavior (Rodríguez-Martos, 2007b).

Procedures

In order to investigate the validity and internal structure of the AUDIT and AUDIT-C scores in this population, a weekly alcohol consumption diary was used as a 'gold standard'. The diary is not only a record of the quantity, frequency, typology of drinks consumed and of drinking patterns but also enables, through the evaluation of these data, the identification and classification of at-risk populations such as binge drinkers.

Data analysis

For the reliability and validity analyses of AUDIT version 20 of the SPSS and FACTOR 9.2 were used.

Reliability. Cronbach's alpha was used as a measure of internal consistency. To determine the correlation between the different sub-scales and the global score, the Spearman correlation coefficient was applied.

To assess *content validity*, the mean scores of two students groups with significantly different alcohol consumption (moderate- and high-risk) were compared. Similarly, the scores on each AUDIT item were compared to the mean scores obtained in the weekly consumption diary for each of the three low-, medium- and high-risk groups of students.

Internal structure validity was investigated by means of exploratory factor analysis (EFA) to assess underlying dimensionality with psychological value, bearing in mind that the original version of AUDIT already has three dimensions or factors. FACTOR 9.2 (Lorenzo-Seva & Ferrando, 2006) was used to check whether the structure obtained in this university population matched the theoretical structure. *Minimum Average Partial (MAP)* (Velicer, 1976) was applied as the method for determining the number of dimensions; *Unweighted Least Squares* (ULS) with Promin rotation was used for extraction; and the Simplimax rotation was used as the most efficient method for obtaining the most suitable cut-off points.

We carried out a multivariate analysis of variance (MANOVA) of the responses to the AUDIT in the three categories of risk established by the weekly diary of alcohol consumption (in SDUs).

The *criterion* or *diagnostic validity* of the AUDIT and AUDIT-C questionnaire scores was assessed on the basis of values obtained with the weekly consumption diary used as a gold standard. The sensitivity and specificity of each item was calculated for the three categories of risk consumption (low, moderate and high) and for BD. ROC curves were ob-

Table 1. *Alcohol consumption patterns among university students (total population and drinkers), by sex.*

Weekly consumption of alcohol and consumption patterns			Men	Women	Total
Total population (N=1309)	Consumption last week	% (n)	73,1 (535)	64,6 (774)	68,1 (1309)
	SDUs last week Mean (SD)	Monday to Wednesday	1,60 (3,7)	0,52 (1,9)***	1,01 (2,9)
		Thursday	1,25 (3,0)	0,79 (2,1)	0,98 (2,5)
		Friday to Sunday	8,14 (9,3)	5,30 (6,3)**	6,29 (8,0)
		Total weekly	10,99 (12,6)	6,60 (8,1)***	8,39 (10,4)
	Weekly consumption pattern (%)	Low-risk consumption[a]	77,2	77,4	77,3
		Moderate-risk consumption[b]	15,0	16,9	16,1
		High-risk consumption[c]	7,9	5,7	6,6
	Binge drinking	≥ 5 SDUs per sitting	38,3	32,7***	35,0
Drinkers (n=891)	Consumption last week	% (n)	73,1 (391)	64,6 (500)	68,1 (891)
	SDUs last week Mean (SD)	Monday to Wednesday	2,18 (4,1)	0,80 (2,3)***	1,41 (3,3)
		Thursday	1,71 (3,4)	1,22 (2,6)	1,44 (2,9)
		Friday to Sunday	11,13 (9,2)	8,20 (6,2)*	9,49 (7,8)
		Total weekly	15,03 (12,5)	10,22 (8,0)***	12,33 (10,5)
	Weekly consumption pattern (%)	Low-risk consumption[a]	68,8	65,0	66,7
		Moderate-risk consumption[b]	20,5	26,2	23,7
		High-risk consumption[c]	10,7	8,8	9,7
	Binge drinking	≥ 5 SDUs per sitting	52,4	50,6***	51,4

Note. SDU (Standard Drink Unit); SD (Standard Deviation). [a] ≤21 SDU men and ≤14 SDU women. [b] 22-27 SDU men and 15-16 SDU women.
[c] ≥28 SDU men and ≥17 SDU women. * p = .018; ** p = .002; *** p = .000.

tained and various cut-off points were considered for identifying optimal sensitivity and specificity. The efficiency of these points was evaluated with the Youden index, and the concordance between observations was established with the Kappa index, using Altman criteria for classification. To evaluate the criterion validity of the AUDIT and AUDIT-C scores for the diagnosis of BD, a benchmark was established of 5 or more SDUs consumed in a single sitting.

Results

Alcohol consumption patterns

The weekly consumption diary shows that 68.1% of students drank alcohol during the previous week, with men being more frequent drinkers (73.1%) than women (64.6%). Taking only those students who had consumed alcohol in the previous week (n=891), the prevalence of *moderate-risk consumption* was 23.7%, while 9.7% was *high-risk*. The average weekly intake was 15.03 SDUs among men, with significantly lower values (p = .000) among women (10.22 SDUs per week) (Table 1).

BD was found independently of whether weekly consumption patterns were low-, moderate- or high-risk; for example 3.9% of men and 4.0% of women had binge drinking episodes despite their consumption being considered *low-risk*.

AUDIT figures show that a quarter of the sample (26.5%) had alcohol consumption problems, of which 20.1% were *high-risk drinkers* and 6.4% were *drinkers with physical-psychological problems and probable ADS*. Among those who had drunk alcohol in the last week, these figures rose to 28.5% and 9.4% respectively (Table 2).

With regard to AUDIT-C, more than half of the drinkers (63.2%) reached the cut-off for *high-risk consumption*, with a predominance (p = .000) of women (36.4%, compared to 26.8% men).

Table 2. *Problems with alcohol consumption by sex according to AUDIT (total population and drinkers).*

AUDIT		Men	Women	Total
		N (%)	N (%)	N (%)
Total population (N=1309)	Low-risk drinker[a]	390 (72,9)	572 (73,9)	962 (73,5)
	High-risk drinker[b]	101 (18,9)	162 (20,9)	263 (20,1)
	Drinker with probable ADS[c]	44 (8,2)	40 (5,2)	84 (6,4)
	Total	535 (100,0)	774 (100,0)	1309 (100,0)
Drinkers (n=891)	Low-risk drinker[a]	249 (63,7)	304 (60,8)	553 (62,1)
	High-risk drinker[b]	98 (25,1)	156 (31,2)	254 (28,5)
	Drinker with probable ADS[c]	44 (11,3)	40 (8,0)	84 (9,4)
	Total	391 (100,0)	500 (100,0)	891 (100,0)

Note. ADS (Alcohol Dependence Syndrome). [a] ≤ 7 men and ≤ 5 women. [b] 8-12 men and 6-12 women. [c] ≥13 men and women.

Reliability study

Internal consistency. The internal consistency (Cronbach's alpha) of AUDIT was 0.75; by domain, the sub-scale *high-risk consumption* yielded a value of 0.83, with 0.79 obtained for *dependence symptoms* and 0.75 for *hazardous consumption*.

The highest values were obtained by questions 1, 2 and 3, which make up the *high-risk consumption* domain, exploring the frequency and quantity of alcohol consumed. Conversely, items 5, 6, 9 and 10 yielded the lowest scores. These questions deal with information regarding dependence symptoms, injuries suffered as a result of drinking, and the worry of others about the amount of alcohol drunk by the subject (Table 3).

Table 3. *Correlation of AUDIT item scores with scale total.*

AUDIT	Media	SD	Inter-element correlation matrix	Inter-element co-variance matrix	Cronbach's alpha if item deleted
Item 1	1,68	1,001	0,706	2,960	0,709
Item 2	0,64	0,856	0,662	2,372	0,718
Item 3	0,66	0,938	0,811	3,187	0,700
Item 4	0,29	0,719	0,610	1,836	0,726
Item 5	0,18	0,448	0,602	1,130	0,736
Item 6	0,12	0,410	0,503	0,864	0,741
Item 7	0,30	0,592	0,593	1,471	0,731
Item 8	0,37	0,638	0,694	1,855	0,723
Item 9	0,10	0,549	0,414	0,951	0,742
Item 10	0,11	0,593	0,369	0,918	0,744
TOTAL	4,45	4,188	1,000	17,542	0,800

Reliability of AUDIT and weekly alcohol consumption diary. Comparing AUDIT to the gold standard of the weekly consumption diary, consistent results were obtained in 90% of cases. The Spearman correlation coefficient was 0.87, pointing to a good level of reliability, and on the basis of the Altman criteria the Kappa value of 0.85 is very good (Table 4).

Reliability of AUDIT-C and weekly alcohol consumption diary. Comparing the short version, AUDIT-C, to the weekly diary measuring consumption in SDUs, reliability was also moderate to good. Spearman's correlation coefficient was 0.57, indicative of a good level of concordance. The Kappa value of 0.5 is moderate according to the Altman criteria (Table 5).

Content validity

For this analysis, students with *moderate-* and *high-risk consumption* were selected. The average AUDIT score in the *moderate-risk consumption* group was 9.45 among men, and 7.92 for women, while the average AUDIT scores for those with *high-risk consumption* were 15.19 and 13.09 for men and women respectively. Statistically significant ($p < .001$) differences were found in AUDIT for the different types of consumption; thus the test is shown to be valid for discriminating between groups of individuals with different consumption patterns.

Analyzing the item scores in the different risk groups, we can see that they increase gradually from low- through moderate- to high-risk groups depending on the types of consumption pattern, except in item 2. This item states: *How many drinks do you have on a day with normal alcohol consumption?* with possible responses being: 0 (one or two), 1 (three or four), 2 (five or six), 3 (from seven to nine), or 4 (ten or more). For this question, the average score in the moderate-risk group is higher than in the high-risk group (1.81 vs. 1.64). The response "five or six drinks" in the *moderate-risk consumption* group represents an average of 24.15 SDUs per week, and 38.74 SDUs per week in the *high-risk consumption* group, which would mean that given an equal number of drinks (five or six), the intake of alcohol (SDUs) is higher in one group than in the other.

Internal structure validity

On analyzing whether the three original dimensions of AUDIT are reflected in our population, three factors are obtained: the first factor consists of items 4, 5, 6, and 7 with a reliability of 0.87; the second is made up of items 1, 2, 3, and 8 with a reliability of 0.92; the third factor covers items 9 and 10 with a reliability of 0.83. The average size of residual correlations (RMSR) was 0.02, a value which shows that the model is of acceptable fit, although the association of items found differs from the original.

When looking at two dimensions, we find one consisting of the first eight items, *risk consumption*, and a second one covering the two last items, *hazardous consumption*, which would explain 66% of the accumulated variance with a reliability of 0.82 and 0.92 respectively. The root mean square correlation (RMSR) was 0.03 (Table 6)

The different risk levels of alcohol consumption patterns are reflected in the responses to the AUDIT questions

Table 4. *Reliability of AUDIT compared to Weekly Alcohol Consumption Diary.*

			Consumption Diary			
			Low-risk consumption[a]	**Moderate-risk consumption[b]**	**High-risk consumption[c]**	**Total**
AUDIT	Low-risk drinkerd	n (%)	952 (54,1)	6 (2,8)	4 (4,7)	962 (73,5)
	High-risk drinkere	n (%)	55 (5,4)	204 (96,7)	4 (4,7)	263 (20,1)
	Drinker with probable ADSf	n (%)	5 (0,5)	1 (0,5)	78 (90,7)	84 (6,4)
	Total	n (%)	1012 (100)	211 (100)	86 (100)	1309 (100)

[a] ≤ 21 SDU men and ≤ 14 SDU women. [b] 22-27 SDU men and 15-16 SDU women. [c] ≥ 28 SDU men and ≥ 17 SDU women. [d] ≤ 7 men and ≤ 5 women. [e] 8-12 men and 6-12 women. f ≥13 men and women. * Spearman correlation (0.87), Kappa (0.85).

Table 5. *Reliability of AUDIT compared to Weekly Alcohol Consumption Diar.*

			Consumption Diary		
			Low-risk consumption[a]	**Moderate-risk consumption[b]**	**Total**
AUDIT-C	Low-risk consumptionc	n (%)	705 (69,7)	4 (1,3)	709 (54,2)
	High-risk consumptiond	n (%)	307 (30,3)	293 (98,7)	600 (45,8)
	Total	n (%)	1012 (100)	297 (100)	1309 (100)

[a] ≤ 21 men and ≤ 14 women. [b] ≥ 22 men and ≥ 15 women. [c] ≤ 3 men and ≤ 2 women. [d] ≥ 4 men and ≥ 3 women. *Spearman correlation (0.57), Kappa (0.50)

Table 6. *Exploratory factor analysis of AUDIT.*

AUDIT	Two factors		Three factors		
	Factor 1	Factor 2	Factor 1	Factor 2	Factor 3
Item 1		0,957		0,647	
Item 2		0,742		0,615	
Item 3		1,028		1,081	
Item 4		0,560	0,618		
Item 5		0,718	1,012		
Item 6		0,591	0,717		
Item 7		0,554	0,498		
Item 8		0,761		0,584	
Item 9	0,832				0,937
Item 10	0,957				0,693
Estimated reliability	0,825	0,923	0,870	0,925	0,833

(especially 3, 5, and 8, according to MANOVA). The variability which was not explained by group differences was 32% in men (Wilks' F42.8 p<0.001) and 25% in women (F75.6 p<0.001). All AUDIT questions were found to be significant in discriminating between different risk patterns of consumption.

Criterion validity

The diagnoses provided by AUDIT and AUDIT-C were compared to the weekly alcohol intake used as the gold standard. The criterion validity of AUDIT for *low-risk drinker, high-risk drinker,* and *drinker with physical-psychological problems and probable ADS* was found to have a high *K* value for both sexes (0.83; 0.83; 0.92 for men and 0.88; 0.88; 0.90 for women); the criterion validity for the three categories of drinker shows strong concordance, with even better results found for women in the sub-group *high-risk drinkers.*

The sensitivity values in AUDIT-C were 98% for men and women, although the *K* values obtained by both sexes were moderate (0.49 and 0.51 respectively) with reference to the Altman criteria.

ROC curves

With regard to AUDIT, the best balance between sensitivity and specificity for detecting *high-risk drinkers* was obtained with a cut-off point of 7.5 for men (sensitivity of 95% and specificity of 93%) and 5.5 for women (sensitivity of 98% and specificity of 95%). For *drinkers with physical-psychological problems and probable ADS*, the best cut-off was 12.5 for both sexes (sensitivity of 95% for men and 86% for women, and specificity of 99% for both).

In the case of *high-risk drinker*, the area under the ROC curve showed very good performance for men (0.963) and excellent performance for women (0.976). For *drinker with physical-psychological problems and probable ADS*, the area under the curve was excellent in both sexes (0.983 for men and 0.973 for women). In terms of validity, comparing the scores with the weekly consumption diary yielded values close to 1 for the areas under the curve of both categories.

For AUDIT-C, the best balance between sensitivity and specificity for *high-risk consumption* was found at 4.5 for men (sensitivity of 91% and specificity of 84%) and 3.5 for women (sensitivity of 86% and specificity of 88%). The area below the curve according to sex showed the test to be very good (0.941 for men, 0.945 for women). In terms of validity, the results yielded values close to 1 for the categories under investigation when comparing scores to the weekly consumption diary.

Analyses of cut-off points

For the AUDIT categories of *high-risk drinker* and *drinker with physical-psychological problems and probable ADS*, the optimal cut-off points were found to be 8 and 13 for men, and 6 and 13 for women respectively. The best cut-offs for *high-risk consumption* in AUDIT-C were 5 for men and 4 for women (Table 7).

Discussion

The socio-demographic characteristics of the sample are similar to those of other studies into alcohol consumption among university students (Adewuya, 2005; Kokotailo et al., 2004; Londoño, García, Valencia, & Vinaccia, 2005; Martín-Montañez et al., 2011; Montaño, Morales, Gómez, Vera, & Gantiva, 2011; Salazar, Ávila, Pérez, & Martínez, 2010; Seguel, Santander, & Alexandre, 2013; Zaldívar, López, García, & Molina, 2011), with women (59.01%) slightly outnumbering men, and an average age of 21.78. A third of these students live away from the family home, and it is this group that presents more frequent moderate- to high-risk consumption patterns, a greater number of high-risk drinkers, and drinkers with physical-psychological problems and probable ADS. These facts highlight the need take into consideration students' living arrangements when planning preventive measures.

Reliability estimates of AUDIT scores using Cronbach's alpha were good, both globally and for each of the subscales, thereby confirming its suitability for screening for alcohol consumption problems in the university context. The reliability values are quite similar to those found in a systematic review which included 10 studies in different contexts (Meneses-Gaya, Waldo, Regina, & Crippa, 2009), in samples of the general population (Alvarado, Garmendia, Acuña, Santis, & Arteaga, 2009; Contel, Gual, & Colom, 1999; Rubio et al., 1998), and in two samples of American (Kokotailo et al., 2004) and Chilean (Seguel et al., 2013) university students, where average values of 0.8 were obtained.

The fact that the highest scores were found in items 1, 2, and 3 (focusing on the quantity and frequency of alco-

hol consumption) and lower scores in items 5, 6, 9 and 10 (measuring the adverse consequences of drinking such as dependence, injuries or the criticism of others) is indicative of alcohol abuse, and is in line with, on the one hand, the changing pattern of alcohol consumption among young people in which binge drinking (BD) plays an important role, and the lower frequency of alcohol dependence in this sector of the population on the other.

The results of the AUDIT subscale for *hazardous drinking* revealed that the prevalence of students who claimed difficulties in giving up alcohol was 6.4% of the total sample and 9.4% for the drinkers subgroup; this highlights the fact that up to a tenth of the university student drinker population is at risk of ADS. A Chilean study of university drinkers (Baader et al., 2014) reported probable ADS of just 1.5%.

With regard to item 2 in AUDIT, the response option "five or six drinks" reveals that weekly consumption is higher among drinkers with *moderate-risk consumption* than with *high-risk consumption* (24.18 SDUs vs. 38.74 SDUs per week). This item reflects the quantity of drinks, not the frequency of consumption, so when analyzing content validity we have to bear in mind that an individual may consume many low-strength drinks every day, while others may have fewer but stronger drinks. Moreover, on validating AUDIT in Catalan and Spanish (Contel et al., 1999), this item performed differently compared to the validation in Spanish by Rubio et al. (1998); a consequence, it was claimed, of the translation. Given these considerations, it would appear advisable to revise item 2 in such a way as to make it possible to analyze frequency and quantity separately. Given the growth of the BD phenomenon, a further improvement would be to specify the frequency parameter more exactly, taking into consideration the number of drinks consumed at a single sitting and not on a whole day; and in terms of quantification, it would be interesting to incorporate the concept of SDUs.

With respect to item 3 in AUDIT: *How often do you have six or more alcoholic drinks at a single sitting?* Kokotailo et al., (2004) in their validation for American university students recommended that this should be reduced to five or more drinks for men and four or more drinks for women. If we remember that BD consists of drinking a quantity of alcohol equivalent to or greater than 5 SDUs in a single sitting, it should be pointed out that this can happen independently of the consumption pattern. In our study, on analyzing the criterion validity of those with high consumption with AUDIT, a moderate *K* value is obtained for both sexes (0.54 for men and 0.59 for women), with a positive predictive value of 82.8% for men and 80.2% for women. Given the above, it would be advisable to redraft this item, reducing it to five or more drinks at a single sitting and, better still, incorporating the concept of five SDUs, thereby more accurately reflecting the BD phenomenon.

The original structure of AUDIT features three dimensions: high-risk consumption (items 1-3), dependence symptoms (items 4-6) and hazardous alcohol consumption (items 7-10). The factor analysis of AUDIT, however, can produce different results depending on the prevalence of the problem in the population under consideration. In our case, the three-dimensional factorial model obtained does not exactly match the original structure since items 7 and 8

Table 7. *Indexes of validity and utility for the AUDIT and AUDIT-C cut-off points.*

	AUDIT				AUDIT-C	
	High-risk drinker C.P.: 8	High-risk drinker C.P.: 6	Drinker with probable ADS C.P.: 13	Drinker with probable ADS C.P.: 13	High-risk consumption C.P.: 5	High-risk consumption C.P.: 4
	Men	Women	Men	Women	Men	Women
S	0,95	0,98	0,95	0,86	0,91	0,86
SP	0,93	0,95	0,99	0,99	0,84	0,88
PPV	0,8	0,85	0,91	0,95	0,63	0,69
NPV	0,98	0,99	0,99	0,99	0,97	0,96
PWC	0,93	0,95	0,99	0,99	0,86	0,88
PBC	0,06	0,04	0,01	0,01	0,14	0,12
LR+	13,54	18,88	117,38	315,23	5,69	7,49
LR-	0,05	0,02	0,05	0,14	0,11	0,15
K	0,83	0,88	0,92	0,90	0,65	0,68
SE	0,93	0,95	0,99	0,99	0,86	0,88
YJ	0,88	0,92	0,94	0,86	0,75	0,75

Note. ADS (Alcohol Dependence Syndrome); C.P. (Cut-off point); S (Sensitivity); Sp (Specificity); PPV (Positive Predictive Value); NPV (Negative Predictive Value); PWC (Percentage Well Classified); PBC (Percentage Badly Classified); LR+ (Positive Likelihood Ratio); LR- (Negative Likelihood Ratio); K (Kappa Coefficient); SE (Standard Efficiency); YJ (Youden's J).

do not remain in the hazardous drinking domain: item 7 is moved to symptoms of probable dependence, and item 8 to high-risk consumption.

We believe that from the point of view of designing intervention programs for the university population, it would be more suitable to adopt a two-factor design where the AUDIT test scores discriminate with great reliability between high-risk and hazardous consumption.

Indeed, in our study university students displayed a prevalence of problematic alcohol consumption of 26.5% (with 20.1% in the *high-risk drinker* category, and 6.4% in *drinker with physical-psychological problems and probable ADS*), and two factors were obtained consisting of items 1-8 and 9-10 respectively.

Other studies of the general population also support a bi-dimensional structure (Contel et al., 1999; Lima et al., 2005; Meneses-Gaya et al., 2009), while in the Chilean university population (Seguel et al., 2013), two components were also established which were linked to consumption itself and to the adverse consequences of excessive consumption.

