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# The Treatment of Dual ADHD: a Drop in the Ocean

## *Tratamiento del TDAH Dual: una Gota en el Desierto*

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Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common mental illnesses in childhood (Polancyk et al., 2007). ADHD can continue into adulthood in around half the patients (Lara et al., 2009) and with a prevalence in this population of between 2.5 and 5% (Kessler et al., 2006, Simon et al., 2009). Some studies suggest that ADHD can have negative impacts at academic, work, social, legal and family levels (Biederman et al. 2012; Klein et al. 2012; Manuzza et al. 2008). Furthermore, childhood ADHD has been linked to an increased risk of substance use in adolescence and adulthood (Carach et al., 2011; Lee et al., 2011). According to population studies, 15% of adult ADHD patients may be affected by substance use disorder (SUD) (Kessler et al., 2006). Among clinical samples, the frequency of SUD is even higher, with some studies describing that at some point in their lives up to 50% of adult ADHD sufferers may develop cannabis dependence, (Torgersen et al., 2006), 45% alcohol abuse or dependence (Biederman et al., 1998), 40% nicotine addiction (Pomerleau et al., 1995), 21% cocaine addiction (Lambert & Hartsough, 1998), and 30% addiction to other substances (Wilens, 2004). Similarly, 23% of SUD patients have comorbid ADHD (van Emmerik-van Oortmerssen et al., 2012). Patients with both ADHD and SUD tend to have a worse prognosis than those who are diagnosed with only one of the two. Indeed, the presence of ADHD in SUD patients has been associated with earlier initiation of substance use, greater consumption and poorer response to treatment (Pérez de los Cobos et al., 2014). The presence of SUD in ADHD sufferers has been linked to an increased risk of criminal behaviour and death by accident (Mannuzza et al., 2008; Dalsgaard et al., 2015).Various theories have been put forward in an attempt to clarify the relationship between ADHD and the development of SUD. This link could be explained by the problems that ADHD patients have to control their own urges, which could lead to increased substance use and the subsequent risk of developing a SUD (Urcelay & Dalley, 2012). It could also be the case that ADHD patients use drugs of abuse to alleviate ADHD symptoms, and given repeated use these drugs create a dependence. This is known as the self-medication hypothesis (Khantzian, 1985; Wilens et al., 2007). In both cases, efficacious treatment of ADHD could reduce drug consumption and improve the SUD. Other factors which have been shown to be involved in the link between ADHD and SUD is the presence of a behaviour disorder and the academic and social impairment associated with ADHD (Molina & Pelham, 2014). Although ADHD and SUD comorbidity is common, little is known as to the efficacy of pharmacological and psychological treatments of either ADHD or SUD among dual patients (Koesters et al., 2009; Pérez de los Cobos 2014), and it is therefore not surprising that these patients do not take easily to treatment for ADHD (Grella et al., 2001; Rowe et al., 2004). With regard to the pharmacological treatment of ADHD in dual patients, a systematic review and meta-anal-

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ysis of randomized clinical trials (RCT) of pharmacological treatments for ADHD implemented on patients with ADHD and substance addiction has recently been published (Cunill et al., 2015). The review identified and included 13 studies with a total of 1,271 patients, and the majority of the RCTs were independent and carried out in USA. The main variables analysed were improvements of ADHD symptoms (assessed by the researcher, self-assessed by the patients and assessed globally), withdrawal from the substance (assessed with objective measurements such as urine tests for drugs and the presence of carbon monoxide (CO) in exhaled air, self-reported by the patient and assessed globally) and treatment discontinuation, defined as the proportion of patients abandoning treatment for whatever reason. These analyses were carried out for all pharmacological treatments and for the different substances abused, in a stratified manner according to the pharmacological treatment and the type of SUD. Five pharmacological treatments were studied: methylphenidate, atomoxetine, pemoline, bupropion and lisdexamfetamine, with a treatment duration of 3 to 16 weeks (mean: 12 weeks). The types of SUD under study were: dependence on nicotine, cocaine, amphetamines, cannabis, alcohol, opioids and also non-specific SUD. Given that in almost half the studies a high risk of bias was detected, mainly due to a high drop-out rate which meant having to work with imputed data sets, the studies were considered to be of low quality methodologically. In addition, bearing in mind that the pharmacological treatments used for ADHD have marked behavioural effects, it cannot be ruled out that the double blind masking of the treatments under study may have failed, leading to possible treatment and detection bias. In terms of results, the meta-analysis found that the pharmacological treatments for ADHD were efficacious in alleviating the severity of ADHD symptoms in patients with SUD (OR= 1.93, 95% confidence interval (CI 95%): from 1.40 to 2.66; p<0,001) both when the assessment was carried out by the researcher or the patient. On stratifying the efficacy results with ADHD symptoms according to the type of pharmacological treatment, it was found that methylphenidate and atomoxetine were more efficacious than placebo, but no differences were found between bupropion, pemoline or lisdexamfetamine and placebo. Results by SUD revealed that pharmacological treatment improved ADHD symptoms in patients with nicotine and alcohol addiction, and in those with a non-specific SUD, but not in those with cocaine, amphetamine or opioid dependence. With regard to the efficacy in treating SUDs, pharmacological approaches did not prove to be any better than placebo in increasing substance abstinence (OR: 1.09; CI 95%: 0.84 to 1.40; p=0.529) irrespective of the type of SUD or treatment. These results were congruent both for objectively assessed and self-reported abstinence. Nor were differences found between pharmacological treatments and placebo in terms of drop-out rates (OR: 1.14, CI 95%: from 0.88 to 1.48, p=0.33), independently of the type of treatment of SUD. There are at least three possible explanations for these none too favourable results which could be of use in the design of future RCTs. The first of these is of a methodological nature and related to the high response rate observed among placebo patients, which would make the detection of a treatment effect more difficult in the group receiving pharmacological treatment. The placebo group's high response rate could be due to due to the fact that these patients were receiving concomitant psychotherapeutic treatment which may have given rise to a positive effect on ADHD symptoms and substance consumption (Pérez de los Cobos et al., 2014).The second reason could be that the doses studied were insufficient for the treatment of dual ADHD patients. A recent RCT carried out on patients with ADHD and cocaine addiction which assessed the efficacy of two doses of mixed amphetamine salts (60 and 80 mg/d) in comparison with placebo over 13 weeks found that the reduction in cocaine use over the course of the study and the proportion of patients managing to stay off the drug in the last three weeks of the study was greater in the group taking the 80 mg/d dose of MAS than among those on 60 mg/d and the placebo patients (Levin et al., 2015). Another RCT which compared the efficacy of high doses of OROS methylphenidate (180 mg/d) with placebo over 24 weeks in male patients with ADHD and amphetamine addiction found that methylphenidate was more efficacious than placebo in improving ADHD symptoms, amphetamine consumption and drop-out rate (Konstenius et al., 2014).The third and final explanation is an attempt to give an account specifically of the results observed regarding substance withdrawal. Even if the SUD is a consequence of ADHD, a small improvement in ADHD symptoms would not have a strong enough effect to bring about a reduction in substance use. Two recent results support this possible explanation. Firstly, a secondary analysis of an RCT assessing the efficacy of OROS methylphenidate in combination with nicotine patches in adult ADHD patients with nicotine dependence found that the methylphenidate achieved higher abstinence rates among those patients who had greater ADHD symptoms reduction (Nunes et al., 2013). Similarly, in the meta-analysis described above a positive correlation was also found between abstinence assessed using objective methods and the efficacy on ADHD, which would support the hypothesis that the greater the improvement in ADHD symptoms, the greater the withdrawal from substances of abuse (Cunill et al., 2015).Although, as has been outlined so far, information regarding the efficacy of pharmacological treatment of ADHD in dual patients is scarce, with serious methodological limitations and somewhat poor results, it can be said that this situation is like an oasis of scientific evidence when compared to the information available on SUD treatment efficacy in patients with dual ADHD, where

we only have observational studies and indirect inferences derived from studies on other populations. Given that ADHD has a negative influence on drug consumption, it is not possible to extrapolate results obtained in other populations without this disorder, and therefore vital that studies be carried out on patients with both ADHD and SUD. The situation regarding the scientific evidence available for psychological treatment among patients with dual ADHD is even more discouraging than that for pharmacological treatment given that there is not a single quality RCT which has investigated the efficacy of psychotherapy in dual patients with ADHD.At this point we need to ask why there are so few RCTs with dual ADHD patients. A possible explanation may be the lack of interest on the part of the pharmaceutical industry to carry out studies with complex patients, such as those with comorbid disorders, once treatment authorization is granted, and this is probably due to a lack of incentive since the regulating agencies do not demand it. In fact, the European Drug Agency (EMA) itself recommends the exclusion of SUD patients from pivotal RCTs of new pharmaceuticals being developed for the treatment of ADHD patients (EMA, 2010). It is unsurprising, therefore, that there are many RCTs with ADHD patients generating redundant information and whose sole raison d'etre is of a commercial nature, while at the same time we lack studies in dual patients (Cunill et al., 2015; Storebo et al.,2015). In the absence of private funding, studies with such patients need to be financed independently, with all the difficulties this involves. In addition, given the complexity of these patients, the high likelihood of unfavourable results may discourage researchers or public agencies from carrying out RCTs on this population.

In sum, the few studies available show that the treatment of ADHD among dual patients results in modest improvements in ADHD symptoms, with a smaller effect size than that observed in patients without SUD (Cunill et al., 2016), without reducing substance consumption nor treatment retention. The review of available studies on patients with dual ADHD, the aim of which was to draw up clinical practice guidelines for the treatment of dual pathology in the adult population (San & Arranz, 2016), has for the first time allowed the formulation of treatment recommendations for patients with ADHD and SUD. Based on the results of this review, we have concluded that pharmacological treatment can be recommended for ADHD to reduce the severity of ADHD symptoms in patients with ADHD and SUD, although this recommendation is weakened by the low quality of the studies available. Conversely, we cannot recommend pharmacological ADHD treatment in order to reduce substance consumption or drop-out rates. Nor can we make any recommendation with regard to the psychological treatment of ADHD nor the treatment of SUD in patients with dual ADHD, given that there are no RCTs focusing on the efficacy of such treatments in dual patients.

## Conflict of interests

The authors declare that they have no conflict of interests.

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# Predictive Capacity of Cloninger's temperament and character inventory (TCI-R) in alcohol use disorder outcomes

## *Capacidad de predicción del inventario de temperamento y carácter de Cloninger (TCI-R) en la evolución de los trastornos por uso de alcohol*

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## Abstract

Objective: to investigate the ability to predict the outcome of alcohol use disorders through Cloninger's temperament and character inventory (TCI-R). Methods: this is a prospective study consisting of 237 outpatients with alcohol use disorders who underwent follow-up treatment for 6 months and whose personality traits were studied using TCI-R. At the end of that period, the scores of each TCI-R trait were analyzed in terms of those who remained in treatment and those who dropped out. Results: The whole group scored highly in novelty seeking (NS) and harm avoidance (HA) and produced low scores in self-directedness (SD), these last traits are considered prominent. The drop-out group scored significantly (p=.004) higher in novelty seeking (NS) than the follow-up group. Also, when the score was higher than the 67 percentile the likelihood of abandoning the treatment was 1.07 times higher. Conclusions: Cloninger's temperament and character inventory is a good instrument to predict the outcome of treatment of patients with alcohol use disorders and the novelty seeking (NS) dimension is strongly related to therapeutic drop-out.

*Keywords*: alcohol dependence; prediction; outcome; personality; temperament; character.

## Resumen

Objetivo: se pretende investigar la capacidad de predicción del inventario de temperamento y carácter de Cloninger (TCI-R) en la evolución de los trastornos por uso de alcohol. Metodología: Es un estudio longitudinal de 237 pacientes con trastornos por uso de alcohol, en tratamiento ambulatorio y seguimiento durante seis meses, cuya personalidad fue estudiada mediante el inventario TCI-R. Se analizó la puntuación de cada una de las dimensiones del inventario TCI-R en función de su situación (retención o abandono) al final del estudio. Resultados: La muestra presentaba puntuaciones elevadas en búsqueda de novedad (BN) y evitación del daño (ED) y baja en autodirección (AD), definidas, estas últimas, como prominentes. El grupo que abandonó presentaba una puntuación significativamente (p= .004) más elevada en búsqueda de novedad (BN) que el grupo en seguimiento; además cuando la puntuación era superior al percentil 67 la probabilidad de abandonar era 1,07 veces superior. Conclusiones: El inventario de temperamento y carácter de Cloninger (TCI-R) es un buen instrumento para predecir la evolución de los pacientes con trastorno por uso de alcohol y la dimensión búsqueda de novedad (BN) está fuertemente relacionada con el abandono terapéutico.

*Palabras clave*: dependencia alcohol; predicción; seguimiento; personalidad; temperamento; carácter.

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Different studies, both prospective and retrospective, have revealed that a range of factors influence the development of alcohol use disorders, such as socio-demographic variables, the clinical characteristics of the disorder, the presence of comorbidity, personality type, cognitive factors such as poor decision-making and the type of treatment (Charney, Zikos and Gill, 2010; Dawson et al., 2005; De Wilde, Verdejo-García, Sabbe, Hulstijn and Dom, 2013).

There is a close relationship between alcohol use and personality disorders that is shown by the high frequency with which each appear together. The prevalence of this association is highly variable and depends, primarily, on the sample studied. In samples of patients with alcohol dependence who attend for treatment, it has been found that between 40 and 50% show some personality disorder (Echeburúa, Bravo de Medina and Aizpiri, 2007; Zikos, Gill and Charney, 2010). However, studies of general population indicate that 28.6% of individuals with an alcohol use disorder over the last twelve months show a personality disorder (Grant et al., 2004); while 42% of those with a personality disorder showed, over their lifetime, alcohol dependence (Trull, Jahng, Tomko, Wood and Sher, 2010). Antisocial, borderline, paranoid, histrionic and dependent personality disorders are those that appear, most frequently, in association with alcohol-use disorders (Agrawal, Narayanan and Oltmans, 2013; Grant et al., 2004; Trull et al., 2010). In an attempt to understand and explain this strong association, recent studies affirm that disorders brought on by substance use, attention deficit and hyperactivity disorder (ADHD), behavioral, anti-social and impulsive disorders form part of a common spectrum, known as externalizing factors (Krueger, Markon, Patrick, Benning and Kramer, 2007).

As for the predictive value of personality disorders, some studies have shown that the persistence of alcohol consumption, after three years of monitoring, is strongly associated with antisocial, borderline and schizotypal personalities (Hasin et al., 2011).

When personality is analyzed from a dimensional point of view, studies stress the role that certain determined traits have on the development, course and therapeutic response of alcohol dependence. Among these traits are impulsiveness, novelty seeking (also known as sensation seeking), extraversion and neuroticism (Dick et al., 2010; Lejuez et al., 2010; Littlefield, Sher and Wood, 2010; Shin, Hong and Jeon, 2012; Simons, Carey and Wills, 2009). Some authors (Dick et al. 2010; Shin et al., 2012) have studied the influx of impulsiveness on the initiation and development of alcohol use disorder and have shown that two dimensions of this, sensation seeking and urgency, predict greater consumption of alcohol and the appearance of problems derived from this, in the future. Other authors (Littlefield et al., 2010; Simons et al., 2009) have shown that negative affective states, exaggerated affective lability and traits of neuroticism have a marked influence on the development of alcohol use disorders, principally on dependence.

One of the most frequently-used instruments in the field of addictive disorders is the Temperament and Character Inventory (TCI) (Cloninger, Svrakic and Przybeck, 1993). The inventory is based on Cloninger's psychobiological model for personality traits (Cloninger, 1987), according to which personality is made up of temperament and character. Temperament refers to the individual differences between the basic automatic responses and emotions. Four temperamental traits, or dimensions are described, which are: Novelty Seeking (NS); Harm Avoidance (HA); Reward Dependence (RD) and Persistence (P). They remain stable throughout life, are genetically determined and have a more or less specific correlation with determined areas of the brain. Character refers to the set of individual values and goals that influence individual behavior and that develop with maturity and learning. There are three character dimensions: Self-Directedness (SD); Cooperativeness (CO) and Self-Transcendence (ST) (Cloninger et al., 1993; Wong and Cloninger, 2010).

Many studies have researched into the personality characteristics of patients with alcohol dependence by means of the TCI, and the results are not conclusive. Some authors find high scores in Harm Avoidance (HA) (Monras, Mondon and Jou, 2008a), while others find them in both Novelty Seeking (NS) and Harm Avoidance (HA) with low scores in Self-Directedness (SD) (Basiaux et al., 2001; Ducci et al., 2007; Nöel et al., 2011; Pedrero et al., 2011). Bearing in mind these findings, some researchers have identified two sub-types of alcoholic patients. Sub-type I is characterized by a high HA score and low ones in NS and SD, while sub-type II shows a high score in NS and low ones in SD and HA and RD (Basiaux et al., 2001; Ducci et al., 2007).

More interesting but, for all that, less researched, is the role that the different dimensions that make up this inventory may have in the prognosis and outcome of alcohol use disorder, that is to say, in abstinence, relapses and adherence to treatment. Works published on this subject, both nationally and internationally, are scarce. Monras, Modnon and Jou (2008b) found in their research that patients with high scores in Persistence (P), Self-Directedness (SD) and Cooperativeness (CO) had better outcomes. Ávila, Pérez, Rodríguez, Recio and Fraile (20132), in a preliminary study, found that abstinence was strongly related to a lower score in Novelty Seeking (NS) and a higher score in Transcendence (T). Finally, Nöel et al. (2011) concluded in the results of their research that individuals with alcohol dependence and with high scores in Novelty Seeking (NS) made poor decisions and were more prone to relapses.

In this paper we propose the hypothesis that high scores in the temperamental dimensions such as NS, HA and

RD, and low scores in the character dimensions SD, CO and ST influence negatively on whether patients continue with treatment. If this hypothesis were to be confirmed, we would be able to state that the TCI is a good instrument for predicting the outcome of alcohol use disorders and would allow for better orientation and more effective therapeutic measures to be adopted.

## Material and Method

### *Participants and procedure*

This research paper is a longitudinal study carried out at the Unidad de Tratamiento del Alcoholismo de Salamanca (Salamanca Alcoholism Treatment Unit) from November 2009 to May 2013.

237 consecutive patients (196 men and 41 women, age 19-70) were included in this study. All of them began outpatient treatment for alcohol use (abuse or dependence), during the period referred to.

The patients were monitored over six months with evaluations programmed for the first, the third and the sixth month. At the end of the study, it was evaluated whether they continued to receive treatment (the follow-up group) or had dropped out (the drop-out group).

Those patients who were unable to respond to the TCI-R inventory because they were unable to understand it were excluded, as were those who responded incorrectly to the validity items, those who showed psychiatric pathology and/or comorbid addiction and secondary severe medical pathology resulting from alcohol consumption.

During the follow-up period, four patients were taken out of the study for the following reasons: two went into a therapeutic community, another was imprisoned and one woman was found to be pregnant.

