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Clinical implications of cognitive impairment and alcohol dependence

Deterioro cognitivo y dependencia alcohólica, implicaciones clínicas

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The fact that the use and abuse of alcohol damages brain tissue, and therefore its functions, has been known for a long time at both clinical and research levels (Bates, Bowden & Barry, 2002; Naim-Feil, Fitzgerald, Bradshaw, Lubman & Sheppard, 2014; Stavro, Pelletier & Potvin, 2013; Wilcox, Dekonenko, Mayer, Bogenschutz & Turner, 2014; Wollenweber et al., 2014). However, there is an ongoing debate about how this damage occurs and what consequences it has on alcohol withdrawal treatment (Horton, Duffy, Hollins Martin & Martin, 2015). Moreover, it is undervalued and not taken into account in healthcare settings where patients are treated for problems related to alcohol use (Horton et al., 2015), although it is estimated that between 9 and 22% of patients diagnosed with dementia abuse alcohol, and dementia is present in 10-24% of alcohol abuse patients (Ridley, Draper & Withall, 2013).

In alcohol-related brain damage (ARBD), two main neurotoxic dimensions are combined which will determine the degree of damage present in each individual, and whether or not this damage falls into the category of dementia (Moretti, Caruso, Dal Ben, Gazzin & Tiribelli, 2017):

Direct neurotoxic effects of alcohol: periods of binge drinking followed by periods of abstinence produce a neurotoxic effect mediated by glutamatergic excitotoxicity (induced through up-regulation of NMDA receptors), a kind of kindling (Golpe, Isorna, Barreiro, Braña & Rial, 2017; Vargas-Martinez, Trapero-Bertran, Gil-Garcia & Lima-Serrano, 2018). Such neuronal damage would be more intense at the level of the hippocampus, hypothalamus and cerebellum, which affects memory and learning capacity (Ridley et al., 2013). Furthermore, the cholinergic function would be affected by this excitotoxicity, leading to increased attention, memory and learning disorders (Ridley et al., 2013). Another area deeply affected is the prefrontal cortex, with subsequent executive dysfunction. Alcohol also appears to be capable of causing brain damage through apoptosis, oxidative stress, mitochondrial damage and altered neurogenesis (Sachdeva, Chandra, Choudhary, Dayal & Anand, 2016).

Thiamine deficiency: poor nutrition, malabsorption in the digestive tract, and liver failure present in patients with alcohol dependence determine the onset of a severe condition: Wernicke's encephalopathy (WE), which, if left untreated, can become chronic and give rise to Korsakoff's syndrome (KS) (Horton et al., 2015). WE is characterized by a confusional state, with vision and gait disorders. KS is characterized by severe anterograde and retrograde amnesia, space-time disorientation, apathy and executive dysfunction, and anxiety; and although most patients improve, an estimated 25% will require chronic residential care (Horton et al., 2015). Such patients present deterioration in social and work lives going beyond mere amnesia and clearly reaching the category of dementia. Neuroimaging studies indicate the presence of damage in diencephalic subcortical structures (thalamus, cerebellum, mammillary

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bodies) and cortical structures (frontal, parietal and cingulate). The combination of both states (WE + KS) is present in 1-2% of all autopsies, and in 10% of those carried out on alcohol abusers (Ridley et al., 2013).

Brain damage associated with these two neurotoxic dimensions, a marked cerebral atrophy with white matter damage and neuronal destruction (Erdozain et al., 2014), is widespread among patients with problems linked to excessive alcohol use and is detected in up to 78% of autopsies (Ridley et al., 2013). In the clinic, a combination of brain damage caused by both dimensions is usually found (Moretti et al., 2017; Ridley et al., 2013; Zahr & Pfefferbaum, 2017) which seems to severely damage the white matter of the prefrontal cortex, the corpus callosum and the cerebellum, and produce neuronal damage in the prefrontal cortex, hypothalamus, and cerebellum (Zahr & Pfefferbaum, 2017). Overall, patients diagnosed with KS present lesions and thus a more severe deterioration in comparison with those that only present damage associated with the direct neurotoxic effects of alcohol (Hayes, Demirkol, Ridley, Withall & Draper, 2016).

Alterations in white matter are partially reversible if prolonged alcohol abstinence can be achieved to allow the restoration of adequate myelination and axonal integrity (Ridley et al., 2013). This recovery would be accompanied by an improvement in cognitive and motor functions. Recovery speed is slow, especially for executive functions, and is linked to the duration of abstinence and the intensity of alcohol use prior to it, rather than to total lifetime use (Ridley et al., 2013). The accumulation over the lifespan of binge drinking episodes followed by withdrawal syndromes, leads to slower and less complete recovery since it produces greater brain damage and with it more cognitive deterioration. This is why lifetime alcohol use is not a risk factor for cognitive deterioration in low-risk users but rather for abusers and dependents (Woods et al., 2016). It is not a question of how much alcohol has been drunk over a lifetime but rather how it has been drunk.

Women appear to be more susceptible to the neurotoxic effects of alcohol and recover more slowly. A higher level of educational attainment seems to exert a protective effect, which could reflect either a better premorbid cognitive level or a greater cognitive reserve achieved through intellectual activity, or both (Ridley et al., 2013). Since all brain structures suffer progressive deterioration with age, when assessing the damage produced by alcohol, age is a confounding factor that should be controlled for with reference values for each age group (Hayes et al., 2016).

After two years of abstinence, both improvement and deterioration stabilize, unlike in other pathologies related to brain damage (Ridley et al., 2013). It is estimated that brain damage caused by thiamine deficiency is more likely to lead to chronification than direct damage produced by alcohol (Sachdeva et al., 2016). If the overall alcohol use in the population is taken into account, a situation similar to that of cardiac risk is observed, yielding a J-shaped risk curve. Light drinking of less than 20 grams of ethanol per day could have a protective effect at the cognitive level, while abusive consumption produces a deterioration (Sachdeva et al., 2016).

When these alterations become chronic and intensify, they enter the dementia spectrum; it is estimated that such cerebral damage is present in 10-24% of the dementia diagnoses in residents of centers for the elderly, reflecting its widespread prevalence, with people under 60 most affected (Ridley et al., 2013).

Unfortunately, patients may present further brain damage associated with a lifestyle which harbors other risk factors, for example traumatic brain injuries due to accidents or violence, the consumption of other toxins, and vascular damage. In addition, given the high comorbidity of psychiatric disorders suffered by patients with alcohol dependence, they can present brain damage accompanied by cognitive deterioration, which is typical of these disorders. A clear example would be depression (Sachdeva et al., 2016)

Assessment of brain damage associated with alcohol use

There are numerous neuropsychological tests that have been used to measure ARBD. According to Aharonovich et al. (2018), the most widely-used are a measurement of global intelligence through the Wechsler scale (WAIS) and its subscales, the FAS verbal fluency test, memory tests such as the WAIS or Rey's complex figure, attentional tests such as the Stroop test or the Trail Making Test (TMT), executive function tests such as the Wisconsin Card Sorting Test (WCST), and even screening tests for dementia such as the Mini Mental State Examination (MMSE) which are not very specific for this type of patient, or others with more validity when used with substance users, such as the ACE-R (Addenbroke's Cognitive Assessment-revised) or the MoCA (Montreal Cognitive Assessment) (Hagen et al., 2016; Hayes et al., 2016).

Although the use of these tests has been heterogeneous and different authors have combined them in non-systematic and non-validated ways, an abundance of studies indicate the presence of disorders in the following cognitive functions: anterograde memory, executive function (decision making, temporal orientation, emotional judgments and verbal fluency) and visuospatial tasks. Working memory and latency time are generally affected. The question as to which cognitive functions are most seriously affected depends on how the two dimensions outlined above , direct damage and thiamine deficiency, interact with the risk factors in each patient (Maharasingam, Macniven & Mason, 2013). Despite the intensity of these disorders, it is estima-

ted that the overall intellectual functioning of these patients is reasonably well preserved, particularly at the level of language, above all when compared to the development of degenerative and vascular dementias (Horton et al., 2015; Ridley et al., 2013; Sachdeva et al., 2016). All affected functions improve after a year of abstinence, with damage to anterograde memory, the most closely linked to thiamine deficit, being the most persistent (Sachdeva et al., 2016).

Cognitive assessment is thought to be appropriate between 1 to 6 weeks after achieving abstinence from alcohol, although some authors recommend 60 days of abstinence first (Hayes et al., 2016).

Consequences of cerebral damage associated with alcohol use

The interference which cognitive damage can cause to the treatment process for achieving alcohol abstinence is of particular concern. Patients with ARBD have motivational and treatment adherence problems derived from their cognitive disorders. Additionally, certain psychotherapeutic procedures such as cognitive and behavioral ones may be affected and their effectiveness diminished due to memory and executive function disorders presented by patients (Sachdeva et al., 2016).

Furthermore, even in its mild forms ARBD may not only affect the treatment of alcoholic withdrawal but also the habits that affect patients' health; it is thus recommended that all patients with problems related to alcohol use are assessed only once they are abstinent, as previously indicated (Hayes et al., 2016).

Treatment of cerebral damage associated with alcohol use

Obviously, the best tool for avoiding ARBD is prevention. Reducing global consumption in the population, delaying the age of alcohol onset and insisting on the treatment of those who already present problems of alcohol abuse are fundamental measures.