In terms of internal validity, the sensitivity and specificity results obtained for AUDIT (sensitivity = 32-96%, specificity = 84-96%) are among the highest published (Barry, & Fleming, 1993; Rubio et al., 1998; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993; Schmidt, Barry, & Fleming, 1995), which demonstrates its utility in screening for alcohol related problems in this sector of the population.

Numerous AUDIT validation studies have achieved good sensitivity and specificity when applying different cut-off points (Adewuya, 2005; Dawson, Grant, & Stinson, 2005; Gache et al., 2005; Knight, Sherritt, Harris, Gates, & Chang, 2003; Kokotailo et al., 2004; Rubio et al., 1998), highlighting the need to establish different cut-offs depending on sex. Given that equal consumption is more likely to have repercussions among women than men, it is advisable to reduce the cut-off point for women when planning interventions (Reinert & Allen, 2002, 2007).

In terms of ROC curves, the area under the curve can be seen as an indicator of the quality of a diagnostic test, and for the category *high-risk drinker* in the case of AUDIT this was 0.96 for men and 0.98 for women, while for *drinker with physical-psychological problems and probable ADS*, the areas were 0.98 for men and 0.97 for women. These values can be considered extremely good, and better than those obtained in the Spanish validation of AUDIT carried out in primary health care (Rubio et al., 1998), where an area of 0.87 was obtained for alcohol use, and the Chilean version (Alvarado et al., 2009), with areas of 0.93 for high risk drinking, 0.88 for hazardous drinking and 0.91 for dependence. Turning to values obtained in studies of university students, the results yielded by the AUDIT validation carried out in the University of Wisconsin were worse, with areas of 0.87 for alcohol consumption and 0.77 for abuse or dependence.

In this study, the most effective cut-off points in AUDIT for problematic alcohol use (*high-risk drinker*) among men was 8 (sensitivity = 95% and specificity = 93%) and 6 for women (sensitivity = 98% and specificity = 95%). In the Spanish validation of the instrument (Rubio et al., 1998), the general cut-off point for detecting problems with alcohol use was 8, but when analyzing sensitivity and specificity by sex, differences were encountered and the cut-off point for men was 9 and higher, with 6 or higher among women. The validation for Catalan and Spanish (Contel et al., 1999) also established a cut-off point of 9 for men but did not detect a different point for women. In an AUDIT validation study carried out exclusively with women in two primary care centers and in a drug dependence center (Pérula et al., 2005), a cut-off point of 6 or higher was obtained.

Taking the results obtained into account, we recommend that the cut-off point for male university students be reduced by one point below the values found in two validation studies in the general population in primary care. This recommendation is supported by a systematic review of AUDIT (Meneses-Gaya et al., 2009), which affirms that its sensitivity and specificity are lower when applying the standard cut-off points to the university population.

Regarding the detection of *drinkers with physical-psychological problems and probable alcohol dependence (ADS)*, the most efficient cut-off point in our study was 13 or higher for both sexes, identical to that recommended in primary care for the general population (Rosón, 2008).

With reference to the criterion validity of AUDIT-C, it may appear contradictory that a test which detects 98% of cases is not useful in detecting high-risk consumption, but it must be pointed out that the low prevalence of consumption among university students generates as many false negatives as true positives, which means that there is only an even probability of detecting positive cases, as reflected in the kappa value.

Despite the reliability estimate for AUDIT-C in this population not being particularly good (Kappa index 0.50), this could be improved for the detection of *high-risk consumption* if cut-off points are raised by one point above those recommended for men (Bush et al., 1998) and women (Bradley et al., 2003). Raising the cut-off points in this way to 5 and 4 respectively significantly increases their predictive power.

The need to detect BD among young people is stressed in the latest report (2011) by the Spanish Observatory on Drugs and Drug Addiction, which describes a high prevalence of this intermittent consumption pattern. Moreover, according to the data provided in EDADES 2011/12, the figures for binge drinking in the last 30 days have risen slightly; 15.2% of those surveyed have consumed alcohol in this way, and this high-risk pattern of consumption is particularly extended among young adults, aged 20-29, of both sexes. The criterion validity or diagnostic validity of detecting binge drinkers with AUDIT is low, with moderate Kappa values obtained for both sexes. AUDIT-C, however, displays good

sensitivity for detecting problems with alcohol use and binge drinking in both men and women (AUDIT: sensitivity of 0.58 for men and 0.64 for women vs. AUDIT-C: sensitivity of 0.81 for men and 0.85 for women)

A possible limitation of this study is the lack of a test-retest analysis, but this was not carried out on organizational grounds and to avoid doubts on the part of the students regarding loss of confidentiality.

In conclusion, its psychometric properties make AUDIT a suitable instrument for the timely detection of problems with alcohol use in the university population, although lowering the cut-off point to 8 for men and revising items 2 and 3 is recommended in order to improve its predictive power in detecting binge drinking. The predictive strength of AUDIT-C would be improved by raising the cut-off points by one for both sexes.

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Conflict of interests

The authors declare no conflict of interests.

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Impulsivity in men with prescription of benzodiazepines and methadone in prison

Impulsividad en varones con prescripción de benzodiacepinas y metadona en prisión

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Abstract

Benzodiazepines and methadone use has been associated with various neuropsychological impairments. However, to the best of our knowledge, no studies have been carried out on the effect of these substances (either separately or combined) on impulsive personality, including studies in prisoners. The aim of this study is to examine the impulsive personality of a sample of 134 male prisoners using the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (Torrubia, Avila, Molto, & Caseras, 2001) and the UPPS-P Scale (Cyders et al., 2007). Some of these were methadone users, methadone and benzodiazepines users, polydrug users in abstinence and non-dependent drug users. The results showed that drug users have greater sensitivity to reward, positive urgency, negative urgency and sensation seeking than non-dependent users. Methadone users showed more sensitivity to punishment and lack of perseverance with respect to other users. No differences were found between methadone+benzodiazepines users and other groups. The secondary aim is to examine which impulsive personality dimensions are related to the two motivational systems proposed by Gray (BIS-BAS) using exploratory factor analysis. Results showed two different components. One component was defined by the subscales sensitivity to reinforcement, positive urgency, negative urgency and sensation seeking. The second component was defined by the subscales sensitivity to punishment, lack of perseverance and lack of premeditation.

Keywords: benzodiazepines; methadone; impulsivity; prison; UPPS-P; SPSRQ.

Resumen

El consumo de benzodiacepinas y metadona se ha asociado a diversas alteraciones neuropsicológicas. Sin embargo, no conocemos estudios sobre el efecto de estas sustancias tanto de forma separada como de forma combinada en rasgos de personalidad impulsiva, y en menor medida en población penitenciaria. El objetivo principal de este estudio es examinar la impulsividad rasgo, medida con el Cuestionario de Sensibilidad al Castigo Sensibilidad a la Recompensa (Torrubia, Avila, Moltó y Caseras, 2001), y la escala de Evaluación del Comportamiento Impulsivo UPPS-P (Cyders et al., 2007), en una muestra de 134 varones de un centro penitenciario con consumo de metadona, metadona y benzodiacepinas, abstinentes de consumo, y no dependientes del consumo de sustancias (criterios DSM-IV). Los resultados mostraron que los grupos de consumidores presentan mayor sensibilidad a la recompensa, urgencia positiva, urgencia negativa y búsqueda de sensaciones que los no consumidores; los grupos de consumo de metadona presentan mayor sensibilidad al castigo y falta de perseverancia. El grupo de no consumidores presenta menor falta de perseverancia que el grupo de metadona y el grupo de metadona+benzodiacepinas. No se han encontrado diferencias específicamente del grupo de metadona+benzodiacepinas con el resto de los grupos. Como objetivo secundario, examinar, mediante análisis factorial exploratorio, qué dimensiones de personalidad impulsiva se relacionan con los dos sistemas motivacionales propuestos por Gray (SIC-SAC). Los resultados mostraron un componente definido por las subescalas sensibilidad al refuerzo, urgencia positiva, urgencia negativa y búsqueda de sensaciones, y un segundo definido por las subescalas sensibilidad al castigo, falta de perseverancia y falta de premeditación.

Palabras clave: benzodiacepinas; metadona; impulsividad; prisión; UPPS-P; SCSR.

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The 2013 report of the European Monitoring Centre for Drugs and Drug Addiction estimated that the average prevalence of problematic opiate use among adults (15-64 years of age) is 0.41%, equivalent to a total of 1.4 million cases in Europe in 2011. A considerable proportion, 48%, of those who began treatments for addiction in Europe in 2011 were consumers of opiates (chiefly heroin). A great deal of research focused on the prevalence and the effects of consuming these illicit substances can be found in the literature, whereas the amount of information available regarding the use of prescribed drugs is substantially smaller. Of these drugs, methadone is the most frequently used, being prescribed in up to 75% of opiate addiction cases. More specifically, in Spanish prisons the prevalence of methadone treatment is 7.9% (2012) of the interned population (Secretary General for Prisons, 2013), and in the same context benzodiazepines are prescribed for 28.7% of inmates (Subdirectorate General for Prison Health, 2007). Furthermore, the prevalence of benzodiazepine consumption among patients in methadone treatment is between 51% and 70% (Jones, Mogali & Comer, 2012), and around 46.5% in Spain (Fernández-Sobrino, Fernández-Rodriguez, & López-Castro, 2009). Despite this high rate of opiate and benzodiazepine consumption, there are relatively few studies of the neuropsychological effects of these medicines, especially benzodiazepines.

Benzodiazepines work at the level of the brain through the GABAA receptors, and their consumption has been linked to neuropsychological problems in relation to visuospatial ability, processing speed and verbal memory (Barker, Greenwood, Jackson, & Crowe, 2004, Stewart, 2005). At the same time, some research on users of the substance has found impulsivity disorders, suggesting behavioral disinhibition (Michel & Lang, 2003), impulsive decision making (Dassanayake et al., 2012; Lane, Tcheremissine, Lieving, Nouvion, & Cherek, 2005), and deficits in response inhibition (Acheson, Reynolds, Richards, & de Wit, 2006).

In various theoretical models of addiction, impulsivity is shown to be a highly relevant marker of vulnerability when explaining addictive processes, both in the analysis of onset and maintenance of substance use (Adan, 2002; Arce & Santisteban, 2006; Cano-Cervantes, Araque-Serrano, & Cándido-Ortiz, 2011; Cortés-Tomás, Giménez-Costa, Motos-Sellés, & Cadaveira-Mahía, 2014; Gullo, Loxton, & Dawe, 2014; Navas, Torres, Cándido, & Perales, 2014; Pattij & De Vries, 2013). The study of impulsivity has been characterized by at least two relatively independent approaches: (i) the study of cognitive impulsivity through neuropsychological tests, and (ii) the study of impulsivity as a character trait using self-report measures (Dougherty, Mathias, Marsh-Richard, Nouvion, & Dawes, 2008; Evenden, 1999, Perry & Carroll, 2008). The latter encompasses two fundamental theoretical assumptions. On the one hand, Gullo et al. (2014) provide evidence of the existence of two factors which explain impulsivity in addictive behavior: "reward sensitivity" and "rash impulsiveness" (Dawe, Gullo, & Loxton, 2004; Dawe, & Loxton, 2004; Franken & Muris, 2006). On the other hand, Whiteside and Lynam (2001), and Cyders and Smith (2007) seek to explain the impulsive personality by using the five-factor model. In this model, they take the five factors constituting impulsivity to be positive urgency, negative urgency, (lack of) premeditation, (lack of) perseverance and sensation seeking. In parallel to these models, Gray and McNaughton (2000) posit the existence of two motivational systems in their neuropsychological model: BAS (behavioral activation system) and BIS (behavioral inhibition system). While some studies have linked the two impulsive personality factors proposed by Gullo et al. to BAS (Dawe et al., 2004; Loxton et al., 2008a), results of other research point to BAS being more closely associated with the urgency and sensation seeking dimensions, and BIS more with the (lack of) motivation and the (lack of) perseverance in the five-factor model (Verdejo-García et al., 2010a).

Taking these theoretical models as a starting point, the literature offers two instruments for measuring impulsive personality. Torrubia, Avila, Moltó and Caseras (2001) propose the use of the Sensitivity to Punishment/Sensitivity to Reward Questionnaire as an instrument which allows the assessment of two personality dimensions: sensitivity to punishment (SP) and sensitivity to reward (SR). Alternatively, Whiteside and Lynam (2001), and Cyders et al. (2007), basing their work on the factor analysis which underlies the five-factor model, recommend the UPPS-P scale of impulsive behavior, while Carlson and Pritchard (2013) suggest that addictive behavior is better explained using a combination of the UPPS-P scale and the SPSR questionnaire than either of them separately.

A variety of studies has investigated impulsivity as a personality trait among substance users and the substance dependent population. Overall, the results of this research show that impulsive personality is affected among consumers of psychostimulants (Albein-Urios, Martínez-González, Lozano, Clark, & Verdejo-García, 2012; Fernández-Serrano et al., 2011; Verdejo-García et al., 2010a), weekly binge-drinkers (Motos, Cortés-Tomás, Giménez-Costa, & Cadaveira-Mahía, 2015), alcoholics (Bravo de Medina, Echeburúa, & Aizpiri, 2007), and cannabis dependents under treatment (Bravo de Medina, Echeburúa, & Aizpiri, 2010). Although the number of studies on opiates is smaller, results also indicate that they could have an effect on the impulsive personality of non-dependent users (Dissabandara, Loxton, Dias, Daglish, & Stadlin, 2012; Nielsen et al. 2012). Nevertheless, as far as we are aware, there are no studies, certainly not with prisoners, into the effects of benzodiazepines and methadone, either separately or combined, on impulsive personality.

An investigation into the character traits among the prison population can be of interest for different reasons. Firstly because of the high prevalence of prescribed benzo-

diazepine/sedative use in this context (Subdirectorate General for Prison Health, 2007). Secondly, given that different studies have highlighted impulsivity as a risk factor in the explanation of criminal behavior (Carroll et al., 2006; Mathias, Marsh-Richard, & Dougherty, 2008; Ratchford & Beaver, 2008), it would be interesting to study the specific dimensions which are affected in this group. Finally, the lack of studies itself provides sufficient reason for investigating the subject in a prison context and, consequently, its potential role in prevention and treatment. The main aim of this study is, thus, to examine the impulsive personality of patients who are prescribed benzodiazepines in methadone maintenance treatment. A secondary objective, taking the theoretical models proposed for the explanation of impulsivity as a starting point, is to attempt to discover which impulsive character traits measured by the UPPS-P scale and SPSR questionnaire are associated with Gray's two motivational systems (BIS/BAS).

Method

Participants

The sample consisted of 134 male prisoners aged 18 to 50 from the Albolote prison in Granada. They were divided into four subgroups, three of which contained substance users and the other non-dependent users (herein referred to as non-users), each with a similar range of ages and years of schooling (see Table 1). The three substance user groups were composed respectively of methadone users (n=33), methadone+benzodiazepine users (n=29) and polydrug users in abstinence (n=43). All of them stated that their preferred method of drug consumption was the smoking of heroin and cocaine. A fourth group (n=29) was composed of individuals who were not dependent on substances (DSM-IV-TR criteria, 2002).

Given that the study was carried out in a closed prison context, the possibility that inmates could take drugs other than those prescribed was limited.

Individuals with a history of traumatic brain damage and neurological disorders and severe acute mental disorder measured by interview were excluded from the study.

Instruments

Impulsivity as a character trait

Impulsive Behavior Scale UPPS-P (Whiteside & Lynam, 2001, Spanish adaptation by Verdejo-García, Lozano, Moya, Alcázar, & Pérez-García, 2010b). This consists of 59 items measuring five personality dimensions which can contribute to impulsive behavior: negative urgency, (lack of) perseverance, (lack of) premeditation, sensation seeking and positive urgency (Smith et al., 2007). The first dimension, negative urgency, assesses the tendency of the subject to give in to strong impulses, especially when these are accompanied by negative emotions such as depression, anxiety or anger. The second dimension, (lack of) perseverance, evaluates the capacity of the individual to persist in carrying out tasks or fulfilling duties despite the boredom or fatigue these may involve. The third dimension, (lack of) premeditation, examines the ability of the person to consider the potential consequences of their behavior before acting. The fourth dimension, sensation seeking, evaluates the individual's proclivity for stimulation or excitement. The final dimension, positive urgency, focuses on the tendency of the subject to give in to impulses when these are preceded by strong positive emotions. Each item was measured using a four-option Likert-type scale from 1 (completely agree) to 4 (completely disagree). The total score for each of the five dimensions was used in the corresponding statistical analysis.

Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSR) (Torrubia et al., 2001). This is a questionnaire of 48 items for evaluating two orthogonal personality dimensions: sensitivity to punishment (SP) and sensitivity to reward (SR). These scales measure the individual differences in the Behavioral Inhibition System (BIS) and the Behavioral Activation System (BAS) of Gray's neuropsychological personality model (Gray & McNaughton, 2000). The first system controls behavior in response to punishment signals, non-reward and new stimuli, and is related to the anxiety dimension (trait). The second system involves behavior in response to reward or non-punishment signals, and is related to the impulsivity dimension of personality. Various studies have shown the SP and SR scales to have adequate psychometric properties (Caseras, Avila & Torrubia, 2003, Verdejo et al., 2010b).

Procedure

The proposed research in prisons was approved by the Directorate General of Penal Institutions.

Participants were recruited for the study by means of individual contacts and through information posters in the different prison units. After informing them of the aims of the study and, in order to enhance the reliability of the information obtained, emphasizing that participation in the study would not have any negative repercussions for them, they signed an informed consent form and received a monetary compensation of €18 for their co-operation plus the possibility of receiving a report of the results.

Given that the instruments were part of a larger protocol aimed at assessing the neuropsychological properties of the sample, the participants were evaluated both individually and collectively.

Statistical analysis

Firstly, to test for the existence of possible differences between the groups in terms of the age and education variables, univariate analyses of variance (ANOVAs) were carried out, together with the non-parametric Kruskal-Wal-

lis test for the age variable. To test for possible differences between the four groups in relation to the UPPS-P scale and the SPSR questionnaire, two multivariate analyses of variance (MANOVAs) were run first of all. This was followed by post hoc univariate ANOVAs on statistically significant results of the MANOVAs in each of the dimensions of the two tests in which significant results had been obtained. Post hoc analyses (Tuckey test) were then carried out to examine possible differences between the four groups in the different dimensions of the two tests. At the same time, the effect size of group differences in the dependent variables was calculated by means of Cohen's *d*. The cutoff value for statistical significance was set at 5%. Finally, in order to test whether the structure of the principal components of impulsivity is maintained, an exploratory factor analysis was carried out with principal component extraction and varimax rotation. Components with eigenvalues greater than 1 were extracted.

Results

With regard to sociodemographic variables, the results showed that there were no statistically significant differences in terms of education. As age was not, however, distributed normally, the non-parametric Kruskal-Wallis test was applied (see Table 1).

The next step was to analyze the potential differences in the groups regarding the dependent variables associated with impulsive personality (UPPS-P & SPSR). Firstly, the MANOVA on the SPSR scores yielded statistically significant differences between the groups, with a Wilks' lambda of [F (6.258)= 5.852; p<.001, η^2= .12]. The subsequent univariate post hoc ANOVAs on the two subscales revealed significant effects in SP [F (3.130)=3.481; p= .018, η^2= .07] and in SR, [F (3.130)=9.528; p< .001, η^2= .18]. The post hoc univariate ANOVAs indicated that there were significant differences only between the non-user and the methadone groups on the SP subscale (p= .034), while with regard to the SR subscale, results showed significant differences existing between the non-user group and the other three groups (p< .001 in all comparisons). The effect sizes obtained (Cohen's delta) were medium to high for all comparisons (values between .74 and 1.20) (see Table 2).

Secondly, the MANOVA on the UPPS-P scores revealed statistically significant differences between the groups, with a Wilks' lambda of [F (15.348)= 4.058; p<.001, η^2=.14]. The univariate ANOVAs for the five subscales showed significant effects in "positive urgency" [F (3.130)=9.058; p<.001, η^2= .17] "negative urgency", [F (3.130)=13.273; p<.001, η^2= .23] "sensation seeking", [F (3.130)=10.467; p<.001, η^2= .19] and "lack of perseverance", [F (3.130)=5.655; p= .001, η^2= .11] No significant results were obtained for "lack of premeditation", [F (3.130)= 1.396; p= .247, η^2= .03]. The post hoc univariate ANOVAs revealed that significant differences existed in the "positive urgency", "negative urgency" and "sensation seeking" subscales between the non-user group and the other three groups (methadone, methadone+benzodiazepines, and in abstinence), with p values of ≤.005. The Cohen's delta values obtained were high in all comparisons (between 1.01 and 1.58). For the "lack of perseverance subscale" the results showed statistically significant differences between the non-user with reference to the methadone and methadone+benzodiazepines groups (p≤.017). The effect sizes obtained were medium to high (0.72 and 0.99) (see Table2).

Finally, exploratory factor analysis yielded a solution with two principal components and eigenvalues above 1 (3.398 & 1.123 respectively) which explained 64.59% of the total variance with good fit to the sample data (Kaiser-Meyer-Olkin KMO= .754, Bartlett's test of sphericity p< .001). The first component explains 33.72% of the variance and is defined by the "SR", "positive urgency", "negative urgency" and "sensation seeking" subscales, with factor loadings greater than .60. The second item explains 30.87% of the variance and is defined by the "lack of perseverance" and "lack of premeditation" subscales, with factor loadings above .80, and the "SP" subscale with a factor load of .47. The correlation matrix is to be found in Table 3. The factor loadings of the subscales in the two components are shown in the rotated factors matrix in Table 4.