### *Evaluation*

The patients were given a structured interview with socio-demographic questions concerning their alcohol consumption patterns and the characteristics of the illness and analytical tests were carried out to determine the biological markers related to their alcohol consumption.

Diagnosis was made according to the criteria of the American Psychiatric Association, included in the Diagnostic Manual DSM-IV-TR.

Before beginning treatment, they were asked to complete the following self-administered questionnaires: 1) the Alcohol Dependence Intensity Scale (EIDA in its Spanish initials) which indicates the individual's degree of alcohol dependency. It is a 30-item questionnaire and answers are on a Likert-type scale of 0-3. It has been validated for use in our country by Rubio, Urosa, Rubio, Ulibarri and Mata (1996). 2) The OCDS (Obsessive Compulsive Drinking Scale) questionnaire on the obsessive-compulsive components of drinking, which has been validated in our country by Rubio and López (1999). It consists of 14 questions, which are also answered on a Likert-type scale, with 5 options and measures the obsessive and compulsive component of the desire for alcohol. This was repeated in each of the programmed evaluations (after the first, third and sixth months). 3) For the TCI, we used the Spanish version (TCI-R) which was revised by Bayón (2004) and validated in this country by Gutiérrez-Zotes et al., (2004). It consists of 240 questions which are answered on a five-point Likert-type scale. In this version, the score for each trait is converted into "T" score (percentiles). Each of the dimensions, whether or not they were prominent, were re-codified. Wong et al., (2010), define as prominent traits those which are in the higher third (percentile 67) or in the lower third (percentile 33).

### *Data analysis*

The statistical analysis was carried out by means of the IBM SPSS Statistics program, version 20 for Windows. For the descriptive analysis, means and typical deviations for the quantitative variables were calculated, and percentages were calculated for the qualitative variables. In the comparative study for the continuous variables the classical Student t-test was used. The qualitative variables were analyzed by means of the Chi-square test.

A logistic regression model was constructed in order to identify which dimensions of the TCI-R questionnaire could predict whether subjects would continue with or drop out of treatment. For the logistic regression analysis, the scores for each dimension were re-codified according to their prominence, in the following way: 0-33 (low prominence), 34-66 (normal prominence) and 67-100 (high prominence).

## Results

### *Characteristics of the sample*

The socio-demographic characteristics, the diagnosis and the severity of the alcohol-use disorder of the sample group are shown in Tables 1 and 2. According to the data, the profile of the sample is male, middle-aged, resident in the city, with a high daily level of alcohol consumption and who presents a diagnosis of moderately severe alcohol dependence, according to the score obtained by means of the EIDA questionnaire.

When these characteristics were analyzed by gender, it could be seen that, significantly, women consumed less alcohol, but the severity of their dependence was greater.

In the TCI-R questionnaire, the sample showed high mean scores in novelty seeking (NS) and, principally, in harm avoidance (HA), and a low mean score in self-directedness (SD), with the latter two acquiring the category of prominent dimensions (Table 3). It is important to highlight that 73.2% of the individuals scored low prominence

in the last dimension (SD), which indicates the presence of a personality disorder.

The women showed the same profile as the men but obtained a significantly lower score in self-transcendence (ST).

### *Follow-up*

After six months of treatment, 60.8% of the subjects continued in treatment while 39.2% had dropped out and the situation of their consumption was unknown (Table 4).

When the sample was analyzed in terms of its adherence to the treatment (the follow-up group and the drop-out group), significant differences came to light between the two. The profile of the subject that dropped out of treatment was significantly younger (41,31± 8,31; p=.01), single, resided in the city, lost control of consumption, with a diagnosis of alcohol abuse and 30% of this group rejected pharmacological treatment (Table 5). As for the result of the TCI-R questionnaire, the group that dropped out showed a significantly higher score in novelty seeking (NS) (p=.004) than the group that followed treatment through.

Table 1. *Socio-demographic traits of the sample group, and by gender*

| | Total (N = 237) % | Males (N = 196) % | Females (N = 41) % | $x^2$ |
|---|---|---|---|---|
| **Gender** | | 82.7 | 17.3 | |
| **Marital status** | | | | .60 |
| Married / partner | 55.9 | 56.1 | 48.8 | |
| Single | 30.0 | 29.6 | 31.7 | |
| Separated | 15.2 | 14.3 | 19.5 | |
| **Residence** | | | | .13 |
| City | 64.6 | 62.8 | 73.2 | |
| Rural | 35.4 | 37.2 | 26.8 | |
| **Alcohol consumption** | | | | .06 |
| Weekdays | 84.0 | 82.1 | 92.7 | |
| Weekends | 16.0 | 17.9 | 7.3 | |
| **Loss of control** | | | | .47 |
| Yes | 45.6 | 45.9 | 43.9 | |
| No | 54.4 | 54.1 | 56.1 | |
| **Diagnosis** | | | | .43 |
| Alcohol dependency | 80.6 | 80.1 | 82.9 | |
| Alcohol abuse | 19.4 | 19.9 | 17.1 | |
| **Treatment** | | | | .053 |
| Yes | 77.2 | 75.0 | 87.8 | |
| No | 22.8 | 25.0 | 12.2 | |

Table 2. *Alcohol use disorder traits of the sample group, and by gender*

| | Total Mean s.d. | Males Mean s.d. | Females Mean s.d. | t student |
|---|---|---|---|---|
| **Age** | 43. 16 ± 9.66 | 43.26 ± 9.78 | 42.68 ± 9.13 | .731 |
| **Grams alcohol/day** | 137.14 ± 54.17 | 142.29 ± 54.78 | 112.49 ± 43.96 | .001* |
| **Total EIDA score ***** | 27.50 ± 14.67 | 26.22 ± 13.79 | 33.63 ± 17.23 | .003* |
| **Total OCDS score** | 14.71 ± 7.77 | 14.23 ± 7.17 | 17.0 ± 9.93 | .038 |
| **AST** | 47.67 ± 122.51 | 51.20 ± 133.93 | 30.21 ± 16.24 | .363 |
| **ALT** | 42.76 ± 64.83 | 46.58 ± 70.41 | 24.09 ± 11.36 | .065 |
| **GGT** | 124.74 ± 214.30 | 133.32 ± 229.99 | 82.09 ± 97.95 | .204 |
| **VCM** | 93.84 ± 6.65 | 93.77 ± 6.27 | 94.19 ± 8.37 | .743 |

Note. EIDA: Alcohol dependency Intensity Scale; CDS: Obsessive Compulsive Drinking Scale; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamiltransferase; MCV: Mean corpuscular volume.
*p < .05

Table 3. *Typical scores (T) on the TCI-R questionnaire and by gender*

| | Total Mean s.d. | Males Mean s.d. | Females Mean s.d. | t student |
|---|---|---|---|---|
| **Novelty seeking** | 62.19 ± 29.98 | 62.15 ± 29.43 | 62.37 ± 32.86 | .966 |
| **Harm avoidance** | 71.97 ± 27.20 | 70.95 ± 27.06 | 76.85 ± 27.69 | .207 |
| **Reward dependence** | 52.87 ± 30.40 | 53.06 ± 30.85 | 51.98 ± 28.45 | .836 |
| **Persistence** | 51.17 ± 32.57 | 52.49 ± 32.75 | 44.88 ± 31.30 | .174 |
| **Self-directedness** | 25.16 ± 26.20 | 26.61 ± 26.37 | 18.27 ± 24.54 | .064 |
| **Cooperativeness** | 47.53 ± 30.62 | 46.60 ± 30.81 | 52.00 ± 29.64 | .305 |
| **Self-trascendence** | 59.51 ± 30.23 | 61.29 ± 29.72 | 50.98 ± 31.55 | .047* |

Note. *p < .05

Table 4. *Outcomes of the sample*

| | 1 month (N = 237) % | 3 months (N = 237) (%) | 6 months (N = 237) (%) |
|---|---|---|---|
| **Follow-up group** | 88.2 | 70.9 | 60.8 |
| Abstinent | 89.47 | 83.93 | 86.80 |
| Non-abstinent | 10.53 | 16.07 | 13.20 |
| **Drop-out group** | 11.8 | 29.1 | 39.2 |

In the logistic regression model that was constructed, it was borne in mind whether the prominence of each dimension was low, normal or high (Table 6). Said model classified 63.7% of the patients. It can be observed that the patients who scored between 67 and 100 for the novelty seeking dimension were 1.07 times more likely to drop out than those who scored between 34 and 66. However, scores of between 0 and 33 acted as a protection factor (odd-ratio=.323), that is to say, they were less likely to drop out than those with normal prominence. As for the prominent dimensions, HA and SD, it is noteworthy that in the drop-out group there was a higher percentage with a low score in HA than in the follow-up group (18.3% versus 9%), although these differences were not significant.

Table 5. *Socio-demographic traits according to follow-up of treatment*

| | Follow-up (N = 144) % | Drop-out (N = 93) % | $x^2$ |
|---|---|---|---|
| **Gender** | | | .561 |
| Male | 82.6 | 82.8 | |
| Female | 17.4 | 17.2 | |
| **Marital status** | | | .036* |
| Married / partner | 61.1 | 45.2 | |
| Single | 24.3 | 38.7 | |
| Separated | 14.6 | 16.1 | |
| **Residence** | | | .018* |
| City | 59.0 | 73.1 | |
| Rural | 41.0 | 26.9 | |
| **Alcohol consumption** | | | .097 |
| Weekdays | 86.8 | 79.6 | |
| Weekends | 13.2 | 20.4 | |
| **Loss of control** | | | .007* |
| Yes | 38.9 | 55.9 | |
| No | 61.1 | 44.1 | |
| **Diagnosis** | | | .016* |
| Alcohol dependency | 85.4 | 73.1 | |
| Alcohol abuse | 14.6 | 26.9 | |
| **Treatment** | | | .047* |
| Yes | 81.2 | 71.0 | |
| No | 18.8 | 29.0 | |

Nota. *p< .05

Table 6. Logistic regression of the TCI-R inventory, according to outcomes and the prominence of each dimension

| | | Follow-up N (%) | Drop-out N (%) | OR (IC 95%) | P_value |
|---|---|---|---|---|---|
| **Novelty seeking** | 0-33 | 46 (31.9%) | 12 (12.9%) | .323 (0.131;0.796) | .010 |
| | 34-66 | 26 (18.1%) | 20 (21.5%) | 1 | |
| | 67-100 | 72 (50%) | 61 (65.6%) | 1.070 (0.527;2.174) | .014 |
| **Harm avoidance** | 0-33 | 13 (9%) | 17 (18.3%) | 2.475 (0.089;6.883) | .083 |
| | 34-66 | 30 (20.8%) | 14 (15.1%) | 1 | |
| | 67-100 | 101 (70.1% | 62 (66.7%) | 1.357 (0.634;2.905) | .432 |
| **Reward dependence** | 0-33 | 40 (27.8%) | 31 (33.3%) | 1.224 (0.602;2.487) | .577 |
| | 34-66 | 51 (35.4%) | 31 (33.3%) | 1 | |
| | 67-100 | 53 (36.8%) | 31 (33.3%) | .836 (0.421;1.662) | .615 |
| **Persistence** | 0-33 | 55 (38.2%) | 34 (36.6%) | 1.231 (0.571;2.653) | .596 |
| | 34-66 | 32 (22.2%) | 18 (19.4%) | 1 | |
| | 67-100 | 57 (39.6%) | 41 (44.1%) | 1.339 (0.630;2.844) | .448 |
| **Self-directedness** | 0-33 | 104 (72.2%) | 69 (74.2%) | 1.296 (0.527;3.158) | .572 |
| | 34-66 | 22 (15.3%) | 11 (11.8%) | 1 | |
| | 67-100 | 18 (12.5%) | 13 (14%) | 1.853 (0.600;5.725) | .284 |
| **Cooperativeness** | 0-33 | 54 (37.5%) | 42 (45.2%) | 1.050 (0.511;2.160) | .894 |
| | 34-66 | 42 (29.2%) | 25 (26.9%) | 1 | |
| | 67-100 | 48 (33.3%) | 26 (28%) | .974 (0.459;2.065) | .945 |
| **Self-transcendence** | 0-33 | 31 (21.5%) | 24 (25.8%) | 1.467 (0.665;3.237) | .343 |
| | 34-66 | 45 (31.3%) | 23 (24.7%) | 1 | |
| | 67-100 | 68 (47.2%) | 46 (49.5%) | 1.310 (0.669;2.566) | .431 |

## Discussion

Our sample group shows, according to the TCI-R questionnaire, two prominent dimensions: HA and SD, with the first being high and the second being low. The high score for HA is a trait of persons who fear uncertainty, are shy and prone to depression and anxiety, while the low SD score appears in people who have difficulties resolving their problems and controlling their emotions, who lack life goals and have a tendency to blame their problems on others (Wong et al., 2010). The NS score is also high, but does not reach the category of prominent. These persons are characterized by their marked exploratory activity, in search of new sensations and rewards, impulsiveness, disorganization and extravagant behavior (Wong et al., 2010).

Various studies carried out both here and abroad have found similar results (Basiaux et al., 2001; Ducci et al., 2007; Milivojevic et al., 2012, Nöel et al., 2011; Pedrero et al., 2011).

The low score in SD, a character trait that is influenced by a person's learning curve and mental development, may be the consequence of personal, family, social and work-place problems and adversities that come up during the development of alcohol dependence. Wedekind, Bandelow, Heitman, Havemann-Reinecke and Engel (2013) studied the personality traits within a sample group of subjects who had alcohol dependence and who had had poor family bonding as children and scored high in HA and significantly low in SD, as in our study, and proposed that these characteristics would cause the subject to be more vulnerable to suffering an alcohol use disorder. Pedrero et al. (2011) have shown that a low SD score is correlated to prefrontal deficits that can bring about poor decision-making and the inability to control the reinforcing effects of alcohol, factors which maintain dependence and mean there is a risk of relapse. In recent years, this aspect (cognitive deterioration and a lack of impulse control owing to lesions in the prefrontal cortex) is being highlighted although its role in the outcome of alcohol dependence is still not very clear (Dos Santos, Quarti, Duarte, Ferrão and Silva, 2014; López-Caneda et al., 2014). However, in our study, neither of these two dimensions is related to the outcome of the sample group; rather, the results of the drop-out group show a tendency that is the opposite of our hypothesis, because the percentage of drop-outs with a low score in SD is greater than in the other group.

As to the predictive capacity of the TCI-R questionnaire, only the high score in NS is strongly related to dropping out of treatment, confirming what other researchers have found (Evren, Durkaya, Evren, Dalbudak and Cetin, 2012; Kravitz, Fawcett, McGuire, Kravitz and Whitney, 1999). However, other researchers such as Monras et al. (2008b), in a study carried out in this country, found that high scores on the P, CO and ST scales favored staying in treatment, a result that this study has not been able to corroborate. A relevant finding of our study is that low scores in the NS dimension have a protection factor, that is to say, they increase the likelihood of staying in treatment.

Apart from personality, there are other factors that influence on treatment drop-out rates, such as the lack of or little motivation to receive treatment, either owing to unawareness of the illness or of the need for treatment, as some studies have indicated (Lucas-Taracena, Maldonado, Tossio-González and Bravo-Ortiz, 2002). The profile of the patient from our sample group who dropped out of treatment, described above, shows traits that suggest having little motivation.

It is necessary to delve further into this line of research, given the contradictions between different papers published and its importance in the development of therapeutic techniques aimed at promoting treatment completion.

In conclusion, the sample group of the present study is characterized by high NS and HA scores and low ones in SD, the latter two being in the prominent category. After six months of monitoring, 62.8% of patients continued in treatment whereas 39.2% had dropped out. This group had a significantly higher score in NS and those with a higher score than the 67 percentile showed a probability of dropping out that was 1.07 times higher than those with a lower score. In our study, we have found that the TCI-R inventory is a good tool for predicting the outcomes of patients with alcohol use disorders and that novelty seeking (NS) is strongly linked to dropping out of therapy.

## Conflict of interests

The authors state that there are no conflicts of interests to declare and that they have not received any grant from any institution, private or public, for the carrying out of this study.

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# Psychotic-like Experiences and Substance Use in College Students

## *Experiencias psicóticas atenuadas y consumo de sustancias en universitarios*

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## Abstract

Psychotic disorders, as well as psychotic-like experiences and substance use, have been found to be associated. The main goal of the present study was to analyse the relationship between psychotic-like experiences and substance use in college students. The sample comprised a total of 660 participants (M = 20.3 years, SD = 2.6). The results showed that 96% of the sample reported some delusional experience, while 20.3% reported at least one positive psychotic-like experience. Some substance use was reported by 41.1% of the sample, differing in terms of gender. Substance users reported more psychotic-like experiences than non-users, especially in the positive dimension. Also, alcohol consumption predicted in most cases extreme scores on measures of delusional ideation and psychotic experiences. The association between these two variables showed a differentiated pattern, with a stronger relationship between substance use and cognitive-perceptual psychotic-like experiences. To some extent, these findings support the dimensional models of the psychosis phenotype and contribute a better understanding of the links between psychotic-like experiences and substance use in young adults. Future studies should further explore the role of different risk factors for psychotic disorders and include models of the gene-environment interaction.

*Keywords:* Substance use; Addiction; Psychosis; Schizotypy; Cannabis; Psychotic-like experiences.

## Resumen

Los trastornos del espectro esquizofrénico, así como las experiencias psicóticas, se han asociado con un mayor consumo de sustancias. El objetivo de este trabajo fue analizar la relación entre las experiencias psicóticas atenuadas y el consumo de sustancias en adultos jóvenes. La muestra la formaron un total de 660 participantes universitarios (M = 20,3 años; DT = 2,6). Los resultados mostraron que un 96% de la muestra informó de alguna experiencia de ideación delirante, mientras que el 20,3% informó de, al menos, una experiencia atenuada de tipo cognitivo-perceptual. El 41,1% de la muestra refirió algún consumo de sustancias, encontrándose diferencias en función del género. Los participantes consumidores informaron de un mayor número de experiencias psicóticas, sobre todo de tipo positivo. Asimismo, el consumo de alcohol predijo, en la mayoría de los casos, las puntuaciones extremas en las medidas de ideación delirante y experiencias pseudo-psicóticas. La asociación entre estas dos variables parece mostrar un patrón diferenciado, encontrándose el consumo de sustancias más relacionado con las experiencias pseudo-psicóticas de tipo cognitivo-perceptual. Estos hallazgos parecen apoyar los modelos dimensionales del fenotipo psicótico y permiten mejorar la comprensión de la relación entre las experiencias psicóticas atenuadas y el consumo de sustancias en adultos jóvenes. Futuros estudios deberían seguir analizando el papel de los factores de riesgo a los trastornos psicóticos, así como incorporar modelos de interacción gen x ambiente.

*Palabras clave:* Consumo de sustancias; Adicción; Psicosis; Esquizotipia; Cannabis; Experiencias psicóticas atenuadas.