Moreover, at the slightest suspicion of WE, a treatment with parenteral thiamine should be administered (up to 1 gram for the first 24 hours of treatment, since it is not effective orally); this can reverse the condition if the treatment starts within the first 48-72 hours. It is also advisable to balance potassium and niacin levels (Sachdeva et al., 2016). Treatment with parenteral thiamin should be continued for 5 days, followed by oral supplementation of 300 mg per day for several weeks (Hayes et al., 2016).

Cognitive remediation is a potentially useful therapeutic tool in patients with ARBD. Studies to date, although not numerous, have yielded improvements in attention, working and episodic memory (Hayes et al., 2016; Sachdeva et al., 2016; Svanberg & Evans, 2013), which appear to have an effect when it comes to improving the capacity for social interaction and consolidating abstinence (Frias-Torres et al., 2018; Hayes et al., 2016). Although the results are not yet powerful enough to make a definitive recommendation, it is possible that boosting the cognitive function of patients with ARBD improves their ability to remain abstinent and is, therefore, a necessary intervention (Bates, Buckman & Nguyen, 2013).

Compensatory psychosocial Interventions in the rehabilitation of patients with ARBD have also been shown to be effective. Such interventions focus on solving everyday problems through the programming of daily activities with the help of professionals and family. Facilitators such as diaries and alarms are used to set the patient's daily activities and to make up for mnemonic deterioration (Hayes et al., 2016).

Memantine, an antagonist with low affinity for the NMDA receptor which is recommended for degenerative dementia, has shown promising results in patients with alcoholic dementia, with improvements in overall cognitive function and quality of life, and a reduction in behavioral disorders. (Sachdeva et al., 2016).

Conclusion

In conclusion, it could be said that brain damage produced by alcohol abuse (ARBD) is scaled, ranging from mild deterioration to dementia. In any case, ARBD worsens treatment response and patient progress. ARBD is associated with two dimensions which usually interact in all cases and are also scaled: the direct neurotoxicity of alcohol linked especially to glutamatergic excitotoxicity and associated with episodes of binge drinking and subsequent abstinence; and on the other hand, thiamine deficit, which gives rise to the WE-KS complex and tends to involve greater severity. ARBD appears to severely damage the white matter of the prefrontal cortex, the corpus callosum, and the cerebellum, and produce neuronal damage in the prefrontal cortex, hypothalamus, and cerebellum. However, ARBD is reversible if a prolonged alcoholic withdrawal of at least 1-2 years can be achieved.

ARBD is associated with disorders in the following cognitive functions: anterograde memory, executive function (decision making, temporal orientation, emotional judgments and verbal fluency) and visuospatial tasks, working memory and latency time. While no battery of cognitive tests validated for ARBD is currently available, it is considered necessary that such a battery cover all the functions that may be susceptible to disorder, and it is recommended that all patients at risk of presenting ARBD be evaluated once they have consolidated a period of abstinence of at least one week.

To date there is no pharmacological or remediation treatment approved for ARBD. Alternatives such as cogni-

tive remediation, psychosocial rehabilitation and memantine have yielded promising preliminary results.

Conflict of interests

The authors declare no conflict of interest for the present study.

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Relationship between alcohol consumption, whether linked to other substance use or not, and antiretroviral treatment adherence in HIV+ patients

Relación entre la adherencia al tratamiento antirretroviral en pacientes VIH+ y el consumo de alcohol, asociado o no al uso de otras sustancias

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Abstract

Hazardous alcohol consumption is a common diagnosis among people living with HIV infection. The relationship between alcohol consumption and poor adherence to antiretroviral therapy has been highlighted in different studies, yet few of them performed a parallel analysis of other substance use. In Spain, alcohol consumption is frequently associated with other substance use, mainly cannabis and cocaine. The aim of this study is to assess the influence of hazardous alcohol consumption both combined with other substances (cocaine, heroin, methadone and/or cannabis) or alone on antiretroviral therapy adherence in our social environment. We performed an observational case-control study including 119 HIV+ individuals. We recruited 40 non-adherent patients, defined by less than 90% compliance according to hospital pharmacy refill data, and corroborated by the *Simplified Medication Adherence Questionnaire* (SMAQ) and referring professional's opinion. Control cases (n=79) were defined as those patients with similar characteristics but considered adherent according to the same parameters. Data collection took place between May 2013 and September 2015. Statistical analysis was performed using a binary logistic regression model. Our results indicate that alcohol consumption decreases adherence to antiretroviral therapy. The use of methadone represents a statistically significant increased risk of poor adherence. No significant differences were found between adherent and non-adherent groups regarding cocaine, heroin or cannabis use in this study. In summary, the detection of substance use and especially alcohol consumption in HIV+ patients can improve the effectiveness of antiretroviral therapy by identifying and treating at-risk individuals for a poor therapeutic adherence.

Keywords: HIV; Highly Active Antiretroviral Therapy (HAART); Medication adherence; Alcohol use; Substance use.

Resumen

El consumo perjudicial de alcohol es un diagnóstico de elevada prevalencia en pacientes VIH+. Distintos estudios han destacado la influencia negativa del mismo sobre la adherencia al tratamiento antirretroviral, aunque pocos de ellos valoran además el consumo de otras sustancias. En España, el consumo de alcohol se presenta frecuentemente en situación de policonsumo, fundamentalmente de cannabis y cocaína. El objetivo es comprobar cómo influye el consumo de alcohol, asociado o no al uso de otras sustancias (cocaína, heroína, metadona y/o cannabis), en la adherencia al tratamiento antirretroviral en nuestro entorno. Se ha realizado un estudio observacional tipo casos y controles sobre una muestra de 119 individuos VIH+. Conforman los casos (n=40) sujetos no adherentes al tratamiento farmacológico según reporte de Farmacia Hospitalaria, corroborado por el *Simplified Medication Adherence Questionnaire* (SMAQ) y la opinión del profesional de referencia. Se consideran controles (n=79) una muestra de pacientes de características similares con buena adherencia terapéutica según los mismos métodos de valoración. La recogida de datos se hizo entre mayo 2013 y septiembre 2015. El análisis estadístico se realizó mediante regresión logística binaria. Los resultados muestran que el consumo de alcohol empeora la adherencia al tratamiento antirretroviral. El uso de metadona supone un incremento estadísticamente significativo del riesgo de no adherencia. No se han encontrado diferencias significativas entre los grupos del estudio respecto a los consumos de cocaína, heroína o cannabis. Por tanto, la detección del consumo de sustancias, especialmente de alcohol, y su abordaje en pacientes VIH+ puede repercutir positivamente en el cumplimiento terapéutico, en beneficio de una mayor efectividad de la terapia antirretroviral.

Palabras clave: VIH; Terapia antirretroviral (TARGA); Adherencia terapéutica; Trastorno por uso de alcohol; Policonsumo.

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The hazardous use of alcohol and other substances is a frequent diagnosis in patients with HIV infection. Several authors have pointed out their high prevalence (Parsons, Starks, Millar, Boonrai & Marcotte, 2014; Skalski, Sikkema, Heckman & Meade, 2013). Although estimates vary between 8% and 42% (Williams et al., 2016), it has been pointed out that the prevalence of heavy drinking (Cortés Tomás & Motos Sellés, 2016) in these patients almost doubles the prevalence in the general population (Galvan et al., 2002).

Apart from the direct harm to the individual's health, other factors have been highlighted among the consequences of alcohol consumption in HIV-positive patients such as the potential increase in the risk of transmission of the virus in situations of alcohol intoxication (Scott-Sheldon et al., 2013), the delay in the diagnosis of the disease (Zarkin, Bray, Babor & Higgins-Biddle, 2004), an increased risk of early cognitive impairment (Anand, Springer, Copenhaver & Altice, 2010) or hepatitis C (Taylor, Denniston, Klevens, McKnight-Eily & Jiles, 2016) and, in general, an increase in morbidity and mortality (Azar, Springer, Meyer & Altice, 2010). In addition, harmful alcohol consumption has been associated with a worsening of immune status independently of treatment (Baum et al., 2010).

In Spain, the rate of new HIV diagnoses continues to be higher than the average for European Union and Western European countries. During 2015, an estimated 9.44 new cases per 100,000 inhabitants (Carlos III Health Institute, 2016) were detected. Since the introduction of highly active antiretroviral therapy (HAART) as the treatment of choice in HIV infection, there has been a significant improvement in the quality and life expectancy of affected individuals (Tancredi & Waldman, 2014; Poorolajal, Hooshmand, Mahjub, Esmailnasab & Jenabi, 2016). The benefits of this regimen, however, are intimately linked to strict treatment compliance, and lack of adherence has been postulated as the first cause of short-term treatment failure (Braithwaite & Bryant, 2010), as well as favouring the development of resistant strains (Cohen, 2006).

There are numerous lines of research regarding factors that may have a negative impact on adherence to antiretroviral therapy, variously highlighting the presence of undesirable side effects of the treatment, emotional stress originating from causes secondary to the core problem treated, lack of social/family support, complexity of the pharmacological regimen, or the lack of efficacy perceived by the patients (Ammassari et al., 2002; Hudelson & Cluver, 2015). Poor treatment adherence has similarly been linked to younger age groups and cognitive impairment (Hinkin et al., 2004), the presence of psychopathology, fundamentally depression (Palepu, Horton, Tibbetts, Meli & Samet, 2004), as well as certain personality traits (Hutton and Treisman, 2008), low socioeconomic status (Bermudez et al., 2016; Peltzer & Pengpid, 2013) and substance use, particularly alcohol (Azar et al., 2010; Palepu et al., 2004).