Table 1. *Descriptive scores, comparisons and significance of the sociodemographic characteristics of the groups*

	Mt (n=33)	Mt+B (n=29)	A (n= 43)	NDS (n=29)	F/Chi squared	p
	M (SD)	***M (SD)***	***M (SD)***	***M (SD)***		
Age	36.06 (4.64)	34.96 (4.54)	31.88 (8.62)	34.57 (7.25)	5.69*	.128
Years of schooling	7 (2.23)	7.48 (1.66)	7.55 (1.85)	8.14 (1.86)	1.79**	.151

Note. Mt= methadone; Mt+B= methadone+benzodiazepines; A=Abstinent; NSD= not substance dependent; M= Mean; SD= Standard Deviation.
*= value of the chi-square statistic (Kruskal-Wallis); **= value of statistic F

Table 2. *Descriptive scores of the four groups in the different dimensions of the UPPS-P and SPSR scales. classified by the two components obtained. with the effect size of the comparisons between pairs of groups (Cohen's delta)*

Instruments	Mt(n=33) M (*ST*)	Mt+B(n=29) M (*ST*)	A (n=43) M (*ST*)	NDS (n=29) M (*ST*)	Tuckey	d
SPSR						
SP	13.84 (4.62)	12.75 (5.96)	10.76 (5.19)	10.17 (5.23)	Mt›A=NSD	0.74 (Mt-NSD)
SR	12.60 (3.91)	12.51 (4.38)	12.46 (4.38)	7.79 (4.12)	NDS‹Mt=Mt+B=A	1.20(Mt-NSD)
						1.11(Mt+B-NSD)
						1.09(A-NSD)
UPPS-P						
Positive urgency	32.69 (8.37)	34.41 (9.39)	30.69 (6.93)	23.96 (8.63)	NDS‹Mt=Mt+B=A	1.02(Mt-NSD)
						1.15(Mt+B-NSD)
						1.01(A-NSD)
Negative urgency	31.33 (6.87)	34.20 (6.72)	30.51(6.10)	23.86(6.33)	NDS‹Mt=Mt+B=A	1.12(Mt-NSD)
						1.58(Mt+B-NSD)
						1.07(A-NSD)
Sensation seeking	32.12 (7.08)	32.75 (7.94)	33.23 (5.33)	24.96 (7.02)	NDS‹Mt=Mt+B=A	1.03(Mt-NSD)
						1.05(Mt+B-NSD)
						1.38(A-NSD)
Lack of perseverance	21.42 (4.67)	20.58 (5.44)	19.20 (3.30)	17.24 (3.57)	NDS‹Mt=Mt+B	0.99(Mt-NSD)
						0.72(Mt+B-NSD)
Lack of premeditation	21.96 (5.23)	22.41 (5.90)	21.55 (4.20)	19.67 (4.95)		

Note. Mt= methadone; Mt+B= methadone+ benzodiazepines; A=Abstinent; NSD= not substance dependent.
SP= Sensitivity to Punishment; SR= Sensitivity to Reward; M= Mean; SD= Standard Deviation.
* Cohen's d ›.80 indicates a large effect size

Table 3. *Intercorrelations between the different dimensions of the SPSR questionnaire and the UPPS-P scale*

Dimension	1	2	3	4	5	6	7
1. SP	-----						
2. SR	.236**	----					
3. Negative urgency	.366**	.527**	------				
4. Lack of premeditation	.077	.199*	.428**	-----			
5. Lack of perseverance	.307**	.341**	.395**	.599**	-------		
6. Sensation seeking	.029	.543**	.460**	.181*	.240**	-------	
7.Positive urgency	.342**	.581**	.759**	.439**	.481**	.471**	------

Nota. N= 134. SC= Sensibilidad al Castigo; SR= Sensibilidad a la Recompensa.
* p ‹ .05. ** p ‹ .01.

Table 4. *Factor loadings extracted from the principal components with a varimax rotation of the UPPS-P scale and SPSR questionnaire dimensions.*

Dimension	Components		Communality (h^2)
	1	2	
SP	164	**.471**	.249
SR	**.820**	.180	.704
Negative urgency	**.675**	**.508**	.714
Lack of premeditation	.069	**.815**	.669
Lack of perseverance	.167	**.832**	.702
Sensation seeking	**.837**	-.002	.700
Positive urgency	**.688**	**.541**	.700
Percentage of variance	33.72	30.87	
Total percentage of variance	64.59		

Note. Factor loadings ›.40 are printed in bold. SP= Sensitivity to Punishment; SR= Sensitivity to Reward.

Discussion

The primary objective of this research was to examine the impulsive personality of prison inmates receiving methadone maintenance treatment and prescribed benzodiazepines. Results showed that substance using groups (methadone, methadone+benzodiazepines and abstinent) displayed greater "sensitivity to reward", positive urgency", "negative urgency" and "sensation seeking" than non-users. It was also found that users in the methadone groups (methadone, methadone+benzodiazepines) exhibited greater "sensitivity to punishment" and "lack of perseverance". No differences specific to the methadone+benzodiazepines group in relation to the other groups were detected. Finally, exploratory factor analysis of the two questionnaires yielded a component defined by the "SR", "positive urgency", "negative urgency" and "sensation seeking" subscales, and a secondary component defined by the "lack of perseverance" and "lack of premeditation" subscales.

The differences between the substance consuming groups and the non-user group in terms of positive and negative urgency, sensation seeking and SR could indicate that these personality traits are generally related to substance use. However, while all the scales have been linked in the literature to addiction, the two "urgency" scales appear to be more consistent in differentiating between addicted and non-addicted groups (Verdejo-García et al., 2007, 2010a) indicating aspects of emotional instability more typical of the greater psychopathological comorbidity found in user groups as opposed to non-users (Billeux et al., 2012; Casares-López et al., 2011). The "SR" scale has also been consistently linked to drug use (Balconi, Finocchiaro, & Campanella, 2014; Stautz & Cooper, 2013), possibly due to its connection with the mesolimbocortical pathway, which mediated by more sensitized dopaminergic transmission among users (Robinson & Berridge, 1993). Finally, although the "sensation seeking" scale is less consistently linked to addiction in the literature (Verdejo-García et al., 2007, 2010a), it also emerges from our study as a trait of impulsivity associated with substance use. This may be explained by the fact that our user groups are characterized by more severe drug use and a greater frequency of involvement in risk situations that this implies, which could also constitute a personality construct typical of prison inmates (Lykken, 1995).

Meanwhile, the groups with methadone users (methadone and methadone+benzodiazepines) displayed a greater lack of perseverance and SP. These data would suggest that the abstinent groups possess the tolerance to frustration and boredom as well as the ability to concentrate on a task required by rehabilitation treatment (with or without specialized support). Methadone user groups, more needy of pharmacological support, also undergo such treatment. Methadone affects the processes of selective attention (Mintzer & Stitzer, 2002; Prosser et al., 2006; and unpublished data obtained in the present sample), and at the same time the powerful processes of response inhibition associated with the "lack of perseverance" scale (Cyders & Coskunpinar, 2011). This indicates the possibility of a common underlying process which differentiates the groups of methadone users from non-users in particular. The higher SP associated with methadone groups may be related to a down-regulation of noradrenergic activity due to the chronic stimulation of the mu opioid receptor affecting how punishment is perceived, as proposed by Ersche et al. (2005).

Finally, with respect to the impulsive personality traits of our groups, we should highlight the fact that no differences were found between them in the "(lack of) premeditation" dimension. This scale has been linked to a decision-making process (Zermatten, Van der Linden, d'Acremont, Jermann, & Bechara, 2005) and is a consistent predictor of such externalizing behaviors as criminality (Gordon & Egan, 2011) or violence in general (Derifenko, DeWall, Metze, Walsh, & Lynam, 2011; Miller, Zeichner, & Wilson, 2012), which suggests that it could be considered as a dimension of impulsivity common to prison inmates and not specific to substance dependence.

The results in relation to our secondary objective bear some similarity to those found in studies (Mitchell et al., 2007; Perales, Verdejo-García, Moya, Lozano, & Pérez-García, 2009; Verdejo-García et al., 2010a) linking BAS more to the urgency and sensation seeking dimensions, and viewing BIS, given its factor loading, as more connected to the lack of premeditation and lack of perseverance dimensions. In our study all substance users, irrespective of the drug preferred, exhibited deficits on all scales included in the first factor emerging from the componential analysis, more closely linked to BAS, and in line with separate research showing that BAS plays an important role in the addiction to different substances, including heroin, methadone, cocaine, ketamine, alcohol and tobacco (Abdi, Roudsari, & Aliloo, 2011; Bijttebier, Beck, Claes, & Vandereycken, 2009; Carlson & Pritchard, 2013; Dissabandara et al., 2012, 2014; Franken, Muris, & Georgieva, 2006; Loxton et al., 2008a; Lyvers, Duff, Basch, & Edwards, 2012; Nielsen et al., 2012). Furthermore, our results would indicate that methadone users have the greatest deficits on the scales comprising the second factor, linked more closely to BIS. However, it is true that the relationship of BIS to substance use is not as well-established in the literature as that of BAS (Bijttebier et al. 2009; Dissabandara et al. 2012; Ersche et al. 2005).

These results have some important clinical implications regarding the inclusion of impulsivity trait evaluation in the processes of assessing and treating addiction disorders. In terms of assessment, our results would facilitate the development of new self-reporting instruments by taking the overlap between the UPPS-P and SPSR scales into account, as well as the dimensions proposed in Gray's model. As far as treatment is concerned, Staiger, Kambouropoulos, and

Dawe (2007) highlight the importance of developing specific treatments depending on the results of personality trait assessment such as, for example, "contingency management" therapy for patients with prominent traits of "reward sensitivity", training in conflict resolution skills, mindfulness, or Linehan's dialectical behavior therapy for "rash impulsivity" traits and cognitive behavior strategies for comorbid anxiety traits. Finally, it has been discovered recently that the scores on the "sensation seeking" scale of the UPPS are potential moderators of motivational enhancement therapy results (Moshier, Ewen, & Otto, 2013).

Alongside its considerable strengths, our study also has some limitations. One of its advantages is the type of sample used, firstly because of its profile of methadone and benzodiazepine consumption, which allows us to discover the separate and combined effects of these substances on the impulsive personality, and secondly by virtue of its prison context. In terms of limitations, we have to highlight the absence of non-prison control groups which could have demonstrated more clearly the variables specific to the criminological context and the potential differences between user groups. In addition, our sample consisted solely of males. While it is true that 92.4% of the Spanish prison population is made up of male inmates (Secretary General of Prison Institutions General Report, 2012), it would be interesting to study whether these results can be extended to the female prison population. Finally, despite being the object of this study and forming part of comprehensive theories, self-report measures do not completely encompass the complex phenomenon of impulsivity. It would therefore be interesting if future studies were complemented by other measurements of impulsivity, whether self-report or laboratory based.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Cross-cultural examination of the five-factor model of drinking motives in Spanish and Canadian undergraduates

Estudio transcultural del modelo de cinco factores de motivos de consumo de alcohol en universitarios españoles y canadienses

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Abstract

This study aims to test the cross-cultural suitability of Modified Drinking Motives Questionnaire-Revised (M DMQ-R) (Grant, Stewart, O'Connor, Blackwell, & Conrod, 2007). The sample included 571 Spanish and 571 Canadian undergraduates between the ages of 18 and 22 (65.8% women). The confirmatory factor analysis demonstrated factorial invariance between samples. The regression analysis showed that social, enhancement and low conformity motives were related to drinking frequency and drinking quantity in the total sample. No moderation effect of country on predicting alcohol consumption was found. The results suggest that M DMQ-R is a suitable instrument for comparing drinking motives across Spanish and Canadian undergraduates, and that motives-focused prevention and treatment programmes developed in one country could be generalised to another.

Keywords: Drinking motives, cross-cultural study, alcohol, M DMQ-R, undergraduates.

Resumen

El objetivo de este estudio es testar la utilidad transcultural del Modified Drinking Motives Questionnaire-Revised (M DMQ-R) (Grant, Stewart, O'Connor, Blackwell, y Conrod, 2007). La muestra incluyó 571 universitarios españoles y 571 universitarios canadienses, de 18 a 22 años de edad (65,8% mujeres). El análisis factorial confirmatorio (AFC) mostró invarianza factorial entre las muestras. Los análisis de regresión mostraron que los motivos sociales, de animación y los bajos motivos de conformidad se relacionaban con la frecuencia y cantidad de alcohol consumida en la muestra completa. El país de origen no moderó la relación de los motivos con el consumo de alcohol. Los resultados sugieren que el M DMQ-R es un instrumento adecuado para comparar los motivos de consumo entre los estudiantes españoles y canadienses, y que los programas de prevención y tratamiento centrados en los aspectos motivacionales del consumo desarrollados en un país pueden generalizarse al otro.

Palabras clave: motivos de consumo, estudio transcultural, alcohol, M DMQ-R, universitarios.

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Alcohol use is related to performance impairment of different tasks (Vinader-Caerols, Monleón, & Parra, 2014) and neurocognitive anomalies in youths (López-Caneda et al., 2014). Harmful alcohol use is also the main risk factor for incident disability-adjusted life years among 10-24-year-oldsyouths (Gore et al., 2011), and is a worldwide problem that results in millions of deaths, including hundreds of thousands of young lives (World Health Organization (WHO), 2011). For these reasons, understanding why young people drink during this stage of life is important for preventing alcohol-related problems.

Drinking motives (reasons for alcohol use) are among the most specific and proximal variables that have been studied as part of an effort to prevent excessive alcohol consumption (Kuntsche, Knibbe, Gmel, & Engels, 2005). Despite the existence of many psychometric instruments developed to assess drinking motives, the Drinking Motive Questionnaire Revised (DMQ-R: Cooper, 1994) and its variants are the most widely used measures (Kuntsche et al., 2005). DMQ-R (Cooper, 1994) includes four drinking motives scales based on the type of reinforcement desired (positive or negative) and source of reinforcement (internal or external). These are social (positive, external), enhancement (positive, internal), conformity (negative, external) and coping (negative, internal) motives. Given that the mechanisms underlying depression-related drinking may differ from those underlying anxiety-related drinking, Grant and colleagues developed the Modified DMQ-R (M DMQ-R; Grant et al., 2007; Mezquita et al., 2011), in which coping-with-anxiety versus coping-with-depression motives had be separated. Several studies have suggested that each one of these five drinking motive categories is related to specific alcohol outcomes in young adults. Enhancement motives are strongly related to drinking at weekends (Kuntsche & Cooper, 2010; Mezquita, Ibáñez, Moya, Villa, & Ortet, 2014) and indirectly with alcohol-related problems through alcohol consumption (Mezquita et al., 2014; Mezquita, Ruipérez, & Stewart, 2010). Social motives are related to frequency and quantity, but not to alcohol-related problems (Grant et al., 2007; Kuntsche et al., 2005). Conformity motives are usually negative related to alcohol use (Grant et al., 2007; Németh et al., 2011), but are positively related to alcohol-related problems (Merrill & Read, 2010). Finally, while coping-with-depression motives are more strongly related to alcohol-related problems (Goldstein, Flett, & Wekerle, 2010; Mezquita et al., 2014), and coping-with-anxiety are related to drinking on weekdays (Mezquita et al., 2014).

Research has also shown vast differences in alcohol use and misuse across countries (WHO, 2014). The highest heavy drinking rates among young European people are found in northern Europe cultures, similarly to those found in some areas of North America like Canada (De Witte & Mitchell Jr., 2012; WHO, 2014). Although drunkenness is increasing in young people from southern European counties like Spain (National Plan of Drugs, 2012), the heavy drinking rates there are still lower than in northern countries (WHO, 2014).

Therefore, the aim of this research was to test whether M DMQ-R (Grant et al., 2007) possesses good psychometric properties across cultures (Spain *vs.* Canada), and whether differences in alcohol use across countries can be explained by differences in drinking motives. Specifically, we investigated cross-national similarities and differences in: 1) the five-factor structure of drinking motives and the internal consistency of the scales; 2) mean levels of drinking motives; 3) the moderation effect of country on the relationship of motives-alcohol outcomes.

Materials and method

Study designs and samples

Canadian participants were drawn from a pool of 868 Dalhousie University undergraduates in 2004 (see Grant et al., 2007 for an extended sample description). Those who indicated that they did not drink alcohol (*N*=109, 12.56%), or did drink, but did not provide complete data in M DMQ-R (*N*=33, 3.80%), and were not of typical university undergraduate age (18-22 years old) (*N*=118, 13.59%), were excluded from the analyses. After matching the two samples (age and gender; see Supplementary Material 1), the final Canadian sample consisted of 571 participants (65.8% women) whose mean age was 18.10 years (SD = 1.06).

Data of the Spanish undergraduates were obtained for the purposes of this cross-cultural study at the Universitat Jaume I of Castellón (east Spain) between 2009 and 2010. Initially there were 1,382 participants. Those who indicated that they did not drink alcohol (*N*=48, 3.47%), did drink, but did not provide complete data in M DMQ-R (*N*=7, 0.51%), did not provide information on their gender or age (*N*=51, 3.69%), or who did not provide information on their drinking patterns (*N*=23, 1.66%), were excluded from the analyses. We deleted the answers provided by participants who did not fall within the 18-22 year age group (*N*=270, 19.54%) before matching both samples on age and gender. The final number of Spanish participants was 571 with the same mean age and percentage of women as the Canadian Sample. In both samples, participation was voluntary and anonymous, and data confidentiality was guaranteed.

Measures

The M DMQ-R (Grant et al., 2007; Mezquita et al., 2011) consists of 28 items. Each contributes to one of five subscales: social, coping-with-anxiety, coping-with-depression, enhancement, or conformity. After considering all the times they drank, participants indicated how often they drank for the reason specified in each item on a 5-point Likert scale ranging from 1 (almost never/never) to 5 (almost always/always).

Subscales are scored as the average across the items within a scale, which allows a direct comparison across subscales.

In addition, two alcohol-related questions were analysed: one asked about frequency (fq) of alcohol consumption in the past 30 days (0 = you did NOT drink alcohol, 1=Once, 2=2 or 3 times, 3=4 or 5 times, 4=6 or more times); the other asked about the quantity (qn) of alcoholic beverages consumed per typical drinking occasion in the past 30 days (0 = you did NOT drink alcohol, 1=One, 2=2 or 3, 3=4 or 5, 4=6 to 9, 5=10 or more).

Statistical analysis

Using the EQS (version 6.1), we explored the questionnaire structure in each sample separately by performing a confirmatory factor analysis (CFA) and calculating the internal consistency of each scale. To test if the factorial structure was invariant between countries, we performed a multi-group CFA with hierarchical steps (Byrne, 2006). As the data showed evidence of kurtosis, we used the heterogeneous kurtosis (HK) estimator. We evaluated the model's goodness of fit using these fit indices: the root mean square error of approximation (RMSEA); the comparative fit index (CFI); the incremental fit index (IFI) (see Byrne, 2006). RMSEA ≤ .10, CFI ≥ .90, and IFI ≥ .90 are considered indicators of an adequate data fit (Weston & Gore Jr, 2006). To compare the adequacy of the multi-group models when constraints between groups were added, we used ΔCFI. To consider that there were no differences between groups, ΔCFI could not exceed .01 (see Byrne, 2006).

Using the SPSS statistic package, version 21, a MANCOVA was calculated to determine cross-national similarities or differences in the mean levels of the five drinking motives after controlling for age and gender. Regression analyses were used to explore if country moderated the associations of drinking motives with drinking frequency and quantity. The following were introduced: age and gender in the first step; the variable "country" (Spain=0; Canada=1) in the second step; the five scales of drinking motives in the third step; the five interactions of country x motive in the last step (see Dawson, 2014).

Results

Testing factorial invariance across countries

The hypothesised correlated five-factor model of drinking motives provided an adequate data fit in the Spanish sample, $\chi^2(340, N = 571) = 1124.67$, $p < .001$; RMSEA= .064; CFI= .936; IFI= .936, and in the Canadian sample, $\chi^2(340, N = 571) = 1136.03$, $p < .001$; RMSEA= .064; CFI= .942; IFI= .942, separately. The standardised loadings of the indicator variables on their hypothesised factors were all salient (i.e., ≥.30) in both samples, save item 1 ("As a way to celebrate") from the social motives scale, which showed a loading of only .24 in the Canadian sample (see Figure 1). The internal consistencies of each scale for both countries (also presented in Figure 1) varied from .65 (coping-with-anxiety, Spanish sample) to .91 (coping-with-anxiety, Canadian sample).

The multi-group analysis showed an adequate data fit, $\chi^2(680, N = 1142) = 2260.92$, $p < .001$; RMSEA = .064; CFI = .939; IFI = .939. The ΔCFI (lower than .01) when we added cross-country equivalence constraints for the factor loadings (ΔCFI = .005), variances of each factor (ΔCFI = .004) and factor covariances (ΔCFI = .001), suggested invariance.

Exploring cross-national similarities or differences in drinking motives

The MANCOVA results indicated that although the informed mean rank order of drinking motives was equal among countries (social > enhancement > coping-with-anxiety > coping-with-depression > conformity), the Canadian undergraduates scored significantly higher in drinking motives ($F(5) = 60.50$, $p < .001$) than the Spanish undergraduates. The *post hoc* Bonferroni analysis showed that these differences were significant ($p < .001$) for the enhancement and coping-with-anxiety motives.

Regression analysis

The regression analysis showed that after controlling for the effect of age and gender, being Canadian predicted a higher drinking frequency (β=.21, $p<.001$), but not a larger drinking quantity (β=-.02, $p>.05$). Both dependent variables were similarly predicted by the social (fq: β=.09, $p<.05$; qn: β=.10, $p<.05$), enhancement (fq: β=.33, $p<.001$; qn: β=.38, $p<.001$) and low conformity (fq: β=-.21, $p<.001$; qn: β=-.14, $p<.001$) motives. In both cases, country did not moderate the relationship of each drinking motive with alcohol use (all the β coefficients were not significant, i.e. $p>.05$).

Discussion

The first aim of the present study was to explore the psychometric properties of M DMQ-R across two samples of young adults from two different countries: Spain and Canada. The multi-group CFA suggested that the M DMQ-R structure is virtually the same in both undergraduate samples. All the alpha coefficients were .65 across countries, or higher, which indicates acceptable internal consistency for all the scales given their small number of items (Loewenthal, 1996). These results are similar to those found in previous cross-cultural studies with other versions of the questionnaire (Kuntsche et al., 2014; Németh et al., 2011), and they suggest that M DMQ-R is a suitable instrument for comparing drinking motives across countries in undergraduate students.