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Substance use and abuse is common amongst patients with disorders along the psychotic spectrum (Buckley, Miller, Lehrer, & Castle, 2009). Substance use and abuse has been associated with poorer clinical evolution, earlier onset, longer duration of untreated psychosis, exacerbation of symptoms, higher number of relapses and hospitalizations and worse adherence to treatment, among other aspects (Broussard et al., 2013; González-Pinto et al., 2011; Henquet et al., 2010; Lambert et al., 2005; Stefanis et al., 2014; Wade et al., 2006; Wisdom, Manuel, & Drake, 2011; Zammit et al., 2008). Furthermore, previous use of certain substances, such as cannabis, for example, apparently increases the subsequent risk of developing psychosis, as well as rates of subclinical psychotic symptoms and psychotic-like experiences, in both the general population (Henquet, Murray, Linszen, & Van Os, 2005; Kuepper et al., 2011; McGrath et al., 2010; Moore et al., 2007) and in family members of patients with psychosis (McGuire et al., 1995). For example, epidemiological studies have found that the start of using cannabis in adolescence increases the probability of experimenting symptoms and disorders of the psychotic spectrum during adulthood (Arseneault et al., 2002) and promotes the persistence of psychotic-like experiences (Mackie et al., 2013). Similar results are found in longitudinal assessments of participants clinically classified as high risk (high risk mental conditions). Nevertheless, there is insufficient evidence to associate substance use with a higher probability of transitioning to psychosis (Addington et al., 2014).

The dimensional approach of the psychotic phenotype suggests that psychotic experiences (e.g., delusional ideation, fantastical beliefs) are distributed along a continuum of gravity, with psychotic symptoms positioned at the extreme (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). These psychotic experiences, though attenuated, are normally distributed among the general population, without necessarily being associated with distress, disability and need for treatment (Linscott & van Os, 2013; McGrath et al., 2015). This series of attenuated experiences, when persistent over time and accompanied by a sense of distress, concern and search for aid, are usually referred to as psychotic-like symptoms (Fonseca-Pedrero, Paino, & Fraguas, 2013; Yung et al., 2007). These types of attenuated experiences are considered a phenotypical marker of vulnerability for disorders of the psychotic spectrum, in general, and for schizophrenia, in particular (Debbané et al., 2015; Linscott & van Os, 2013). Therefore, it is possible that the identification of this series of subclinical experiences will allow the early detection and identification of participants who are vulnerable to a serious mental disorder, such as psychosis. Likewise, these types of psychotic-like experiences could be combined with other risk markers (proximal or distal), for example, substance use and abuse, trauma or growing up in an urban environment (van Os, Kenis, & Rutten, 2010), for the purpose of examining possible underlying aetiological mechanisms and for improving early detection and prevention strategies and programmes. The possible effect of substance use among high risk individuals or those vulnerable to psychosis could be impacted by different factors, such as: age of first use, pattern and frequency of substance use or pre-existent vulnerability (Casadio, Fernandes, Murray, & Di Forti, 2011; Valmaggia et al., 2014).

Previous studies have associated attenuated psychotic experiences with substance use and abuse, especially cannabis (Barkus, Stirling, Hopkins, & Lewis, 2006; Mackie et al., 2013; Saha et al., 2011; Schubart et al., 2011; van Os et al., 2002). The results seem to indicate that this association is more probable and increases among those participants with a certain, latent predisposition, or who report a family history of psychosis (Henquet, Krabbendam, et al., 2005; Stowkowy & Addington, 2013; van Os et al., 2002). In a longitudinal study, van Os et al. (2002) found that the use of cannabis predicted the presence of psychotic symptoms three years later, as well as their degree of severity and need for treatment. In another epidemiological study carried out in Australia, Saha et al. (2011) found that delusional experiences were associated with a higher use of tobacco, cannabis and alcohol. These studies analysed the role of attenuated positive psychotic experiences (e.g., delusional ideation or hallucinations), though the effect of attenuated negative psychotic experiences (e.g., flat affect or inability to feel pleasure) are not analysed in depth (Schubart et al., 2011).

Convergent results have been found when the relationship between schizotypal traits and substance use is examined (Barkus et al., 2006; Davis, Compton, Wang, Levin, & Blanco, 2013; Fumero, Santamaría, & Navarrete, 2009; Najolia, Buckner, & Cohen, 2012; Nunn, Rizza, & Peters, 2001). Schizotypal traits are intimately related with psychotic-like experiences and sometimes the terms are used interchangeably (Kwapil & Barrantes-Vidal, 2015). Both constructs are normally distributed among the general population within a continuum of severity of psychosis. However, schizotypal traits bring together a larger series of attenuated psychotic symptoms (e.g., positive, negative and depressive dimensions) and greater stability (trait). On the other hand, psychotic-like experiences more frequently refer to positive symptoms that are temporary in nature (state). As occurs in studies on psychotic-like experiences, individuals with higher scores on measures of schizotypy that participate in longitudinal follow-ups have a greater likelihood of developing substance abuse disorders (Kwapil, 1996). Likewise, transversal studies have reported that schizotypal traits are predictors of alcohol and tobacco use among college students in Spain (Fumero et al., 2009). In this regard, several studies indicate that users of cannabis and/or alcohol obtain lower scores on the negative dimension of schizotypy in comparison with non-users (Nunn et al., 2001; Skosnik, Park, Dobbs, & Gardner, 2008), though other studies do not find this association (Barkus et al., 2006; Dumas et al., 2002;

Fridberg, Vollmer, O'Donnell, & Skosnik, 2011; Schiffman, Nakamura, Earleywine, & LaBrie, 2005), or even find a positive association (Bailey & Swallow, 2004; Davis et al., 2013).

As may be observed, studies that analyse the association between psychotic-like experiences and substance use in non-clinical samples of young adults are inconsistent. Furthermore, the role of negative psychotic-like experiences has not yet been studied in depth. Therefore, it is necessary to carry out new research to understand and explore the relationship between these types of attenuated experiences and substance use, during the developmental stage of young adulthood, especially vulnerable for psychosis. Within this research context, the main purpose of this study was to examine the relationship between psychotic-like experiences and substance use in a young adult sample of college students. The hypothesis is that a high percentage of individuals will report substance use and attenuated psychotic experiences. Likewise, in accordance with previous studies, another hypothesis is that substance users will present a higher frequency of psychotic-like experiences, both positive and negative, in comparison with non-users, and that this association will be stronger with cognitive-perceptual psychotic-like experiences.

## Method

### Participants

An incidental sample of college students has been used. The sample was comprised of 660 participants, 195 males (29.5%), pursuing different courses of study at the University of Oviedo (Teaching, Criminology, Psychology, Medicine, Speech-Language Pathology, Computer Science, Economics and Physiotherapy). The average age of the participants was 20.3 years (*SD* = 2.6), ranging between the ages of 17 and 30. The average number of years of education was 16.8 (*SD* = 2.3). As regards civil status, 81.6% of the sample was single, 16.2% was married, 0.6% was divorced and 1.7% left this status unreported. As regards employment, 86.6% of the participants were unemployed, 12.6% were employed, and 1.2% left employment status unreported. The criteria for exclusion from this study was: a) presence of a serious mental illness (e.g., psychosis, bipolar disorder); and b) presence of a neurological disorder.

### Instruments

*Questionnaire on substance use.* To evaluate substance use, a series of *ad hoc* questions referring to the use of alcohol and drugs were formulated, specifically: cannabis, inhalants, cocaine, designer drugs and heroine/morphine. As regards alcohol consumption, data was gathered to classify the participants as non-drinker, drinker or ex-drinker. Participants classified as drinkers were asked to specify the amount of alcohol consumed in grams per day, in four categories: less than 10, between 11 and 20, between 21 and 50 and more than 51. Likewise, information was also gathered on other substances, such as Cannabis/Marihuana/Hashish, Inhalants, Cocaine, Designer drugs/Methamphetamines/Ecstasy/LSD and Heroine/Morphine. For each, information was collected as to age of initial use in years, duration of use in months and days of use in the last month. These questions were formulated in line with earlier studies (Dumas et al., 2002; Najolia et al., 2012) and used scales that were previously validated (Soto-Brandt et al., 2014).

*Evaluation Scale for the Community Assessment Psychic Experiences-42* (CAPE-42) (Stefanis et al., 2002). The CAPE is comprised of 42 items that evaluate three dimensions of psychotic symptoms: Positive (20 items), Negative (14 items) and Depressive (8 items). Each question is answered on a Likert scale of four points ranging from *Almost never* (1) to *Almost always* (4). When the participant selects the answers *Sometimes*, *Often* or *Nearly always*, the level of distress that results of that experience must also be indicated on a Likert scale of four points (0 = *Not distressed*; 3 = *Quite distressed*). This study used the version adapted to Spanish and validated in accordance with international standards (Muñiz, Elosua, & Hambleton, 2013). Scores obtained in previous studies present suitable levels of reliability and different evidences of validity (Barragan, Laurens, Blas Navarro, & Obiols, 2011; Fonseca-Pedrero et al., 2011; Fonseca-Pedrero, Paino, Lemos-Giráldez, & Muñiz, 2012b).

*Peters et al Delusions Inventory-21* (PDI-21) (Peters, Joseph, Day, & Garety, 2004). The PDI-21 is a self-report designed to assess delusional experiences and propensity for delusions. The PDI comprises 21 items with dichotomous Yes/No answers. The total score is obtained by adding the positive responses of each item, wherefore the maximum possible score is 21 points. A higher score is indicative of greater delusional symptoms or propensity for delusions. Likewise, each item has three subscales measuring the degree of conviction, preoccupation and distress. These three subscales are scored using a Likert scale with five categories (1-5). This study used the Spanish version of the PDI-21, with suitable psychometric properties (Fonseca-Pedrero, Paino, Santarén-Rosell, Lemos-Giráldez, & Muñiz, 2012; López-Ilundain, Pérez-Nievas, Otero, & Mata, 2006).

*State-Trait Anxiety Inventory* (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). The STAI is a self-report comprised of 40 items designed to evaluate two independent concepts of anxiety: State and Trait. Each scale is comprised of a total of 20 items with a Likert answer scale of four points according to intensity (0 = *Almost never/Not at all*; 3 = *Very much so/Almost always*). The total score for each scale ranges between 0-60 points. This study used the Spanish version of the STAI (Spielberger, Gorsuch, & Lushene, 2008). The Spanish version presents internal consistency levels that range between 0.84-0.93, and its validity has been analysed previously (Fonseca-Pedrero, Paino, Lemos-Giráldez, & Muñiz, 2012a; Guillén-Riquelme & Buela-Casal, 2011).

### Procedure

The instruments were administered to the sample as a group, in groups of 10 to 45 students, during in-class hours and in a room prepared for this purpose. The study was presented to the participants as a research project on diverse personality traits, guaranteeing the confidentiality of their answers as well as the voluntary nature of their participation. Self-reports were always administered under the supervision of a researcher. All participants gave their informed consent to participate in the research project. This study is framed within a line of research related with early detection of serious psychological disorders in young adults. The study was approved by the Ethics Committee of the University of Oviedo.

### Data analysis

First, descriptive statistics were calculated for the PDI-21 and the CAPE-42 instruments. Second, the prevalence of self-reported psychotic experiences and substance use were analysed. Third, different Multivariate Analysis of Covariance (MANCOVA) were performed, controlling the effect of the covariables gender, anxiety state and anxiety trait. Scores on the PDI-21 and the CAPE-42 were the dependent variables, while use and non-use of substances were the independent variables, as well as global dichotomous polydrug use (non-users versus users of some type of substance). Given their low prevalence in this study, the effects of neither inhalants nor heroine were analysed. Wilks's *Lambda* value was used to estimate possible statistically significant differences between all variables. The effect size was calculated using the partial *eta-squared* (partial $\eta^2$).

Fourth, scores obtained in the PDI-21 and the CAPE-42 were dichotomized to carry out different hierarchical binary logistic regression analyses. Participants with scores equal to or greater than the 90th percentile, or participants with a percentile equal to or lower than 10, were selected. The effects of gender, anxiety state and anxiety trait were also controlled. Covariables were introduced in the first step of the model. The fixed variables selected were consumption of alcohol, cannabis, cocaine and designer drugs. The method for estimation used was the Forward Wald; the odds ratio and its confidence interval (95%) were calculated. The Hosmer Lemeshow test was used to evaluate the goodness of fit of the binary logistic regression model. The SPSS Statistics 15.0 package was used for data analysis (*Statistical Package for the Social Sciences,* 2006).

## Results

### Descriptive statistics and prevalence of psychotic-like experiences and substance use

The descriptive statistics referred to the scores obtained in the CAPE-42 may be consulted in a previous study (Fonseca-Pedrero, Paino, et al., 2012b). The statistics of the PDI-21 were: *M*= 4.30; *SD*=2.18; range 0-18; Cronbach's alpha= 0.91.

The percentage of participants that responded affirmatively (*Often* or *Almost always*) in the answer options of the positive dimension of the CAPE-42 ranged between 0.6% (item 24) and 20.3% (item 6), though it is true that almost all of the percentages were close to 2%. In the PDI-21, 96% of the participants positively reported having experienced delusions at least once.

In relation to substance use, participants reported the following: A total of 32.4% ($n$ = 215) of the participants considered themselves drinkers. The percentage by type of consumption for drinking was: 26.1% ($n$ = 172) under 10 g/day, 3.5% ($n$ = 23) between 11-20 g/day, 1.8% ($n$ = 12) 21-50 g/day, 0.3% ($n$ = 2) over 51 g/day and 0.9% ($n$ = 6) ex-drinker. A total of 20.2% ($n$ = 133) of the sample reported using cannabis, 0.6% ($n$ = 4) inhalants, 7.7% ($n$ = 51) cocaine, 2.6% ($n$ = 17) designer drugs, and 0.2% ($n$ = 1) heroine. In global terms, 41.1% of the sample reports some type of substance use, distributed as follows: 0 = 58.9% ($n$ = 153), 1 = 23.2% ($n$ = 153), 2 = 14.4% ($n$ = 95), 3 = 2.3% ($n$ = 15), 4 = 1.1% ($n$ = 7), and 5 = 0.2% ($n$ = 1). As to consumption, disregarding substances with lower prevalence (heroine and inhalants), the number of substances was distributed as follows: 0 = 58.9% ($n$ = 389), 1 = 24.2% ($n$ = 153), 2 = 14.7% ($n$ = 97), 3 = 2.3% ($n$ = 15), and 4 = 0.9% ($n$ = 6). If only the consumption of the substances cannabis, cocaine and designer drugs are considered, 75% of the sample reported no consumption.

Consumption patterns showed differential variations depending on gender for alcohol consumption (dichotomized consumption vs. non-consumption) ($\chi2$ (1) = 30.78, $p$ = 0.001), cannabis ($\chi2$ (1) = 21.31, $p$ = 0.001), inhalants ($\chi2$ (1) = 9.59, $p$ = 0.001), and designer drugs ($\chi2$ (1) = 4.58, $p$ = 0.032). In these cases, reported substance use was higher in males than in females. Statistically significant differences were not found neither in cocaine use ($\chi2$ (1) = 1.57, $p$ = 0.209) nor in heroin use ($\chi2$ (1) = 0.42, $p$ = 0.517).

### Association between psychotic-like experiences and substance use

Then, the relationship between the subscales and the total scores obtained in the PDI-21 and the CAPE-42 and use or non-use of substances was analysed. Table 1 presents the mean scores depending on use, as well as global polydrug use. The results showed statistically significant differences in a majority of the comparisons carried out. The Wilks's $\lambda$ value revealed statistically significant differences depending on the factors Alcohol ($\lambda$ = 0.974, $F$(4.652) = 4.289, $p$ = 0.002, partial $\eta^2$ = 0.026), Cannabis ($\lambda$ = 0.971, $F$(4.652) = 4.90, $p$ = 0.001, partial $\eta^2$ = 0.029), Designer drugs ($\lambda$ = 0.978, $F$(4.652) = 3.735, $p$ = 0.005, partial $\eta^2$ = 0.022), and total use ($\lambda$ = 0,969, $F$(4.652) = 5.130, $p$ < 0.001, partial $\eta^2$ = 0.031). Statistically significant differences were not found for the Cocaine factor ($\lambda$ = 0.961, $F$ (4.652) = 4.010, $p$ = 0.348, partial $\eta^2$ = 0.007). In any case, the substance user group obtained

Table 1. *Mean scores in the Peters et al. Delusions Inventory-21 (PDI-21) and in the Community Assessment Psychic Experiences-42 (CAPE-42), per substance use*

| | **PDI-21 Total** | | **CAPE-42 Positive** | | **CAPE-42 Depressive** | | **CAPE-42 Negative** | | **CAPE-42 Total** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Use | Non-use | Use | Non-use | Use | Non-use | Use | Non-use | Use | Non-use |
| Alcohol | | | | | | | | | | |
| Mean | 3.95 | 5.02 | 24.53 | 26.15 | 13.38 | 13.73 | 22.62 | 23.51 | 60.52 | 63.38 |
| *SD* | 2.60 | 3 | 3.56 | 5.76 | 2.67 | 2.98 | 4.57 | 4.93 | 8.69 | 10.56 |
| Cannabis | | | | | | | | | | |
| Mean | 4.04 | 5.32 | 24.71 | 26.42 | 13.42 | 13.78 | 22.69 | 23.75 | 60.82 | 63.95 |
| *SD* | 2.58 | 3.27 | 3.86 | 6.12 | 2.79 | 2.73 | 4.59 | 5.08 | 8.88 | 11.05 |
| Cocaine | | | | | | | | | | |
| Mean | 4.24 | 5.04 | 24.94 | 26.37 | 13.46 | 13.88 | 22.89 | 23.08 | 61.29 | 63.33 |
| *SD* | 2.81 | 2.24 | 4.38 | 5.11 | 2.81 | 2.41 | 4.75 | 4.14 | 9.48 | 8.73 |
| Designer drugs | | | | | | | | | | |
| Mean | 4.27 | 5.47 | 24.96 | 28.47 | 13.49 | 13.47 | 22.93 | 22.06 | 61.38 | 64 |
| *SD* | 2.77 | 2.85 | 4.35 | 6.78 | 2.79 | 2.29 | 4.72 | 4.1 | 9.43 | 9.51 |
| Any use | | | | | | | | | | |
| Mean | 3.84 | 4.96 | 24.39 | 26.01 | 13.32 | 13.73 | 22.45 | 23.56 | 60.16 | 63.31 |
| *SD* | 2.56 | 2.95 | 3.44 | 5.47 | 2.72 | 2.85 | 4.59 | 4.8 | 8.67 | 10.16 |

Note. *SD:* Standard Deviation; Alcohol: Non-use n = 445, Use n = 215; Cannabis: Non-use n = 527, Use n = 133; Cocaine: Non-use n = 609, Use n = 51; Designer drugs: Non-use n = 643, Use n = 17; Any use: Non-use n = 389, Use n = 217.

higher total mean scores in the PDI-21 and the CAPE-42, compared with the non-user group.