It has been posited that adherence to antiretroviral therapy should be understood as a dynamic process in which modifiable risk factors are linked to better or worse compliance (Lazo et al., 2013). In recent years, many authors have focused especially on the impact of alcohol consumption on treatment adherence (Vagenas et al., 2015). Various systematic reviews consistently support the relationship between both factors (Azar et al., 2010, Vagenas et al., 2015; Hendershot, Stoner, Pantalone & Simoni, 2009). Moreover, the consumption of alcohol or other substances may also influence adherence to other medical treatments related to diseases or infections common to HIV-positive patients (Gonzalez, Barinas & O'Cleirigh, 2011). Consequently, treatment intervention programmes have been proposed to decrease alcohol consumption and improve pharmacological compliance, which would translate into an overall improvement in the course of HIV disease (Parry et al., 2014). Thus, it has been pointed out that the transition from active substance use to abstinence would be consistently associated with improved treatment adherence (Lucas, Gebo, Chaisson & Moore, 2002).

In Spain, alcohol consumption is often associated with the use of other substances. According to the household survey on alcohol and drugs (Encuesta Domiciliaria sobre Alcohol y Drogas) carried out by the Spanish Ministry of Health (OEDT, 2015), alcohol is involved in practically all cases of polydrug use: 94.3% of cannabis users and 96.8% of cocaine users also drink alcohol. In addition, among those whose primary substance is alcohol, cannabis is used by 11.1%, and cocaine by 2.7%.

There is evidence that the influence on treatment adherence may vary depending on the substance used and the pattern of consumption (Azar et al., 2015; Gonzalez et al., 2011), although the types of substance and the mechanisms that link their use to decreasing adhesion have not been studied in depth (Gonzalez, Mimiaga, Israel, Andres Bedoya & Safren, 2013). In a study carried out by Parsons et al. (2014) on a sample of 557 HIV-positive individuals over 50 years of age, the combined use of alcohol with cannabis or cocaine was associated in a statistically significant way with an increase in forgetting medication when compared to alcohol consumption in isolation.

Treatment adherence requires careful attention to dose times and, in many cases, the coordination of multiple medications, which involves mechanisms related to cognition, planning and decision making. Elements such as lifestyle instability (Tucker et al., 2004), physical and psychic vulnerability, or difficulties in self-control mediated by substance use may interact to weaken adherence. In addition, some patients may discontinue treatment during episodes of consumption if they perceive it to be incompatible with substance use (Kalichman et al., 2015).

Despite the above, which is based on international data, references in the literature regarding the impact of alcohol consumption on adherence to antiretroviral therapy in HIV-positive patients in Spain are limited (Ortego, Huedo-Medina, Vejo & Llorca, 2011; Pérez-Valero et al., 2016a; Pérez-Valero et al., 2016b). The aim of the present study is to assess whether hazardous alcohol use is linked to poor adherence to antiretroviral therapy in HIV-positive patients once adjusted for use of other substances (cocaine, heroin, methadone and/or cannabis), and to determine the role they play in adherence in a specific care setting and in the cultural context of the Spanish population.

Methodology

Participants

The study population consisted of adult patients undergoing regular outpatient follow-up at the infectious disease centre of a third-level hospital (Ramón y Cajal University Hospital, Madrid), who had been receiving HAART for at least the previous twelve months, dispensed in all cases by the hospital pharmacy. All participants gave informed consent prior to taking part in the study. Regular follow-up was defined as attending at least two scheduled appointments in the previous year (Tripathi, Youmans, Gibson & Duffus, 2011). Exclusion criteria were the presence of acute infectious or active oncological processes, as well as refusal to participate or voluntary withdrawal from the study in compliance with informed consent. In addition, cases with an inconsistency between the SMAQ questionnaire results and/or the opinion of the referring professional regarding adherence according to the hospital pharmacy were excluded from the study. The study was approved by the Clinical Research Ethics Committee of the Hospital before being carried out.

Procedure

This is an observational case-control study. Non-adherent HAART patients make up the cases, and a sample of patients with similar characteristics and good therapeutic adherence are the controls. The selection of cases was carried out by consecutive sampling of a list of non-adherent patients routinely generated on a monthly basis by hospital pharmacy. The controls were selected by consecutive sampling of the patient list for outpatient appointments. Non-adherent patients were considered to be those who, according to the hospital pharmacy refill data, had collected less than 90% of their antiretroviral treatment medication prescribed during the previous year. Adherent patients were those collecting 95% or more of their doses during the last year, according to hospital pharmacy (Paterson et al., 2000). Patients whose adherence was equal to or greater than 90% but less than 95% were excluded from the study on the basis of lack of unanimity in the literature as to the limits of this differentiation (Viswanathan et al., 2015). All the individuals participating in the study were given a semi-structured clinical assessment interview created ad hoc for the purpose. The SMAQ questionnaire - a brief instrument asking patients six questions about their therapeutic compliance and validated for use in patients with HIV infection (Knobel et al., 2002) - was included in order to corroborate the assessment of treatment adherence according to hospital pharmacy. The assessment process was carried out in its entirety by the researchers. Data collection took place between May 2013 and September 2015.

Variables of the study

Socio-demographic variables such as age, sex, race, marital status, socioeconomic status, educational and work status were included, among others. In addition, a register of variables regarding HIV infection status and treatment was drawn up, which included the progression in time from the beginning of follow-up and treatment, the number of pills and antiretroviral treatment shots per day, as well as whether or not the taking of medication was supervised. Regarding substance use, a history of alcohol, cannabis, cocaine, heroin and methadone (therapeutic use) was recorded covering the 12 months prior to the assessment, with the frequency of their use and the daily amount consumed being taken into account.

Statistical analysis

The descriptive values and the frequencies of the variables included in the study were obtained in the statistical analysis. Some of the variables were recoded so as not to lose power in the analysis, without this entailing a substantial loss of information and preserving a clinical sense. Cases with financial difficulties with or without external aid, or the impossibility of keeping up payments or debt repayment, or the threat of eviction were classified as having problematic or hazardous socioeconomic status. Alcohol consumption was dichotomously categorized into non-problematic and hazardous consumption, according to the criteria established by the World Health Organization (WHO, 1992). For the remaining substances, their continuous use was considered positive, regardless of the pattern of consumption (all individuals presented at least weekly use). For the description of quantitative variables which did not meet normal distribution criteria, the median and the interquartile range (IQ25-75) were chosen. For the comparative analysis of raw data, the Mann-Whitney U test was used, while the Pearson chi-square statistic was applied to qualitative variables. In both cases, a significance level of $p = 0.05$ was selected.

Finally, we carried out the multivariate analysis using binary logistic regression. The Enter method was used for including the predictor variables in the equation. Variables which in the raw analysis were shown to have a link to treat-

ment adherence were included in the model, and these focus our study in relation to substance use, together with the other variables recommended in the specialised literature. Included in this analysis are: age, gender, socioeconomic level, length of follow-up, number of pills prescribed per day, and use of alcohol, cannabis, cocaine, heroin and methadone.

Results

Descriptive results and raw analysis

Sociodemographic and clinical characteristics of the sample.

A total sample of 119 subjects was analysed, with 40 cases and 79 controls. The median age of the population as a whole was 48.5 years (IQ: 44.3-52.8). The median years of follow-up and treatment time were, respectively, 16.5 (IQ: 9-21) and 15 (IQ: 7-19). The set of subjects took a median of 3 pills per day (IQ: 1-3). Other qualitative data characterising the overall sample are presented in Tables 1 and 2.

The number of males in the control group was 52 (65.8%), with 27 males in the group of cases (67.5%) (Table 3). The median age of the sample was 47.6 (42.5-50.6) in the case group and 49.1 (45.3-53.5) in the control group, with a median follow-up in years in the case group of 17.5 (9.8-22.0) and 15.0 (8.0-21.0) in the controls (Table 4).

The comparative analysis shows that the higher socioeconomic status of the control group is statistically significant. Similarly, among the cases a greater degree of treatment supervision by third parties is evident (Table 3). Regarding the quantitative variables, statistically significant differences between cases and controls were only found in terms of the number of pills per day (Table 4).

Table 1. *Sociodemographic variables of whole sample.*

		n	%
Sex	Male	79	66.4%
	Female	40	33.6%
Race	Caucasian	99	83.2%
	Other	20	16.8%
Marital status	With partner	46	38.7%
	Other	73	61.3%
Employment	In work	53	44.5%
	Unemployed	66	55.5%
Profession	Unqualified	54	46.2%
	Qualified	63	53.8%
Socioeconomic level	Stable	90	75.6%
	At risk	29	24.4%
Supervised treatment	Never	98	82.4%
	Sometimes/always	21	17.6%

Table 2. *Substance use variables of whole sample.*

	Yes	No
	n (%)	n (%)
Alcohol use	27(23.3)	89 (76.7)
Cannabis use	39 (32.8)	80 (67.2)
Cocaine use	29 (24.4)	90 (75.6)
Heroin use	8 (6.7)	111 (93.3)
Methadone use	17 (14.3)	102 (85.7)
Polydrug use	36 (30.3)	83 (69.7)

Table 3. *Sociodemographic variables compared - cases and controls.*

		Controles	Cases	Pearson test	
		n (%)	n (%)	χ^2	Sig.
Sex	Male	52 (65.8)	27 (67.5)	0.033	0.855
	Female	27(34.2)	13(32.5)		
Race	Caucasian	70 (88.6)	29 (72.5)	4.928	0.026
Marital status	With partner	28 (35.4)	18 (45.0)	1.023	0.312
	Other	51 (64.6)	22 (55.0)		
Employment	Unemployed	41 (51.9)	25 (62.5)	1.208	0.272
Profession	Unqualified	31 (40.3)	23 (57.5)	3.148	0.312
	Qualified	46 (59.7)	17 (42.5)		
Socioeconomic level	Stable	69 (87.3)	21 (52.5)	17.490	0.000
	At risk	10 (12.7)	19 (47.5)		
Treatment supervision	Never	71 (89.9)	27 (67.5)	9.146	0.002
	Sometimes/always	8 (10.1)	13 (32.5)		

Variables related to the use of substances.