In both countries, positive reinforcement drinking motives were more strongly endorsed than negative reinforcement drinking motives, as in previous studies with the four-factor DMQ-R (social > enhancement > cope > con-

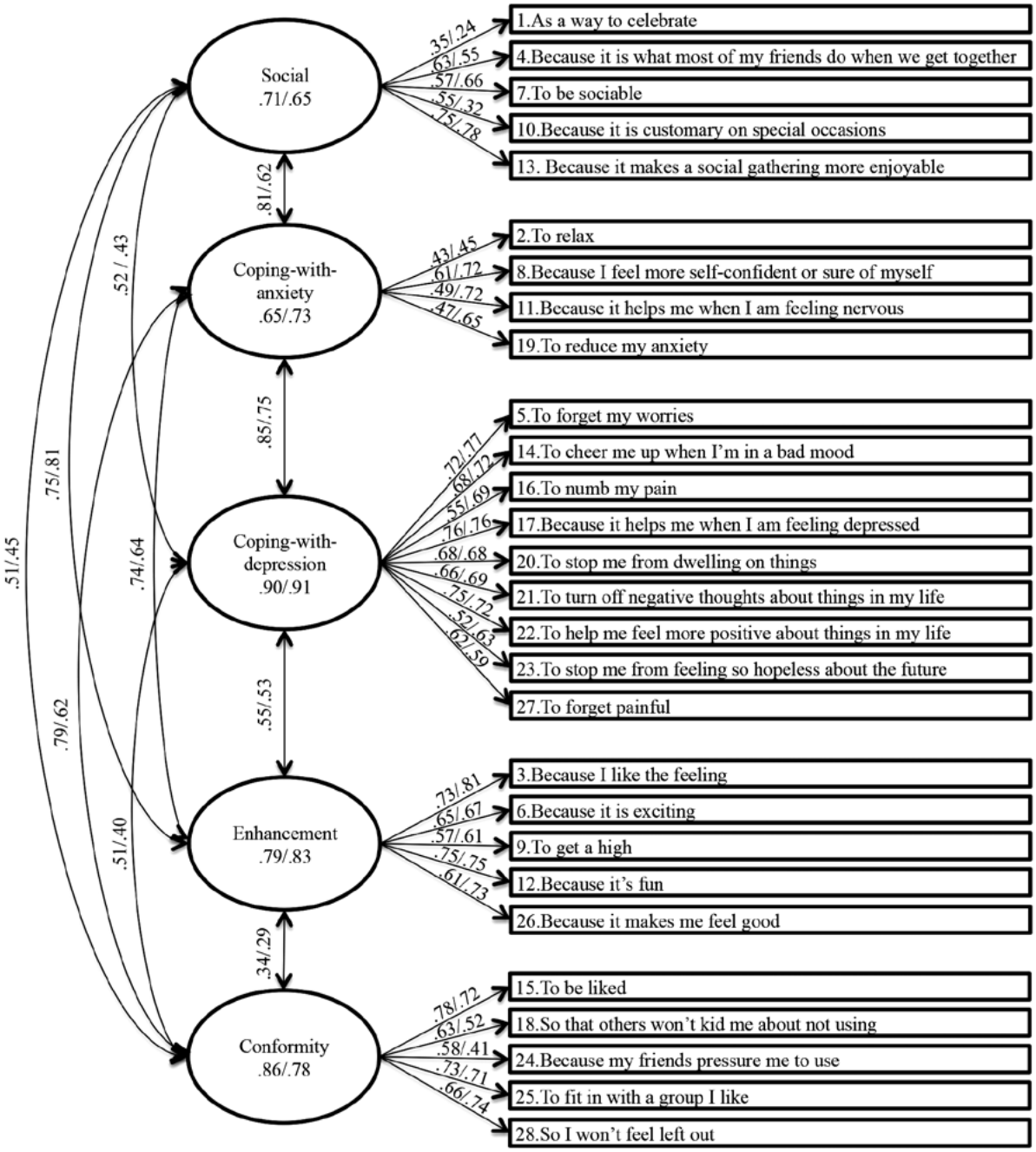

Figure 1. CFA in Spanish (before the slash) and Canadian (after the slash) undergraduates. Above unidirectional arrows, factor loadings. Above bidirectional arrows, correlations. All the parameters were significant at p ‹.001. In circles, Cronbach's alphas.

formity) (Kuntsche et al., 2014; Németh et al., 2011). Coping-with-anxiety motives were more strongly endorsed than coping-with-depression, similarly to those found in previous and independent samples of Spanish adults, clinical samples and undergraduates (Mezquita et al., 2011, 2014).

The regression analysis results showed that in the overall sample higher enhancement motives, lower conformity motives and, to a lesser extent, social motives were related to greater alcohol use (quantity and frequency). This result is consistent with previous studies in which "drinking for fun" or "because it is exciting" is the strongest predictor of alcohol use among young adults, while other positive reinforcement motives, social motives, usually show a moderate or non-significant relationship with alcohol use (Grant et al., 2007; Kuntsche et al., 2008; Németh et al., 2011). The negative regression coefficient between conformity and alcohol use has also been consistently found in the present and previous studies (Grant et al., 2007; Mezquita et al., 2011; Németh et al., 2011). This suggests that what is unique to conformity motives (i.e., not shared with other drinking motives) is negatively associated with overall alcohol use.

In addition, when differences among countries were explored, no moderation effect of country was found on the relationship of motives-alcohol outcomes, which is similar

to those found among European young adults (Kuntsche et al., 2014; Németh et al., 2011), even when being Canadian was associated with higher drinking frequency. This result is especially relevant because it suggests that the relation between motives and alcohol outcomes is consistent, at least with drinking frequency and drinking quantity, and that similar prevention and treatment programmes may be applied among different countries.

It is possible that the higher level of enhancement and coping-with-anxiety motives reported by the Canadian undergraduates could be responsible for the higher heavy and binge drinking level found in Canadian samples compared with southern Europe ones as cultures where drinking to intoxication are less common (De Witte & Mitchell Jr., 2012). However, future research works are required to test this hypothesis.

The main limitation of the present study was that we did not assess other drinking patterns apart from drinking frequency and drinking quantity. The inclusion of binge drinking and others variables, such as alcohol-related problems, drinking on weekdays, and drinking at weekends, would also be relevant, and especially so in internal drinking motives as previous studies found that coping-with-anxiety, coping-with-depression and enhancement motives relate differently with them (Mezquita et al., 2011, 2014; Studer et al., 2014).

To summarise, the results of this research suggest that M DMQ-R has suitable psychometric properties, can be used for comparing drinking motives, and should be used in future research to explore differences in alcohol use patterns (e.g. binge drinking, weekend alcohol use, etc.) across countries, at least among Spanish and Canadian undergraduates.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Supplementary material 1. Matching process.

With the aim of controlling the differences between the original samples in age (Spain: N = 983, mean age = 19.43 [SD = 1.34] years; Canada: N = 608, mean age = 18.66 [SD = 1.04] years; $t = 12.02$, $p < .001$), we pseudo-randomly matched the samples as follows: In each age/gender group (e.g., 18 year old women), we used the sample (Canadian or Spanish) with fewer participants as the primary sample unit (i.e., Spanish in the 18 and 19 year old groups, Canadian in the 20, 21 and 22 year old groups) and randomly found a match for each successive case from the other sample. We then used SPSS to delete the remaining participants in each age/gender group. The total number of participants deleted was 37 in Canada vs. 412 in Spain, resulting in final samples of 571 participants from each country.

Gender differences in addiction severity

Diferencias de género en la gravedad de la adicción

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Abstract

Gender has been associated with substance use disorders (SUD). However, there are few studies that have evaluated gender differences in a global and a standardized way, and with a large sample of patients with SUD. Our goal is to analyze the role of gender in addiction severity throughout multiple life domains, using the Addiction Severity Index-6 (ASI-6). A naturalistic, multicenter and prospective study was conducted. A total of 221 patients with SUD (80.1% men) were interviewed with the ASI-6. Our results indicate that the Recent Summary Scores (RSSs) of men and women are similar, with the exception of Psychiatric and Partner- Problems, where women showed higher severity (p = .017 and p = .013, respectively). Statistically significant gender differences were found in certain aspects of the ASI-6 domains: men have more problems of physical health, legal issues, and alcohol and other substance use; and woman score higher in problems of mental health, social network, subjective evaluations of SUD consequences, and treatment needs. These results should be taken into account to improve the identification, prevention, and treatment of SUD.

Keywords: Addiction severity; Gender differences; ASI-6; Substance use disorder.

Resumen

Se ha descrito que el género es un factor que condiciona los trastornos por uso de sustancias (TUS). Sin embargo, hay pocos estudios que hayan evaluado esas diferencias de género de manera global, estandarizada y en una muestra amplia de pacientes con TUS. Nuestro objetivo es analizar el rol del género en la gravedad de la adicción a través de los diversos dominios de vida mediante el Addiction Severity Index-6 (ASI-6). Se llevó a cabo un estudio naturalístico, multicéntrico y prospectivo con una muestra compuesta por 221 pacientes con TUS (80,1% hombres). Los participantes fueron entrevistados con el ASI-6. Los resultados han mostrado que las Puntuaciones Sumarias Recientes (PSRs) son similares entre hombres y mujeres a excepción de las correspondientes a Salud mental y Pareja- Problemas, donde las mujeres presentan mayor gravedad (p = 0,017 y p = 0,013, respectivamente). Por otra parte, se han encontrado diferencias estadísticamente significativas en diversos aspectos concretos de las áreas contempladas por el ASI-6, que indican que los hombres presentan más problemas en cuanto a salud física, cuestiones legales y uso de alcohol y drogas, y la mujeres en salud mental, red social y la valoración subjetiva sobre las consecuencias del TUS y la necesidad de tratamiento. Estos resultados deben tenerse en cuenta a la hora de implementar una mejora en la identificación, prevención y tratamiento de los TUS.

Palabras clave: Gravedad de la adicción; Diferencias de género; ASI-6; Trastorno por uso de sustancias.

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Previous data have shown that the gender can modulate the different clinical aspects of substance use disorders (SUD), including prevalence, expression of symptoms, comorbidity, clinical course, severity, choice of treatment, and prognosis (Grella & Lovinger, 2012; Miquel, Roncero, López Ortiz, & Casas, 2011). Thus, women begin consuming at lower doses than men, but their evolution towards abuse and dependence is faster ("telescoping effect") (Alvanzo et al., 2011) and they have greater chances of relapse during withdrawal (Becker & Hu, 2008). On another hand, as noted by Miquel et al. (2011), although there are more men than women with dual pathology (87.5% vs. 12.5%, respectively) in general psychiatry units, the proportion is reversed in drug units (47.5% of women had dual pathology compared to 30.3% of men). In addition, in men, the most prevalent comorbid diagnoses are psychotic and bipolar disorders, whereas in women, they are anxiety and affective disorders (Miquel et al., 2011). This comorbidity of SUD may be predictive of low performance, family difficulties, therapeutic non-compliance, legal issues, etc. (Miquel et al., 2011; Najt, Fusar-Poli, & Brambilla, 2011; Schwinn, Schinke, & Trent, 2010). In terms of physical health problems, female consumers have poorer general health, report more chronic problems, receive more prescriptions and take more medication than men (Green, Grimes Serrano, Licari, Budman, & Butler, 2009; Grella & Lovinger, 2012).

Substance use has been associated with criminal behavior, both in men and women (Green et al., 2009; Palmer, Jinks, & Hatcher, 2010). Traditionally, men show higher rates of violence and crimes against property than women (Castillo-Carniglia, Pizarro, Luengo, & Soto-Brandt, 2014; McMurran, Riemsma, Manning, Misso, & Kleijnen, 2011). However, for several years, the rates of women with legal problems resulting from substance abuse have been increasing significantly (Messina, Grella, Cartier, & Torres, 2010; Palmer et al., 2010).

The study of the relationship between employment and gender in people with SUD has revealed differences that may be mediated by different social roles such as parenthood, child care, the division of homework, etc. (Huang, Evans, Hara, Weiss, & Hser, 2011; Thompson & Petrovic, 2009). For example, male consumers have a longer history of working life and are more predisposed to work than women (Hogue, Dauber, Dasaro, & Morgenstern, 2010).

Moreover, the family may constitute a significant source of protection against substance abuse, and family factors related to substance use may be different for men and women (Kopak, Chen, Haas, & Gillmore, 2012). Women with SUD report more family conflicts, tend to live with their children, and are more likely to be divorced or widowed than are men (Green et al., 2009).

But as seen above, the literature reports gender differences in specific problems caused by SUD, and, to our knowledge, there are no studies that have evaluated these differences globally and comprehensively, with a standardized instrument allowing the determination of possible differences in the severity of these problems in a sample of patients with SUD. Taking the literature reports into account, we hypothesized that there will be gender differences in specific aspects of different life areas of people with SUD, but this is not sufficient to have an impact on the severity profile of the different life domains. Our goal is to examine the impact of gender on addiction severity in the different life domains through the Addiction Severity Index-6 (ASI-6).

Method

Participants

The total sample was made up of 221 patients, of whom 177 (80.1%) were men and 44 (19.9%) women, who presented a SUD (dependence) and who were receiving treatment in one of the 8 centers participating in the project (Unidad de Tratamiento de Conductas Adictivas, SERGAS, Orense; Clínica Asturias, Gijón; Hospital Ramón & Cajal, Madrid; Hospital Sant Pau, Barcelona; Unidad Asistencial de Drogodependencias, Carballo- La Coruña; Centro de Atención a Drogodependencias San Juan de Dios, Palencia; Centro de Salud Mental Retiro, Madrid; Centro de Salud Mental Teatinos, Oviedo). The inclusion criteria were: (a) being of age, (b) having a main diagnosis of SUD (dependence) according to the International Classification of Diseases ([ICD-10], World Health Organization, 1992) criteria, (c) initiating or changing treatment, and (d) signing the informed consent form. The only exclusion criterion was not signing the informed consent form.

Assessments

Four assessments were performed in the study. The first was performed when including the patient, after he or she had signed the informed consent, and follow-ups were performed at 1, 3, and 6 months. This work only shows the data from the baseline assessment. All patients were administered the Spanish version of the Addiction Severity Index (ASI-6) (Cacciola, Alterman, Habing, & McLellan, 2011; Díaz Mesa et al., 2010).

Addiction Severity Index (ASI-6)

The ASI-6 is a semi-structured and hetero-applied interview that multi-dimensionally assesses addiction severity understood as need for treatment. It consists of 257 items that collect demographic information and data about housing, and assess seven problem areas: physical health, employment and resources, alcohol and drugs, legal status, family and social relationships, and psychiatric area. These problem areas have a similar structure: firstly, objective items to describe the patient's situation in that area and to identify and quantify possible problems; and secondly, subjective items about the patients' appraisal of their life situation in the last 30 days and the importance to them of treatment to solve those situations (rated as none, slight, moderate, substantial or extreme).

The ASI-6 provides a severity profile of the last 30 days made up of the Recent Summary Scores (RSSs) in the 9 primary and 6 secondary scales. These scores are obtained using a mathematical algorithm that only uses some of the items (objective and subjective) that constitute each problem area. The RSSs have a theoretical range from 0 to 100, such that the higher the score, the greater the severity, although the feasible range is specific to each score (see Table 1).

Design

Data for this article were taken from a naturalistic, multicenter, longitudinal, prospective study with a 6-month follow-up. The design features are described in more detail in Casares et al. (2011). The study was approved by the Ethics Committee for the Research Clinic of the Central University Hospital of Asturias (ref. nr. 45/2005) and follows the guidelines of the Helsinki Declaration of 1975, revised in 1983. We obtained informed consent for participation in the study from all the participants and/or their legal representatives before inclusion in the study.

Data analysis

Descriptive analysis (distribution of means and frequencies as a function of the nature of the variables) was carried out to establish the characteristics and profile of the total sample and differentiated by gender. Subsequently, statistically significant differences were established as a function of gender using bivariate analyses (Chi-square with Yates' correction and Fisher's exact test, and Student's t for independent samples). To perform the most appropriate analyses, the five response options of the subjective items were recoded according to their frequency distributions as: None (none and slight), Moderate (moderate) and Extreme (considerable and extreme). We established a 95% confidence level and used the statistical package for Social Sciences SPSS-15.

Results

Sample profile

The mean age of the sample was 41.4 years (SD = 11.5). In terms of marital status, 43.0% were married or living as a couple. In the last 30 days, 61.4% had been in hospital, in a hospitalization unit for alcohol or drugs or a psychiatric unit, prison, a therapeutic community, or a protected flat. Concerning education, 49.3% had compulsory studies (elementary, primary, and secondary). Regarding employment status, 47.3% was active either part-time or full-time. Alcohol was the main substance of reference in the treatment for 54.3% of the participants. Table 2 presents the socio-demographic and consumption data of the patients differentiated by gender. We found no statistically significant gender differences in any of them.

Table 1. *Structure and Scores of the Addiction Severity Index v. 6.0 (ASI-6).*

Assessed problem areas	**Scales** - 9 primary scales (1.1 to 1.9) - 6 secondary scales (2.1 to 2.6)*		**Feasible RSS range**
1. Physical health	PRIMARY	1.1. Physical health	29 – 78
2. Employment and resources		1.2. Employment	21 – 53
3. Alcohol use		1.3. Alcohol	38 – 77
4. Drug use		1.4. Drugs	31 – 77
5. Legal situation		1.5. Legal	43 – 79
6. Family and social relationships		1.6. Family - Children	48 – 79
		1.7. Family/Social network - Support	27 – 73
		1.8. Family/Social network - Problems	36 – 78
	SECONDARY	2.1. Partner - Support	32 – 57
		2.2. Partner - Problems	47 – 77
		2.3. Adult relatives - Support	41 – 68
		2.4. Adult relatives - Problems	44 – 67
		2.5. Friends - Support	37 – 59
		2.6. Friends - Problems	46 – 70
7. Psychiatric	P	1.9. Psychiatric	31 – 79

Note. RSS: Recent Score Summary; P: Primary
* Secondary scales and their scoring ranges are shaded in gray.

Table 2. *Socio-demographic and Consumer Profile according to Gender.*

	Men (n = 177)	**Women (n = 44)**	**p**
Mean Age – years (SD)	41.9 (*DT* = 11.7)	39.6 (*DT* = 10.9)	0.242
Civil status - n (%)			0.162
Married / Living as a couple	77(43.5)	18 (40.9)	
Divorced / Separated	30 (16.9)	4 (9.1)	
Single	67 (37.9)	19 (43.2)	
Widowers	3 (1.7)	3 (6.8)	
Housing in the last 30 days - n (%)			
Alone	28 (90.3)	3 (9.7)	
Spouse/Partner	71 (81.6)	16 (18.4)	
Children< 18 years	28 (73.7)	10 (26.3)	
Parents	58 (85.3)	10 (14.7)	
Other adult relatives	28 (71.8)	11 (28.2)	
Other non-adult relatives	7 (77.8)	2 (22.2)	
Hospital Unit (drugs)	6 (66.7)	1 (100)	0.490
Prison	3 (33.3)	1 (100)	0.197
Restricted or supervised housing	5 (83.3)	1 (16.7)	0.346
Hostel/street	7 (58.3)	0 (0)	0.261
Studies achieved [n (%)]			0.313
Compulsory (Elementary, Primary, Secondary)	85 (48.3)	23 (53.5)	
High school /Vocational training	69 (39.2)	14 (32.6)	
University (Degree/Postgraduate)	18 (10.2)	6 (14.0)	
None	4 (2.3)	0 (0.0)	
Work situation n (%)]			0.315
Full-time/part-time	79 (44.9)	25 (56.8)	
Unemployed and actively seeking	28 (15.9)	8 (18.2)	
Outside of the labor market	69 (39.2)	11 (25.0)	
Main consumption substance [n (%)]			0.359
Alcohol	92 (52.0)	28 (63.6)	
Cannabis	11 (6.2)	2 (4.5)	
Cocaine	33 (18.6)	7 (15.9)	
Opiates	39 (22.0)	6 (13.6)	

Note. There were no statistically significant gender differences in any of the variables.

Profile of addiction severity according to the RSSs on the ASI-6 scales

Men and women both showed greater severity on the primary scale of Employment, and on the secondary scales of Partner - Support and Friends - Support. Regarding the impact of gender on the severity of the addiction profile, we only found statistically significant differences in the primary scale of Psychiatric and the secondary scale of Partner - Problems. In both cases, there was higher severity in the women (Table 3).

Physical health

As regards the presence of chronic diseases related to substance use (HIV, tuberculosis, hepatitis, and cirrhosis or other liver diseases), there were no statistically significant gender differences. However, 39.8% of the men compared to 23.3% of the women reported other chronic diseases, and the differences were statistically significant, $\chi 2 = 4.066$, $p = .044$. On another hand, 13.6% of the men and 2.3% of the women received a pension due to physical disease or disability, $\chi 2 = 4.513$, $p = .034$. We also found statistically significant differences in the mean number of times that they had been hospitalized for physical health problems: 2.26 times for the men and 1.51 times for the women, $t = 2.066$, $p = .041$.

Employment and resources

Statistically significant differences were found, $\chi 2 = 24.138$, $p = .007$, in terms of the type of work currently per-

Table 3. *Differential RSS Profile as a Function of Gender.*

Scales		Men (SD)	Women (SD)	Student's t	p
PRIMARY	1.1. Physical health	45.1 (9.2)	42.8 (10.3)	1.403	0.162
	1.2. Employment	38.4 (13.1)	36.1 (11.7)	1.031	0.307
	1.3. Alcohol	51.7 (9.0)	54.1 (9.3)	-1.507	0.133
	1.4. Drugs	40.6 (10.9)	38.6 (9.4)	1.048	0.296
	1.5. Legal	47.0 (3.3)	47.2 (3.7)	-0.353	0.725
	1.6. Family - Children	49.7 (5.0)	50.4 (6.0)	-0.682	0.496
	1.7. Family/Social network - Support	45.0 (12.5)	44.2 (9.2)	0.465	0.643
	1.8. Family/Social network - Problems	43.6 (8.9)	49.0 (9.2)	-1.751	0.081
SECONDARY	2.1. Partner - Support	43.0 (11.4)	43.6 (11.4)	-0.329	0.742
	2.2. Partner - Problems	48.9 (6.6)	52.4 (8.2)	-2.570	0.013
	2.3. Adult relatives - Support	49.2 (8.9)	46.6 (8.3)	1.746	0.082
	2.4. Adult relatives - Problems	49.1 (7.0)	50.9 (7.9)	-1.530	0.128
	2.5. Friends - Support	48.1 (9.0)	47.8 (10.3)	0.178	0.860
	2.6. Friends - Problems	48.8 (6.2)	48.3 (5.5)	0.472	0.637
P	1.9. Psychiatric	44.1 (9.2)	48.1 (8.4)	-2.406	0.017

Note. RSS: Recent Score Summary; P: Primary.

formed. Out of the sample, women predominated in sectors of technical and administrative professions and domestic cleaning (specialized, executive, administrative and management professions, sales, clerks and administrative support, services and domestic employees), whereas men carried out manual labor (precision production, trades and repairs, machine operators and supervisors, carriers and removals, manual workers, cleaning equipment, helpers and laborers). The longest full-time work interval was 116.22 (SD = 120.8) months for the men versus 75.7 (SD = 91.7) months for the women, t = 2.401, p = .019.