The results of the univariate analysis of variance showed statistically significant differences for the Alcohol factor in all scores, with the exception of the depressive dimension of the CAPE-42 ($p < 0.05$). As to the alcohol consumption pattern (depending on g/day), statistically significant differences were found between the different groups ($\lambda = 0.933$, $F(20.2150) = 2.284$, $p < 0.001$, partial $\eta^2 = 0.017$). Specifically, statistically significant differences were found in the total score of the PDI-21 ($F(5.651) = 5.946$, $p < 0.001$, partial $\eta^2 = 0.044$) in its Positive dimension ($F(5.651) = 4.604$, $p < 0.001$, partial $\eta^2 = 0.011$), and in the total score obtained in the CAPE-42 ($F(5,651) = 3.899$, $p < 0.001$, partial $\eta^2 = 0.029$). The tendency found was that non-drinkers obtained lower mean scores compared with the remaining groups (except for ex-drinkers or more than 50 g/day), and that the user group of 21-50 g/day obtained higher mean scores compared with the rest of the groups. As to use of cannabis and total polydrug use, participants who positively reported use also obtained higher mean scores in the mentioned self-reports, compared with the substance non-user group ($p < 0.05$). On the other hand, participants who reported designer drug use only presented statistically higher mean scores compared with non-users in the positive dimension of the CAPE-42 ($F(4.652) = 7.183$, $p < 0.001$, partial $\eta^2 = 0.011$).

### *Prediction of psychotic-like experiences and substance use*

Finally, different binary logistic regression analyses were performed, selecting those participants who obtained extreme scores in the PDI-21 and the CAPE-42. The effects of gender, anxiety state and anxiety trait were also controlled. Table 2 displays the results of the binary logistic regression analyses. As shown, the variable alcohol use was statistically significant in the majority of the estimated models. Cannabis use only predicted the total score for participants with extreme scores in the PDI-21. None of the different types of substance use resulted in statistically significant predictions of scores in the negative dimension of the CAPE-42. Cocaine and designer drugs failed to predict extreme scores in neither the PDI-21 nor the CAPE-42.

## Discussion and conclusions

The main goal of this study was to examine the relationship between psychotic-like experiences and substance use in a sample of college students. The results showed that 96% of the sample reported some type of experience of delusional ideation, while 20.3% reported at least one positive type of psychotic-like experience. Furthermore, 41.1% of the sample reported some type of substance use. Participants who were users of any substance, with the exception of cocaine,

Table 2. *Binary logistic regression models for substance use that predict extreme scores in the PDI-21 and the CAPE-42, controlling for the effect of gender and anxiety*

| Variable | Use type | *B* | Standard error | Wald | g.l. | *p* | *Odds ratio* | Confidence interval 95% | $R^2$ Nagelkerke |
|---|---|---|---|---|---|---|---|---|---|
| PDI-21 Total | | | | | | | | | |
| | Alcohol | 3.161 | 0.787 | 16.12 | 1 | 0.001 | 23.59 | 5.04-110.30 | 0.557 |
| | Cannabis | 1.434 | 0.677 | 9.48 | 1 | 0.034 | 4.195 | 1.112-15.22 | 0.591 |
| CAPE Positive | | | | | | | | | |
| | Alcohol | 0.875 | 0.444 | 3.875 | 1 | 0.049 | 2.399 | 1.004-5.371 | 0.457 |
| CAPE Depressive | | | | | | | | | |
| | Alcohol | 2.230 | 0.077 | 9.073 | 1 | 0.003 | 10.172 | 2.248-46.018 | 0.831 |
| CAPE Total | | | | | | | | | |
| | Alcohol | 1.572 | 0.747 | 4.429 | 1 | 0.035 | 4.816 | 1.114-20.822 | 0.796 |

reported a higher number of subclinical psychotic experiences, especially of a cognitive-perceptual type. Likewise, alcohol use predicted, in most cases, extreme scores on measures of delusional ideation (PDI-21) and of psychotic-like experiences (CAPE-42). These findings seem to support dimensional models of the psychotic phenotype and enable for increasing our understanding of the relationship between psychotic-like experiences and substance use in non-clinical young adults.

First, the findings of this study indicate that psychotic experiences are not strictly limited to the clinical population, but rather may be normally distributed among the general population, below the clinical threshold, suggesting the possibility of a continuum between clinical and subclinical phenotypes of psychosis (Linscott & van Os, 2013; van Os et al., 2009). Previous studies have reached similar conclusions, analysing both non-clinical adolescents and adults of the general population (Debbané et al., 2015; Fonseca-Pedrero, Santarén-Rosell, Paino, & Lemos Giraldez, 2013; Ibáñez-Casas et al., 2015; McGrath et al., 2015). For example, a study carried out by McGrath et al. (2015), with a sample of 31,261 adults from 18 countries, found that the average prevalence of psychotic-like experiences was of 5.8%, with hallucinations experienced by 5.2% and delusional experiences by 1.3%. Likewise, substance use was quite common among this sample, with results similar to, or even lower than, those reported in previous studies (Fumero et al., 2009; Hernández-Serrano, Font-Mayolas, & Gras, 2015). According to the 2013/2014 Home-based Interviews on Alcohol and other Drugs (EDADES, 2015), the most-used drugs are alcohol (78.3% have consumed alcohol in the last twelve months), tobacco (40.7%) and hypnosedatives (12.2%). Likewise, as to the use of cannabis, 9.2% of those surveyed reported having tried it *at least once over the last year*, while 6.6% *at least once over the last month*. Specifically, 2.2% of the Spanish population meets the required criteria for diagnosing problematic cannabis use.

Second, participants who used some type of substance, with the exception of cocaine, reported a higher number of attenuated psychotic experiences. Specifically, effect sizes were higher for use of alcohol and cannabis. The results of this study are convergent with those reported in earlier publications on psychotic-like experiences (Barkus et al., 2006; Mackie et al., 2013; Saha et al., 2011; Schubart et al., 2011; van Os et al., 2002), as well as schizotypy (Barkus et al., 2006; Davis et al., 2013; Fumero et al., 2009; Najolia et al., 2012; Nunn et al., 2001). For example, Saha et al. (2011) found that psychotic-like delusional experiences were related with a higher use of tobacco, cannabis, and alcohol. Likewise, participants with disorders due to cannabis use were more prone to report subclinical psychotic experiences. This association was more prominent in individuals with an age of initial use of 16 years or under. To the contrary, the pattern of association between delusional experiences and alcohol use or dependence were less consistent. Nevertheless, individuals with disorders due to alcohol use at an early age were more prone to report these types of psychotic-like experiences (Saha et al., 2011).

Per these results, participants that use substances report more psychotic-like experiences when compared with non-users, though the nature of the association is unclear and is, apparently, quite complex. Different hypotheses may be proposed. It is possible that those participants with these types of experiences recur to substances to mitigate or alleviate their impact (e.g., dysphoria, self-medication or reverse causation). Likewise, it is plausible that the substance use itself predisposes the user for psychotic experiences (causal relationship). Also, the existence of a bidirectional

relationship is possible (a combination of both hypotheses) or that, simply, an association exists. In this regard, current models consider that the relationships between substance use and psychotic experiences, symptoms, and disorders are complex, dynamic, and multifactorial (e.g., age of initial use, frequency of use, protective factors, family history of disorders), as the paths for developing heterogeneous psychotic symptoms (Henquet, Di Forti, Morrison, Kuepper, & Murray, 2008).

Third, the results derived of the logistic regression analyses prove that alcohol use, once having controlled for the effect of certain covariables, was the most powerful predictive variable for the group with extreme scores in psychotic-like experiences. In almost all of the cases, high odds ratio were found. Compared with the remaining patterns, alcohol users with a moderate-high consumption (21-50 g/day) obtained the highest average scores. Given the reduced sample size in this study, conclusive data cannot be drawn for the severe consumption group (more than 50 g/day). Likewise, the association between type of consumption and psychotic-like experiences revealed a differentiated pattern, detecting a stronger association with cognitive-perceptual psychotic-like experiences and a weaker one with negative psychotic-like experiences. Previous studies analysing the role of negative traits of schizotypy or negative psychotic-like experiences yielded similar, though inconsistent, results. For example, some studies reflect the existence of an association between the negative dimension and use of drugs on a subclinical level (Bailey & Swallow, 2004; Davis et al., 2013); however, it is likewise true that other studies indicate that users of cannabis and alcohol obtain lower scores on the negative dimension of schizotypy in comparison with non-users (Nunn et al., 2001; Skosnik et al., 2008), or do not find this association (Barkus et al., 2006; Dumas et al., 2002; Fridberg et al., 2011; Schiffman et al., 2005). In general terms, these results seem to reveal the existence of a differentiated pattern of association between this series of experiences and subclinical psychotic traits and substance use (e.g., use, frequency and age of initial use), though this issue requires further research given that results vary depending on the type of study, sample, measurement instruments, and statistical analysis performed.

These types of psychotic-like experiences could be combined with other risk markers, such as, for example, substance use and abuse, stress, trauma or growing up in an urban environment (van Os et al., 2010), to examine possible underlying aetiological mechanisms of disorders of the psychotic spectrum (Henquet et al., 2008). Some theoretical models hypothesize that the cumulative or synergic presence of different environmental risk factors, depending on an individual's developmental stage and predisposition or vulnerability, may favour the transformation of certain psychotic-like experiences into abnormally persistent ones, in the future comprising clinical symptoms and the subsequent need for treatment (Cougnard et al., 2007). For example, epidemiological studies have found that the start of using cannabis in adolescence increases the probability of psychotic symptoms and disorders during adulthood (Arseneault et al., 2002) and contributes to their persistence over time (Mackie et al., 2013). In the same way, it seems that when the use of cannabis interacts with other risk factors, such as traumatic experiences, the likelihood of having psychotic symptoms increases (Cougnard et al., 2007; Harley et al., 2010). Other models, based on studies using animals, also postulate on the effect that cannabinoids may cause on different dopamine and/or cannabinoid receptors (especially at the level of the prefrontal cortex, striate cortex and hippocampus), as well as with regards to their capacity for modifying the glutamatergic system and for triggering a wave of biochemical changes, perhaps neurotoxic and, likewise, increasing the risk for developing psychotic disorders (Bossong & Niesink, 2010; Rocchetti et al., 2013).

The following limitations must be taken into account when interpreting the results of this study. First, the use of an incidental sample of college students, mostly female. In this regard, the characteristics of the sample affect the validity of the results, as well as their possible generalisation to other populations of interest. Second, the problems inherent to self-reporting, wherefore the use of external reporters would have been interesting (e.g., interviews) to analyse the presence of mental disorders among study participants, or laboratory measures (e.g., blood analyses) to verify substance use. Third, the transversal nature of this study cannot be overlooked, which prevents the possibility of inferring cause-effect relationships. Fourth, substance use has been associated with neurocognitive deficits (López-Caneda et al., 2014) and physiological effects (Vinader-Caerols, Monleon, & Parra, 2014), aspects that may modulate the results. Finally, the administration of measurement instruments for analysing the depressive affective state would have been interesting.

Future research should perform longitudinal studies and determine the predictive value of substance use in developing disorders along the psychotic spectrum and include neuroscientific models accounting for complex and dynamic interactions established in the gene x environment interaction, for purposes of improving early detection strategies and for the early detection and identification of individuals at risk of these disorders.

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# Persistent psychotic symptoms after long-term heavy use of mephedrone: A two-case series

## *Síntomas psicóticos persistentes después del uso abusivo prolongado de mefedrona: una serie de dos casos*

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## Abstract

Mephedrone (4-methylmethcathinone) is a synthetic stimulant drug of the cathinone class. Similar effects to those of cocaine and ecstasy are reported by users, with a high addictive potential. Given its increasing rate of consumption in Europe, it is getting more and more attention from the addiction field. In spite of that, little is known about the long-term consequences of prolonged heavy use. The two following cases might depict some of them.

Case 1 was a middle-age man who reported three years of intravenous use of mephedrone. He used to binge for several days in a row. Psychotic symptoms appeared after a few months, especially paranoid delusions. Sent to aftercare in a therapeutic community, delusions kept reappearing after prolonged abstinence. A good response to risperidone was observed.

Case 2 was a young man who used mephedrone heavily for two years, always snorted. Upon admission to the therapeutic community, the patient reported auditory hallucinations that partially remitted with olanzapine. Both cases showed a good insight and no personality deterioration.

Given its similarities to other substances that are known to induce psychotic symptoms, and the increasing consumption of mephedrone around Europe, similar cases are expected in the near future. Conventional antipsychotic treatment seems a reasonable pharmacological approach.

*Keywords:* mephedrone; cathinone; drug dependence; psychosis; heavy use; new psychoactibe substances.

## Resumen

La mefedrona (4-methylmethcathinone) es un estimulante sintético del grupo de las catinonas. Los usuarios refieren efectos similares a los de la cocaína y el éxtasis, con un potencial adictivo elevado. Dada la creciente tasa de consumo en Europa, cada vez recibe más atención desde el campo de las adicciones. No obstante, poco se sabe sobre las consecuencias a largo plazo de su consumo abusivo. Los dos siguientes casos pueden servir para mostrar alguna de ellas.

El caso 1 es un hombre de mediana edad, quien refería un consumo intravenoso de mefedrona de 3 años de duración. Su patrón de uso consistía en atracones que duraban varios días. Tras varios meses de consumo, aparecieron síntomas psicóticos, especialmente delirios paranoides. Tras ser enviado a una comunidad terapéutica, los síntomas psicóticos se continuaron produciendo pese a mantener una abstinencia prolongada. Se observó una buena respuesta a la risperidona. El caso 2 es un hombre joven, con un consume abusivo de 2 años de duración, vía nasal. A su llegada a la comunidad terapéutica, el paciente refirió alucinaciones auditivas que remitieron parcialmente con olanzapina. Ambos casos mostraron una buena conciencia de enfermedad, así como ausencia de deterioro en su personalidad.

Dadas las similitudes bioquímicas con otras sustancias con potencial para inducir síntomas psicóticos, y el creciente consumo de mefedrona en Europa, casos similares son esperables en un futuro cercano. El uso de antipsicóticos convencionales parece una estrategia razonable de tratamiento.

*Palabras clave:* mefedrona; catinona; dependencia a sustancias; psicosis; consumo abusivo; nuevas sutancias psicoactivas.

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Mephedrone, a synthetic cathinone, was initially synthesized as early as 1929 (European Monitoring Center for Drugs and Drug Addiction, 2010). However, its appearance in the context of human recreational consumption dates back only a few years. It displays strong stimulant and entactogen effects, similar to those of cocaine and MDMA (Winstock et al., 2011). Its addictive potential remains high, with some cases of dependence already reported in the literature (Bajaj, Mullen & Wylie, 2010).

Noteworthy, its consumption has dramatically increased in the past few years, reaching, in some countries, levels similar to those of other stimulants, such as cocaine, amphetamines and ecstasy (European Monitoring Center for Drugs and Drug Addiction, 2010). Despite all that, little is known in the actual literature about mephedrone use disorders, its natural history, treatment or adverse effects in the long run.

The biggest population-based study to date (Winstock et al., 2011), with a cross sectional design conducted with club drug users, excluded the investigation of psychotic symptoms associated with its consumption. However, given its biochemical similarity to other psychosis-inducing substances, as well as the specific body of evidence emerging around synthetic cathinones, it would be reasonable to expect such symptoms in the context of mephedrone consumption. As it is the case with other drugs, it would be also relevant to investigate whether psychotic symptoms are related to intoxication, withdrawal or whether they may persist after prolonged abstinence (and in such instances, the risk or association with illnesses such as schizophrenia).

To try to shed some light into these questions, we present two cases of mephedrone addiction with long-term heavy use, who presented persistent psychotic symptoms after prolonged abstinence, treated in a therapeutic community.

## Case 1

A 40 year old, white, single male, with university education and a stable high-qualified job came to our rehabilitation centre accompanied by his family. No previous psychiatric history, neither personal nor familial, was reported. Only occasional cocaine use figured among his substance use records. Three years ago, after a relationship break-up, the patient started using mephedrone. Initially snorted, it soon became an intravenous use, usually associated with sexual activity. The patient reported a heavy use, being able to binge for five consecutive days, usually two to three times per month. The usual amount he used in a day of binge was between 1 and 3 grams.

After a severe deterioration in both his psychological and physical health status, with the emergence of persecution and reference delusions, the patient started an outpatient treatment. Given the lack of success in achieving and maintaining abstinence, he was transferred to our Therapeutic Community, where he spent 4 months. Upon admission, no antipsychotics were administered, given the fast remission of his delusional ideas once he became fully abstinent. The insight the patient displayed about them was fairly good. However, in the last weekend-permissions before discharge, he reported delusional beliefs again. They lasted only a few minutes, and again, his insight was good, so no medication was considered necessary. Finally, once back in the community, these brief, self-limited psychotic symptoms, mainly delusional beliefs of persecution and reference, kept reappearing. Therefore, risperidone 1 mg each night was prescribed, with complete remission up until the moment of writing this paper, three months after discharge of our therapeutic community.

## Case 2

A 26 year old, white, single male with university education and a high-qualified job came to our Therapeutic Community accompanied by his family after two years living abroad in the UK, where heavy use of mephedrone (always snorted, usually between 1 and 2 grams), on a daily basis, had taken place. The patient had no previous psychiatric history. Occasional use of cocaine was also reported. The patient described heavy use of alcohol in recent years. Upon admission, the patient reported auditory hallucinations, with no behavioural or affective impact. His insight regarding the origin of these psychotic symptoms was fairly good. High dose of olanzapine (up to 30 mg per day) was started, with gradual resolution of the hallucinations, although at the time of writing this paper, the patient is still in our Therapeutic Community and minor hallucinations of a few seconds duration are still present. No other psychotic symptoms were observed.

## Discussion

This report about the psychopathological consequences of long-term heavy-use of mephedrone is in line with previous publications outlining similar effects of mephedrone on heavy users (Dragogna, Oldani, Buoli & Altamura, 2014). Besides the usual consequences of addiction itself (social, organic and psychological deterioration) both cases presented persistent psychotic symptoms after months of abstinence to the substance. The fact that no previous psychiatric history existed in both cases, tentatively leads to a drug-related origin.

Given its biochemical similarities with amphetamines and other stimulants, and their well-known potential to induce psychotic symptoms (Bramness et al., 2012), it is not striking to observe such symptoms after long-term heavy use of mephedrone. A recent body of evidence is emerging, specifically related to synthetic cathinones, its biochemical and neurological toxicity, its behavioural consequences and its

psychiatric and physiological effects (Gregg & Rawls, 2014; Weaver, Hopper & Gunderson, 2015 ). Given its novelty, however, most of the data provided by this research is related to the acute consequences of consumption. The available evidence suggests that psychotic symptoms are related dysfunctions in the dopaminergic system (Martínez-Clemente et al., 2014). Besides dopamine, other systems such as the serotoninergic might also be relevant parts in the overall toxicity of the drug.

Despite the novelty and the short-term nature of these findings, a tentative comparison with the case of methamphetamine might be made to foresee the long-term consequences of mephedrone use, since methamphetamines, biochemically related to synthetic cathinones, are one of the drugs with the highest potential to induce psychotic symptoms beyond intoxication, withdrawal and prolonged abstinence (Lichlyter, Purdon & Tibbo, 2011).