Hazardous alcohol use was evident in 15 of the cases (37.5%), compared to 12 subjects (15.8%) in the control group (p = 0.009).

As the analysis of qualitative variables shows, the cases present a profile characterised by higher intakes of each substance assessed except for cannabis, where there are no differences with respect to the controls. Therapeutic use of methadone was observed in 12 of the cases (30.0%), in contrast to 5 subjects in the control group (6.3%) (p = 0.000). The difference in cocaine use was also statistically significant (p = 0.005). In the case of heroin, there were differences between both groups, with p = 0.073 (Table 5).

Logistic regression

Table 6 shows the results of the logistic regression analysis, where the variables that influence treatment adherence in a statistically significant way are highlighted. The applied model correctly classifies about 80% of the subjects, with greater specificity than sensitivity (Hosmer and Lemeshow test: cases = 55.7%, controls = 90.0%, overall = 78.3%) and explains 44.2% of the variability in adherence.

Substance use.

From the above data, it can be deduced that hazardous alcohol consumption represents an average increase of 4.330 (95% CI: 1.157-16.206) in the risk of poor adherence to antiretroviral therapy in a statistically significant way (p = 0.030) as against abstinence or non-detrimental use once adjusted for the variables indicated. The use of methadone increases this risk by 5.074 (95% CI: 1.056-24.379). In contrast, the consumption of cannabis, cocaine or heroin is not significantly associated with decreasing treatment adherence.

Sociodemographic and clinical data.

The results indicate increased risk of non-adherence for males, those in worse socioeconomic situations, and with antiretroviral therapy regimens consisting of a greater number of pills per day.

Discussion

It follows from the above that hazardous alcohol consumption significantly worsens adherence to antiretroviral

Table 4. *Clinical variables and statistical significance of comparisons - cases and controls.*

		n	Median	Interquartile range		Mann-Whitney U
				Q25	Q75	Sig.
Age	Cases	40	47.66	42.50	50.61	0.086
	Controls	79	49.10	45.31	53.47	
Years of follow-up	Cases	40	17.50	9.75	22.00	0.171
	Controls	78	15.00	8.00	21.00	
Years of treatment	Cases	40	17.00	8.25	20.00	0.094
	Controls	78	13.00	5.00	19.00	
Number of pills per day	Cases	40	3.00	3.00	4.00	0.001
	Controls	79	2.00	1.00	3.00	

Table 5. *Substance use and statistical significance of the comparisons - cases and controls.*

	Controls	Cases	Pearson test	
	n (%)	n (%)	χ^2	Sig.
Alcohol use	12 (15.8)	15 (37.5)	6.917	0.009
Cannabis use	24 (30.4)	15 (37.5)	0.611	0.434
Cocaine use	13 (16.5)	16 (40.0)	7.987	0.005
Heroin use	3 (3.8)	5 (12.5)	3.207	0.073
Methadone use	5 (6.3)	12 (30.0)	12.151	0.000
Polydrug use	14 (17.7)	22(55.0)	17.489	0.000

Table 6. *Logistic regression, 'Enter' method.*

	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI
Age	-0.092	0.044	4.348	1	0.037	0.912	0.837 – 0.995
Sex	-1.346	0.612	4.834	1	0.028	0.260	0.078 – 0.864
Years of follow-up	0.063	0.041	2.293	1	0.130	1.065	0.982 – 1.154
Nº pills per day	0.515	0.203	6.469	1	0.011	1.674	1.126 – 2.491
Socioeconomic level	1.347	0.581	5.374	1	0.020	3.844	1.231 – 12.001
Alcohol use	1.465	0.673	4.735	1	0.030	4.330	1.157 – 16.206
Cannabis use	-0.646	0.588	1.209	1	0.272	0.524	0.165 – 1.659
Cocaine use	0.380	0.715	0.283	1	0.595	1.463	0.360 – 5.943
Methadone use	1.624	0.801	4.112	1	0.043	5.074	1.056 – 24.379
Heroin use	-0.517	1.088	0.226	1	0.635	0.596	0.071 – 5.035
Constant	-2.282	3.062	0.556	1	0.456	0.102	

therapy. This confirms in our own care context and cultural environment what has previously been broadly and consistently described in the literature in other contexts (Azar et al., 2010; Vagenas et al., 2015; Hendershot et al., 2009). Furthermore, the association between alcohol use and lack of adherence is maintained in our research after adjustment for other substance use, so that in the sample studied, alcohol weakens adherence independently of the use of other substances.

A negative influence of the use of methadone on adherence is also evidenced, although doubts as to the meaning of this result exist. The therapeutic use of methadone could, at least in our country, correspond to clinically more deteriorated individuals or to those with a lower socioeconomic profile (Ladero, Orejudo & Carrobles, 2005), which would explain worse adherence and would be congruent with the results obtained. Nevertheless, previous studies have suggested that adherence to a methadone treatment program may lead to an improvement in adherence to antiretroviral therapy in comparison to untreated parenteral drug users (Malta, Strathdee, Magnanini & Bastos, 2008), especially in marginal areas with a high prevalence of this type of consumption (Azar et al., 2015).

Conversely, the present study finds no significant association between the use of cannabis, cocaine or heroin and a decrease of treatment adherence, which differs globally from findings previously reported in the literature in other contexts (Hinkin et al., 2004; Azar et al., 2015). However, the absence of a link between cannabis use and noncompliance has already been pointed out by other authors (Rosen et al., 2013; De Jong, Prentiss, McFarland, Machekano & Israelski, 2005). In this sample, moreover, there are no significant differences in the raw analysis between cases and controls in such consumption. Regarding the use of heroin or cocaine, it is estimated that the absence of a statistically significant relationship could be due to the small number of individuals that admit to using these drugs, although there is controversy about the capacity of patients to report such consumption (Van Dorn, Desmarais, Swartz, Young & Sellers, 2014).

From the results, it can be concluded that the subjects in worse socioeconomic situations are at greater risk of treatment noncompliance. This would be congruent with other findings described in the literature. It is known that structured social support and a fixed address facilitate adherence (Ruiz-Pérez et al., 2006), thus underlining the importance of psychosocial factors on overall health status and the need to deepen research in this field, which has gained importance in recent years (Ruiz-Pérez et al., 2006; Beer, Mattson, Bradley & Skarbinski, 2016).

In the group of subjects classified as non-adherent, there is a higher percentage of treatment supervision by third parties, which should probably be understood as a consequence of the baseline situation of noncompliance. The superiority - in terms of immunological control of infection and adherence - of supervised medication administration for substance users compared to self-medication has been demonstrated in both randomized studies and systematic reviews (Binford, Kahana & Altice, 2012).

Various authors have previously found that more complicated treatment regimens (greater number of pills per day) worsened treatment adherence (Ammassari et al., 2002; Stone, Jordan, Tolson, Miller & Pilon, 2004; Nachega et al., 2014).

The present study confirms, in our context, most of the findings published in the literature. The reliability of treatment adherence data, in which the objective and quantitative hospital pharmacy reports are consolidated by the SMAQ instrument and the opinion of the referring professional, as well as the inclusion of different consumption and sociodemographic variables can be seen as strengths of the study.

Among its limitations, it should be noted that its statistical power is diminished due to the small sample size, as well as the low incidence of heroin and cocaine use, which appears to limit the role of these variables in our sample. It must be emphasised that data regarding the individual history of substance use were obtained solely via an interview with the patient. In addition, given the requirements of regular outpatient follow-up, it is likely that subjects with more acute consumption patterns and more severe markers of social and clinical deterioration have been excluded from this study. It should be assumed that the results obtained may be applied and extrapolated only to those populations that share a similar profile. It is therefore recommended that the study be extended to populations in environments with greater problems in accessing health care, with more acute consumption patterns or greater psychosocial deterioration in order to study the impact of alcohol and other substances on treatment adherence in subjects with this profile.

Substance use was measured qualitatively, following the WHO criteria for hazardous drinking in the case of alcohol, and quantitatively, without assessing whether patients met criteria for the diagnostic categories of substance abuse or dependence. However, considering the damage linked to the use of substances on a continuum rather than assigning it to static entities increases sensitivity in the detection of the influence of hazardous use in non-adherence, and is the line followed by the current DSM-5.

It should be noted that the adherence estimate according to the hospital pharmacy refill data is based on the withdrawal or otherwise of the medication, and not strictly on its consumption. Other limitations include the inability to determine whether medication was taken at the correct time, whether extra medication was taken in compensation, or whether pills were lost (Berg & Arnsten, 2006). Nevertheless, this method has been shown to be highly specific but not very sensitive, thus the use of complementary methods in the present study decreases the risk of a possible overestimation of adherence (Henegar et al., 2015).