Alcohol and drugs

We found statistically significant differences in the age at onset of alcohol use such that the men began to drink at a significantly lower mean age (16.0 years, SD = 5.1) than the women (18.5 years, SD = 7.3), t = -2.119, p = .039. Of the men, 27.7% had presented problems to control, reduce, or refrain from drinking alcohol or had spent a longer time drinking compared to 43.2% of women, $\chi2 = 3.974$, p = .046. In addition, significantly fewer men (21.5%) than women (43.2%) had medical or psychological, occupational, legal or domestic problems due to alcohol use, $\chi2 = 8.680$, p = .003. We also found statistically significant differences in the perception of craving or the impulse to drink as a problem, present in 27.3% of the men compared with 45.5% of the women, $\chi2 = 8.241$; p = .004. Considering a daily abusive intake of 5 units of standard drink (USDs) for men and 4 for women, as established in the ASI-6, the men reported a mean regular abusive consumption of 13.02 (SD =12.9) years, and the women of 7.84 (SD =9.0) years, t = 2.794, p = .006.

Regarding illegal drugs, no age differences in the onset for any substance, in days of consumption or abuse, either lifelong or in the last 30 days, were found. No age differences were found for the consumption of sedatives, cocaine, stimulants and hallucinogens. Only in the case of inhalants, age at onset was lower for men (18.2 years, SD = 5.090) compared to women (26.4 years, SD = 9.370), t = -2.448, p = .026. In terms of the lifelong regularity of consumption, men consumed the following substances for significantly more years than women: marijuana (4.7 years, SD = 7.1, vs. 1.7 years, SD = 4.5, respectively), t = 3.311, p = .001, heroin (3.1 years, SD = 5.8, vs. 0.9 years, SD = 2.6, respectively), t = 3.678, p ≤ .001, and methadone (1.2 years, SD = 3.107, vs. 0.4 years, SD = 1.706, respectively), t = 2.296, p = .023. We found no gender differences in the prevalence of abuse of any of the substances. However, regarding the use of secondary drugs (without a diagnosis of abuse), again men presented consumption patterns significantly more frequently than did women in some substances. Thus, among those who consumed marijuana, 56.5% of the men compared to 35.9% of the women, $\chi2 = 5.414$, p = .020, had consumed it more than 50 days over their lifetime, and 31.2% of the men compared with 13.6% of the women had consumed heroin on more than 50 occasions, $\chi2 = 5.418$, p = 0.020. In terms of risk behavior related to substance use, 23.3% of the men had injected drugs at some point in their lives, whereas of the women, only 9.3% had done so, $\chi2 = 4.085$, p = .043.

No significant differences in economic problems derived from gambling were apparent. However, in the last 30 days, the men had gambled significantly more than the women in games like the lottery, the coupon, football pools, slots ma-

Table 4. *Differences in Social and Family Relations as a Function of Gender.*

	Men	Women	Statistical test	p
In the last 30 days				
Has spent time in person with partner- n (%)	107 (97.3)	28 (87.5)	5.052[a]	0.025
Has had some contact with partner (calls, internet, etc.) - n (%)	108 (98.2)	26 (81.3)	13.367[a]	0.000
Has argued with partner - n (%)	43 (39.4)	18 (64.3)	5.563[a]	0.018
The partner has a problem with alcohol or drugs - n (%)	10 (9.2)	10 (35.7)	12.586[a]	0.000
Close friends have problems with alcohol or drugs - n (%)	29 (27.6)	2 (8.0)	4.280[a]	0.039
Has talked to friends about feelings or problems - n (%)	72 (67.3)	23 (92.0)	6.134[a]	0.013
Has gone to religious services or activities promoted by the religious community – n (%)	14 (7.9)	8 (18.2)	4.148[a]	0.042
Lifelong				
Someone he/she knows physically abused or assaulted him/her - n (%)	33 (18.9)	27 (38.6)	7.807[a]	0.005
Someone he/she knows sexually abused or assaulted him/her- n (%)	4 (2.3)	10 (23.8)	26.171[a]	0.000
Months since the last time - M (SD)	55.2 (61.5)	240.3 (117.1)	-3.272[b]	0.006
Months since he/she saw how someone was killed, attacked, or seriously harmed - M (SD)	139.9 (133.8)	62.1 (47.2)	2.927[b]	0.006

Note.
[a] χ^2
[b] Student's *t*

chines, bingo, betting on racing, casinos, etc., or any other illegal gambling (2.8 times, SD = 6.3, vs. 0.6 times, SD = 2.0, respectively), t = 3.892, p ≤ .001).

Legal situation

At the legal level, men had significantly more problems than women. Of the men, 44.1% had been in jail/prison even though only for a few hours at some point in their lives, whereas of the women, only 20.5% had been in jail, $\chi2$ = 8.232, p = .004. In the case of arrests, 48.0% of the men and 25.0% of the women had been arrested, $\chi2$ = 7.573, p = .006.

Family and social relationships

As shown in Table 4, in the last 30 days, a greater proportion of men than of women had spent time with their partners, had had contact with them, and had close friends with current problems of alcohol or drugs. Moreover, in the last 30 days, a higher percentage of women than of men had argued with their partners, their partner had drug or alcohol problems, and they had talked more with friends about their problems and feelings. In addition, a higher percentage of women than men had suffered physical assault or abuse (38.6% vs. 18.9%, respectively, $\chi2$ = 7.807, p = .005) and sexual abuse (23.8% vs. 2.3%, respectively, $\chi2$ = 26.171, p ≤ .001) at some time in their lives.

Mental health

The women's level of mental health was significantly worse than the men's. Thus, a higher percentage of women had tried to commit suicide at some time in their lives (28.6% vs. 10.1%), $\chi2$ = 9.612, p = .002, and had felt depressed or low or had had sleeping problems in the past 30 days (65.9% vs. 46.1%), $\chi2$ = 5.462, p = .019. In addition, women were assessed or treated for emotional or psychological problems for the first time at a younger age than men [24.8 years, SD = 9.3, vs. 30.3 years, SD = 11.9), t = 2.293, p = .024.

Subjective assessment of severity and the need for treatment

As shown in Table 5, the women were significantly more concerned about their alcohol consumption, the abusive and traumatic events experienced, and their psychological problems, and they granted more importance to treatment for their consumption and their social relationships with other adults, and for the abuse and trauma suffered. The women also showed a higher tendency than the men to worry about their physical health and the problems associated with drugs. They also considered that achieving abstinence from alcohol, getting treatment for their psychological problems, and feeling more satisfied with their adult relationships was more important than did the men. Furthermore, we observed in the men a tendency to experience more pain or physical discomfort, and they granted more importance to its treatment, and to the need for job counseling, treatment to cease using substances, and counseling in their relation with their children. They felt their current legal problems were more severe, they were more concerned about their relationships with other adults, and they were more satisfied with their free or leisure time.

Discussion

The main goal of this study was to examine gender differences in addiction severity in the different life areas assessed by the ASI-6. In relation to the addiction severity profile, when observing the RSSs, there are few differences, and these show that women's profile is significantly more severe in the life domains related to mental health and couple problems. However, when considering different items of the ASI-6 individually, the men in this study have more problems related to substance use in all life areas, except for those concerning psychological status and the area of social relations, in line with the findings of other studies (Cotto et al., 2010; Kopak et al., 2012; Najt et al., 2011; Palmer et al., 2010).

A global and comprehensive, standardized and universally accepted assessment instrument was used in this study, which has shown that there is no differential addiction severity profile as a function of gender, except for the scales of Mental health and Partner– Problems.

Physical health

The men reported having been hospitalized several times, and a higher proportion of men than of women received a pension for physical-related problems. Among the scarce previous studies, it was found that women have poorer health status (Green et al., 2009; Grella & Lovinger, 2012), although in those cases, the samples were limited to patients with opioid abuse.

Employment and resources

Substance use influences the socio-economic area (Neale, Nettleton, & Pickering, 2014). In our sample, we detected a labor market pattern characterized by the predominance of manual work in men, and of technical, administrative, and commercial professions and domestic work in women. On another hand, women had worked less in full-time jobs, as other studies have shown (Green et al., 2009; Huang et al., 2011). More research is needed to understand how the SUD affects men and women in the workplace (Huang et al., 2011).

Alcohol and drugs

Regarding substance use, coinciding with the literature, men begin consuming at earlier ages, and their consumption is more abusive and regular (Alvanzo et al., 2011; Buu et al., 2014; Green et al., 2009). For their part, the women in the sample, like those from other studies, considered craving as a problem and reported more difficulties to control their alcohol use and more problems associated with

Table 5. *Subjective Assessment of Severity and the Need for Treatment in the past 30 Days*

	Men n (%)			Women n (%)			χ^2	p
	None	Moderate	Extreme	None	Moderate	Extreme		
Physical health								
Pain or physical discomfort	103 (58.9)	43 (24.6)	29 (16.6)	27 (61.4)	12 (27.3)	5 (11.4)	0.754	0.686
Concern about physical health	109 (62.3)	29 (16.6)	37 (21.1)	28 (63.3)	4 (9.1)	12 (27.3)	1.906	0.386
Importance of treatment for physical health	100 (57.5)	12 (6.9)	62 (35.6)	25 (58.1)	3 (7.0)	15 (34.9)	0.008	0.996
Employment and resources								
Importance of job counseling	114 (65.5)	11 (6.3)	49 (28.2)	25 (61.0)	6 (14.6)	10 (24.4)	3.177	0.204
Alcohol use								
Concern about problems with alcohol	128 (72.7)	9 (5.1)	39 (2.2)	19 (43.2)	3 (6.8)	22 (50.0)	14.626	0.001
Importance of treatment to quit drinking	94 (53.4)	12 (6.8)	70 (39.8)	14 (32.6)	3 (7.0)	26 (60.5)	6.423	0.040
Importance of achieving / maintaining abstinence from alcohol	85 (48.3)	13 (7.4)	78 (44.3)	14 (31.8)	3 (6.8)	27 (61.4)	4.282	0.118
Drug use								
Concern about drug-related problems	130 (75.6)	6 (3.5)	36 (20.9)	32 (76.2)	1 (2.4)	9 (21.4)	0.132	0.936
Importance of treatment to quit using substances	96 (54.9)	8 (4.6)	71 (40.6)	28 (65.1)	2 (4.7)	13 (30.2)	1.597	0.450
Importance of achieving / maintaining abstinence from substances	86 (49.1)	8 (4.6)	81 (46.3)	26 (61.9)	1 (11.1)	15 (35.7)	2.316	0.314
Legal situation								
Severity of judicial problems	146 (84.9)	2 (1.2)	24 (14.0)	36 (87.8)	0 (0.0)	5 (12.2)	0.585	0.746
Family and social relationships								
Satisfaction provided by adult relationships	59 (33.5)	57 (32.4)	60 (34.1)	11 (25.0)	14 (31.8)	19 (43.2)	1.617	0.445
Concern about problems in adult relationships	103 (58.2)	30 (16.9)	44 (24.9)	21 (48.8)	12 (27.9)	10 (23.3)	2.749	0.253
Importance of treatment for adult relationships	103 (58.5)	20 (11.4)	53 (30.1)	17 (39.5)	11 (25.6)	15 (34.9)	7.462	0.024
Satisfaction with leisure	78 (44.1)	55 (31.1)	44 (24.9)	26 (59.1)	9 (20.5)	9 (20.5)	3.347	0.188
Concern about abuse and traumatic events	162 (94.7)	0 (0.0)	9 (5.3)	30 (73.2)	7 (17.1)	4 (9.8)	31.982	0.000
Importance of treatment for traumatic/abusive events	160 (93.6)	2 (1.2)	9 (5.3)	30 (73.2)	2 (4.9)	9 (22.0)	14.793	0.001
Additional need for problems with children	126 (95.5)	2 (1.5)	4 (3.0)	32 (97.0)	0 (0.0)	1 (3.0)	0.506	0.776
Difficulty in relationship with children	131 (99.2)	1 (0.8)	0 (0.0)	30 (96.8)	1 (3.2)	0 (0.0)	1.262	0.261
Importance of counseling for relationship with children	123 (93.9)	3 (2.3)	5 (3.8)	28 (90.3)	2 (6.5)	1 (3.2)	1.465	0.481
Mental health								
Concern for psychological problems	79 (45.7)	27 (15.6)	67 (38.7)	13 (31.0)	4 (9.5)	25 (59.5)	5.992	0.050
Importance of psychological treatment	77 (43.8)	24 (13.6)	75 (42.6)	12 (27.3)	5 (11.4)	27 (61.4)	5.169	0.075

consumption (Shand, Degenhardt, Slade, & Nelson, 2011; Thompson & Petrovic, 2009). In our study, we detected a higher percentage of men who injected drugs. This could be because women basically inject with their partners, whereas men have a broader network of family and friends who consume (Werb et al., 2013).

It was found that men had gambled more frequently in the last month, which could be attributed to the vulnerability shared by SUD and pathological gambling, and the differential characteristics of impulsiveness, emotional arousal, and response to stress as a function of gender, etc. (Estévez Herrero, Herrero Fernández, Sarabia Gonzalvo, & Jáuregui Bilbao, 2014; Pilver, Libby, Hoff, & Potenza, 2013; Verdejo-Garcia, Lawrence, & Clark, 2008).

Legal situation

Although, in accordance with other studies (Green et al., 2009; Haas & Peters, 2000), there were more men than women who had been in prison or had been arrested, the severity profile of the Legal Scale did not yield significant gender differences.

Family and social relationships

A broad range of research indicates that the family environment is more dysfunctional in women with SUD than in men (Kopak et al., 2012; Shand et al., 2011). According to our study, there are no major differences in problems in the family setting or in the severity scores of this area, and such problems are limited to the couple context, where the women did present higher severity. According to Cranford, Tennen, and Zucker (2015), following the theory of role incompatibility, consumption would be more incongruent with adult social roles like marriage in the case of women, which could generate more couple problems.

There are no data on the social network of adults with SUD. In our study, men had more friends with problems related to alcohol or other substances than did women. This could be because women tend to make new friends or remake contact with people who do not consume, whereas men have more trouble making new nonconsumer friends, to which is added the lack of family support (Neale et al., 2014).

The higher prevalence of traumatic events in women with SUD than in men (Shand et al., 2011), as well as the greater likelihood of sexual abuse (Neale et al., 2014; Shand et al., 2011) is well documented in the literature. In this sample, the women had been assaulted physically and sexually more frequently than the men, but it was striking that the men had been sexually assaulted a shorter time ago.

The spiritual or religious aspect in SUDs, although less studied, seems to play a considerable role in the treatment and recovery process (Alterman, Cacciola, Dugosh, Ivey, & Coviello, 2010). These data would explain why the women in our sample reported attending religious events more frequently than the men.

Psychiatric area

Although until now, there have been conflicting data on the comorbidity of SUD with other psychiatric diagnoses and gender differences, among people with SUD, mental health problems and thoughts and attempts of suicide seem more prevalent in women (Araos et al., 2014; Saiz et al., 2014; Shand et al., 2011). In this sense, the analyzed sample confirms that there are more women who are depressed and who have attempted suicide, but no differences appeared in the rest of symptoms assessed by the ASI-6. Although other studies found similar results, none of them offers an explanation (Miquel et al., 2011). The severity scores in the area of mental health confirm that women have a worse mental health profile, so the psychological consequences of substance use are higher in women than in men.

Subjective assessment of severity and the need for treatment

To our knowledge, there are no studies on the differences in subjective experiences about the consequences of SUD in the different domains. When was asked for subjective assessment, in our study, the women were significantly more concerned about their consumption of alcohol, stressful life events experienced, and psychological problems, and they granted more importance to the treatment of their consumption and their social relationships with other adults, and of the abuses and traumatic events suffered.

Limitations

Firstly, the low proportion of women in the study sample should be noted. Second, we included patients with all types of substance dependence and, as expected, the legal substance (alcohol) was overrepresented compared to the rest. Finally, it should be taken into account that memory bias, motivations, social desirability, and the subjective perceptions of the interviewed subjects may have influenced the scores obtained. Therefore, it is necessary to be cautious when generalizing the results found in the study.

Conclusion

Our study reveals the existence of gender differences in multiple specific aspects evaluated by the ASI-6. However, these differences are minimized when considering the severity profile of the ASI-6. Nevertheless, women showed a more severe addiction profile in the mental health components and in couple problems, in line with their subjective evaluations of concern and need for treatment of psychological and social aspects.

These findings are of great interest to clinical practice because personalized intervention programs should be developed to attend to each patient differentially and globally, in this case, a function of gender.

However, further studies are needed that allow the establishment of causal relationships to explain severity differences between men and women, as well as prospective studies that include larger and more homogeneous samples regarding gender and substances.

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Conflict of interest

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

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Internalizing and externalizing personality and subjective effects in a sample of adolescent cannabis users

Personalidad internalizante y externalizante y efectos subjetivos en una muestra de adolescentes consumidores de cánnabis

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Abstract

Cannabis is the illicit substance most widely used by adolescents. Certain personality traits such as impulsivity and sensation seeking, and the subjective effects experienced after substance use (e.g. euphoria or relaxation) have been identified as some of the main etiological factors of consumption. This study aims to categorize a sample of adolescent cannabis users based on their most dominant personality traits (internalizing and externalizing profile). Then, to make a comparison of both profiles considering a set of variables related to consumption, clinical severity and subjective effects experienced. From a cross-sectional design, 173 adolescents (104 men and 69 women) aged 13 to 18 asking for treatment for cannabis use disorder in an Addictive Behavior Unit (UCAD) from the hospital were recruited. For the assessment, an *ad hoc* protocol was employed to register consumption, the Millon Adolescent Clinical Inventory (MACI) and the Addiction Research Center Inventory (ARCI) 49-item short form were also administered. Factor analysis suggested a two-profile solution: Introverted, Inhibited, Doleful, Dramatizing (-), Egotistic (-), Self-demeaning and Borderline tendency scales composed the internalizing profile, and Submissive (-), Unruly, Forceful, Conforming (-) and Oppositional scales composed the externalizing profile. The comparative analysis showed that the internalizing profile has higher levels of clinical severity and more subjective effects reported than the externalizing profile. These results suggest the need to design specific intervention strategies for each profile.

Keywords: Adolescents; Cannabis; Internalizing personality; Externalizing personality; Subjective effects.

Resumen

El cánnabis es la sustancia ilícita más consumida por los adolescentes. Determinados rasgos de personalidad, como la impulsividad y la búsqueda de sensaciones, así como los efectos subjetivos experimentados tras el consumo (p.e. euforia o relajación), se han identificado como algunos de los principales factores etiológicos de consumo. Este estudio tiene por objetivo categorizar a una muestra de adolescentes consumidores de cánnabis en función de sus rasgos de personalidad más predominantes (perfil internalizante y externalizante) para, posteriormente, realizar una comparación de ambos perfiles a partir de un conjunto de variables asociadas al consumo, la gravedad clínica y los efectos subjetivos experimentados. A partir de un diseño transversal, se reclutaron 173 adolescentes (104 hombres y 69 mujeres) de 13 a 18 años, que demandaron tratamiento por Trastorno por Uso de Cánnabis en la Unidad de Conductas Adictivas (UCAD) del Hospital. Para la evaluación se utilizó un protocolo *ad hoc* para registrar el consumo, el Inventario Clínico para Adolescentes de Millon (MACI) y la versión abreviada del *Addiction Research Center Inventory* (ARCI)-49. El análisis factorial sugirió una solución en 2 perfiles: las escalas Introvertido, Inhibido, Pesimista, Histriónico (-), Egocéntrico (-), Autopunitivo y Tendencia límite forman el perfil internalizante, y las escalas Sumiso (-), Rebelde, Rudo, Conformista (-) y Oposicionista el externalizante. El análisis comparativo mostró que el perfil internalizante presenta mayores niveles de gravedad clínica y reporta más efectos subjetivos que el externalizante. Estos resultados sugieren la necesidad de diseñar estrategias de intervención específicas para cada perfil.

Palabras clave: Adolescentes; Cánnabis; Personalidad internalizante; Personalidad externalizante; Efectos subjetivos.

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Cannabis is the most widely used illicit substance consumed by adolescents worldwide (United Nation Office on Drugs and Crime, 2014). In Spain, survey conducted among school students between the ages of 14 and 18 reveals that 33.6% have consumed it at least once in their lives, 22.6% in the last year, 16.1% in the last 30 days and 2.7% on a daily basis, with a higher percentage of adolescent boys consuming than adolescent girls (3.8% vs. 1.5%) (Spanish Observatory on drugs, 2014).

An early onset age for use is related to a greater risk of problematic use (Martínez-Lorca & Alonso-Sanz, 2003), the later use of other illicit drugs (Swift et al., 2012), of the presence of cerebral alterations (DuPont & Lieberman, 2014; Jacobus & Tapert, 2014), of cognitive processing (Alameda-Bailén, Salguero-Alcañiz, Merchán-Clavellino, & Paíno-Quesada, 2014; Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010; Grant, Chamberlain, Schreiber, & Odlaug, 2012) and motor functions being affected (Hall & Degenhardt, 2009), with the exacerbation of psychopathological symptoms in adulthood (Arias et al., 2013; Chen et al., 2011; Cuenca-Royo, Torrens, Sánchez-Niubó, Suelves, & Domingo-salvany, 2013; Muro i Rodríguez, 2015; Rubino, Zamberletti, & Parolaro, 2012) and with a higher probability of academic failure (Volkow, Baler, Compton, & Weiss, 2014).