Given the increasing rate of consumption in Europe, especially in the UK (European Monitoring Center for Drugs and Drug Addiction, 2010), and the highly addictive properties of the substance (Weaver et al., 2015), one should consider that the implications might be relevant, as more and more cases are expected in the years to come. Indeed, there are already some reports suggesting that club drugs are one of the most prevalent substances seen in the Emergency Department (Nogué, Amigó & Galicia, 2014)

Although one suffered from delusions and the other from hallucinations, it is also worth mentioning that insight remained partially good in both case studies, and no personality deterioration, more ascribed to schizophrenia-like psychosis, was observed. The duration of consumption had been 3 and 2 years, respectively, therefore it remains unknown what would have happened if heavy use would have continued unchanged. In this scenario, it could be useful to think of a critical consumption threshold, assuming that, beyond a critical point, consumption might lead to persistent psychotic symptoms, and if continued, a chronic psychotic illness might ensue (Lichlyter et al., 2011).

Case series must be interpreted with caution, given their relevant limitations. The most relevant are its observational nature and the lack of control subjects. Therefore, it is not possible to fully establish a real and valid connection between drug use and the symptoms observed. For example, it can not be ruled out that drug use and symptoms onset were merely related by chance. Moreover, two other serious limitations must be taken into account when interpreting this report. First, as it is not implemented in routine clinical practice, upon admission, no toxicological evidence was gathered regarding the actual presence of mephedrone in patients' urine. Therefore, this report is based on patients' self-reports. Although this fact may diminish validity, it is a common methodological approach in the addiction field. Second, both patients had also used cocaine in the past, also a well-known psychosis-inducing substance. Nonetheless, both reported mephedrone to be, by far, their main substance of abuse. This fact reasonably allows for the described psychopathological symptoms to be subscribed to mephedrone. There remains also the possibility of an alcohol-related origin for the hallucinations of case 2, which should then be labelled as alcohol hallucinosis. However, given the relatively young age of the patient and that no withdrawal or intoxication symptoms were observed during his stay in the Clinic, we considered it reasonable to discard this diagnosis.

Finally, regarding the treatment of psychotic symptoms associated with mephedrone, the little evidence this case series offers suggests that second generation antipsychotics, as in other substance-induced psychotic symptoms, might be useful.

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## Conflict of interests

None of the authors have any conflict of interest to disclose regarding the present report.

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# Segmental hair testing to disclose chronic exposure to psychoactive drugs

## *Análisis segmentario del pelo para detectar la exposición crónica a drogas psicoactivas*

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## Abstract

This study presents the case of a 4-year-old healthy child admitted to the paediatric ward for suspected accidental intoxication due to ingestion of narcoleptic drugs (methylphenidate, sertraline and quetiapine), taken on a regular basis by his 8-year-old brother affected by Asperger syndrome.

Intoxication can be objectively assessed by measurements of drugs and metabolites in biological matrices with short-term (blood and urine) or long-term (hair) detection windows.

At the hospital, the child's blood and urine were analysed by immunoassay (confirmed by liquid chromatography-mass spectrometry), and sertraline and quetiapine and their metabolites were identified. The suspicion that the mother administered drugs chronically prompted the analysis of six, consecutive 2-cm segments of the child's hair, using ultra-high performance liquid chromatography-tandem mass spectrometry, thereby accounting for ingestion over the previous 12 months. Quetiapine was found in the first four segments with a mean concentration of 1.00 ng/mg ± 0.94 ng/mg hair while sertraline and its metabolite, desmethyl-sertraline, were found in all segments with a mean concentration of 2.65 ± 0.94 ng/mg and 1.50 ± 0.94 ng/mg hair, respectively. Hair analyses were negative for methylphenidate and its metabolite (ritalinic acid).

Biological matrices testing for psychoactive drugs disclosed both acute and chronic intoxication with quetiapine and sertraline administered by the mother.

*Keywords:* Segmental hair testing; Children; Antidepressants; Antipsychotics; Ultra-high performance liquid chromatography-tandem mass spectrometry.

## Resumen

Se presenta el caso de un niño sano de 4 años de edad que ingresa en la sala de hospitalización pediátrica por la sospecha de una intoxicación accidental debido a la ingesta de fármacos narcolépticos (metilfenidato, sertralina y quetiapina), que tomaba de forma pautada su hermano de 8 años de edad que padecía un síndrome de Asperger.

La evaluación objetiva de la intoxicación se puede realizar con la determinación de los fármacos y sus metabolitos en matrices biológicas con una ventana de tiempo corta (sangre y orina) o larga (pelo).

En el hospital se realizó un análisis de sangre y orina mediante inmunoanálisis (confirmado mediante espectrometría líquida-cromatografía de masas) y se identificó la presencia de sertralina y quetiapina y sus metabolitos. Con la sospecha de administración crónica de fármacos al niño, se procedió al análisis del pelo con cromatografía líquida de ultra-alto rendimiento-espectrometría de masas en tándem. El pelo se dividió en 6 segmentos consecutivos de 2 cm de longitud, de forma que permitieron estudiar la ingesta de los fármacos durante los últimos 12 meses. En los primeros 4 segmentos se encontró quetiapina con una concentración media de 1,00 ng/mg ± 0,94 ng/mg de pelo y en todos los segmentos se encontraron sertralina y su metabolito, desmetil-sertralina, con una concentración media de 2,65 ± 0,94 ng/mg y 1,50 ± 0,94 ng/mg de pelo, respectivamente. El análisis de pelo resultó negativo para metilfenidato y su metabolito (ácido ritalínico).

La detección en matrices biológicas de fármacos psicoactivos demostró la intoxicación aguda y crónica por quetiapina y sertralina, administradas por la madre.

*Palabras clave:* Análisis segmentario del pelo; Niños; Antidepresivos; Antipsicóticos; Cromatografía líquida de ultra-alto rendimiento-espectrometría de masas en tándem.

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Given the severity of paediatric mood and anxiety disorders and their psychosocial and functional consequences, clinical practice demands the development of complementary approaches for difficult cases, such as combining antidepressants with other psychotropic drugs (Díaz-Caneja, Espliego, Parellada, Arango and Moreno., 2014). Paediatric psychiatric polypharmacy, defined as the receipt of multiple daily psychiatric medications for the same or for different conditions, has been increasing (Hilt et al., 2014). Antidepressants have become one of the drug classes most frequently prescribed in combination and are commonly co-prescribed with stimulants and antipsychotics in children and adolescent affected by psychiatric disorders (Díaz-Caneja et al., 2014). Concerns about this include a lack of research evidence supporting the effectiveness of most medication combinations, poorly defined side effects from medication combinations (Hilt et al., 2014). Side effects were particularly more common in medication combinations including either selective serotonin reuptake inhibitors (SSRIs) or antipsychotics (Hilt et al., 2014).

Non compliance, but specially or excessive consumption and also criminal forced parental administration, mainly in combination, has been demonstrated in some cases and may lead to potential severe side effects (Binchy, Molyneux and Manning, 1994; Gaillard et al., 2011; Pawłowicz, Wasilewska, Olanski and Stefanowicz, 2013).

The objective assessment of intoxication can be disclosed by drug and metabolites measurement in biological matrices for short-term (blood and urine) or long-term (hair) time window, with hair testing particularly successful in paediatric chronic intoxications (Garcia-Algar et al., 2005; Joya et al., 2009; Joya et al., 2011; Papaseit, Garcia-Algar, Simo, Pichini and Farre, 2013; Pichini et al., 2006; Pichini et al., 2014a; Pichini et al., 2014b; Pichini et al., 2014c).

In addition, segmental hair analysis can disclose a month to month (considering 1 cm segment cuts) eventual repeated chronic exposures and, in some instances, identify patterns of drug use/administration (Pichini et al., 2006; Thieme, Baumer, Sachs and Teske, 2013).

We report a case of a child admitted to the hospital for suspected psychoactive drugs intoxication and found chronically intoxicated by segmental hair testing.

## Method

### *Case report*

A 4 years old child was admitted to the paediatric ward of the hospital with lower extremity pain and clumsiness. The day before his admission the family noticed increasing drowsiness and gait alterations. The initial exam on the emergency room he was exhausted, drowsiness, afebrile and presented cough and thick nasal discharge. The child was admitted with the diagnosis of encephalitis versus drug intoxication (two years ago he had been admitted for an episode of encephalitis that resolved over a three months period). A blood cell count, liver and renal function test including the determination of lactates and ammonia and cerebrospinal fluid analysis were done with normal results a head CT was also performed being normal. Specific gas chromatography mass spectrometric analysis of blood and urine revealed the presence of sertraline and quetiapine, two of the three psychoactive drugs (the other was methylphenidate) taken by the 8 years old brother affected by Asperger syndrome.

Once hospitalized, the child presented a wide range of symptoms such as persistent drowsiness, generalized weakness, slurred speech, urinary incontinence and constipation. During the first four days he experienced miosis, lacrimation and blepharospasm. During four days clinical symptoms changed gradually: no deep reflexes from the second day, an erythematous flush in the upper third of the trunk, head and neck, dystonic movements of the extremities, extrapyramidal signs and generalized tonic seizures with mydriasis scarcely reactive to light that resolved with diazepam. He was then admitted to the intensive care unit (ICU) for further management and monitoring. Few hours after the transfer to the ICU the child experienced a gradual recovery of vigilance and muscle tone, mydriasis resolved, he was able to sit alone, to grasp objects, to move them from hand to hand, and to lift them. An improvement in the language, including the comprehension of simple commands was observed. After 24 hours the child was able to walk.

The severe symptomatology, a previous similar episode, and the two drugs present in blood and urine samples prompted to ask for a segmental hair testing with the high suspicion of chronic non accidental administration by the mother of methylphenidate, sertraline and quetiapine administered also to his treated brother.

### *Sample collection, preparation and analysis*

Child hair, measuring 12 cm, was cut in 6 segments of 2 cm, representing a time window of approximately 2 months per segment for as total of 12 months. Hair samples were analyzed for the presence of methylphenidate, sertraline and quetiapine and their metabolites (ritalinic acid and desmethyl-sertraline) and any other eventual drug of abuse. At the time of analysis, the metabolite of quetiapine: 7-hydroxy-quetiapinestandard was not available. Briefly, hair samples (20 mg) were reduced in short cuts and after decontamination with dichloromethane and methanol they were added with 10 µl internal standard (promethazine 2 µg/ml) and treated with 500 ml M3 buffer reagent (Comedical, Trento, Italy) for an hour at 100 °C. Then, the treated samples were cooled at room temperature and 100 µ L of the M3 extract was diluted with 900 µ L of water before a sample volume of 10 µL was analysed by ultra-high performance liquid chromatography–tandem mass spectrometry. Chromatography was carried out

in reversed phase using a Acquity UPLC HSS C18 column (2.1 mm × 150 mm, 1.8 µ m) using a linear gradient elution with two solvents: 0.1% formic acid in acetonitrile (solvent A) and 0.1% formic acid in waters (solvent B). Solvent A was maintained 10% for the first 0.50 min. It was increased to 55% from 0.50 to 4.00 min, held at 55% from 4.0 to 6.00 min, and then decreased back to 10% from 6.00 to 6.10 min and held at 10% from 6.10 to 10.00 min for re-equilibration. The flow rate was kept constant at 0.40 mL/min during the analysis. The separated analytes were detected with a triple quadrupole mass spectrometer operated in multiple reaction monitoring (MRM) mode via positive electrospray ionization (ESI). The applied ESI conditions were the following: capillary voltage 3.0 kV, desolvation temperature 600 °C, source temperature 150 °C, cone gas flow rate 60 L/h, desolvation gas flow rate 1100 L/h and collision gas flow rate 0.13 mL/min. Cone energy voltages, MRM transitions, and collision energy voltages were established for each analyte and the values are listed in Table 1. The method was validated as elsewhere described (Pichini et al., 2014a) and applied with limit of quantification at 0.1 ng/g, and limit of detection at 0.04 ng/g. Linearity ranged from 0.1 to 10 ng/g. Imprecision was lower than 10%, analytical recovery ranged between 70.1% and 95.3% and process efficiency was 80.9%. All analytes under investigation showed no significant ion suppression/enhancement (less than 10% analytical signal suppression due to matrix effect).

Table 1. *Ultra-performance liquid chromatography tandem mass spectrometry parameters for the multiple reaction monitoring (MRM) acquisition mode*

| Analytes | Retention time (min) | MRM transitions | | | | | |
|---|---|---|---|---|---|---|---|
| | | Quantification | | | Confirmation | | |
| | | m/z | CV (V) | CE (eV) | m/z | CV (V) | CE (eV) |
| Ritalinic acid | 2.99 | 220.3 › 84.2 | 30 | 16 | 220.3 › 174.2 | 30 | 20 |
| Methylphenidate | 3.51 | 234.3 › 84.1 | 26 | 18 | 234.3 › 56.1 | 26 | 32 |
| Quetiapine | 4.16 | 384.2 › 221.2 | 26 | 36 | 384.2 › 253.2 | 26 | 20 |
| Desmethyl-sertraline | 5.48 | 292.2 › 159.0 | 8 | 28 | 292.2 › 275.1 | 8 | 16 |
| Sertraline | 5.68 | 306.2 › 159.1 | 14 | 30 | 306.2 › 275.1 | 14 | 14 |
| Promethazine (IS) | 4.84 | 285.2 › 198.1 | 22 | 28 | | | |

## Results

The results of hair testing on six 2.0 cm length strands collected after child admission to the hospital are shown in Table 2. Methylphenidate and its metabolite, ritalinic acid were absent in all the examined segments while quetiapine was present in the hair segments corresponding to the past eight months and sertraline and its metabolite desmethyl-sertraline were present in all segments representing the past twelve months.

Quetiapine concentration decreases from 2.29 ng/mg in the proximal segment to 0.10 ng/mg to the distal segment.

Sertraline and its metabolite, desmethyl-sertraline, were found in all segments. However, sertraline concentration was quite stable in the distal segments and increasing just in the segments corresponding to the past four months while metabolites concentration were decreasing from the proximal to the distal strand.

## Discussion

Hair testing in the four years child hospitalized with neurological symptoms of possible intoxication revealed chronic intoxication with two psychoactive drugs: quetiapine and sertraline, due to criminal administration by the mother of drugs prescribed to his brother.

Published data on quetiapine and sertraline concentration in hair are scarce. Only one published paper could be found that reported quetiapine concentration in hair of adults treated with dosages between 200 and 1200 mg (Binz, Yegles, Schneider, Neels and Crunelle, 2014). Quetia-

Table 2. *Psychoactive drugs in hair sample from intoxicated child*

| Segment (cm) | Methylphenidate (ng/mg) | Ritalinic acid (ng/mg) | Quetiapine (ng/mg) | Sertraline (ng/mg) | Desmethyl-sertraline (ng/mg) |
|---|---|---|---|---|---|
| 0-2 | nd | nd | 2.29 | 4.28 | 3.79 |
| 2-4 | nd | nd | 1.23 | 3.28 | 1.89 |
| 4-6 | nd | nd | 0.40 | 2.07 | 0.87 |
| 6-8 | nd | nd | 0.10 | 2.25 | 1.66 |
| 8-10 | nd | nd | nd | 1.88 | 0.41 |
| 10-12 | nd | nd | nd | 2.13 | 0.39 |

pine concentrations ranged from 0.35 to 10.21 ng/mg hair with 7-hydroxy-quetiapine concentrations from 0.02 to 3.19 ng/mg hair in two cm or longer hair segments. Individuals showed a trend in quetiapine concentration that matches to our one: a linear decrease from proximal to distal segment. The authors hypothesized the effect of cosmetic hair treatments (eg. shampoos and other products) as a reason for concentration decrease, more plausible than a change in compliance or dosage. This was in accordance with the internationally accepted effect of cosmetic hair treatments and sweat influence in decreasing xenobiotic concentration from proximal to distal hair segments (Jurado, Kintz, Menendez and Repetto, 1997). Similarly, only one paper reported sertraline concentration in human post-mortem hair with sertraline concentrations ranging from 0.6 to 1.6 ng/mg hair with desmethyl-sertraline concentrations ranging from 0.5 to 2.6 ng/mg hair of death person (Wille et al., 2009).

Although data on hair testing for quetiapine and sertraline in children are lacking, from obtained results we could conclude that child was treated repeatedly with the two drugs. The clinical manifestations of antipsychotic drug toxicity generally include varying degrees of central nervous system depression, anticholinergic effects, pupillary changes, seizures, hypotension, and cardiac conduction abnormalities (Cobaugh et al., 2007). In addition, many patients who overdose on selective serotonin reuptake inhibitors are asymptomatic (Sarko, 2000). Symptoms, when they do occur, are usually self-limited and consist of tachycardia, drowsiness, tremor, nausea, agitation, visual hallucinations, diaphoresis, flushing and vomiting (Grenha, Garrido, Brito, Oliveira and Santos, 2013; Myers, Dean and Krenzelok, 1994; Pao and Tipnis, 1997).

In our case report, infant symptoms resulting from ingestion of psychotropic drugs and chronic exposure was established on the basis of the presence of quetiapine and sertraline in hair. The peak in drug concentration occurs in the 0 to 2-cm section of hair for both quetiapine and sertraline, suggesting that these drugs were accidentally or intentionally or forcedly ingested in a non negligible amount before acute intoxication and consequent hospitalization.

The main clinical implications of this case are related to the usefulness of hair analysis to disclose chronic consumption or exposure to drugs of prescription (and also to drugs of abuse) related to overdose, combination or polypharmacy.

## Conclusion

Hair testing is complimentary to blood and urine testing in disclosing suspected chronic intoxication to toxic xenobiotics in presence and/or absence of acute one. Furthermore, segmental hair analysis can provide information as to whether the substance was taken regularly before the alleged incident or if the substance had been ingested only in a short timeframe that corresponded to the moment of the incident.

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## Conflicts of interests

The authors declare that there are no conflicts of interests.

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# Alcoholism and its treatment approach from a citizen perspective

## *El alcoholismo y su abordaje desde una perspectiva ciudadana*

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## Abstract

*Introducción*: El objetivo del estudio es describir el consumo de alcohol de la población general española, conocer la opinión que tienen los ciudadanos de su consumo, del alcoholismo y de su abordaje terapéutico.

*Métodos*: Estudio descriptivo transversal mediante encuesta telefónica que se realizó en mayo de 2015. Se seleccionó una muestra representativa de la población adulta española a quien se le preguntó acerca de su patrón de consumo de alcohol, percepción de riesgo, opinión acerca del alcoholismo, y consecuencias del consumo, y abordaje terapéutico. Se diseñó un cuestionario ad hoc utilizando el AUDIT-C para determinar el patrón de consumo. Se realizó un análisis descriptivo e inferencial según las características socio-demográficas.