Among the limitations of the study it should finally be stressed that the analysis of the sample presented lacks variables related to the presence or otherwise of psychopathology (Torrens, Mestre-Pintó, Montanari & Vicente, 2017) as well as the cognitive status of the participants. The possibility of selection and survival biases inherent in the study design should also be taken into account. No patients were excluded for non-consent. Data on patients excluded on other grounds were not collected.

It is well known that adherence to antiretroviral therapy plays a vital role in preventable morbidity and mortality in HIV-positive patients (Braithwaite & Bryant, 2010). In light of the results obtained, it is therefore essential to address the possible existence of substance use - especially of alcohol - in the daily clinical setting, questioning the type, frequency and amount of the substance consumed in order to be able to carry out measures that reduce the impact of consumption on treatment compliance (Parsons et al., 2014). In addition to improving the detection of possible risk patterns, it would be important to provide patients with access to specific resources to treat these problems (Gonzalez et al., 2013). Based on the above, new research should focus on the behavioural, structural, social or psychological factors related to adherence in different groups of substance users in order to develop specific interventions (Azar et al., 2015).

Conclusions

The study highlights the importance of alcohol consumption as a factor negatively affecting adherence to antiretroviral therapy. This importance is maintained even when the consumption of other substances is considered, and adjustments are made for other variables that influence adherence, such as being male, having a problematic socioeconomic situation or a regimen with a high number of pills. The assumption that treatment adherence is a dynamic and modifiable process justifies intervention at different levels in order to minimise the factors associated with its decline. Carefully exploring the use of alcohol (and other substances) is essential in the treatment of patients with HIV and highly active antiretroviral therapy (HAART), and could thus facilitate the advancement of better outcomes for the disease, with decreases in morbidity, mortality and the risk of virus transmission, as well as the development of resistant strains. In studies with HIV-positive subjects, the great degree of heterogeneity among patients must be taken into account. Therefore, in clinical practice it will be important to individualise each case and to identify which factors, both risk and protective, can condition adherence to antiretroviral therapy.

Conflict of interests

The authors state that there is no conflict of interest with regard to the present study. Enriqueta Ochoa Mangado states that in recent years she has received funding as a speaker and has collaborated on projects by *Lundbeck, Servier, Reckitt Benckiser / Indivior,* and *Ferrer-Brainfarma.*

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Exploring the direct or inverse association of physical activity with behavioral addictions and other self-regulation problems

¿Protege o predispone la actividad física a las adicciones conductuales y otros problemas de autorregulación?

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Abstract

This cross-sectional survey study had the aim of clarifying the relationships between leisure time physical activity (LTPA) and non-drug-related self-regulation problems (non-drug-related SRPs), including behavioral addictions, and the role of impulsive personality traits therein. Spanish university students (N = 329; M_{age} = 21.20) completed questionnaires for each of these constructs.

Fitness and Bodybuilding LTPA was negatively associated with video gaming-related SRPs, r = -.13, p = .019, 95% CI (bootstrapped) [-.23, -.02], and positively associated with sex-related SRPs, r = .16, p = .005, 95% CI (bootstrapped) [.04, .30]. Endurance LTPA was associated with higher scores in eating-related SRPs, r = .17, p = .003, 95% CI (bootstrapped) [.02, .31]. The proportion of participants presenting scores above the clinically significant threshold in eating-related SRPs was 2.64 times higher for respondents in an Excessive Endurance LTPA cluster compared to the other respondents, Fisher's exact test, p = .017, OR = 3.10, 95% CI [1.26, 7.63], and the proportion of participants reporting vomiting to control weight was 2.12 times higher, Fisher's exact test, p = .040, OR = 2.43, 95% CI [1.06, 5.57]. The associations were largely independent of impulsive personality traits.

We identified an elevated risk of eating pathology in a subgroup of participants with anomalously high participation in endurance physical activity. This overlap is consistent with the *secondary dependence* hypothesis of exercise addiction.

Keywords: Leisure time physical activity; Physical exercise; Exercise addiction; Self-regulation; Behavioral addiction; Impulsivity; Impulsive personality traits.

Resumen

Este estudio tuvo como objetivo aclarar las relaciones entre la actividad física de ocio (AFO) y los problemas de autorregulación (PARs) no relacionados con drogas, incluyendo las adicciones conductuales, y el papel de los rasgos de personalidad impulsiva. Estudiantes universitarios españoles (N = 329, M_{age} = 21,20) completaron cuestionarios para cada uno de estos constructos.

La AFO de gimnasio y musculación se asoció negativamente con los PARs relacionados con videojuegos, r = -0,13, p = 0,019, 95% CI (*bootstrapped*) [-0,23, -0,02], y positivamente con los PARs relacionados con sexo, r = 0,16, p = 0,005, 95% CI (*bootstrapped*) [0,04, -0,30]. La AFO de resistencia se asoció positivamente con los PARs relacionados con la alimentación, r = 0,17, p = 0,003, 95% CI (*bootstrapped*) [0,02, 0,31]. La probabilidad de presentar puntuaciones potencialmente clínicas en PARs de alimentación fue 2,64 veces mayor para los encuestados en un grupo de AFO de resistencia excesiva en comparación con los otros encuestados, prueba exacta de Fisher, p = 0,017, OR = 3,10, 95% CI [1,26, 7,63], y la probabilidad de vomitar para controlar el peso fue 2,12 veces mayor en ese mismo grupo, prueba exacta de Fisher, p = 0,040, OR = 2,43, 95% CI [1,06, 5,57]. Las asociaciones fueron en gran medida independientes de los rasgos de personalidad impulsiva.

Identificamos un riesgo elevado de patología alimentaria potencialmente clínica en un subgrupo de participantes con niveles anormalmente altos de actividad física de resistencia. Esta superposición es consistente con la hipótesis de *dependencia secundaria* en la adicción al ejercicio.

Palabras clave: Actividad física de ocio; Ejercicio físico; Adicción al ejercicio; Autorregulación; Adicción conductual; Impulsividad; Rasgos de personalidad impulsiva.

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Physical activity (PA) is widely acknowledged as beneficial for mental and physical health. However, a long-lasting debate has been going on with regard to the potentially risky correlates of participation in sports. More specifically, abnormally intense or frequent PA shows parallelisms with self-regulation problems (SRPs; Bratland-Sanda et al., 2011). Self-regulation requires the control of habits, urges, and cravings, so that poorly self-regulated behaviors may interfere with well-being (Vohs & Baumeister, 2011). Some of these SRPs, including excessive PA, have been conceptualized as behavioral addictions (e.g. Grant, Potenza, Weinstein, & Gorelick, 2010).

Thus PA may be used as a strategy to address mental health issues, but, at the same time, certain PA patterns could overlap with or be a precursor of self-regulation problems. With this two-sided prospect in mind, we explored the potential relationships between amounts of leisure time physical activity (LTPA) and subjective complaints associated with non-drug-related self-regulation problems (SRPs), as well as the possible involvement of impulsive personality traits in such relationships.

Most SRPs as well as certain PA patterns have been found to be associated with impulsive personality traits (Evenden, 1999; Joseph, Alonso-Alonso, Bond, Pascual-Leone, & Blackburn, 2011; Knezevic-Budisin, Pedden, White, Miller, & Hoaken, 2015; Lejoyeux, Tassain, Solomon, & Adès, 1997; Perry & Carroll, 2008; Raymond, Coleman, & Miner, 2003; Verdejo-García, Lawrence, & Clark, 2008). In accordance with the "Urgency, Premeditation, Perseverance, Sensation Seeking" model (UPPS-P; Whiteside & Lynam, 2001), impulsivity comprises: (a) negative urgency, i.e., the tendency to experience strong reactions under conditions of negative affect; (b) positive urgency, i.e., the proneness to act rashly under intense positive affect; (c) sensation seeking, i.e., the tendency to pursue new and exciting activities; (d) lack of premeditation, i.e., the tendency to not think of the consequences of an action before engaging in it; and (e) lack of perseverance, i.e., the inability to stay focused on attention-demanding tasks (Cyders et al., 2007).

Impulsive personality traits can play different hypothetical roles in the relationships between LTPA and non-drug-related SRPs. On the one hand, the *strength model of self-control*[1] predicts that the availability of self-control resources underlies low levels of impulsive personality traits, facilitates self-regulation, and prevents self-regulation problems (Baumeister & Tierney, 2011; Baumeister, Vohs, & Tice, 2007). In accordance with this prediction, individuals with reduced self-control resources are more prone to impulsive acts and SRPs (Billieux, Gay, Rochat, & Van der Linden, 2010; Verdejo-García et al., 2008; Wills & Dishion, 2004; Wills, Iasi, Don Mendoza, & Ainette, 2007). Concurrently, high self-control is associated with a low level of sedentary behavior and increased levels of participation and performance in PA, via a higher tolerance to fatigue and an orientation toward long-term benefits (Dorris, Power, & Kenefick, 2012; Joseph et al., 2011; Wills et al., 2004; Wills et al., 2007). In other words, high levels of self-control (manifested in low impulsive personality traits) could predict both engagement in LTPA and decreased risk of non-drug-related SRPs.