The etiology of cannabis use – sporadic or problematic – in the adolescent population is multi-causal (Hemphill et al., 2011), with several risk factors being involved: namely individual factors (Magallón-Neri et al., 2012; Szerman, Goti, Díaz, & Arango, 2014; ter Bogt et al., 2014), familial factors (Becoña, Fernández del Río, Calafat, & Fernández-Hermida, 2014; Brière, Fallu, Descheneaux, & Janosz, 2011; Creemers et al., 2015), school factors (Guxens, Nebot, Ariza, & Ochoa, 2007; Hall & Degenhardt, 2009) and factors related to the personal environment (European Monitoring Centre for Drugs and Drug Addiction, 2014; Peñafiel, 2009; Szerman et al., 2014).

Among the individual risk factors, certain personality traits stand out (Belcher, Volkow, Moeller, & Ferré, 2014; Gunnarsson, Gustavsson, Tengström, Franck, & Fahlke, 2008; Marquez-Arrico & Adan, 2013) such as high levels of impulsiveness, sensation-seeking, dissocial traits, and a low predisposition to harm avoidance (Gunnarsson et al., 2008; Munno, Saroldi, Bechon, Sterpone, & Zullo, 2015; Walther, Morgenstern, & Hanewinkel, 2012), which are aggravated by continuous use (Chakroun, Doron, & Swendsen, 2004). Deficits in emotional regulation and negative affectivity have also been associated with use (Chabrol, Melioli, & Goutaudier, 2014; Creemers et al., 2009). In studies that have been carried out among adolescent users and non-users using the Millon Adolescent Clinical Inventory (MACI) (Millon, 1993) it has been observed that the consumers showed higher scores on the *Unruly*, *Forceful*, *Oppositional* and *Borderline* personality scales (Becoña et al., 2011; Fantin, 2006) and lower scores on the *Submissive* and *Conforming* scales (Faúndez & Vinet, 2009). However, studies of adolescents are scarce, possibly owing to the lack of consensus on the applicability of the construct of personality at early ages or in adolescence (Adshead, Brodrick, Preston, & Deshpande, 2012).

In order to help the study of personality, some authors have suggested encompassing it within the internalizing and externalizing dimensions (Achenbach & Edelbrock, 1984) and the research shows that they do explain the greater part of the associations between personality patterns, psychopathological indicators and clinical dysfunction in patients (Cosgrove et al., 2011; Harford et al., 2013; Hink et al., 2013; Hopwood & Grilo, 2010).

Elsewhere, several studies determine that the problematic use of cannabis is also related to the subjective experience that is obtained by its use (Zeiger et al., 2010). Subjective effects are characterized in two sub-types: 1) positive effects; linked to agreeable sensations such as euphoria, relaxation or sensorial alteration, and 2) negative effects; linked to disagreeable experiences such as anxiety, paranoia, hallucinations, sadness or nausea. Cannabis users may report both (Block, Erwin, Farinpour, & Braverman, 1998; Scherrer et al., 2009; Zeiger et al., 2012). These effects have shown themselves to be good predictors of cannabis abuse or dependency (Pedrero Pérez, 2003; Zeiger et al., 2012). Among the adolescent population it has been observed that the subjective positive experiences before the age of 16 are linked to cannabis dependency in adulthood (Fergusson, Horwood, Lynskey, & Madden, 2003). More recently, it has been observed that experiencing subjective positive and negative effects, known as "high response", is linked to a tendency to develop cannabis dependency (Scherrer et al., 2009) and to the presence of higher levels of use of other illegal substances (Zeiger et al., 2012).

Given the importance of personality traits in the onset and maintenance of use and of the subjective effects on the development of problematic cannabis use, as well as the paucity of the data existing n the subject, this study is presented with the following objectives. Firstly, to discriminate between the personality traits that are present in a clinical sample of adolescent cannabis users by means of the categorization into two personality profiles: internalizing and externalizing. Secondly, to make a comparison of both profiles by means of a set of variables that are associated with consumption, such as: gender, age of onset of consumption, age of regular consumption, age at which treatment was sought, hourly use patterns, clinical seriousness and the subjective effects experienced after use.

Methods

This is an exploratory, cross-sectional study.

Sample

In order to carry out the present research, a total of 173 adolescents who had come to the Unidad de Conductas Adictivas (Addictive Behaviors Unit) of the Hospital's Psychiatric and Psychological Service (anonymized for peer review) seeking treatment for cannabis use.

The inclusion criteria for the sample were: 1) to be under the age of 18, and 2) to show signs of cannabis abuse or dependency. On the other hand, the exclusion criteria were: 1) having an acute mental pathology that prevented the subject from understanding the questionnaires.

The final sample was made up of a total of 173 subjects: 60.1% (n = 104) adolescent boys and 39.9% (n = 69) adolescent girls, with an average age of 15.67 (SD= 1.23).

Regarding the academic background, of the 173 subjects, 70.5% (n = 22) were studying, 69.4% (n = 120) had been held back a year and 29.5% (n = 51) had dropped out. At the time of evaluation the sample group were either in, or had been in, the following school years: 13.3% (n = 23) in the 2nd year of compulsory secondary education (CSE) 27.7% (n = 48) in the 3rd year of CSE, 31.2% (n = 54) in the 4th year of CSE, 8.7% (n = 15) in the 1st year of senior high school (SHS) 0.6% (n = 1) in 2nd year of SHS, 8.1% (n = 14) in vocational courses leading to professional qualifications (VCPQ), 0.6% (n = 1) at university and 9.8% (n = 17) in other academic situations.

Evaluation tools / Analysis

In order to gather the necessary information for the research, the socio-demographic variables referring to gender, age and academic level were collected. Variables relating to the use of cannabis were obtained by means of an *ad hoc* protocol in which the onset age of consumption, the age at which use became regular, the age when treatment was sought and the hourly use pattern (before entering class, during recess, midday, afternoons/evenings, before going to sleep) were all registered.

In order to determine whether there was Substance Use Disorder, the Spanish version of the Substance Abuse Supplement of the *Kiddie-Schedule for Affective Disorders & Schizophrenia, Present & Lifetime Version* (K-SADS-PL) semi-structured diagnostic interview was used; (Kaufman et al., 1997; Ulloa et al., 2006) which is based on the criteria of the DSM-IV. The K-SADS.PL is designed to analyze episodes of psychopathology in children and adolescents (from the age of 6 to 17) both in the past and in the present. The reliability coefficients of the Spanish version of the scale go from 0.76 for major Depressive Disorder to 1 for Dissocial Disorder.

In order to evaluate personality patterns and the clinical severity of the patients the Spanish version of the Millon Adolescent Clinical Inventory (Millon, 1993) was used. The MACI is a questionnaire that is designed to analyze personality traits in adolescents (from the age of 13 to 19), which consists of 160 true-false items and is arranged into 31 scales, 27 clinical and 4 non-clinical. These are: Twelve *Personality Patterns Scales* which reveal personality styles that arise during child development and stabilize during adolescence (*Inhibited, Doleful, Submissive, Dramatizing, Egotistic, Unruly, Forceful, Conforming, Oppositional, Self-demeaning, and Borderline tendency*). Eight scales of *expressed concerns* focused on areas of adolescent development (*Identity Confusion, Self-Devaluation, Body Disapproval, Sexual Discomfort, Peer Insecurity, Social Insensitivity, Family Discord and Childhood Abuse*). Seven scales of *clinical syndromes* that involve highly prevalent disorders among adolescents: (*Eating Dysfunctions, Substance-Abuse Proneness, Delinquent Predisposition, Impulsive Propensity, Anxious Feelings, Depressive Affect, Suicidal Tendency).* One scale of validity of the protocol (*Reliability*) and three modifying indices that allow for certain response tendencies to be controlled (*Disclosure, Desirability, Debasement*); (Faúndez & Vinet, 2009). This tool was validated among the Spanish population and the reliability coefficients of the scales were between 0.65 (*Sexual Discomfort*) and 0.91 (*Self-Devaluation*). Among the personality pattern scales, the coefficients go from 0.69 (*Submissive*) to 0.90 (*Self-demeaning*); (Millon & Aguirre, 2004). In the sample for this study, the reliability coefficient for all the items was of 0.66.

In order to study the subjective effects that adolescents experience when consuming cannabis, the Spanish version of the short-form *Addiction Research Center Inventory* (ARCI)-49 (Martin, Sloan, Sapira, & Jasinski, 1971) was administered, as this is one of the most widely-used questionnaires in the field of clinical testing of substances with potential for abuse (Poudevida, Farré, Roset, & Camí, 2003). This questionnaire consists of 49 true-false questions and is made up of 5 scales that differentiate 5 subjective effects: 1) the *Morphine-Benzedrine Group* (BMG) scale, which measures the effect of *Euphoria*, 2) the *Pentobarbital-Chlorpromazine-Alcohol Group* (PCAG) scale, which measures the *Sedation* effect, 3) the *Lysergic Acid-Diethylamide* (LSD) scale, which measures *Dysphoria* and psychotomimetic changes, 4) the *Benzedrine Group*, which measures the *Stimulant-sensitive* scale and 5) the A scale, or *Amphetamine Group*, which measures *Amphetaminic* effects. This instrument was validated among the Spanish population and the reliability coefficients were of between 0.87 for the PCAG scale; 0.81 for MBG, 0.55 for LSD, 0.79 for BG and 0.49 for A (Lamas, Farré, Llorente, & Camí, 1994). In the sample group for the current study, the reliability coefficient for the 49 items was 0.78.

Procedure

The research was carried out entirely at the Hospital's Unidad de Conductas Adictivas de adolescentes (Adolescent Addictive Behaviors Unit) and was anonymized for peer revision.

Prior to the work being undertaken, approval was obtained from the hospital's Ethics Commission, taking

into account the internal ethics regulations and those of the World Medical Association and the 1975 Declaration of Helsinki with its successive amendments (CIOMS and WHO, 1993) and all participants gave their written consent after being duly informed of the project, its aims, the confidentiality agreement and personal data protection. Participation in the study was not remunerated.

All participants were assessed by the unit's clinical psychologist over two sessions of approximately 45 minutes' duration. In the first session, the psychological anamnesis was conducted and participants' socio-demographic and use data were recorded (*ad hoc* protocol). In the second session, the MACI and ARCI-49 questionnaires were administered to the participants and were later checked to make sure they had been duly completed.

Statistical Analysis

Version 18 of the *Statistical Package for the Social Sciences* (SPSS), (SPSS Inc., 1988) was used for the statistical analysis of the data gathered.

In order to analyze the prevalence of the different socio-demographic characteristics and the variables associated with use that were considered, both descriptive and frequency-distribution analyses were carried out.

Next, the MACI personality pattern scales were categorized into profiles by means of factor analysis carried out through the extraction of the principal elements and VARIMAX rotation from which the internalizing/externalizing profiles were obtained. Once these had been obtained, the sample was distributed over both profiles by means of a K-means cluster analysis and the differences between these were analyzed according to the socio-demographic variables and the variables related to consumption. In order to do this, a comparison of means was performed using Student t test for independent samples (for the quantitative variables) and the Chi-square test, calculated from 2X2 contingency tables (for the nominal variables).

The statistical significance of all the tests was considered with a probability level of 5% or lower, with the exact significance that the SPSS offered always being indicated.

Results

Descriptive analysis of the sample

Regarding the use of cannabis, the average age of onset into use was 13.01 (SD = 1.63). The average age of regular use was 13.80 (DE = 1.51). The average age at which treatment was sought was 15.67 (DE = 1.23).

Regarding the hourly use pattern, of the whole sample (n = 173), some 63.6% (n = 110) smoke before going into school, 54.3% (n = 94) smoke during recess, 64.7% (n = 112) smoke at midday after class, 69.9% (n = 121) smoke during the afternoon/evening and 31.8% (n = 55) smoke before going to bed.

Exploratory factor analysis of the MACI

An exploratory factor analysis (EFA) was carried out to determine whether the Personality Pattern scales of the MACI could be represented by means of a two-profile structure: internalizing and externalizing (Hopwood & Grilo, 2010; Newman, Larsen, Cunningham, & Barry, 2015).

The Kaiser-Meyer-Olkin measure of sampling adequacy indicated that the relationship between the MACI personality patterns is notable (KMO = .856), and the Bartlett test for homogeneity of variances showed that the factor analysis (X^2 = 1902.944, p < .001) can be applied.

The Principal Components Analysis (PCA) indicated 2 factors with their own value that was greater than 1 (5.356, 3.732). A two-factor model was extracted which explains the variance of 75.73%; 44.12% with the first component and 31.62% with the second.

The rotated components matrix (Varimax) suggested the following cluster. The internalizing profile is made up of the Introverted, *Introverted, Inhibited, Doleful, Dramatizing* (negative sign), *Egotistic* (negative sign), *Self-demeaning* and *Borderline tendency* scales. The externalizing profile is made up of the *Submissive* (negative sign), *Unruly, Forceful, Conforming* (negative sign) and *Oppositional* scales. The negative values attached to the submissive and conforming scales indicate that a low score determines that they belong to the externalizing profile (see Table 1).

Analysis of the K-means cluster

Starting from the K-means cluster analysis, we classified the two profiles obtained by means of the factor analysis (internalizing and externalizing). In cluster 1, the internalizing profile, 49.1% (n = 85) of the participants are grouped. Cluster 2, the externalizing profile, is made up of 50.1% (n = 88) of the participants. The variance analysis

Table 1. *Exploratory Factor Analysis of the MACI Personality Pattern Scales.*

Scales	Component	
	Internalizing	Externalizing
Dramatizing (4)	-.864	
Introverted (1)	.844	
Egotistic (5)	-.841	
Self-demeaning (8B)	.835	
Doleful (2B)	.832	
Inhibited (2A)	.789	
Borderline tendency (9)	.692	
Unruly (6A)		.863
Forceful (6B)		.846
Submissive (3)		-.843
Conforming (7)		-.795
Oppositional (8A)		.647

of one factor (ANOVA) indicates that all of the scales are significantly different between the clusters, except *Forceful* (p = .488) which is the scale on which both clusters are most similar.

Comparative analysis between the internalizing and externalizing profiles

For the variables referring to age of onset, age of regular use and age at which treatment was sought, there are no statistically significant differences between the internalizing and externalizing profiles (see Table 2).

Regarding gender, of the total number of internalizing participants (n = 85), 58.8% are male and 41.2% (n = 35) are female. Of all the externalizing participants (n = 88), 61.4% are male compared to 38.6% (n = 34) who are female. There are no statistically significant differences between profiles by gender.

Regarding hourly use patterns, of the externalizing participants, 64.8% (n = 57) smoke before entering class and 59.1% (n = 52) during recess as opposed to 62.4% (n = 53) and 49.4% (n = 56) of the internalizing participants, respectively. In the same way, on leaving school at midday, 65.9% (n = 56) of the internalizing participants smoke as opposed to 63.6% (n = 56) of the externalizing participants. Of all the internalizing participants (n = 85), some 72.9% (n = 62) smoke during the afternoon/evening as opposed to 67% (n = 59) of the externalizing participants.

Table 2. *Comparison between profiles by onset age for use, age of regular use and age at which treatment was sought.*

Age	**Total sample** (N = 173)	**Internalizing** (n = 85)	**Externalizing** (n = 88)					
	Mean	SD	Mean	SD	Mean	SD	t	p
Onset age for use	13.01	1.63	13.02	1.57	13	1.69	-.533	s.i.
Age of regular use	13.80	1.51	13.74	1.48	13.86	1.53	.095	s.i.
Age at which treatment was sought	15.67	1.23	15.76	1.21	15.58	1.24	.986	s.i.

Note. s.i.: statistically insignificant differences according to the t Student test (p › .05).

Table 3. *Comparison between profiles by hourly use patterns.*

Hourly pattern	**Total sample** (N = 173)	**Internalizing** (n = 85)	**Externalizing** (n = 88)					
	n	%	n	%	n	%	Chi Squared	p
Before entering class								
Yes	110	63.6	53	62.4	57	64.8		
No	63	36.4	32	37.6	31	35.2	.109	s.i.
During recess								
Yes	94	50.3	42	49.4	50	59.1		
No	79	45.7	43	50.6	36	40.9	1.633	s.i.
At midday								
Yes	112	64.7	56	65.9	56	63.6		
No	61	35.3	29	34.1	32	36.4	.096	s.i.
In the afternoon/ evening								
Yes	121	69.9	62	72.9	59	67		
No	52	30.1	23	27.1	29	33	.715	s.i.
Before going to sleep								
Yes	55	31.8	34	40	21	23.9		
No	118	68.2	51	60	67	76.1	5.192	.023

Note. s.i.: statistically insignificant differences according to the Chi Squared test (p › .05).

Table 4. *Comparison between profiles by the MACI expressed concerns and clinical syndromes scales.*

MACI	Total sample (*N* = 173)	Internalizing (*n* = 85)		Externalizing (*n* = 88)				
	Mean	SD	Mean	SD	Mean	SD	t	p
Identity Confusion	54.49	22.69	64.35	20.43	44.97	20.70	6.197	‹.001
Self-Devaluation	48.33	20.54	62.45	16.26	34.69	14.01	12.038	‹.001
Body Disapproval	47.80	22.13	58.78	23.45	37.19	14.37	7.330	‹.001
Sexual Discomfort	35.18	23.95	34.45	25.18	35.89	22.83	-.3 94	s.i.
Peer Insecurity	38.39	21.54	47.95	22.22	29.15	16.27	6.365	‹.001
Social Insensitivity	79.11	25.82	68.21	26.31	89.64	20.54	-5.981	‹.001
Family Discord	69.25	20.04	70.04	20.61	68.50	19.57	.502	s.i.
Childhood Abuse	57.21	21.07	67.68	19.41	47.10	17.43	7.342	‹.001
Eating Dysfunctions	48.95	20.36	58.25	19.72	39.98	16.68	6.586	‹.001
Substance-Abuse Proneness	86.69	17.66	90.12	16.85	83.39	17.88	2.545	.012
Delinquent Predisposition	83.87	22.96	76.49	23.51	90.99	20.09	-4.363	‹.001
Impulsive Propensity	76.94	25.33	76.60	24.17	77.26	26.52	-.171	s.i.
Anxious Feelings	21.43	16.81	22.95	18.84	19.95	14.54	1.174	s.i.
Depressive Affect	42.05	21.47	56.46	16.87	28.14	15.44	11.523	‹.001
Suicidal Tendency	52.23	18	62.36	14.88	42.43	15.14	8.729	‹.001

Note. s.i.: statistically insignificant differences according to the t Student test (p › .05).

However, there are statistically no significant differences between the profiles for any of these four variables. Against that, 40% (n = 34) of the internalizing participants smoke before going to sleep as opposed to 23.9% (n = 21) of the externalizing participants, this difference being statistically significant (p = .023) (see Table 3).

Expressed Concerns (MACI)

For the *Expressed Concerns* category on the MACI, there are statistically significant differences between the profiles with the internalizing participants scoring significantly higher than the externalizing ones on the scales of: *Identity Confusion* ($t_{(171)}$ = 6.197, p < .001, *IC 95%* 13.21 – 25.56, d = 1), *Self-devaluation* ($t_{(171)}$ = 12.038, p < .001, *IC 95%* 23.20 – 32.30, d = 1.8), *Body Disapproval* ($t_{(171)}$ = 7.330, p < .001, *IC 95%* 15.77 – 27.39, d = 1.1), *Peer Insecurity* ($t_{(171)}$ = 6.365, p < .001, *IC 95%* 12.97 – 24.63, d = 0.9) and *Childhood Abuse* ($t_{(171)}$ = 7.342, p < .001, *IC 95%* 15.04 – 26.11, d = 1.1).

In the same way, there are statistically significant differences between the profiles with the externalizing participants scoring significantly higher than the internalizing ones on the scale of: *Social Insensitivity* ($t_{(171)}$ = -5.981, p < .001, *IC 95%* -28.49 – -14.35, d = 0.9).

On the *Sexual Discomfort* and *Family Discord* scales there are no statistically significant differences observed between the internalizing and externalizing profiles (see Table 4).

Clinical Syndromes (MACI)

For the *Clinical Syndromes* category on the MACI statistically significant differences may be observed in favour of the internalizing participants who score significantly higher than the externalizing ones on the scales of: *Eating Dysfunctions* ($t_{(171)}$ = 6.586, p < .001, *IC 95%* 12.79 – 23.74, d = 1.08), *Substance-abuse Proneness* ($t_{(171)}$ = 2.545, p = 0.012, *IC 95%* 1.51 – 11.95, d = 0.4), *Depressive Affect* ($t_{(171)}$ = 11.523, p < .001, *IC 95%* 23.471 – 33.174, d = 1.8) and *Suicidal Tendency* ($t_{(171)}$ = 8.729, p < .001, *IC 95%* 15.42 – 24.44, d = 1.3).

At the same time, there are statistically significant differences between the profiles in which the externalizing participants score significantly higher than the internalizing ones on the scale of: *Delinquent Predisposition* ($t_{(171)}$ = -4.363, p < .001, *IC 95%* -21.05 – -7.93, d = 0.65).

On the scales of *Impulsive Propensity* and *Anxious Feelings* no statistically significant differences are observed between the internalizing and externalizing profiles (see Table 4).

Subjective Effects (ARCI)

Regarding the subjective effects of use as measured on the ARCI, significant differences are found between the profiles with the internalizing participants scoring significantly higher than the externalizing ones on the scales that measure the effects of: *Sedation* (PCAG) ($t_{(169)}$ = 3.103, p =

Table 5. *Comparison between profiles by the ARCI Subjective Effects scales.*

ARCI	Total sample (*N* = 173)	Internalizing (*n* = 85)		Externalizing (*n* = 88)				
	Mean	SD	Mean	SD	Mean	SD	t	p
Sedation	3.54	3.37	4.34	3.66	2.78	2.89	3.103	.002
Euphoria	7	3.17	7.34	3.24	6.65	3.08	1.405	s.i.
Dysphoria/ Disagreeable physical effects	0.89	2.50	1.31	2.57	0.49	2.38	2.155	.033
Stimulant-sensitive	1.47	2.87	1.49	3.35	1.44	2.30	0.107	s.i.
Amphetaminic effects	4.45	1.95	4.63	2.01	4.27	1.89	1.204	s.i.

Note. s.i.: statistically insignificant differences according to the t Student test (p › .05).

.002, *IC 95%* 0.56 – 2.55, d = 0.78) and *Dysphoria* (LSD) ($t_{(167)}$ = 2.155, p = .033, *IC 95%* 0.06 – 1.57, d = 0.5).