*Resultados*: El 22,1% presentan un consumo de riesgo, siendo mayor en los hombres y los jóvenes. Mayoritariamente el alcoholismo es considerado una enfermedad y más del 75% de los ciudadanos coinciden que el alcohol tiene consecuencias negativas en la salud a nivel sociolaboral y familiar. La percepción de riesgo que tienen los ciudadanos de su consumo es mayor de lo esperado (37,6%). El 67,7% considera al médico de familia capacitado para atender los problemas relacionados con el consumo de alcohol, sobre todo entre las mujeres y los ciudadanos de mayor edad.

*Conclusiones:* El consumo de riesgo es muy prevalente entre los ciudadanos españoles sobre todo entre los jóvenes (31,8%). Existe una alta autopercepción de riesgo del consumo de alcohol. La mayoría de ciudadanos coinciden que el médico de familia está capacitado para tratar el alcoholismo.

*Palabras clave:* alcohol; detección; prevención; tratamiento; percepción de riesgo.

## Resumen

*Introduction:* The main objective of the study is to describe alcohol consumption in the general Spanish population, to discover citizens' opinion on their alcohol consumption, on alcoholism and on treatment approaches.

*Methods:* In 2015 a cross-sectional study was carried out by means of a telephone survey. A representative sample was selected. Participants were asked about their alcohol consumption, their perception of risk regarding their pattern of alcohol consumption, about their opinion on alcoholism, alcohol consequences and the treatment approach. A questionnaire was designed. The Alcohol Use Disorders Identification Test-C was used to define the pattern of alcohol intake. A descriptive and an statistical inference analysis were done.

*Results:* 22.1% were classified as risky drinkers, with a higher proportion in young males. The majority of individuals think that alcoholism is an illness, and more than 75% agree that alcohol has negative consequences on health, social functioning, occupational functioning and family relationships. Furthermore, the perception of risk that citizens have regarding their own drinking pattern is high (37.6%). 67.7% considered that the general practitioner can manage alcoholism, with females and older people believing this most strongly.

*Conclusions:* Alcohol consumption is very prevalent in the Spanish population, especially in young people (31.8%). The perception of alcohol risk is high. The majority agree with the fact that general practitioners are well prepared for treating alcohol problems.

*Keywords:* alcohol; screening; prevention; treatment; risk perception.

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Alcohol consumption is the third biggest risk factor in terms of worldwide morbi-mortality (World Health Organization, 2011). It is also responsible for 6.8%-9.6% of disability adjusted life years (Degenhardt et al., 2013; Patel et al., 2015) and for more than 200 illnesses and conditions (World Health Organization, 2011). Worrying changes have been observed in recent years in alcohol consumption patterns in Spain, for example the rise in binge drinking, mainly among women. Binge drinking is also one of the most serious prognostic factors in alcoholism (Dawson, Li, & Grant, 2008; Gmel, Kuntsche, & Rehm, 2011). This consumption pattern requires more specific treatments than the normal short intervention (Rubio et al., 2015), and need to include two factors heavily linked to binge drinking: the subject's expectations regarding alcohol consumption, and the perception of risk which this substance can have on the individual's health (Cortés, Gimenez-Costa, Motos, & Cadaveira, 2014). These two aspects have been little explored in the general population. The few studies of risk perception regarding alcohol consumption focus on aspects other than self-perception of the subject's own consumption of alcohol, such as a comparison between the perception of risks involved in alcohol consumption as opposed to other substances (Delegación del Gobierno para Plan Nacional sobre Drogas, 2013), or the risk perception of alcohol consumption in the general population (Bischof, Bischof, Meyer, & Rumpf, 2015; Karlsson, 2012). There has been no research into the self-perception of risk or the concern of the citizens regarding their own consumption of alcohol, despite this being considered to be a relevant prognostic marker (Bertholet, Faouzi, Studer, Daeppen, & Gmel, 2013; Bischof et al., 2015).

Alcoholism is a chronic disease (Erdozain & Callado, 2014) with an estimated prevalence of 5.4% and 1.5% among adult European men and women respectively, which amounts to around 12 million people affected in Europe alone. In Spain, it is estimated that 202,010 citizens suffer from this pathology (1,2% of men and 0,2% of women) (Rehm, Shield, Rehm, Gmel, & Frick, 2012). These figures are equivalent to other treatable chronic medical conditions such as schizophrenia (0.3-0.8%) (Ayuso-Mateos, Gutierrez-Recacha, Haro, & Chisholm, 2006; Moreno-Küstner et al., 2016) or HIV (0,3%) (UNAIDS, 2014).

Alcoholism is a health problem with far-reaching social implications. It is extremely stigmatizing, to a greater degree than other mental disorders such as schizophrenia or depression (Schomerus et al., 2011), or medical diseases in which lifestyle habits play an important role, for example diabetes mellitus or hypertension. The stigma has clinical relevance in that it has been linked to lower self-efficacy in rejecting alcoholic beverages (Schomerus et al., 2011). In general, it should be borne in mind that greater acceptance of people with mental disorder in society has a positive influence on their prognosis, with the suicide rate, for example, being reduced to general population levels (Schomerus et al., 2015). Furthermore, viewing mental disorders as a continuum appears to be linked to lower levels of stigmatization (Schomerus, Matschinger, & Angermeyer, 2013). With regard to alcohol consumption, the term "heavy use over time" has recently been proposed with the aim of reducing the stigmatizing label of alcoholism and give greater importance to the quantity of alcohol consumed over time, which is the factor with a direct link with morbi-mortality (Rehm et al. 2013). DSM-V diagnostic criteria also incorporate the idea of a continuum in psychiatric diagnoses with the aim of reducing the stigma attached to mental health.

The stigma surrounding the disease is among the reasons behind the low treatment access rates (15.3%) (Hasin & Grant, 2015; Luoma et al., 2007; Wolstenholme et al., 2013), despite being a medical condition for which effective pharmacological treatments and psychological interventions are available (Kaner et al., 2009; Rösner et al., 2010; Smedslund et al., 2011). Treatment access rates in Spain are slightly higher than among our European neighbors (7.6%), though still much lower than for other mental illnesses such as schizophrenia (82.2%), major depression (54.6%), bipolar (60.1%), general anxiety (37.7%) or obsessive-compulsive disorders (75.4%) (Robert, Saxena, Levav, & Saraceno, 2004).

The aims of this study are: 1) to describe the pattern of alcohol consumption in the target population; 2) to describe and explore citizens' perceptions of their own levels of alcohol consumption and the associated sociodemographic and clinical factors; 3) to describe and explore the beliefs of citizens regarding alcoholism and its effects, as well as the opinions of health professionals in charge of dealing with alcoholism. We expect to find a pattern of consumption similar to that observed in the general population and a low perception of risk regarding citizens' own consumption. Understanding what citizens think of their own consumption, what their opinions are regarding alcoholism and its consequences, and the factors involved are necessary elements to better understand the stigma surrounding the illness and, thus, design effective population-based prevention strategies.

## Methods

### *Study design and population*

A transverse observational descriptive study was carried out. The sample was taken from the target adult population (18 to 65 years of age) throughout Spain. A representative sample of 4250 individuals was selected (2136 men and 2114 women) from the Spanish population using a stratified random sampling approach with homogenous fixing for each autonomous community and proportionally adjusted for sex and age. The sample yielded a sampling fraction of 0.14% with a sampling error of 1.3% (confidence interval

of 95.5%). The baseline data for the sampling frame was the ongoing census of Spain's National Statistics Institute on January 1, 2014. A total of 13.6% of those contacted by telephone refused to take part in the survey, and 0.2% did not complete the telephone survey.

### *Assessment*

Individuals were assessed by telephone. The questionnaire design included socioeconomic data (age, sex, level of income, and employment) and the level of consumption. AUDIT-C was used to determine the quantity and frequency of consumption. A standard drink unit (SDU) was considered to be equivalent to 10 grams of pure alcohol (Gual, Martos, Lligoña, & Llopis, 1999).

Based on the results obtained by AUDIT-C, the level of drinking risk was determined by the following criteria: 1) no consumption (0 points), low risk (1-3 points, or 4 points but all on the first question), moderate risk (4 or 5 points), high risk (6 or 7 points), very high risk (8-12 points). Subjects were also asked how they perceived their own level of risk and how worried they were about their own consumption. In addition, they were asked for their opinion about alcoholism, whether or not it was an illness or a vice, and about its positive or negative effects on physical or mental health, and on family, social and work environments. Finally, citizens were asked as to the type of health professional who should treat alcohol problems (specialist, primary health-care personnel o others), and about their perception of primary health-care professionals and their role in the treatment of alcohol consumption.

### *Statistical analysis*

The data were weighted by age, sex and autonomous community of origin. A descriptive analysis was carried out, with continuous quantitative variables described by their means and categories by number of subjects and percentages. Responses of the type "doesn't know/didn't answer" were excluded from the analysis.

In order to compare categorical variables across groups, Chi-square or Fischer exact tests were used depending on the distribution of the variables. A value of $p < 0.05$ was set to establish statistical significance with application of the Bonferroni correction for multiple comparisons. Bivariate analysis was carried out on the sociodemographic data and risk level of alcohol consumption as independent variables, with other variables considered as dependent. A variety of multivariate analyses were run to determine the relationship between self-perception of risk relating to own consumption (very low and low vs moderate, high and very high), perception of own consumption, opinions held on the concept of alcoholism, the place where it should be treated and by which healthcare professionals, and the sociodemographic and clinical variables. The following variables were recategorized: age (using 35 as the cut-off in the

Table 1. *Sociodemographic data of patients interviewed and results of the citizen survey (n=4250)*

| | n (%) |
|---|---|
| **Sex (men)** | 2136 (50.3) |
| **Age (years)** | |
| ≤ 35 | 1450 (34.1) |
| › 35 | 2800 (65.9) |
| **Educational level** | |
| Primary | 920 (21.7) |
| Secondary | 1527 (36) |
| University | 1790 (42.3) |
| **Employment** | |
| Employed | 2381 (56.2) |
| Student | 443 (10.4) |
| Other situation | 1415 (33.4) |
| **Income level** | |
| Equal to or below €2000/month | 2440 (63.3) |
| Above €2000/month | 1412 (36.7) |
| **Risky consumption according AUDIT-C** | |
| No consumption | 938 (22.5) |
| Low risk | 2310 (55.4) |
| Moderate risk | 664 (15.9) |
| High risk | 205 (4.9) |
| Very high risk | 51 (1.2) |
| **Self-perception of risk of drinking** | |
| Very low, low | 2433 (73.8) |
| Moderate | 811 (24.6) |
| High, very high | 54 (1.6) |
| **Have you worried at some point about the amount of alcohol you consume?** | |
| Yes | 345 (37.6) |
| **In your opinion, what is alcoholism?** | |
| A vice | 361 (8.5) |
| An illness | 3623 (87.1) |
| Both | 174 (4.2) |
| **If you knew someone with alcoholism, where should s/he go for treatment?** | |
| Primary care | 1333 (33.5) |
| Specialized care | 1209 (30.4) |
| Other | 1436 (36.1) |
| **Do you consider that the GP is the right health professional to deal with alcohol problems?** | |
| Yes | 2764 (67.6) |
| **Negative consequences of alcohol consumption (agree completely)** | |
| Mental health problems | 3381(79.7) |
| Physical health problems | 3326 (78.3) |
| Accidents | 3901 (91.9) |
| Problems in the family environment | 3617 (85.1) |
| Problems at work | 3528 (83.1) |
| Problems in the social environment | 3045 (71.8) |

same way as was done in the EDADES study), occupational activity, level of income, level of alcohol consumption risk, alcohol consumption frequency, amount of alcohol consumed per sitting, frequency of binge drinking, perception of alcohol consumption, negative and positive alcohol consequences.

## Results

A total of 4250 citizens were interviewed. The sociodemographic characteristics of the sample can be seen in Table 1.

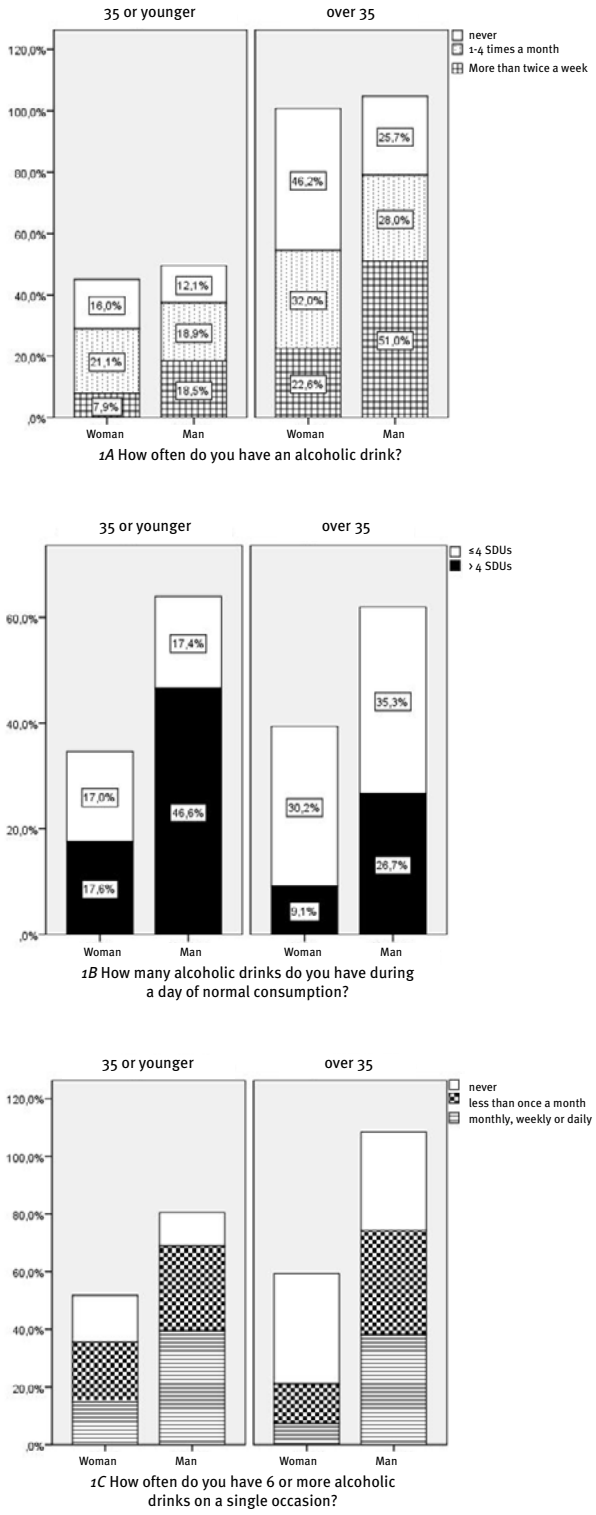
### *Alcohol consumption pattern and high-risk consumption*

Alcohol consumption in the previous year was reported by 77.5% (n=3230), with 23.6% drinking on more than two days per week, 5.1% consuming more than 4 SDUs per sitting, and 10.7% drinking more than 5 SDUs once a month or more frequently. Figure 1A shows how consumption increases with age in both sexes, although more sharply in the case of men, while young men drink a larger amount per sitting (Figure 1B). In terms of binge drinking, it can be seen that the number of people never doing this grows with age, although it is more prevalent among men (Figure 1C).

We can see statistically significant differences on comparing frequency of consumption and quantity consumed by sex , age (Table 2), occupational and income levels. Those who typically drink less frequently are students (17.6% versus 23.8% versus 25.1%, Chi2=79.2, p<.001), and those with an income above €2000 drink the greatest number of times per week (27.3% versus 21.2%, Chi2=59.5, p<.001). Students drink more than 4 SDUs more frequently than people in work or other occupational situations (12.2% versus 4.3% versus 4%, chi2= 42.9, p<.001). No statistically significant differences, however, were found in relation to income levels. Men and younger people consume 5 drinks or more per sitting proportionally more often (Table 2), as do students (24.3% versus 8.8% versus 9.2%, Chi2=115.9, p<.001).

Of those who reported their own alcohol consumption pattern, 22.1% met the risky consumption criteria, with 32.7% of men and 11.3% of women being high-risk drinkers (chi2=227.8, p<.001). Young people make up 31.8% of high-risk drinkers, compared to 17% of those over 35 years of age (chi2=119.2, p<.001). Given that they are in the youngest group of drinkers, students also presented the highest percentage of risky consumption, while no differences were found as a function of income level.

*Figure 1.* AUDIT-C according to sex and age




### *Self-perception of consumption*

When asked about how they saw their own alcohol consumption, 73.8% said that it was low or very low. Table 3 shows that being male with high-risk consumption increases the likelihood of considering one's own consumption as risky. Table 1 shows that 37.6% expressed concern about their own alcohol consumption, with men being twice as likely to worry about this than women (Table 2). However, when adjusted for sociodemographic and high-risk consumption variables, it can be seen that men are less likely to worry about their own consumption than women (OR=0.65 CI95% 0.46-0.92). There were no significant differences for the rest of the variables analyzed.

Table 2. *Differences of sex and age in the variables studies (n=4250)*

| | Sex | | | | | | Age | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Women | | Men | | | | ≤35 | | >35 | | | |
| | n | % | n | % | $x^2$ | p-value | n | % | n | % | $x^2$ | p-value |
| **How often do you have an alcoholic drink?** | | | | | | | | | | | | |
| Never | 584 | 27.7 | 355 | 16.7 | 216.2 | ‹.001 | 264 | 18.2 | 675 | 24.2 | 77.1 | ‹.001 |
| 1-4 times/month | 1219 | 57.8 | 1080 | 50.7 | | | 920 | 63.5 | 1379 | 49.4 | | |
| More than twice a week | 305 | 14.5 | 695 | 32.6 | | | 264 | 18.3 | 736 | 26.4 | | |
| **How many alcoholic drinks do you have during a day of normal consumption?** | | | | | | | | | | | | |
| ≤4 SDUs | 1458 | 97 | 1627 | 93.1 | 27.3 | ‹.001 | 1062 | 90.9 | 2023 | 97.1 | 61.7 | ‹.001 |
| › 4 SDUs | 44 | 3 | 122 | 6.9 | | | 107 | 9.1 | 59 | 2.9 | | |
| **How often do you have 6 or more alcoholic drinks on a single occasion?** | | | | | | | | | | | | |
| Never | 1155 | 76.5 | 972 | 54.9 | 180.6 | ‹.001 | 591 | 49.9 | 1535 | 73.3 | 182.6 | ‹.001 |
| Less than once a month | 227 | 18.3 | 525 | 29.7 | | | 402 | 34 | 19.1 | 24.1 | | |
| Monthly. weekly or daily | 78 | 5.2 | 272 | 15.4 | | | 190 | 16.1 | 160 | 7.6 | | |
| **Risky consumption according to AUDIT-C** | | | | | | | | | | | | |
| No risk | 1837 | 88.7 | 1411 | 67.3 | 277.8 | ‹.001 | 976 | 68.2 | 2272 | 83 | 119.2 | ‹.001 |
| Risky | 234 | 11.3 | 686 | 32.7 | | | 455 | 31.8 | 466 | 17 | | |
| **Have you worried at some point about the amount of alcohol you consume?** | | | | | | | | | | | | |
| Yes | 70 | 29.7 | 275 | 40.3 | 8.1 | 0.004 | 171 | 37.9 | 174 | 37.2 | 0.1 | 0.79 |
| **In your opinion. what is alcoholism?** | | | | | | | | | | | | |
| A vice | 122 | 5.9 | 239 | 11.5 | 43.2 | ‹.001 | 179 | 12.6 | 182 | 6.6 | 48.2 | ‹.001 |
| An illness | 1874 | 90.2 | 1749 | 84 | | | 1195 | 84.4 | 2427 | 88.5 | | |
| Both | 81 | 3.9 | 94 | 4.5 | | | 42 | 3 | 132 | 4.8 | | |
| **If you knew someone with alcoholism. where should s/he go for treatment ?** | | | | | | | | | | | | |
| Primary care | 681 | 34.2 | 652 | 32.8 | 14.6 | .001 | 377 | 28 | 956 | 36.4 | 36.1 | ‹.001 |
| Specialized care | 551 | 27.7 | 658 | 33.1 | | | 478 | 35.4 | 731 | 27.8 | | |
| Other | 758 | 38.1 | 678 | 34.1 | | | 494 | 36.6 | 941 | 35.8 | | |
| **Do you consider that the GP is the right health professional to deal with alcohol problems ?** | | | | | | | | | | | | |
| Yes | 1310 | 64.2 | 1453 | 71 | 21.8 | ‹.001 | 875 | 62 | 1889 | 70.6 | 31.6 | ‹.001 |

Note. Values of p≤(.05/12)=.0042 are considered statistically significant. SDU: Standard Drink Unit.