On the other hand, the *PA dependence hypotheses* conceive some cases of anomalously high participation in sports as instances of a specific type of SRP, so-called *primary PA dependence* (i.e., exercise addiction). Alternatively, PA can be a strategy to deal with the consequences of other clinical or subclinical primary problems, so-called *secondary PA dependence* (de Coverley Veale, 1987; Landolfi, 2013). Accordingly, PA-dependent individuals would exercise routinely to excess[2], often ignoring injury and neglecting work, family, and friends (de Coverley Veale, 1987). This condition is frequently reported among runners and other endurance sports people (Allegre, Souville, Therme, & Griffiths, 2006; Breuer & Kleinert, 2009). Assuming it could be regarded as a primary SRP, excessive PA would be expected to present some level of co-occurrence with other problematic behaviors in this category. This type of overlap is observed, for example, between substance abuse and problem gambling (Navas, Torres, Vilar, et al., 2014; Petry, Stinson, & Grant, 2005), or between harmful alcohol consumption and excessive internet use (Navas, Torres, Cándido, & Perales, 2014; Yen, Ko, Yen, Chen, & Chen, 2009). Extending the parallelism, at least some excessive exercisers (in whom excessive exercise tends to an addictive pattern) would be expected to present impulsivity characteristics similar to the ones observed in other addictive behaviors, with sensation seeking signaling early exposure, and negative urgency as a predictor of disordered behavior (Billieux et al., 2007; Dick et al., 2010; Navas, Torres, Cándido, & Perales, 2014; Navas, Torres, Vilar, et al., 2014).

Of particular interest is the specific relationship between dysregulated eating behavior and excessive endurance LTPA (Grandi, Clementi, Guidi, Benassi, & Tossani, 2011; Lichtenstein, Christiansen, Elklit, Bilenberg, & Støv-

1 Self-control is a component of self-regulation (the ability to regulate behavior at the service of longer-term goals), namely the top-down cognitive mechanism by means of which drives, habits, and urges are inhibited.

2 There is no consensus on the existence of PA dependence. Therefore, no diagnostic category exists in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013). Actually, the DSM–5 only recognizes gambling disorder as a behavioral (non-substance) addiction. In order to avoid controversy, we use the term "excessive LTPA" for cases reporting very high levels of LTPA participation compared to mean LTPA values, in a purely descriptive fashion and without any clinical connotations.

ing, 2014). In putative cases of primary PA dependence, dieting and weight loss would be expected to be strategies to increase performance, whereas secondary PA dependence can occur among people with eating disorders, where PA is a means to lose weight (Adams & Kirkby, 2001; de Coverley Veale, 1987).

Our overarching research aim was thus to explore the potential relationships between practice patterns of different forms of LTPA and non-drug-related SRPs (including behavioral addictions), and the role impulsive personality traits play in these relationships. Few studies exist about the relationships between LTPA and SRPs, apart from substance abuse (e.g. Lisha & Sussman, 2010). Furthermore, the importance of PA modalities has not yet been exhaustively considered (Allegre et al., 2006; Breuer et al., 2009; Ziemainz et al., 2013). However, athletes practicing distinct types of LTPA mostly differ in their personal exercise motivation and aims (Ford, 2007; Kondric et al., 2013; NIH, 2011), and it has been found that these underlying motives may influence the associations with drug-related SRPs (Kondric et al., 2011). Considering the absence of direct evidence, our expectation about the direction of relationships remains open. An association in which low impulsive personality trait scores contribute simultaneously to a higher likelihood of participation in LTPAs and to a lower probability of presenting non-drug-related SRPs would be in line with the strength model of self-control (Baumeister et al., 2011; Baumeister et al., 2007). On the contrary, a direct positive relationship of endurance LTPA with non-drug-related SRPs as well as with impulsive personality traits would support the PA dependence hypothesis. More specifically, an association between potentially clinical eating-related SRPs and excessive LTPA would support the secondary PA dependence hypotheses (de Coverley Veale, 1987).

Methods

Participants

Participants were students at the University of Granada, Spain. Being a university student was the only inclusion criterion. Meeting the intended sample size required for the statistical analyses, the final sample consisted of 329 students with ages between 18 and 41 years (M_{age} = 21.20; *SD* = 3.50). The sample consisted of 183 female and 146 male students. Participants were following degrees in Sports Sciences (n = 125), Psychology (n = 116), Sociology (n = 42), Speech-Language Therapy (n = 18), a Master's degree (n = 4) or others (n = 22). Most participants (n = 227) were in the first year of their degree.

Design and Procedure

For the cross-sectional survey study we recruited the participants through convenience sampling at various departments of the University of Granada, without compensation. All participants received information about the aims of the study and gave their informed consent prior to participation. The participants completed a set of paper-and-pencil self-report questionnaires in class. Instructions were given by members of the research team. The procedure was approved by the Ethics Committee of the University of Granada (*Vicerrectorado de Política Científica e Investigación*) with reference number 2014-901.

Measures

We measured LTPA by means of the *Cuestionario sobre la Participación en Actividades Deportivas por Tipo* (Questionnaire of Participation in Sports Activities per Type; CPAD-T). We adapted the Global Physical Activity Questionnaire (GPAQ) of the World Health Organization to measure the patterns of participation in LTPA (Armstrong & Bull, 2006; Bull, Maslin, & Armstrong, 2009), specified by type of sport. The scale contains the forty most practiced LTPAs in Spain according to results from a survey carried out by the Supreme Council for Sports of the Spanish Government (García & Llopis, 2011), and the option "other physical activity, namely…". Based on the measurement system of the GPAQ, respondents were asked to indicate which of the LTPAs they presently practiced, how many days a week they practiced this activity during a typical week, and how many hours and minutes on a typical day—a day on which they practiced a certain LTPA. Students from the Sports Sciences faculty filled out the questionnaire twice, in order to separate academic PAs from activities practiced in their leisure time. Here, only the latter were used for the analyses, since our focus was on leisure time practice, and mandatory PA could distort the results. The GPAQ is used extensively in the scientific field and has good psychometric properties (Armstrong et al., 2006).

In order to boil down the number of LTPAs assessed with the CPAD-T questionnaire to a manageable set of dimensions, we extracted the combination of dimensions that best accounted for correlations among different LTPAs with a principal component analysis (PCA; see Appendix A for a detailed description of the analysis). Table 1 shows the factor loadings after rotation. Based on literature (Ford, 2007; García et al., 2011; Kondric et al., 2013; NIH, 2011) we identified the components as Opposition LTPA (Factor 1); Ski, Skate, and Board LTPA (Factor 2); Non-Intrusive Endurance LTPA[3] (Factor 3); Fitness and Bodybuilding LTPA (Factor 4); Aerobics LTPA (Factor 5); Competitive Individual LTPA (Factor 6); and Swimming LTPA (Factor 7).

Subsequently, we carried out a k-means cluster analysis with Euclidean distance measure on the Non-Intrusive Endurance LTPA factor scores, in order to discriminate a

3 With Non-Intrusive Endurance LTPA we refer to PAs that are usually practiced to sustain physical condition and supposed to minimally interfere with daily life.

Table 1. *Factor Loadings From Principal Component Analysis With Varimax Rotation for Leisure Time Physical Activities (LTPA) of the Questionnaire of Participation in Sports Activities per Type* (N = *329)*

	Rotated factor loading						
LTPA	1	2	3	4	5	6	7
Padel tennis	**.73**	.04	-.02	-.00	.01	.17	.14
Tennis	**.66**	-.16	-.00	-.07	.08	.13	.20
Soccer	**.60**	.19	.02	.16	-.16	-.27	-.20
Winter sports	.00	**.76**	.08	-.03	.08	.10	.25
Skating	.01	**.73**	-.08	.01	-.07	-.05	-.21
Fitness at home	.02	-.20	**.73**	-.17	.08	-.06	-.21
Running	.05	.07	**.61**	.36	-.23	.06	.08
Hiking	-.17	.32	**.58**	-.03	.06	.04	.46
Bodybuilding	.00	-.13	.00	**.79**	-.13	.06	-.02
Fitness at gym	-.12	.18	-.01	**.63**	.42	-.12	.03
Aerobics	-.16	-.11	-.09	.11	**.72**	-.02	.10
Basketball	-.18	-.09	-.06	.13	**-.59**	-.01	.16
Athletics	.05	-.06	-.12	.05	-.10	**.82**	.07
Cycling	.16	.24	.29	-.06	.12	**.58**	-.22
Swimming	.28	-.03	-.06	.01	-.07	-.05	**.75**
Initial eigenvalue	1.75	1.60	1.30	1.24	1.15	1.05	1.03
% of variance	11.68	10.65	8.64	8.24	7.66	6.98	6.87

Note. Boldface indicates highest factor loadings. Factor 1 = Opposition LTPA; Factor 2 = Ski, Skate, and Board LTPA; Factor 3 = Non-Intrusive Endurance LTPA; Factor 4 = Fitness and Bodybuilding LTPA; Factor 5 = Aerobics LTPA; Factor 6 = Competitive Individual LTPA; Factor 7 = Swimming LTPA.