On the scales that measure the effects of *Euphoria* (BMG), *Stimulant-sensitive* (BG) and those of the *Amphetaminic* type (A) no statistically significant differences are observed between the internalizing and externalizing profiles (see Table 5).

Discussion

This study was carried out to discriminate between personality traits of a sample of adolescent cannabis users, by means of the categorization of the participants into internalizing and externalizing profiles in order to, later, make a comparison of both profile groups in terms of certain variables relating to consumption, clinical severity and subjective effects of the same.

The results of the research support the existence of significant differences in the personality traits of adolescent cannabis users. Two personality profiles, internalizing and externalizing, have been obtained on which the dimensional construct of personality in adolescent cannabis users is based (Hopwood & Grilo, 2010). It is worth noting that the distribution of the sample over the profiles was balanced, since the number of participants that each profile included was similar and, therefore, the results appear to indicate that, in a clinical sample of adolescent cannabis users neither profile predominates over the other.

The results obtained show that the adolescents with an internalizing profile are characterized by scoring higher on the *Introverted*, *Inhibited*, *Doleful*, *Self-demeaning* and *Borderline tendency* scales, and by very low scores on the *Dramatizing* and *Egotistical* scales. The adolescents with an externalizing profile, for their part, reach higher scores on the *Unruly*, *Forceful* and *Oppositional* scales, and very low scores on the *Conforming* and *Submissive* ones (Hopwood & Grilo, 2010). No statistically significant differences were observed between the personality profiles in terms of gender. This fact was also observed in Hopwood and Grilo's paper and may be explained by the fact that both studies were carried out with clinical samples, where comorbidity with externalising disorders is much higher than in the general population (Chi, Sterling, & Weisner, 2006; Hopwood & Grilo, 2010).

Focusing on age, it is notable that in the sample studied, the average onset age of use is 1.8 years before the average onset age in the general population (Spanish Observatory on Drugs, 2014). The same occurs with the age at which a regular pattern of use is established, also one year before that of the reference population (Spanish Observatory on Drugs, 2014). This fact is explained once more by the clinical characteristics of the sample group, since they are adolescent users whose use is frequent and problematic, and requires treatment (Creemers et al., 2009). These results ratify, as has been widely described in the literature, that an early onset age predicts later problematic use (Martínez-Lorca & Alonso-Sanz, 2003).

Between the personality profiles no differences are observed for the onset age, the age at which use becomes regular and the age at which treatment is sought. The homogeneity of these results could once again be explained by the clinical characteristics of the sample group since the participants were recruited at a specific unit and share aspects such as the chronology of use and the severity of the addictive pathology.

If we focus on the hourly use patterns, the frequency with which both profile groups consume during school hours stands out. At the same time, 69.4% of the sample group have been held back a year at school and 29.5% have dropped out altogether. The use of cannabis, therefore, seems to be significantly related to problems with academic performance as has been observed in other studies (Hall & Degenhardt, 2009; Volkow et al., 2014). On the other hand, the internalizing profile reports higher frequency of use before going to sleep, a facet that has been

described in other studies as one of the main effects sought when consuming (Schofield et al., 2006).

The clinical severity of both profile groups was evaluated by means of the Expressed Concerns and Clinical Syndromes scales on the MACI. In the sample group studied, the adolescents with an internalizing profile obtained higher scores on most of the scales when compared with the externalizing profile. Looking at the internalizing profile, the observed data point in the same direction as previous studies (Casullo & Castro, 2002; Fantin, 2006; Szerman et al., 2014). Specifically, the *Depressive Affect* and *Suicidal Tendency* have been described as traits that are highly prevalent among substance users (Chabrol et al., 2014). Contrasting with this, the *Social Insensitivity* and *Delinquent Predisposition* scales are highlighted in the externalizing profile, and have been observed in studies in which samples of adolescent users have been compared with samples of adolescent non-users (Fantin, 2006; Faúndez & Vinet, 2009). On the other hand, both profiles score high in *Family Discord*. As has been indicated in the literature, the presence of problems within the family is associated with substance use (Brière et al., 2011). The highest scores obtained, regardless of the profile group to which the adolescents belong, are: *Social Insensitivity*, *Substance-abuse Proneness*, *Delinquent Predisposition*, and *Impulsive Propensity*. As has been described in the literature, the most dissocial and impulsive traits are most prevalent among the adolescent consuming population (Becoña et al., 2011; Fantin, 2006; Faúndez & Vinet, 2009).

Regarding the subjective effects, both profiles show a greater Euphoria effect, an effect that is widely described in the literature and is most associated with the reasons for consumption, problematic use, abuse and dependence (Block et al., 1998; Scherrer et al., 2009; Zeiger et al., 2010). On the other hand, the internalizing group show higher scores for the *Sedation* and *Dysphoria* effects. This may be defined, as Scherrer et al., 2009, described it, as a "high response", as both positive and negative effects are experienced. The "high response" has been associated with a greater tendency to use and with the development of dependency (Scherrer et al., 2009). We believe, therefore, that in view of the scarcity of literature that links personality and subjective effects it is necessary to carry out further studies in which this association is considered.

Among the limitations of the present study we find, firstly, the small size of the sample group, which limits the statistical potential of the results. Secondly, the sample group is clinical and the results obtained cannot therefore be extrapolated to the general population. Therefore, any generalization of the results to population samples of adolescent users with cannabis use patterns that are less problematic should be approached with caution. Thirdly, the instruments used for the evaluation, the MACI and ARCI-49 questionnaires, are self-administered and the results could be skewed by a tendency of the adolescents to minimise or maximise symptomology. Lastly, the scarcity and the heterogeneity of the studies of personality and of the subjective effects of consumption, specifically among the adolescent population of cannabis users, make any comparison of the results obtained difficult. This is, nevertheless, one of the main contributions that this study makes to the existing literature, more so if we consider that the results obtained are consistent with empirical research and the background theoretical antecedents.

In this study it has been observed that the categorization by means of the personality traits of two profiles -internalizing and externalizing- allows us to characterize a clinic sample of adolescent cannabis users. The expression of the clinical severity and of the subjective effects is different according to the personality traits. Thus, the internalizing profile shows greater clinical complexity: higher use at night time, more prevalence of expressed concerns and of clinical syndromes and a greater experience of subjective effects. Knowing the internalizing/externalizing personality profile is useful when it comes to proposing interventions aimed at this type of population. Discriminating between the subjective effects of cannabis allows us to know the functions of use and to propose an approach that is aimed at the factors that maintain it.

For the future, and basing what we say on the results obtained, we propose that it is necessary for new lines of research to be opened that are related to our study and that will respond to the existing scarcity and widen the debate around personality and the subjective effects in adolescents who consume substances. If that were to be the case, we could point to the interest in increasing the size of the sample group in order to be able to contrast the results obtained and enhance the statistical potential of the same. It would, also, be desirable to protocolize the evaluation of personality, as a part of the initial assessment, in order to be able to draw up interventions that are more effective and more suited to the characteristics of these patients.

Conflict of interests

The researchers declare no conflict of interests.

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Orally ingestion of krokodil in Spain: report of a case

Consumo de krokodil por vía oral en España: a propósito de un caso

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Abstract

The krokodil use disorder is an addictive pathology with quite severe organic effects, especially at the skin level, that causes severe and degenerative necrosis of blood and muscle tissue. Though this disorder has a low prevalence in Spain, compared to the large number of consumers in other countries such as Ukraine or Russia, its consumption is slowly but gradually expanding in countries of the European Union and America. The simplicity of the process of obtaining the substance from desomorphine, together with its high availability and low cost, contribute toward consumers' self-sufficiency. This article presents the case of a user of krokodil and reviews the clinical symptoms of oral ingestion.

Keywords: Krokodil; Substance use; Oral ingestion; Desomorphine.

Resumen

El trastorno por uso de krokodil es una de las patologías adictivas con mayores repercusiones orgánicas, principalmente a nivel cutáneo, produciendo una grave y degenerativa necrosis del tejido sanguíneo y muscular. Se trata de un trastorno con escasa prevalencia en España, frente al elevado número de consumidores en otros países como Ucrania o Rusia, si bien se está produciendo una lenta aunque gradual expansión del consumo en países de la Unión Europea y del continente americano. El sencillo proceso de obtención de la sustancia desde la desomorfina, unido a la elevada disponibilidad y bajo coste, configura el proceso de autoabastecimiento de los consumidores. En este artículo revisamos un cuadro clínico, presentando el caso de un paciente que consume krokodil por vía oral.

Palabras clave: Krokodil; Uso de sustancias; Vía oral; Desomorfina.

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Desomorphine or krokodil is one of the most-frequently consumed substances in some countries of northern Europe and the former Soviet Union, and is quickly expanding through the United States and South America. At the same time, given its high addictiveness, low cost and ready availability, as well as the incidence of serious organic pathologies associated with its use, its social and health-related repercussions for the user demand attention (Heimer, 2013). Despite the start of its consumption in Russia, Ukraine and Georgia at the end of the last century, clinical interest in the use of krokodil is currently under focus due to its potential organic deterioration and addictiveness for the user. Determinant factors also exist behind the great social alarm and media coverage given to the process of krokodil use as a whole. One of these aspects is the easy access to the substance, starting with the rudimentary, home-based synthesis of krokodil; another determinant is the dissemination of the users' serious clinical symptoms exhibited by media sources and the Internet (Gahr et al., 2012). Over the last five years, a growing number of reports on the prevalence of substance use claim a notable reduction of inhaled opium and parenteral consumption of heroin in Russia, Ukraine, Kazakhstan and Georgia, while at the same time reporting a notable increase of the use of drugs containing codeine (*Solpadeine, Codterpin* or *Codelac*) used for producing desomorphine (Savchuk, Barsegyan, Barsegyan & Kolesov, 2008). The ongoing economic crisis of these countries, together with the relative availability of legal precursors at pharmacies, promotes, to date, a culture of homemade substances, like alcohol, krokodil or -as an example of the abovementioned- the use of *Pervitin* (methamphetamine) in Prague since the early 1980s (Zabransky et al., 2012).

This self-supply model differs from that of other countries, where drug trafficking dominates drug production and distribution. Apparently economic factors are the determinants of krokodil use (Grund, 2002), as there is already proof of the home-based manufacturing of desomorphine in areas with high unemployment rates and economic problems, as is the case in some states of the United States, Mexico and Holland (Kwint, Kruizinga, Kaal & Bootsma, 2013).

The molecule dihydrodesoxymorphine: C17H21NO2, desomorphine, or the brand name *Permonid*, is similar to the opioid synthesized in 1932 in the United States by the chemist Lyndon Frederic Pequeño. Desomorphine is a derivative of morphine with the elimination of the 6-hydroxyl group and the reduction of the 7,8 double bond. Traditional synthesis of desomorphine is based on α-chlorocodide, in turn obtained by provoking a reaction of thionyl chloride with codeine. Through catalytic reduction, the α-chlorocodide produces dihydrodesoxycodeine, which through demethylation leads to the formation of desomorphine (Eddy, Halbach & Braenden, 1957) (Figure 1). Given its structural similarity to morphine, it is suggested that desomorphine is a potent *mu* opioid agonist with higher toxicity and analgesic power of between 5-10 greater than morphine. The effect of desomorphine is produced approximately two minutes after consumption, and lasts, on the average, between 60 and 90 minutes (Eddy & Howes, 1935).

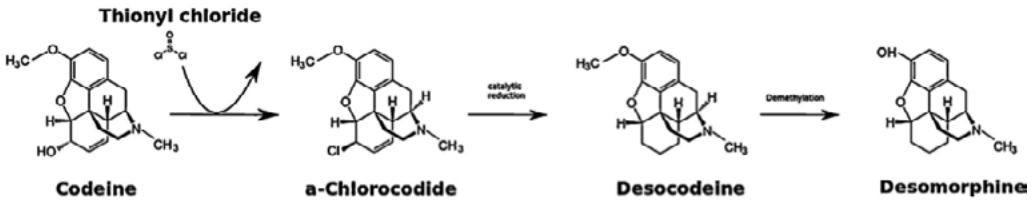
Figure 1.

The leading and diverse medical purposes for which desomorphine or *Permonid*® was sold as hydrobromic acid salt included analgesic, antitussive and even sedative uses. However, its side effects (hypotension, urinary retention, vomiting and drowsiness) together with a fast development of addiction in humans, resulted in its withdrawal from the market (Matiuk, 2014).

The neologism krokodil arises from its pronunciation similar to chlorocodide, as well as for the lesions users suffer at the epithelial level, which with a greenish hue and scaly appearance remind us of the skin of a crocodile. Elaborating the substance is simple and inexpensive. In most cases, patients manufacture krokodil in their own home by combining hydrochloric acid, iodine and red phosphorus with codeine, though different preparations, like organic solvents or tropicamide, cheapen the process. This procedure is similar to the synthesis of methamphetamine from pseudoephedrine (Abdala, Grund, Tolstov, Kozlov & Heimer, 2006).

The main ingestion routes of krokodil are oral and parenteral, the latter entailing serious consequences for the organism, including HCV and HIV infections and even provoking endocarditis. Injuries associated with the injection of krokodil are considered serious and are unprecedented within physical consequences of drug use. The main focus of clinical concern, and the greatest complication resulting

Figure 1. Synthesis of desomorphine using codeine



of the use of krokodil, are its effects on blood tissue: abscesses, phlebitis, thrombophlebitis, hemorrhages and ulcers that appear close to the injection site, as well as damage to muscles, soft tissues and bones, with fast necrosis and gangrene. In most cases, interventions for these conditions require extremely complicated surgeries with serious aftermaths, such as surgically removing the main veins from arms or legs, sometimes requiring amputation or skin grafts (Demidova & Mokhachev, 2011). The toxic effects of krokodil are not only limited to muscular vascular lesions; the substance's toxic components, like iodine, damage the thyroid and muscles, and phosphorus seriously deteriorates cartilage (Harris, 2013). In turn, these toxic compounds damage the neurological and endocrine systems, as well as the organs that intervene in the metabolism of chemical products and heavy metals used in the substance's synthesis. The initial symptoms appear just a few days after the first intravenous krokodil injection and include organic symptoms, the most common of which are: pneumonia, meningitis, periodontitis and osteomyelitis. This process and the organic symptoms together result in users' gradual physical deterioration with very high mortality rates, though not all users experiment the extreme harm associated with krokodil (Grund, Latypov & Harris, 2013).

The psychological consequences of use are usually not as defined. Together with the evident and progressive process of substance dependency there also coexists notable neurological damage, speech impediments, loss of motor skills, altered memory, mood disorders and even psychotic episodes (Matiuk, 2014).

Clinical case presentation

Our case is a 34-year-old male user of the services provided by CIBE in Castellón de la Plana, with prenatal and perinatal developmental stages unmarked by any events worth highlighting. As to medical evaluations, no data of interest are detected, with a medical examination and blood test completed in September 2014, with no relevant alterations in blood range parameters. He has a secondary level education level, is currently unemployed, and his stable partner inhales cocaine regularly. As an adult, he was imprisoned for 5 months. The most noteworthy fact of his family background is his father's alcohol use disorder.

His first experimental use of cannabis and alcohol began during adolescence, snorting cocaine at age 19, followed by habitually smoking cocaine and heroin as of the age of 20, while occasionally abusing of benzodiazepines ingested orally. The patient underwent different detoxification treatments at the Hospital Detoxification Unit and addiction treatment programs at the In-patient Drug Addiction Unit, was discharged and now alternates periods of abstinence and active use. Currently, the patient undergoes no type of treatment and has a disorder from using benzodiazepines, cocaine and smoking heroin.

As to the reason for his visit, the patient mentions having acquired and consumed krokodil orally, combined with a caffeinated beverage as a recreational experiment. He mentions the substance's distinct bitter taste, even when dissolved in the mix, and mentions detecting its effects 20 minutes after ingesting it. The patient describes the effects as itchiness across the entire body, increased temperature of the stomach that rises up toward the head, sweating, altered breathing and an evident slowing down, headache and a noticeable sensation of relaxation and sedation of the rest of the body. The patient describes this like "the effect of heroin but much more physical, stronger" and despite his previous experience with opioid use, describes these symptoms as more greatly affecting the organs while disassociated from the intoxication or abstinence syndrome inherent to heroin. Interference on behavior of these is minimal, as the patient can continue with his normal functions. At the same time, he does not report any serious alterations to his judgment, will or consciousness, though he does mention symptoms of moderate anxiety and slight depersonalization.

Two hours after the ingestion, the patient experiences vomiting and stomach ache and progresses from feeling slightly feverish to having fever, congruent with a possible indigestion or gastroenteritis. The patient does not associate this with the use of krokodil and evolves favorably, under the care of the primary care system during three days.

Discussion

This case entails the oral ingestion of krokodil, wherefore we detect the first case of krokodil use in Spain. Seemingly, the expansion to Europe of krokodil use is associated with the economic crisis, as this is possibly the cause behind the appearance of the first use in Spain, where an increased use of amphetamine derivatives, such as α-Hydroxybutyric acid (GHB) or ketamine (Nogué, Amigó & Galicia, 2014), has also been detected.

In this case, the oral ingestion of the substance is worth highlighting, as opposed to the higher prevalence of the parenteral route, given the scarce evidence of alternate forms of use (Merkinaite, Grund & Flimpond, 2010). In an initial phase, the physical symptoms and mental effects as perceived by the patient are verified, while confirming the use of opioids with a urine drug test. It would be convenient to perform more specific toxicological analyses for purpose of detecting new, emerging drugs or substances that fall beyond the scope of classical analysis types. The detected symptoms are inherent to the effects of opioid use, yet simultaneously display other, less-specific symptoms. These clinical symptoms detected in the patient after consumption could comprise a lighter version of the symptoms of intoxi-

cation by opioids with effects on the central nervous system and digestive system.

Krokodil consumption presents serious physical symptoms associated with the ingestion route, mainly as regards parenteral ingestion, such abscesses, phlebitis, thrombophlebitis, hemorrhages and ulcers (Rhodes, 2009). However, the patient does not show signs of intravenous krokodil injection but rather, the possible consequences of consumption associated with oral ingestion. The patient was monitored since 2008 by the CIBE assistance unit, without having been detected any type of psychopathological alteration in previous periods of intervention, assessment and follow-up. Nevertheless, psychopathological repercussions of occasional krokodil use are not significant.

The expansion and use of krokodil is a reality in Europe, and given this case, we can confirm the start of its use in Spain. For this reason, healthcare professionals, at both levels of primary care and emergency rooms, as well as mental health and addiction-related services, must be watchful to detect intoxications, abstinence syndromes or physical and/or psychopathological effects of its use.

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

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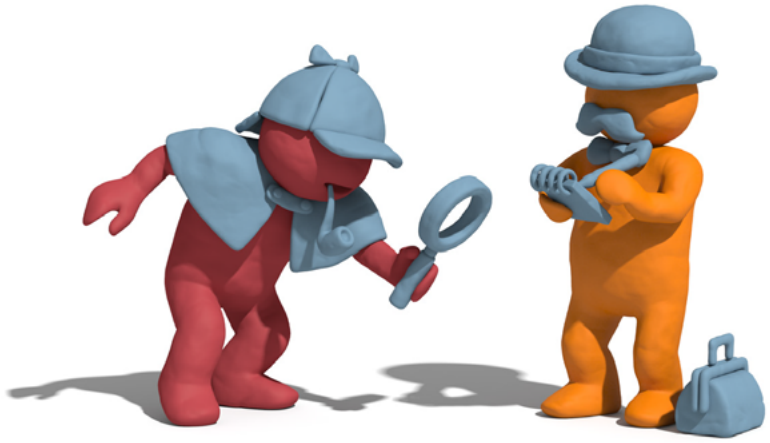

EFICACIA PARA SENTIRSE BIEN

FARMACOCINÉTICA[1, 2]

EFICACIA[1]

SIN SUPLEMENTACIÓN ORAL[3]

MONOTERAPIA[1, 4, 5]

TOLERABILIDAD CONTRASTADA[3, 7 *]

METABOLISMO HEPÁTICO LIMITADO[3]

CLARIDAD DE PENSAMIENTO[8]

FLEXIBILIDAD DE PAUTA POSOLÓGICA[3]

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

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1. NOMBRE DEL MEDICAMENTO. Xeplion 25 mg suspensión inyectable de liberación prolongada. Xeplion 50 mg suspensión inyectable de liberación prolongada. Xeplion 75 mg suspensión inyectable de liberación prolongada. Xeplion 100 mg suspensión inyectable de liberación prolongada. Xeplion 150 mg suspensión inyectable de liberación prolongada. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** Xeplion 25 mg suspensión inyectable. Cada jeringa precargada contiene 39 mg de palmitato de paliperidona equivalentes a 25 mg de paliperidona. Xeplion 50 mg suspensión inyectable. Cada jeringa precargada contiene 78 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. Xeplion 75 mg suspensión inyectable. Cada jeringa precargada contiene 117 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. Xeplion 100 mg suspensión inyectable. Cada jeringa precargada contiene 156 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. Xeplion 150 mg suspensión inyectable. 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 FARMACEUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). **4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas.** 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 tercera dosis se debe administrar un mes después de la segunda dosis de inicio. La dosis de mantenimiento mensual recomendada es de 75 mg; algunos pacientes pueden beneficiarse de dosis inferiores o superiores dentro del rango recomendado de 25 a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. Los pacientes con sobrepeso u obesos pueden requerir dosis situadas en la parte superior del intervalo (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. El ajuste de la dosis de mantenimiento se puede hacer mensualmente. Al realizar ajustes de la dosis, se deben tener en cuenta las características de liberación prolongada de Xeplion (ver sección 5.2), dado que el pleno efecto de las dosis de mantenimiento puede no resultar evidente durante varios meses. *Cambio desde 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. Algunos pacientes se pueden beneficiar de una retirada gradual. Xeplion debe iniciarse según se describe al principio de la sección 4.2 anterior. *Cambio desde Risperidona inyectable de acción prolongada.* Al realizar el cambio de tratamiento de los pacientes desde risperidona inyectable de acción prolongada, inicie el tratamiento con Xeplion en lugar de la siguiente inyección programada. A partir de entonces, Xeplion se debe continuar en intervalos mensuales. No es necesario seguir el régimen de dosificación inicial de una semana incluyendo las inyecciones intramusculares (día 1 y 8, respectivamente) según se describe en la sección 4.2 anterior. Los pacientes previamente estabilizados con diferentes dosis de risperidona inyectable de acción prolongada pueden alcanzar una exposición similar a paliperidona en estado estacionario durante el tratamiento de mantenimiento con dosis mensuales de Xeplion según se describe a continuación:

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

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

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

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	No conocidas
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, cistitis, infección de oídos, infección de ojos, amigdalitis, celulitis, acarodermatitis, absceso subcutáneo	onicomicosis	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, anemia, disminución del hematocrito, aumento del recuento de eosinófilos	agranulocitosis[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], cetoacidosis 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 consciencia, disminución del nivel de consciencia, 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, acufenos, dolor de oído		
Trastornos cardiacos		bradicardia, taquicardia	fibrilación auricular, bloqueo auriculoventricular, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, anomalías del electrocardiograma, palpitaciones	arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	embolismo pulmonar[a], trombosis venosa, isquemia[a], rubor	
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión pulmonar, sibilancias, dolor faringolaríngeo, epistaxis	síndrome de apnea del sueño[a], hiperventilación[a], neumonía por aspiración[a], congestión del tracto respiratorio disfonía[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, fecaloma, disfagia, queilitis[a]	

Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas	ictericia[a]	
Trastornos de la piel y del tejido subcutáneo		erupción cutánea	urticaria, prurito, alopecia, eccema, 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	rabdomiolisis[a], aumento de la creatina fosfoquinasa en sangre, anomalía postural[a], inflamación de las articulaciones, debilidad muscular	
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales				síndrome de abstinencia neonatal (ver sección 4.6)[a]	
Trastornos del aparato reproductor 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, malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción mamaria	
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[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		

[a]Referido a "Hiperprolactinemia" a continuación. [b]Referido a "Síntomas extrapiramidales" a continuación. [c]En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con Xeplion comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,47% en todos los pacientes tratados con Xeplion. [d]**Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóveo. **Trastornos menstruales incluyen:** menstruación irregular, oligomenorrea. [e]Observado 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 raros ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de Xeplion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección.* La reacción adversa relacionada con el lugar de la inyección notificada con mayor frecuencia fue el dolor. La mayoría de estas reacciones se notificaron con gravedad de leve a moderada. Las evaluaciones del dolor en el sitio de la inyección en los sujetos, basada en una escala analógica visual, indican que el dolor tiende a disminuir en frecuencia e intensidad con el tiempo en todos los estudios de fase 2 y 3. Las inyecciones en el músculo deltoides se perciben como un poco más dolorosas que las correspondientes inyecciones en el glúteo. Otras reacciones en el lugar de la inyección fueron en su mayoría de intensidad leve e indujeron 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, hiperinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreatetosis, atetosis y miodonía), distonía (incluye distonía, hipertonía, torticolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo orofaríngeo, pleurotótonos, espasmo lingual y trismo) y temblor. Hay que destacar que se incluye un espectro más amplio de síntomas que no tienen forzosamente su origen en el trastorno extrapiramidal. *Aumento de peso.* En el estudio de 13 semanas de duración que incluyó un régimen de dosificación inicial de 150 mg, la proporción de sujetos con un aumento anormal de peso ≥7% mostró una tendencia relacionada con la dosis, con una tasa de incidencia del 5% en el grupo placebo, en comparación con tasas del 6%, 8%, y 13% en los grupos tratados con 25 mg, 100 mg y 150 mg de Xeplion, respectivamente. Durante el período abierto de transición/mantenimiento de 33 semanas de duración del ensayo de prevención de recidivas a largo plazo, el 12% de los pacientes tratados con Xeplion cumplieron este criterio (aumento de peso de ≥7% desde la fase doble ciego hasta el final del estudio); la media (DE) del cambio de peso desde el nivel basal del periodo abierto fue de +0,7 (4,79) kg. *Hiperprolactinemia.* En ensayos clínicos, se observaron medianas de aumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un aumento de los niveles de prolactina (p. ej., amenorrea, galactorrea, alteraciones de la menstruación, ginecomastia) se notificaron en <1% de los sujetos. Efectos de clase. Con antipsicóticos puede aparecer prolongación del QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicable, parada cardiaca y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, incluidos casos de embolismo pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del intervalo QT y síntomas extrapiramidales. Se han notificado Torsades de pointes y fibrilación ventricular en un paciente en relación con la sobredosis de paliperidona oral. En caso de sobredosis aguda, se debe tener en cuenta la posibilidad de que estén implicados varios medicamentos. Administración: Al evaluar el tratamiento necesario y la recuperación hay que tener en cuenta la naturaleza de liberación prolongada del medicamento y la prolongada vida media de eliminación de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio deben tratarse con las medidas terapéuticas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales intensos, se administrará medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros antipsicóticos. Código ATC: N05AX13. Xeplion contiene una mezcla racémica de paliperidona (+) y (-). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D2. Paliperidona también bloquea los receptores adrenérgicos alfa1 y bloquea, en menor medida, los receptores histaminérgicos H1 y los adrenérgicos alfa2. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D2 potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos catalepsia y reduce las funciones motrices en menor medida que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. *Tratamiento agudo de la esquizofrenia.* La eficacia de Xeplion en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Las dosis fijas de Xeplion en estos estudios se administraron en los días 1, 8, y 36 en el estudio de 9 semanas de duración, y, además, el día 64 en los estudios de 13 semanas de duración. No fue necesario administrar suplementos antipsicóticos orales adicionales durante el tratamiento agudo de la esquizofrenia con Xeplion. El criterio principal de eficacia del estudio se definió como una reducción de las puntuaciones totales de la Escala de los Síndromes Positivo y Negativo (PANSS), como se muestra en la siguiente tabla. La PANSS es un inventario multi-elemento validado compuesto por cinco factores destinados a evaluar los síntomas positivos, los síntomas negativos, el pensamiento desorganizado, la hostilidad/excitación incontrolada y la ansiedad/depresión. La función se evaluó mediante la escala de Funcionamiento Personal y Social (PSP). La PSP es una escala homologada que mide la capacidad del paciente para desempeñar sus actividades personales y sociales en cuatro áreas del comportamiento: las actividades socialmente útiles (incluidos el trabajo y el estudio), las relaciones personales y sociales, el cuidado personal y los comportamientos disruptivos y agresivos. En un estudio de 13 semanas de duración (n=636) que comparó tres dosis fijas de Xeplion (inyección inicial en el deltoides de 150 mg seguida por tres dosis en el glúteo o en el deltoides de cualquiera de 25 mg/4 semanas, 100 mg/4 semanas o 150 mg/4 semanas) con placebo, las tres dosis de Xeplion fueron superiores a placebo en términos de la mejoría de la puntuación total de la PANSS. En este estudio, tanto los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntuación de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de Xeplion en el día 8. Los resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de Xeplion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

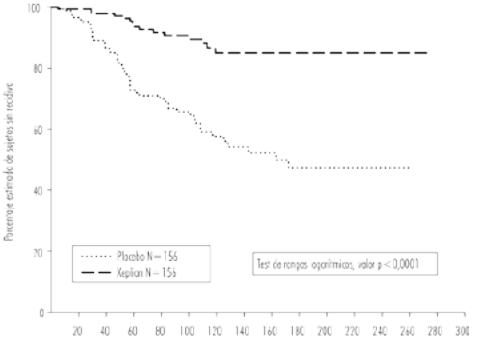
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (días 8 y 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a las de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (ClCr=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (ClCr=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (ClCr =10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{∞}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. No se recomienda ajustar la dosis únicamente en función de la edad. Sin embargo, puede ser necesario realizar el ajuste de la dosis debido a las disminuciones en el aclaramiento de creatinina relacionadas con la edad (ver Insuficiencia renal más arriba y la sección 4.2). Peso. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de Xeplion. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. No se evaluó el tabaquismo con Xeplion. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte mesivamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas mecho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Xeplion 50 mg suspensión inyectable de liberación prolongada: PVL: 180,64 €; PVP: 226,55 €; PVP (IVA): 235,61 €. Xeplion 75 mg suspensión inyectable de liberación prolongada: PVL: 234,82 €; PVP: 285,73 €; PVP (IVA): 297,16 €. Xeplion 100 mg suspensión inyectable de liberación prolongada: PVL: 289,04 €; PVP: 339,95 €; PVP (IVA): 353,55 €. Xeplion 150 mg suspensión inyectable de liberación prolongada: PVL: 433,56 €; PVP: 484,47 €; PVP (IVA): 503,85 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** Xeplion 25 mg: EU/1/11/672/001. 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.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 05/2016. 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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Autoría. Es muy importante que únicamente se consideren autores aquellos que han hecho sustanciales contribuciones: 1) a la concepción y diseño, adquisición de datos, o el análisis e interpretación de datos; 2) a la redacción del artículo o a su revisión crítica; y 3) que ha dado su aprobación de la versión que se publicará. Los autores deben asegurarse de que partes significativas del material aportado no ha sido publicado con anterioridad. En caso de que puedan tener dudas sobre el cumplimiento de esta norma, deberán presentar copias de lo publicado o de lo presentado para publicación a otras revistas antes de poder ser considerado el artículo para su revisión. En caso de dudas sobre alguno de los aspectos anteriores los autores deben consultar el acuerdo de Farmington al que está adherida la revista Adicciones (Anexo 1), las normas de "Sponshorship, authorship, and accountability" del International Committee of Medical Journal Editors (www.icmje.org/sponsor.htm) o las normas de publicación de la American Psychological Association, 6ª edición (2010) (www.apastyle.org). El editor de la revista puede dirigirse a los autores del artículo para que especifiquen cual ha sido la contribución de cada uno de ellos.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

Copyright y permisos. Los derechos de copyright de todos los artículos publicados en la revista Adicciones pasan a ser propiedad de la revista. La cesión de derechos será firmada por el autor o autores cuando envían su manuscrito para su consideración de publicación. Los autores se comprometen a acompañar el manuscrito de todos los permisos correspondientes para reproducir material previamente publicado que se va a incluir en el manuscrito, como texto, tablas, figuras, etc.

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Este medicamento está sujeto a seguimiento adicional, lo que agilizará la detección de nueva información sobre su seguridad. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas. Ver la sección 4.8, en la que se incluye información sobre cómo notificarlas. **1. NOMBRE DEL MEDICAMENTO** Selincro 18 mg comprimidos recubiertos con película. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA** Cada comprimido recubierto con película contiene 18,06 mg de nalmefeno (como dihidrato de hidrocloruro). Excipiente con efecto conocido: cada comprimido recubierto con película contiene 60,68 mg de lactosa. Para consultar la lista completa de excipientes, ver sección 5.1. **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), 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, durante este periodo de dos semanas, junto con una intervención psicosocial dirigida a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. Durante los ensayos clínicos pivotales la principal mejoría se observó durante las 4 primeras semanas. Se debe evaluar la respuesta del paciente al tratamiento y la necesidad de mantener farmacoterapia con regularidad (p. ej., mensualmente). 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. *Poblaciones especiales* Población de edad avanzada (≥ 65 años de edad) No se recomienda el ajuste de la dosis para este grupo de pacientes (ver sección 4.4). Insuficiencia renal No se recomienda el ajuste de la dosis para los pacientes con insuficiencia renal leve o moderada (ver sección 4.4). Insuficiencia hepática No se recomienda el ajuste de la dosis para los pacientes con insuficiencia hepática leve o moderada (ver sección 4.4). Población pediátrica No se ha establecido la seguridad y eficacia de Selincro en niños y adolescentes de < 18 años. No se dispone de datos. 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. **4.3 Contraindicaciones** Hipersensibilidad al principio activo o a alguno de los excipientes incluidos en la sección 5.1. 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 m^2). Pacientes con historia reciente de síndrome de abstinencia del alcohol agudo (incluyendo alucinaciones, convulsiones y delirium tremens). **4.4 Advertencias y precauciones especiales de empleo** Selincro no está indicado en pacientes cuyo objetivo terapéutico sea la abstinencia inmediata. La reducción del consumo de alcohol es un objetivo intermedio en el camino hacia la abstinencia. Administración de opiáceos En una situación de urgencia en la que se deban administrar opiáceos a un paciente que toma Selincro, la cantidad de opiáceo requerida para lograr el efecto deseado puede ser superior a la habitual. El paciente se debe someter a un estricto control para detectar síntomas de depresión respiratoria como consecuencia de la administración de opiáceos, así como otras reacciones adversas. Si se precisan opiáceos en una urgencia, la dosis siempre se debe ajustar de forma individual. Si se requieren dosis excepcionalmente altas, será necesaria una estrecha observación. El tratamiento con Selincro se debe interrumpir temporalmente 1 semana antes del uso previsto de opiáceos (p. ej., cuando se vayan a utilizar analgésicos opioides en una intervención quirúrgica programada). El médico prescriptor deberá advertir a los pacientes de la importancia de informar a su médico de la última toma de Selincro en caso de que sea necesario el uso de opiáceos. Se debe tener precaución cuando se utilicen medicamentos que contengan opiáceos (p. ej., antitusígenos, analgésicos opioides (ver sección 4.5)). Comorbilidad Trastornos psiquiátricos Se han registrado efectos psiquiátricos en estudios clínicos (ver sección 4.8). Si los pacientes presentan síntomas psiquiátricos no asociados al inicio del tratamiento con Selincro, y/o que no son transitorios, el médico prescriptor deberá considerar otras causas de los síntomas y valorar la necesidad de continuar el tratamiento con Selincro. Selincro no se ha investigado en pacientes con enfermedad psiquiátrica inestable. Se debe proceder con precaución al prescribir Selincro a pacientes con comorbilidad psiquiátrica presente como el trastorno depresivo mayor. Trastornos convulsivos Se dispone de experiencia limitada en pacientes con antecedentes de trastornos convulsivos, incluidas las convulsiones por abstinencia de alcohol. Se recomienda precaución si se inicia un tratamiento para reducir el consumo de alcohol en estos pacientes. Insuficiencia renal o hepática Selincro se metaboliza principalmente en el hígado y se elimina predominantemente por la orina. Por lo tanto, se debe tener precaución cuando se prescriba Selincro a pacientes con insuficiencia renal o hepática leve o moderada, por ejemplo, realizando controles más frecuentes. Se debe proceder con precaución al prescribir Selincro a pacientes con valores altos de ALAT o ASAT (> 3 veces el LSN), ya que estos pacientes fueron excluidos del programa de desarrollo clínico. Pacientes de edad avanzada (≥ 65 años de edad) Se dispone de datos clínicos limitados sobre el uso de Selincro en pacientes ≥ 65 años de edad con dependencia del alcohol. Sea debe tener precaución al prescribir Selincro a pacientes ≥ 65 años de edad (ver sección 4.2). Otras Se recomienda precaución si Selincro se administra conjuntamente con un inhibidor potente de la enzima UGT2B7 (ver sección 4.5). Lactosa Los pacientes con intolerancia hereditaria a galactosa, insuficiencia de lactasa de Lapp o problemas de malabsorción de glucosa o galactosa no deben tomar este medicamento. **4.5 Interacción con otros medicamentos y otras formas de interacción** No se han llevado a cabo estudios de interacción farmacológica *in vivo*. Según estudios *in vitro*, no se prevén interacciones clínicamente relevantes entre el nalmefeno, o sus metabolitos, y medicamentos administrados simultáneamente metabolizados por las enzimas más comunes CYP450 y UGT o transportadores de membrana. La administración conjunta con medicamentos que sean inhibidores potentes de la enzima UGT2B7 (p. ej., diclofenaco, fluconazol, acetato de medroxiprogesterona, ácido meclofenámico) puede aumentar significativamente la exposición a nalmefeno. Es improbable que esto suponga un problema con el uso ocasional, pero si se inicia un tratamiento a largo plazo simultáneo con un inhibidor potente de la UGT2B7, no se puede descartar la posibilidad de un aumento en la exposición a nalmefeno (ver sección 4.4). Por el contrario, la administración conjunta con un inductor de la UGT (p. ej., dexametasona, fenobarbital, rifampicina, omeprazol) puede dar lugar a concentraciones plasmáticas subterapéuticas de nalmefeno. Si se toma Selincro de manera simultánea con agonistas opioides (p. ej., algunos tipos de antitusígenos y antigripales, determinados antidiarreicos, y analgésicos opioides), puede que el paciente no se beneficie del agonista opioide. No existe ninguna interacción farmacocinética clínicamente relevante entre el nalmefeno y el alcohol. Se produce un pequeño deterioro en la función cognitiva y psicomotora tras la administración de nalmefeno. No obstante, el efecto de la combinación de nalmefeno y alcohol no superó la suma de los efectos de cada uno de ellos por separado. El consumo simultáneo de alcohol y Selincro no previene los efectos de la intoxicación del alcohol. **4.6 Fertilidad, embarazo y lactancia** Embarazo No hay datos o estos son limitados (menos de 300 resultados en embarazos) relativos al uso de nalmefeno en mujeres embarazadas. Los estudios en animales han mostrado toxicidad en la reproducción. No se recomienda Selincro durante el embarazo. Lactancia Los datos farmacodinámicos/toxicológicos disponibles en animales muestran que nalmefeno/metabolitos se excretan en la leche. Se desconoce si nalmefeno se excreta en la leche materna. No se puede excluir el riesgo en recién nacidos/lactantes. Se debe decidir si es necesario interrumpir la lactancia o interrumpir/abstenerse de iniciar el tratamiento con Selincro tras considerar el beneficio de la lactancia para el niño y el beneficio del tratamiento para la madre. Fertilidad En estudios de fertilidad en ratas, no se observaron efectos de nalmefeno sobre la fertilidad, el apareamiento, el embarazo o los parámetros espermáticos. **4.7 Efectos sobre la capacidad para conducir y utilizar máquinas** No se ha estudiado la influencia de nalmefeno sobre la capacidad para conducir y utilizar máquinas. Selincro puede provocar reacciones adversas como náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, relacionadas con el inicio del tratamiento y tuvieron una corta duración. La influencia de Selincro sobre la capacidad para conducir y utilizar máquinas es nula o insignificante. **4.8 Reacciones adversas** Resumen del perfil de seguridad Más de 3.000 pacientes han sido expuestos a nalmefeno en estudios clínicos. En general, el perfil de seguridad concuerda en todos los estudios clínicos realizados. Las frecuencias de las reacciones adversas en la Tabla 1 se calcularon basándose en tres estudios aleatorizados, a doble ciego y controlados con placebo en pacientes con dependencia del alcohol (1.144 pacientes expuestos a Selincro a demanda y 797 expuestos a placebo a demanda). Las reacciones adversas más frecuentes fueron náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración. En los estudios clínicos se comunicaron estados confusionales y, en raras ocasiones, alucinaciones y disociación. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración (de unas pocas horas a unos pocos días). La mayoría de estas reacciones adversas se resolvieron con el tratamiento continuo y no recurrieron con la administración repetida. Si bien estos acontecimientos tuvieron generalmente una corta duración, podrían tratarse de psicosis alcohólica, síndrome de abstinencia alcohólica o enfermedad psiquiátrica comórbida. Tabla de reacciones adversas Las frecuencias se definen como: muy frecuentes (≥1/10), frecuentes (≥1/100 a <1/10), poco frecuentes (≥1/1.000 a <1/100), raras (≥1/10.000 a <1/1.000), muy raras (<1/10.000) o frecuencia no conocida (no puede estimarse a partir de los datos disponibles). Notificación de sospechas de reacciones adversas Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del sistema Español de Farmacovigilancia de medicamentos de Uso Humano: https://www.notificaram.es. **4.9 Sobredosis** En un estudio en pacientes diagnosticados de ludopatía, se investigaron dosis de nalmefeno de hasta 90 mg/día durante 16 semanas. En un estudio en pacientes con cistitis intersticial, 20 pacientes recibieron 108 mg/día de nalmefeno durante más de 2 años. Se ha registrado la toma de una dosis única de 450 mg de nalmefeno sin cambios en la tensión arterial, la frecuencia cardiaca y respiratoria o la temperatura corporal. No se ha observado un patrón atípico de reacciones adversas en estos contextos, si bien la experiencia es limitada. En caso de sobredosis, se recomienda realizar un tratamiento sintomático y someter al paciente a observación. **5. DATOS FARMACÉUTICOS 5.1 Lista de excipientes** Núcleo del comprimido Celulosa microcristalina Lactosa anhidra Crospovidona, tipo A Estearato de magnesio Recubrimiento del comprimido Hipromelosa Macrogol 400 Dióxido de titanio (E171) **5.2 Incompatibilidades** No procede. **5.3 Periodo de validez** 3 años. **5.4 Precauciones especiales de conservación** Este medicamento no requiere condiciones especiales de conservación. **5.5 Naturaleza y contenido del envase** Blísters transparentes de PVC/PVdC/aluminio en cajas de cartón. Tamaños de envases de 7, 14, 28, 42, 49 y 98 comprimidos recubiertos con película. Puede que solamente estén comercializados algunos tamaños de envases. 5.6 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. **6. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN** H. Lundbeck A/S Ottiliavej 9 DK-2500 Valby Dinamarca **7. 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. **8. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN** Fecha de la primera autorización: 25 de Febrero de 2013. **9. PRESENTACIÓN Y PRECIO PVP (IVA)** Selincro 18 mg, envase con 14 comprimidos. P.V.P 63,04 € P.V.P iva 65,57 €. **10. CONDICIONES DE DISPENSACIÓN POR LA SEGURIDAD SOCIAL** Con receta médica. Especialidad reembolsable por el Sistema Nacional de Salud. Con visado de inspección. Cícero de aportación reducida. **11. 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/.

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
Muy frecuente	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

1. Ficha Técnica de Selincro®. Lundbeck España SA. En: http://www.emea.europa.eu/ema. **2.** François C, et al. PLoS One. 2015 Jun 8;10(6):e0129289.

*Rasca la zona plateada para descubrir el caso de **Álex**.*

Álex, 43 años.

Se siente cansado con facilidad y sufre fuertes resacas. Aumentó su consumo de alcohol debido a su alto grado de responsabilidad y estrés en el trabajo como consecuencia de la presión por incrementar los ingresos familiares tras el nacimiento de su hijo. El alcohol se ha convertido en su vía de escape de la realidad del día a día.

Empieza a beber desde que se levanta, ingiriendo un promedio de 5 cervezas diarias o más entre semana y a menudo una caja el fin de semana.

¿Qué haría en su lugar?

*Caso fictício.

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