### *Opinions about alcohol*

The great majority (87.1%) believe that alcoholism is an illness or an addiction, while 8.7% see it as a vice. Citizens on incomes below €2000 (10% versus 5.5%, chi2= 36.7, p<.001) and students (13.3% versus 7.2% versus 9.8%, respectively; chi2 =26.9, p<.001) are the groups who more frequently categorize alcoholism as a vice (Table 2).

The multivariate analysis confirms that the probability of seeing alcoholism as an illness is double in women and people over 35 years of age (OR=2.5 (CI95% 1.9-3.2); (OR=2.1 (CI95% 1.6-2.8). Those with only a primary education are less likely than university students to see alcoholism as an illness (OR= 0.31 CI95% 0.2-0.4).

The majority of those surveyed did not consider alcohol to be beneficial (n=2478, 59%), with 37.3 (n=1567) believing it to be good if consumed in moderation, while 3.7% (n=158) thought it was always beneficial.

Table 1 shows the percentage of citizens surveyed who agree completely (point 5 on the Likert scale) with the questions relating to the negative consequences of alcohol consumption. More than 70% believe it has negative consequences.

Table 3. *Link between the perception of risk regarding consumption (very high/high/moderate versus very low/low) and the sociodemographic and clinical variables*

| | OR | CI 95% | |
|---|---|---|---|
| | | Minimum | Maximum |
| Age (above 35 years of age vs younger people) | 0.8 | 0.6 | 1.0 |
| Sex (Men in relation to women) | 1.3 | 1.1 | 1.6 |
| Education(1) | 1.0 | 0.7 | 1.3 |
| Education(2) | 1.1 | 0.8 | 1.4 |
| Income | 1.2 | 1.0 | 1.5 |
| Employment(1) | 0.8 | 0.6 | 1.1 |
| Employment (2) | 1.0 | 0.7 | 1.5 |
| High-risk consumption | 7.2 | 5.9 | 8.7 |
| Constant | 0.2 | | |

Note. OR: Odds ratio. CI: Confidence Interval. Education(1): Primary versus secondary education: education(2): university versus primary. Employment(1): employed versus students; employment(2): others versus students.

### *Opinions about healthcare professionals treating alcoholic patients*

The general practitioner is seen by 67.7% (n=2764) to be suitable for treating alcoholism, with 33.5% (n=1333) declaring that someone suffering from alcoholism should go to a primary care facility, while 30.4% (n=1209) think that they should go to a specialized medical service (psychologist, psychiatrist, mental health or drug addiction centers) and 36.1% (n=1936) to other facilities or services. The chief reason for visiting the GP as a suitable professional was the fact that they could refer the patient to the relevant specialist (35.2%, n=974), followed by familiarity with the patient's situation and medical record (19%, n=526), with the third reason put forward being that they are professionals with the qualifications to deal with alcoholism (18.6%, n=515). Just over half of those surveyed (57.8%, n=2417) confirmed that their GP had asked them on some occasion about their alcohol consumption.

Women, older people, employed people (69.4% versus 60.4% versus 66%, chi2=14.3, p=.001) and those with higher income levels (71.6% versus 64.4%, chi2=20.7, p<.001) more frequently consider primary healthcare professionals as suitable for treating alcoholism (Table 2). After adjusting for the various sociodemographic and clinical variables, we find that these differences are maintained for those over 35 years of age (OR=1.3 CI95% 1.2-1.6) and people in higher income brackets (OR=1.2 CI95% 1.1-1.5), with a slightly higher likelihood, however, that men will find primary care professionals to be suitable for treating alcoholism (OR=1.3 CI95% 1.2-1.6).

Men above 35 years of age and in work (63.6% versus 34.2% versus 55.2%, chi2 = 136.4, p<.001), remember more frequently having been asked about their alcohol consumption by a primary healthcare professional. There were no statistically relevant difference with regard to level of income.

## Discussion

Alcohol consumption is highly prevalent among the Spanish population (77.5% in the last year), with a high level of risky drinking (22.1%). Citizens are aware of the detrimental effects of alcohol, and the perception of risk regarding one's own consumption is greater than expected (37.6%). There are differences in alcohol consumption patterns depending on age and sex. Women consume less and drink less frequently than men. Younger people drink greater amounts but less frequently. Men and high-risk drinkers are more likely to view their own consumption as being high, although women tend to worry more about the alcohol they drink. Men, young people, and those with lower educational and income levels are more likely to see alcoholism as a vice. The majority of citizens believe that people with alcohol related problems should go to primary healthcare facilities for treatment, and they also believe that professionals working there are well prepared to treat this disease.

The prevalence of alcohol consumption found in our study matches the findings in the 2013 report from the Spanish Survey on Alcohol and Drugs (EDADES: Encuesta sobre Alcohol y Drogas en España) (78.3%). Our data for men and women (83.3% and 72.3% respectively) also match the EDADES survey (83.2% and 73.4%) (Delegación del Gobierno para Plan Nacional sobre Drogas, 2013). Subjects under 35 years of age have a greater tendency to drink than those above 35, especially in the form of binge drinking (16.1% versus 7.6%), and these results are similar to those in the EDADES survey (22.1% versus 11.0%.) (Delegación del Gobierno para Plan Nacional sobre Drogas, 2013). Population data show that there are differences in consumption patterns in terms of age and sex. Men drink more than women and the drink patterns change with age. Younger people tend to drink less frequently but in larger amounts, while the opposite is true among those over 35. These data coincide with previous studies (Delegación del Gobierno para Plan Nacional sobre Drogas, 2013; Miquel et al.,2015; Motos Sellés, Cortés Tomás, Giménez Costa, & Cadaveira Mahía, 2015). The level of high-risk consumption, however, is considerably higher (22.1%) than that found in the EDADES survey (4.9%), although it must be remembered that the criteria as to what constitutes high-risk drinking is different in both surveys. While in our study AUDIT-C was used, the EDADES study used the full version of AUDIT (10 questions and a cut-off score of 8). Furthermore, our findings are similar to those of other research in the Spanish primary healthcare context, i.e. 18.3% (Segura Garcia, Gual Solé, Montserrat Mestre, Bueno Belmonte, & Colom Farran, 2006). High-risk consumers are more frequently found among men and the under-35s, which is similar to the findings of the EDADES survey (Delegación del Gobierno para Plan Nacional sobre Drogas, 2013). Being young and male as predictors of high-risk drinking are constant variables in various studies and cultures as diverse as Malaysia, Australia,

USA, UK, Korea, Spain or Brazil (Antai, Lopez, Antai, & Anthony, 2014; French, Sargent-Cox, Kim, & Anstey, 2014; Mutalip, Kamarudin, Manickam, Abd Hamid, & Saari; Silveira et al., 2012). In our study we found a greater proportion of high-risk drinkers among students when compared to other occupations, which matches prior research (Arrieta Vergara, 2009; Miquel et al., 2015), although these differences are measured by age.

The perception of risk regarding the consumption of a substance (e.g. alcohol) is usually measured through comparison with other substances (Hampson, Severson, Burns, Slovic, & Fisher, 2001; Slovic, 1983) or by considering the risk of consumption in general rather than one's own. Drinking is seen as risky behavior by 80-90% of those surveyed in different countries (Delegación del Gobierno para Plan Nacional sobre Drogas, 2013; Karlsson, 2012). In our case, the perception of risk is much lower, although it is true that we are referring to the risk of subjects' own consumption rather than any specific behavior in the population as a whole (26.2% think their alcohol consumption is moderate to high, and 37.6% worry about their level of consumption). Our figures show that it is men and students who are more concerned about their drinking patterns. The fact that men have a more pronounced sense of risk has already been reported in earlier studies (Bischof, Bischof, Meyer, & Rumpf, 2015), and yet this does not agree with the data from the EDADES study (Delegación del Gobierno para Plan Nacional sobre Drogas, 2013). This may again be due to the fact that our study focuses on the perception of own risk. Thus it would seem that women are more concerned about risky patterns of consumption in general, but that men are more worried about the risk to themselves. More complex analyses and future research should explore this relationship between the perception of risk relating to one's own consumption and consumption in general. It is worth pointing out that this is not a minor point and that risk perception of alcohol consumption has been linked to consumption patterns and the risk of developing problems in the future (Haug, Ulbricht, Hanke, Meyer, & John; Robinson, Jones, Christiansen, & Field, 2014).

The majority of those surveyed see alcoholism as an illness (87.1%). This statistic is substantially better than that reported in many other countries, for example in Germany (52-56%) or Brazil (18.8%) (Peluso & Blay, 2008; Schomerus et al., 2013; Schomerus, Matschinger, & Angermeyer, 2014). Alcoholism is most frequently viewed as a vice by men, young people, students, people with lower academic and income levels. In other countries this level of stigmatization is only exceeded among women, which suggests that they tend to perceive more stereotypes (Schomerus, Matschinger, Lucht, & Angermeyer, 2014). If this were confirmed by studies focusing on this particular aspect, it would mean that this population group would need to be specifically included in new strategies to reduce stigmatization and improve access to treatment. The widespread perception in our study of alcoholism as an illness is not reflected in greater access to treatment. An alternative explanation is that while the majority of patients see that treatment for alcoholism is only focused on abstinence, this is not an objective that 45.7% initially set for themselves (Adamson, Heather, Morton, & Raistrick, 2010; Heather, Adamson, Raistrick, & Slegg, 2010); some studies suggest that this is one of the principal barriers to treatment (Wallhed Finn, Bakshi, & Andreasson, 2014).

Not many people believe alcohol to be beneficial (41%), with men, those in higher income brackets and high-risk drinkers being more likely to label it thus. The perception of the negative effects of alcohol consumption on physical and mental health, and its consequences for social, family and work relationships is always above 70%. It seems that identifying alcohol as positive does not rule out an appreciation of the negative effects of consumption. At the same time, this highlights the contrast between perceiving the value of "social" drinking and the stigma of "excessive" consumption.

Citizens believe primary healthcare doctors to be professionals prepared to treat alcoholism and its associated problems. Men, people in higher income brackets and older people believe that someone suffering from alcoholism should first see their GP. The differences observed in the study match the fact that older people in general make more use of primary healthcare than younger people (Cherpitel, 1999; Rodríguez Artalejo et al., 2000). It thus appears logical that those who receive more primary healthcare and know their GPs better also see them as suitable for managing alcoholism. People trust their family doctors to take responsibility for the treatment of the disease or refer patients to specialized centers when necessary, and thus believe the primary healthcare system to be the first level of treatment in guaranteeing the health of the citizens. In the case of alcohol, primary healthcare professionals should be ready to identify and treat patients with high-risk or hazardous consumption based on scientific evidence and approach treatment in such a way as to offer patient-centered care (Bradley & Kivlahan, 2014; Smedslund et al., 2011). In less than 10 years (2006-2015) the percentage of Spanish patients remembering that their GP had asked them about their alcohol consumption has risen from 48.9% to 57.8% (Segura Garcia et al., 2006). This may reflect the multiple efforts made to improve early identification of risky alcohol consumption, especially in the primary healthcare system (Colom, Scafato, Segura, Gandin, & Struzzo, 2014; Keurhorst et al., 2013; López-Pelayo et al., 2014).

Our study suffers from some weaknesses. Given the transversal nature of the research, causal interpretations are limited; nevertheless, the majority of studies in Spain (EDADES, ESTUDES, Encuesta Nacional de Salud) and Europe (EMCDDA) use similar methodologies. Furthermore, it is based on the self-reports of citizens, which, even though it is a metho-

dology recommended for pivotal pharmaceutical studies, limits the reliability of the data (EMCDDA, 2015; "New drug to treat alcoholism," 2004). Finally, nor does it gather data on the perception of alcoholism or of one's own drinking with validated instruments due to the lack of such instruments for the type of assessment attempted in our study. The main advantages of our study are the size and representativeness of our sample. In addition, it explores issues not frequently addressed in prior research such as the perception of one's own alcohol consumption and the role of the GP in treating alcoholism, which is all useful in improving access to treatment and successful care. It also suggests that certain population groups are more susceptible to treatment for reducing the stigmatization of alcohol related disorders. In conclusion, drinking patterns are determined by age and sex of those surveyed, with young men displaying a more episodic pattern of consumption, while men over 35 are more regular consumers. This matches the observation that there are more high-risk drinkers among young men. People who took part in the survey presented a higher than expected level of self-perception regarding the risks of alcohol consumption. Despite the stigma surrounding the illness, citizens generally see it as an illness rather than vice, believe primary healthcare professionals to be qualified to address problems with alcohol, and consider that alcohol consumption also has important negative effects in different contexts.

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## Conflict of interests

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# Regulating gambling to prevent addiction: more necessary now than ever

## *Regular el juego para prevenir la adicción: hoy más necesario que nunca*

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## Abstract

The American Psychiatric Association published the 5th Edition of DSM in May 2013, in which the gambling disorder is included within the category of addictive disorders -a long-standing and recurrent demand from the clinical, social and scientific fields. Nevertheless, the harmful effects of gambling have not been considered by the Government, which is the main area of addiction prevention.

The present article is a proposal for the regulation of gambling by the Government through the different levels of the State (national, regional and even local), which has the ultimate goal of preventing gambling addiction. This proposal has been presented to the Chamber of Deputies of the Congress, as part of the Congress-Senate Joint Committee for the Study of Drug Problems. The proposed regulation is based on the evidence provided by scientific studies on the prevention of addiction.

*Keywords:* Gambling Addiction; Prevention; Gambling Regulation; Gambling Disorder; Responsible Gambling.

## Resumen

En mayo de 2013 apareció la quinta edición de la clasificación de los trastornos mentales (DSM-5) de la American Psychiatric Association (APA, 2013), en la cual se incluye el trastorno de juego dentro de la categoría de trastornos adictivos, que es algo que era demandado desde hace décadas desde los ámbitos clínicos, sociales y científicos. El juego de azar, que según la propia APA tiene la misma consideración que las drogas o el alcohol en cuanto a la activación de los circuitos cerebrales de recompensa y a las consecuencias clínicas del trastorno del juego, no tiene, sin embargo, esa consideración desde el principal ámbito desde donde se debe llevar a cabo la prevención de la adicción, que es en los poderes públicos.

El trabajo que presentamos es una propuesta de regulación del juego para llevar a cabo desde la Administración mediante acciones de gobierno que competen a diferentes niveles de la misma (estatal, autonómico e incluso local), con el objetivo final de prevenir la adicción al juego. Dicha propuesta ha sido presentada tanto a la Dirección General de Ordenación del Juego como a la Cámara del Congreso de los Diputados, esta última en el marco de la Comisión Mixta Congreso-Senado para el Estudio del Problema de las Drogas. En este trabajo se defiende la propuesta de regulación desde la evidencia que proporcionan los estudios científicos en materia de prevención de las adicciones.

*Palabras clave:* Adicción al Juego; Prevención; Regulación del Juego; Trastorno de juego; Juego Responsable.

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## The current state of play

The latest edition of the DSM-5 (APA 2013) included what had long been a recurrent demand, the recognition of pathological gambling as an addictive disorder, putting it into the same category as drug dependency, alcoholism or smoking (Petry, 2006a; Potenza, 2006). Something similar may occur with the case of addiction to on-line video games, a disorder the DSM-5 calls Internet Gaming Disorder and that is currently included in Section III of the manual (Carbonell, 2014).

Despite the fact that, as far as pathological gambling is concerned, there has been no significant conceptual change since the DSM-III-R (Chóliz, 2014a), the justification given by the APA for its definition of gaming disorder as an addictive disorder could not be more explicit, since *"gambling behaviors activate reward systems similar to those activated by drugs of abuse and produce some behavioral symptoms that appear comparable to those produced by the substance use disorders"* (APA, 2013, p. 481).

Currently, gambling as an economic and social activity is going through a period of rapid expansion in Spain (Jiménez-Murcia, Fernández-Aranda, Granero and Menchón, 2014), especially since the appearance and development of new forms of on-line gambling, something that is reflected in successive reports by the Directorate General for the Regulation of Gambling (DGOJ). In 2014, the Spanish spent €30,053,000 million on legal gambling activities, which is approximately 2.8% of GDP. Of that amount, some 23.4% (€7,032,000) was spent on new, online forms of gambling (DGOJ, 2015).

Despite the magnitude of the phenomenon and the evident implications gambling activity has on pathological gambling, prevention programs are scarce, partial and on many occasions lack adequate evaluation. There is, nevertheless, an extensive and objective scientific literature that analyzes the variables that have a greater prevalence in the emergence/appearance of problem gambling (Williams, West and Simpson, 20112).