Table 2. *Demographic Characteristics per Cluster Distinguished on Endurance Leisure Time Physical Activity (LTPA;* N = *329)*

	Cluster 1: Low–Normal Endurance LTPA (*n* = 287)				Cluster 2: Excessive Endurance LTPA (*n* = 42)			
Characteristic	%	*M*	*SD*	*Mdn*	%	*M*	*SD*	*Mdn*
Age (years)		21.25	3.60	2.17		21.01	2.68	20.17
Gender (female)	55.7				54.8			
Degree (Sports Sciences)	39.0				31.0			
Years of education attendance		14.27[a]	2.82[a]	14.00[a]		13.88	2.97	13.50
Education level mother		1.75[b]	0.95[b]	2.00[b]		1.81	1.04	2.00
Education level father		1.82[c]	0.99[c]	2.00[c]		1.83	0.99	2.00

Note. [a]*n* = 278. [b]*n* = 285. [c]*n* = 284.

group of participants who practiced endurance LTPA at very high to excessive levels compared to the rest of the sample. We labeled the clusters Low–Normal Endurance LTPA (Cluster 1; $n = 287$) and Excessive Endurance LTPA (Cluster 2; $n = 42$). Demographic characteristics per cluster are shown in Table 2. In Appendix B, we explain the analysis in more detail. Table B.1 displays intercluster differences in participation in each LTPA.

For the measurement of the non-drug-related SRPs we used the questionnaire MULTICAGE CAD-4 (Pedrero Pérez et al., 2007). The questionnaire consists of 32 items assessing alcohol-, drug-, video gaming-, sex-, eating-, gambling-, internet-, and spending-related SRPs. Here, we only used the non-drug-related variables. All items are dichotomous (yes/no). In each SRP subscale, zero or one affirmative answers indicate non-existence of a clinically relevant problem, two affirmatives indicate a possible existence of a problem, three a very probable, and four an almost definite existence of a problem (a score of 2 or higher is considered clinically significant). The questionnaire is easily applicable and presents adequate psychometric and discriminative properties (Pedrero Pérez et al., 2007).

In order to test the incidence of problematic eating behavior as a function of LTPA participation, we identified individuals with eating-related SRP scores above a clinically significant threshold: We divided scores on the eating-related SRP variable into 0–1 indicating a low probability, and 3–4 indicating a high probability of clinical problems.

Participants who scored 2 were not included, in order to diminish the possibility of false positives.

Impulsivity was assessed with the Spanish brief UPPS-P Impulsive Behavior Scale (Cándido, Orduña, Perales, Verdejo-García, & Billieux, 2012; Whiteside, Lynam, Miller, & Reynolds, 2005), based on the model explained above. Each trait is measured by four items, scored on a four-point Likert scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*). Psychometric properties are satisfactory and can be found in Cándido et al. (2012).

Statistical Analyses

For the first hypothesis regarding the relationships between LTPA and non-drug-related SRPs, we conducted a partial correlation analysis including LTPA factors, non-drug-related SRP scores, and impulsive personality traits. Demographic variables (gender, age, years of education attendance, and education level completed by the mother) entered the analysis as control variables. These variables have been previously found to be associated with drug-related SRPs (Gardner, 1994; Lamptey, 2005), and, in the present study, correlated either with LTPA or with non-drug-related SRP scores. Whether a participant studied at the faculty of Sports Sciences or not also entered the analysis as a covariate (for a detailed description of the analyses see Appendix C).

For the second set of hypotheses we explored the potential clinical correlates of the different LTPA patterns showed by the Low–Normal Endurance LTPA and Excessive Endurance LTPA clusters three-way. First, we compared the proportion of individuals who presented clinically significant scores on the eating-related SRPs across the two endurance LPTA groups with the use of a Fisher's exact test. Second, we analyzed differences between groups per MULTICAGE CAD-4 eating-related SRP item, again using Fisher's exact tests. Finally, we compared the two groups on each of the impulsive personality traits by conducting independent samples *t* tests.

We performed all analyses using IBM SPSS Statistics 20, and applied a .05 significance criterion.

Results

Sample characteristics

The most popular LTPAs, practiced by at least 15 participants, both female and male students, from the faculty of Sports Sciences as well as other faculties, were running (36.4%, including jogging and trail running), soccer (23.7%), bodybuilding (21.9%, including weight lifting), aerobics (17.9%, including corporal expression, dancing, steps, pilates, yoga, acrobatics, pole dance, spinning, and similar guided LTPAs), fitness at home (17.6%), cycling (16.4%), fitness at gym (14.0%), padel tennis (13.7%), hiking (13.7%, including trekking and mountaineering), swimming (8.5%), winter sports (7.6%), basketball (7.3%), tennis (7.0%), athletics (4.6%), and skating (4.6%). Some participants practiced more than one activity, while some others ($n = 54$) did not practice any LTPA. The mean time spent in LTPA was 8.08 h/week ($SD = 8.13$). The sample median was 6 hours and the middle 50% of the respondents spent between 1.5 and 12 hours in LTPA. The frequencies categorized by gender and faculty are shown in Table 3.

Table 4 displays the frequency distributions of non-drug-related SRPs in the sample (according to the

Table 3. *Practiced Leisure Time Physical Activity in Hours per Week (*N *= 329)*

	Faculty of Sports Sciences						Other faculties					
Gender	*n*	%	*M*	*SD*	*Mdn*	*IQR*	*n*	%	*M*	*SD*	*Mdn*	*IQR*
Female	39	11.9	8.92	7.00	6.25	14.00–4.50	144	43.8	4.73	5.45	3.00	7.19–0.06
Male	86	26.1	12.63	9.02	11.21	16.00–6.38	60	18.2	9.06	7.10	7.00	14.77–1.50

Table 4. *Non-Drug-Related Self-Regulation Problem (SRP) Scores of MULTICAGE CAD-4 Questionnaire (*N *= 329)*

	Video gaming		Sex		Eating		Gambling		Internet		Spending	
SRP score	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
0	281	85.4	267	81.2	191	58.1	311	94.5	124	37.7	246	74.8
1	28	8.5	39	11.9	76	23.1	11	3.3	90	27.4	48	14.6
2	15	4.6	16	4.9	31	9.4	4	1.2	64	19.5	23	7.0
3	2	0.6	4	1.2	18	5.5	2	0.6	30	9.1	9	2.7
4	2	0.6	2	0.6	12	3.6	0	0.0	20	6.1	2	0.6
Missing	1	0.3	1	0.3	1	0.3	1	0.3	1	0.3	1	0.3
M (SD)	0.22 (0.36)		0.28 (0.67)		0.73 (1.08)		0.08 (0.36)		1.18 (1.21)		0.39 (0.79)	

MULTICAGE CAD-4 questionnaire). All distributions were positively skewed: The majority of the sample reported low scores on the non-drug-related SRP variables. As mentioned above, a score of 2 or higher indicates the possible existence of a non-drug-related SRP. As shown by the means and the relatively large number of risk scores of 2 or higher, quite some respondents showed potential eating- (18.5%) and internet-related (34.7%) SRPs, of whom a large part very probably presented those problems (score of 3 or 4): respectively 9.1% and 15.2%.

Impulsive personality traits measured with the UPPS-P range between 1 (*low impulsive personality traits*) to 4 (*high impulsive personality traits*). The mean scores were: negative urgency, $M = 2.38$ ($SD = 0.74$); positive urgency, $M = 2.47$ ($SD = 0.61$); sensation seeking, $M = 2.58$ ($SD = 0.75$); lack of premeditation, $M = 1.98$ ($SD = 0.56$); lack of perseverance, $M = 1.77$ ($SD = 0.59$). The overall mean was 2.24 ($SD = 0.42$). One participant did not fill in the scale.

Relationships between variables of interest

We used partial correlations to explore the associations between the variables of interest. The possible confounders described in Appendix C (gender, age, studying at the faculty of Sports Sciences or not, years of education attendance, and education level completed by the mother) were entered in the analyses as control variables. The correlations are shown in Table 5, with hypotheses-relevant associations presented in bold. An inverse relationship between LTPA and non-drug-related SRPs appeared only for Fitness and Bodybuilding LTPA and video gaming-related SRPs. We found a positive relationship for the same factor Fitness and Bodybuilding LTPA and sex-related SRPs. Finally, as predicted, a positive correlation emerged for Non-Intrusive Endurance LTPA and eating-related SRPs.

In these associations between LTPA and non-drug-related SRPs we found a possible involvement or moderating effect of impulsive personality traits only for sensation seek-

Table 5. *Partial Intercorrelations Among Measures of Leisure Time Physical Activity (LTPA), Non-Drug-Related Self-Regulation Problems (SRPs), and Impulsive Personality Traits* (N = *329)*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Opposition LTPA	—																	
2. Ski, Skate, & Board LTPA	-.07	—																
3. Non-Intrusive Endurance LTPA	.02	.03	—															
4. Fitness & Bodybuilding LTPA	-.13*	-.02	.01	—														
5. Aerobics LTPA	.11°	.04	.00	.08	—													
6. Competitive Individual LTPA	-.03	.00	.01	-.02	.00	—												
7. Swimming LTPA	.01	.10°	-.01	-.01	-.02	-.02	—											
8. Video gaming-related SRPs	.01	-.02	.02	**-.13***	-.06	.06	.02	—										
9. Sex-related SRPs	-.06	.06	-.02	**.16****	-.02	-.04	-.01	.09	—									
10. Eating-related SRPs	-.06	-.01	**.17****	.04	**.10°**	.07	-.02	-.01	.07	—								
11. Gambling-related SRPs	.05	-.09	-.03	.09	.06	-.01	-.03	.06	.18**	.07	—							
12. Internet-related SRPs	.03	-.03	.06	.04	-.04	.01	-.03	.16**	.17**	.17**	.06	—						
13. Spending-related SRPs	-.02	-.01	-.01	.06	.00	-.06	-.03	.12*	.32**	.16**	.06	.22**	—					
14. Negative urgency	-.02	.00	.00	.03	.00	.02	-.07	.06	.19**	.21**	.10°	.15**	.18**	—				
15. Positive urgency	-.08	.08	.04	.09	-.01	.03	-.02	.03	.23**	.15**	.15*	.15**	.24**	.50**	—			
16. Sensation seeking	.00	.17**	-.01	**.17****	-.03	.17**	.00	-.06	**.26****	.07	.11*	.11°	.12*	.19**	.41**	—		
17. Lack of premeditation	-.05	.09	-.02	.07	.04	-.04	.02	.07	.19**	-.01	.00	.11°	.08	.23**	.33**	.29**	—	
18. Lack of perseverance	.01	-.12*	-.05	-.04	-.04	-.04	-.05	.12*	.15**	.05	.20**	.21**	.18**	.11°	.25**	.05	.27**	—

Note. Boldface indicates highest hypotheses-related correlations. Control variables were age, gender, studying at the faculty of Sports Sciences or not, years of education attendance, and education level completed by the mother. ° $p < .10$. * $p < .05$. ** $p < .01$.

ing in the positive relationship between Fitness and Bodybuilding LTPA and sex-related SRPs. As shown in Table 5, sensation seeking correlated both with Fitness and Bodybuilding LTPA and with sex-related SRPs.