## Basic principles of gambling regulation

The need for gambling addiction prevention programs to be implemented by the Government of Spain is based on the following principles:

- Gambling is an activity the can have health risks since, despite personal differences in vulnerability (Clark, 2014; Lobo et al., 2014), and even genetic predisposition factors, both the structural characteristics of gambling (Parke and Griffiths, 2007) and the conditions in which it takes place (Williams, West and Simpson, 2012) are factors that can determine the development of gambling disorder among the population (Parke and Griffiths, 20079.
- A gambling disorder can have serious consequences both for the gambler and for their family; in an important percentage of cases (approximately 25% of pathological gamblers) they commit illegal acts in order to obtain money to be able to continue gambling (Granero et al., 2014).
- As with any other health problem, and particularly in the case of addictive disorders, the most effective way of dealing with the problem is to implement prevention programs (Dickson-Gillespie, Rugle, Rosenthal and Fong, 2008) bearing in mind that:
  a. Prevention programs must be carried out from different spheres, even though gambling policies (Government initiatives aimed at regulating gambling) have been shown to be the most effective ways of preventing excessive gambling (Williams, West and Simpson, 2012).
  b. Once the disorder has developed, the person is incapable of controlling their gambling behavior, which is dominated by impulsiveness (Blanco et al., 2009), even when informed of the negative consequences of excessive gambling. Suitable external control is, therefore necessary, the most effective form of which are gambling policies.
  c. The prevention of gambling addiction is incompatible with the promotion of excessive gambling (Williams, 2014), which makes regulating policies on the part of the Government even more necessary given that gambling, as an economic activity, bases its business model on a high level of consumption (Chóliz, 2014b). However, at the current time we find that it is difficult to legislate in gambling matters in such a way as to prevent disorders associated with it, in much the same way that it is difficult to legislate against alcohol and alcoholism (Rodríguez-Martos, 2007).

Despite all the aforementioned, the appearance of gambling disorders is a complex problem that also depends on other factors of vulnerability that must be borne in mind (Clarke, 2014), even though this is something that goes beyond the scope of this paper and corresponds to other sectors (education, health etc.) to develop prevention programs that address the different variables (biological, psychological etc.).

## Gambling regulation proposal

The proposal for the regulation of gambling that we present is built around three core ideas, which include the principal variables responsible for gambling addiction whose addictive potential could be reduced by means of adequate gambling policies (see Figure 1):

- The regulation of advertising and promotional strategies
- The regulation of opportunities to gamble, whose most relevant variables are the availability and accessibility of gambling activities, and

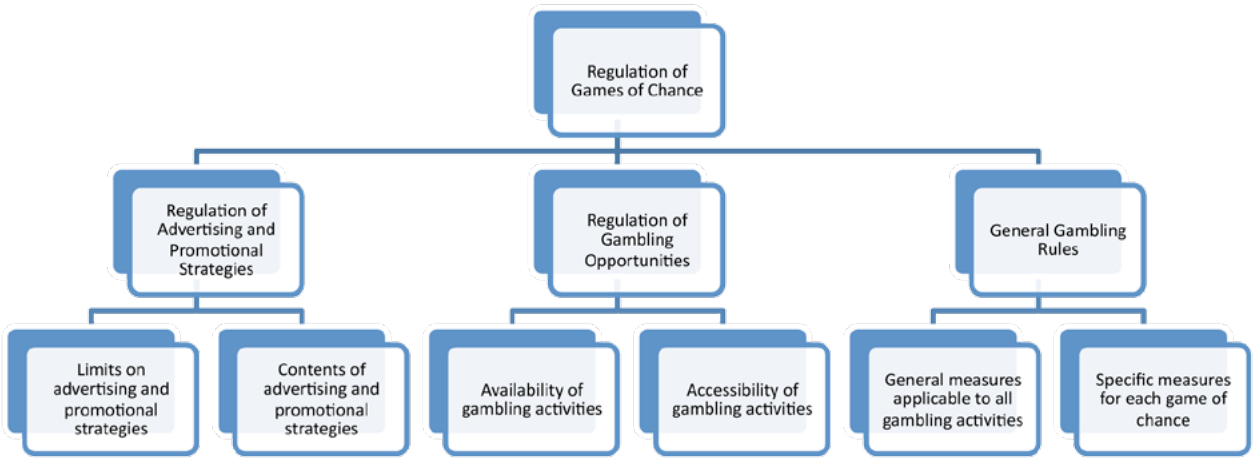


*Figure 1.* General framework of the process for regulating gambling

- The regulation of the structural characteristics of gambling activities themselves, with the aim of reducing the addictive potential of the same.

Below, we outline the different specific actions that could be taken to address each of these core ideas:

### *Gambling advertising and promotional strategies.*

Despite the fact that it is necessary to introduce specific regulations aimed at the advertising of gambling activities in order to prevent the appearance of disorders derived from the same (Binde, 2014), the emergence of online gambling in Spain has been accompanied by an increase in advertising and promotional techniques (this was in fact happening even before it was legalized) in the absence of specific rules and regulations governing advertising on the part of successive governments.

For that reason it is necessary to implement an advertising rulebook, or code, which should be revolve around two essential aspects: the limits of advertising and the contents of the same.

**Advertising limits.** As a general strategy, gambling advertising should be limited to the spaces in which gambling takes place: bingo halls, casinos, bookmakers' shops, betting shops and the gambling websites themselves in the case of online gambling. In the event of this general limitation not being put in place, there should be a series of regulatory measures, such as the following:

– ***Limitations in the press and audiovisual communication media.*** Advertising should be restricted to certain time slots (on radio and TV), or sections (of the printed press). In accordance with the General Law on Audiovisual Communication (Ley General de Comunicación Audiovisual), both on radio and television, and in Internet, the time slot should be restricted to the hours between 22:00 and 06:00 the following day.

– ***Regulation of online gambling advertising.*** Regarding the advertising of online gambling via Internet, this should be subject to specific regulation, since the way Internet itself functions can make advertising not only intrusive but also turn it into a technique that encourages people to play when gambling sites open automatically, even when the user is engaged in other web activity. Thus, in Internet, online gambling advertising should remain within gambling web pages themselves, and only once the user has entered them, with banners, links to pages outside those webs (as happens in the electronic press), pop-up gambling windows etc. all being explicitly prohibited.

**Advertising contents.** Gambling is a potentially addictive activity, that shares certain traits with smoking and alcoholism, but one that also has some singularities that should be borne in mind.

– ***Aspects of regulation common to other addictions.*** As is the case with alcohol advertising, gambling publicity should not be aimed at minors, and nor should minors be used to promote gambling activities; gambling should not be associated with career success nor should it give the impression that it favors a good mood or helps to resolve conflicts etc.; unrestrained gambling should not be encouraged nor should the fact of not gambling be portrayed in a negative light; clear rules governing sponsorship or other indirect ways of promoting gambling etc. should be established

– ***Specific regulatory aspects.*** One of the main variables that affects the addictive potential of gambling is the way in which it is presented, since this arouses cognitive biases and errors that, at the same time, have fundamental relevance on the development and maintenance of the addiction (Sharpe, 2002). For that reasons, neither advertising nor promotional techniques should employ strategies that lead to such cognitive biases or errors that themselves encourage gambling disorder. The main biases and promotional techniques that should

be eliminated in the case of gambling are: expertise bias (induced by the so-called "welcome bonuses"), "big win" prizes (induced by an accumulation of small wins) (Weatherly, Sauter and King, 2004), the "near miss" (Habib and Dixon, 2010), etc.

### *Opportunities to gamble.*

The opportunity to consume is one of the most relevant variables both in the development of an addiction and in the relapses that occur in recuperated addicts (Marlatt and Gordon, 1989, 1985). In the case of gambling, the two main variables involved are the *availability* of gambling activities in the immediate environment and the *accessibility* of the same for gamblers.

**Availability.** Availability refers both to the supply of gambling activities and the proximity of gambling outlets or establishments where gambling takes place. There is a positive relationship between the availability of gambling and the appearance of cases of pathological gambling (Welte, Wieczorek, Barnes, Tidwell and Hoffman, 2004), between the problems of excessive and pathological gambling and the proximity of gambling outlets (Pearce, Mason, Hiscock and Day, 2008), with the number of games (Grun and McKeigue, 2000) or with the density of gaming machines (Storer, Abbott and Stubbs, 2009). Specific regulatory measures aimed at availability would be as follows:

- Both presential and online gambling should take place in gambling halls that are duly authorized for this activity. This would imply the removal of both "type B" slot machines (commonly known as fruit machines or "one-armed bandits") and the more recent models of betting machines from establishments such as bars and restaurants.
- The awarding of licenses to gambling halls based on geographical criteria but, in any case, reducing the number of those already in existence.

**Accessibility.** Accessibility refers to the ease with which gambling activities can take place. It is considered to be one of the main variables in the development of problematic gambling (Thomas, Sullivan and Allen, 2008). The principal dimensions that should be subject to regulation on the part of the Government would refer to the requisites demanded and the conditions that are established in order to be able to gamble, even for types of gambling that are widely available. Some of the specific measures that could be carried out in this sense are:

- A General Register of Interdictions for all types of gambling in Spain (both presential and online) and the possibility of carrying it out from the State Administrations, or on the part of first-degree relatives, according to the principle of precaution.
- Identification by means of the National Identity Card for any type of gambling and the issue of a receipt in the case of lotteries.
- Providing proof of identity in order to be able to take part in any electronic and online gambling:
  - Building an electronic ID Card reader into all "type B" slot machines and all other gambling and betting machines.
  - The enabling of a system for credible identification for online gambling by means of a password obtained from Government offices, which must be periodically renewed. The enabling of a system for obtaining a password for foreigners via the Spanish consulate in their country of origin.

### *A General Set of Gambling Regulations*

Despite the fact that the structural characteristics that affect gambling addiction are many and varied, any set of regulations should select those that are especially relevant and clearly operationalize the way in which they should be regulated, with the aim of reducing the addictive potential of gambling. In this sense, the most addictive gambling activities are those that have high playing and reinforcement rates (Parke and Griffiths, 2007; Welte, Barnes, Wieczorek, Tidwell and Hoffman, 2007), as well as immediacy in response (Chóliz, 2010). Looking at different modalities of gambling, electronic gambling, or EGMs (Electronic Gaming Machines) are the ones that maximize these characteristics and are considered to be the most addictive (Brooks, Ellis and Lewis, 2008; Dowling, Smith and Thomas, 2005; Welte et al., 2007), for which reason their being regulated is especially important.

On the other hand, the conditions in which gambling activities are carried out also condition enormously the addictive potential of the same, strengthening its effects in some cases (Welte et al., 2004). This could be the form of payment (in cash or by card), the location, the possibility of consuming other substances (alcohol, tobacco), etc. But, without any doubt, one of the principal factors that can encourage the addictive potential of gambling is the use of Internet as a tool (Petry, 2006b), since the Web fosters the main variables that are responsible for the addictive potential of gambling; availability, accessibility, immediacy, short time-cycles etc. (Griffiths 2003; Griffiths, Parke, Woods and Parke, 2006), In fact, one of the clearest proofs of this is that online gamblers show higher addiction rates that those who take part in presential gambling (Wood and Williams, 2009; Wood, Williams and Parke, 2012), which makes the regulation of online gambling one of the immediate objectives that need to be carried out to protect vulnerable people (Monaghan, 2009), especially given that until now, existing legislation has been incapable of suitably regulating online gambling to protect pathological gamblers or young people who are at risk of addiction (Schoen, Hughes, Lewis and Marmon, 2007). In fact, in a recent study carried out in Spain, it was shown that there has been a notable increase in the number of pathological gamblers for whom the principal cause of

their disorder is online gambling and, in the case of gamblers below the age of 26, the main cause of their problem is online gambling, even more so than the "type B" machines (Chóliz, 2015).

Following are some of the principal measures proposed for dealing with the problems of excessive gambling and addiction.

**General measure: loss limitation.** Loss limitation, also known as pre-commitment, has shown its effectiveness both in addiction prevention and in the promotion of responsible gambling (Bernhard, Lucas and Jang, 2006; Focal Research Consultants, 2007, 2010; Griffiths, 2012; Omnifacts Bristol Research, 2007; Parke, Rigbye and Parke, 2008; Productivity Commission, 2010; Responsible Gambling Council, 2009; Schrans, Grace and Schellinck, 2004; Williams, 2010). The way of making this operational in General Gambling Regulations would be to impede a player from losing more than a previously-fixed amount of money. The amount in question would be determined by the Government and reflected in the General Gambling Regulations. Control over the amounts would be by means of a smartcard, described below.

Two types of loss limitation are foreseen:

- Overall gambling losses. Daily, weekly and monthly limits on losses would be fixed, which will reflect the total amount of money that it is possible to lose taking into account all the games in which bets are placed. These limits would be established by the Government in the General Gambling Regulations.
- Losses incurred in specific games. Before starting any electronic gambling session, there should be the option of pre-fixing the maximum amount that the player is prepared to lose. Said amount should be lower than that which the Government will have established as a daily limit for gambling losses.

The "Intelligent Gambling Card" (IGC, TIJ in its Spanish initials) is the tool which would allow for many of the gambling control techniques to be put into practice. It is a smart card, that would store the most relevant information concerning gambling activities, with the aim of preventing excessive spending. It should contain, therefore, the basic personal and gambling data of its owner (frequency of play, spending, losses etc.). it would be a necessary device for participating in gambling activities, accompanied by the National Identity Card and would be issued by the Government.

Without any pretensions to being exhaustive, and bearing in mind both the technical properties and the specific procedure for action that should be indicated in detail in the General Gambling Regulations, some of the most relevant characteristics of the IGC should be as follows:

- It should be a personal and non-transferable card to be used together with the electronic National Identity Card for use in electronic gambling. A registration system should also be put in place for use in gambling halls and in other sectors where non-electronic gambling takes place.
- The card will register all gambling activity, the time and the day in which they were carried out as well as the daily, weekly and monthly gains and losses.
- In order to obtain the card, the user should identify themselves by, for example, going in person to an office of the Regional or Local Government and proving their identity by means of the National Identity Card. It should have an expiry date of between three and six months from the date of issue and, once that time has elapsed, be renewed by means of the previous process, thus guaranteeing the identity of the player.
- In the General Gambling Regulation, daily, weekly and monthly loss limits will be clearly fixed. As soon as the cardholder reaches those limits, the IGC will be blocked for the time fixed in the Regulation.

It should be borne in mind that this is not a credit card, but rather a gambling control card. Electronic and other gambling machines will continue to function with their habitual mechanisms, but will control excessive spending.

**Specific measures for each game of chance.** These are specific rules aimed at mitigating the effect that the variable structures have and which depend on each specific form of gambling or game. For that reason, these measures may need to be, unlike those described above, aimed solely at one type of game or just some of them. They are technical modifications that involve certain variables which have been shown to influence on the development or maintenance of gambling addiction.

Some of the most significant are the following:

- Delay of the reward in electronic games, pre-drawn lotteries, casino games etc. It is a question of increasing the time-cycle between: a) the placing of the bet or wager and the result (gain or loss); or b) between the result and the payout.
- Reducing the time-cycle of betting. With this measure the aim is to diminish the player's absorption in the game. Some of the preventive strategies that impede this excessive absorption are the following:
  - Banning "live betting". Betting should be closed before the competition on which bets are placed begins.
  - Single bets in the case of online betting. Banning combined or accumulator bets etc. In particular, banning cross betting owing to the risk of addiction and safety of the player (Chóliz, 2013).
  - A ban on playing several online poker games simultaneously. With this measure the aim is to hinder professional players from carrying out strategies against novices or occasional players who are at a disadvantage because they lack the techniques and the technological tools that professionals have available.

- Limiting big payouts. Some of the measures to be taken are:
  - A ban on the interconnection of machines, such as combined bingo machines, that excessively increase prizes.
  - Putting a limit on the percentage given to prizes, especially in online betting and gambling, which is currently very high in some cases, and gives rise to patterns of excessive gambling.

## Conclusions

Gambling policy, that is to say, the regulatory mechanisms of the State applied to games of chance, are the basis on which the rest of preventive measures sit (Williams, West and Simpson, 2012). Some of the dimensions to be regulated, such as availability and accessibility, have a proven and close relationship with the emergence of problems of excessive gambling and gambling disorders (Grun and McKeigue, 2000; Pearce et al., 2008; Werte et al., 2004), while others are probably effective and their effectiveness would need to be shown once they have been implemented within a system of regulation. These measures are not only necessary in order to prevent the emergence of gambling addiction, but also to help control those who already suffer the disorder. The responsibility for developing and implementing them corresponds to the powers that be, even if that should be complemented by educational, family and community measures, or action on the part of the health services.

It is a proposal that, though plausible and, with the right measures, probably effective, must be continually subject to a process of evaluation of its effects, with the aim of refining the procedures and techniques proposed. Certain objective evaluation criteria need to be established, such as how to proceed in evaluating the emergence of gambling disorders or of the demand for help before and after the application of the measures; selecting specific population groups in which to observe the effect of the measures established; implementing in a sequential way some of the measures and observing the effect they have on the general population or on specific milieus etc.

The principal goals of this proposal for regulation of gambling are none other than the prevention of gambling addiction and the reducing of the risks of those who already show maladaptive gambling patterns, and has the aim of reconciling the participation in a recreational activity with the preservation of the higher right of public health.

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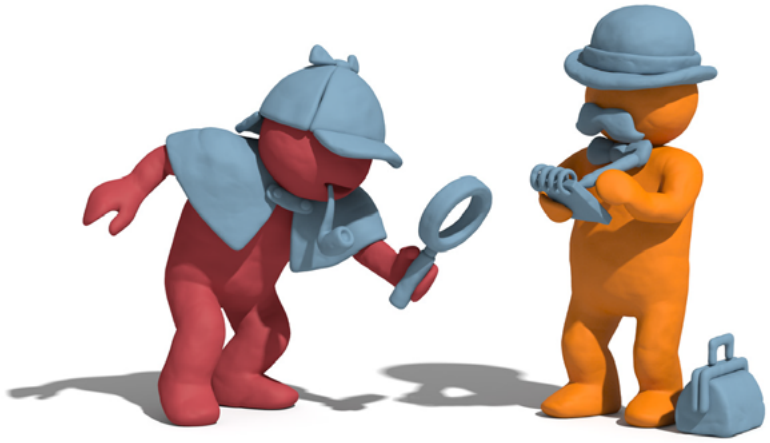
MENSUAL suspensión inyectable de liberación prolongada

# XEPLION®

palmitato de paliperidona



# 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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PHARMACEUTICAL COMPANIES OF Johnson&Johnson

PHES/XEP/0315/0010(1) Mayo 2016

**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).

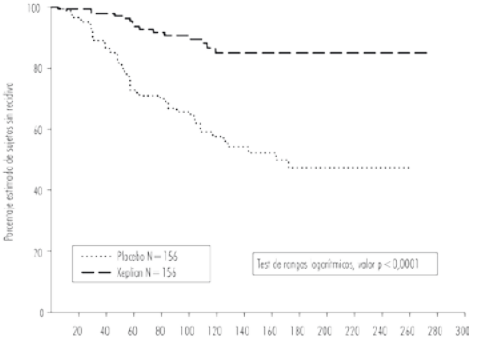
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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

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

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

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

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

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

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

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

## PRESENTACIÓN DE LOS TRABAJOS

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

## ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

**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.

Selincro®
nalmefeno

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 **Lucía**.*

# Lucía, 58 años.

Padece obesidad, hipertensión y diabetes. Está sometida a una gran presión y responsabilidad en casa y en el trabajo. Su consumo de alcohol se inició hace varios años pero se vio incrementado tras divorciarse de su marido.

Ingiere 7 o más bebidas al día (una botella de vino a menudo seguida de cerveza o licores).

## ¿Qué haría en su lugar?

*Caso fictício.

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