Eating-related SRPs in Excessive Endurance LTPA practitioners

In the Low–Normal Endurance LTPA cluster (n = 287) 7.7% showed a score of 3 or higher on eating-related SRPs, versus 19.0% of the Excessive Endurance LTPA cluster (n = 42). An analysis of the data with a Fisher's exact test, in which we excluded individuals who scored 2 on the eating-related SRP subscale, as explained above, yielded a significant association between endurance LTPA cluster and eating-related SRPs, p = .017, OR = 3.10, 95% CI [1.26, 7.63]. Supporting the hypothesis, the proportion of respondents presenting scores above the clinically significant threshold in eating-related SRPs (3-4 MULTICAGE scores in the eating disorders subscale, as opposed to individuals with 0-1 scores) was 2.64 times higher in the Excessive Endurance LTPA cluster.

Fisher's exact tests carried out with the whole sample (N = 329) showed that the clusters significantly differed in affirmative answers only on the first item of the eating-related SRP variable, "Have you ever provoked vomiting to avoid weight gain?", p = .040, OR = 2.43, 95% CI [1.06, 5.57].The proportion of individuals indicating "yes" was 2.12 times higher for the Excessive Endurance LTPA cluster. Confirming the previously reported partial correlations (Table 5), t tests showed no significant intercluster differences with regard to the impulsive personality traits: The lowest p-value was p = .201.

Discussion

Summarizing the main results, data unveiled a very limited number of associations between LTPA and non-drug-related SRPs and behavioral addictions in a community sample of university students. The higher an individual's practice levels of Fitness and Bodybuilding LTPA, the lesser video gaming-related and the more sex-related SRPs were reported. High participation in endurance LTPAs was associated with more eating-related SRPs, and specifically with vomiting as a strategy to control weight. Furthermore, a considerable amount of positive relationships supported the hypothesized association between impulsive personality traits and non-drug-related SRPs. However, we did not find clear associations between impulsive personality traits and LTPAs that could, in turn, be responsible for a relationship between LTPAs and non-drug-related SRPs.

The strength model of self-control (Baumeister et al., 2011; Baumeister et al., 2007) predicts inverse relationships between LTPA participation and non-drug-related SRPs. In partial accordance with this model, we found lower levels of Fitness and Bodybuilding LTPA participation to correlate with higher levels of video gaming-related SRPs. However, although the model proposes availability of self-control resources to be at the core of SRPs and regular engagement in effortful activities (Dorris et al., 2012; Joseph et al., 2011), in our study we did not find any indications of impulsive personality traits being responsible for the association. Alternatively, the *displacement* hypothesis could account for the inverse association between Fitness and Bodybuilding LTPA and video gaming-related SRPs. This proposition states that time spent in sedentary behaviors displaces time that could be spent in PA (Ballard, Gray, Reilly, & Noggle, 2009; Mansoubi, Pearson, Biddle, & Clemes, 2014). Consistent with our results, Ballard and colleagues (2009) found a negative relationship between time dedicated to video gaming and PA levels.

The Fitness and Bodybuilding LTPA factor was positively related to sex-related SRPs, with high sensation seeking simultaneously correlating with both constructs. To our knowledge, a relationship between PA and excessive sexual behavior has never been directly analyzed. However, previous research suggests (1) an association between bodybuilding (Litt & Dodge, 2008; McCreary & Sasse, 2000), even to excess (Hale, Roth, DeLong, & Briggs, 2010; Hurst, Hale, Smith, & Collins, 2000), and drive for muscularity, especially reported among men (McCreary, 2012; McCreary et al., 2000); (2) associations of muscularity (in men) and thinness (in women) with ideals of attractiveness (Murnen & Don, 2012; Murray, Rieger, Touyz, & De la Garza García, 2010); and (3) an association between drive for attractiveness and frequency of sexual intercourse (Brody, 2004; Filiault, 2007; Swami, Diwell, & McCreary, 2014). Our results suggest the possibility that Fitness and Bodybuilding LTPA practice can be associated with not only an enhanced sexuality, but also with its potential negative consequences in the form of SRP symptoms of hypersexuality.

Besides drive for attractiveness, an alternative (not necessarily incompatible) explanation comprises the existence of a common personality factor associated with both behaviors. In accordance with that possibility we found sensation seeking to correlate with both Fitness and Bodybuilding LTPA and sex-related SRPs. Higher levels of sensation seeking have been found before among fitness club members (Lichtenstein et al., 2014), and sensation seeking has been reported as a robust predictor of risky sexual behavior (e.g., Hoyle, Fejfar, & Miller, 2000; Zapolski, Cyders, & Smith, 2009).

The primary PA dependence hypothesis was not confirmed: We did not find impulsive personality trait markers (which were expected to be mainly negative urgency and sensation seeking; Billieux et al., 2007; Dick et al., 2010; Navas, Torres, Cándido, & Perales, 2014; Navas, Torres, Vilar, et al., 2014) to potentially underlie positive associations between excessive endurance LTPA measures and non-drug-related SRPs. However, in accordance with the

secondary PA dependence hypothesis (de Coverley Veale, 1987), higher scores on the Non-Intrusive Endurance LTPA factor (containing running, fitness at home, and hiking) correlated with signs of eating-related SRPs. Moreover, belonging to a cluster of individuals showing very high practice patterns of this type of LTPA (labeled here as Excessive Endurance LTPA) more than doubled the probability of presenting symptoms of eating-related SRPs above the clinically significant threshold, compared to Low–Normal Endurance LTPA participants. This is consistent with prior research, indicating that excessive endurance PA participation and disordered eating patterns often go hand in hand (Allegre et al., 2006; Grandi et al., 2011; Lichtenstein et al., 2014). Moreover, as a novel result, we found that vomiting as a weight-control strategy distinguished between Low–Normal Endurance LTPA and Excessive Endurance LTPA participants.

The impulsive personality trait negative urgency correlated with eating-related SRPs. This result is consistent with reports of negative urgency as a strong predictor of psychopathology, especially in the realm of SRPs (Billieux et al., 2007; Dick et al., 2010). The potential association of eating-related SRPs and sensation seeking, proposed by previous researchers as a signal of early exposure to potentially addictive substances (e.g., Cyders, Flory, Rainer, & Smith, 2009), as well as with overeating and obesity (e.g. Schag, Schönleber, Teufel, Zipfel, & Giel, 2013), has not been found here. This suggests that the type of eating-related SRPs detected in the current sample and found to be related to excessive LTPA is not the type that has been described as food addiction (e.g. Lerma-Cabrera, Carvajal, & Lopez-Legarrea, 2016), but is more closely linked to clinical or subclinical forms of anorexia and bulimia. The relationship between excessive LTPA and vomiting also points in that direction.

Strengths and Limitations

The conclusions presented are potentially affected by a number of limitations. Foremost, future (longitudinal) research is needed in order to examine directions of the correlational findings in our cross-sectional self-report study. Another limitation is the fact that, given the exploratory nature of the study, some hypotheses were rather open. Because we used no methods for alpha adjustment, this could be deemed fishing. Even so, this does not apply to the remarkable association found between endurance LTPA and eating-related SRPs, which we expected based on a very specific hypothesis.

Furthermore, we based the hypotheses in part on PA dependence models (e.g., de Coverley Veale, 1987), although, for PA, characteristics of addiction have not been measured: Purely behavioral measures are not necessarily associated with PA dependence attitudes (Adkins & Keel, 2005; Mond, Hay, Rodgers, & Owen, 2006). A mayor strength is the adaptation of the GPAQ (Armstrong et al., 2006) without altering its measurement system, which allowed us to assess sport modalities: The importance of sport types in relation to self-regulation issues has scarcely been paid any attention to in prior research.

The generalizability of the results is supported by the most practiced LTPAs being very comparable to the most practiced sports in Spain (García et al., 2011). Moreover, in a study with a population of all ages (Rodríguez Monje, Pedrero Pérez, Fernández Girón, Gallardo Alonso, & Sanz Cuesta, 2009) very similar–heavily skewed–distributions of non-drug-related SRP were found. A larger sample size in our study may have yielded more respondents with potentially clinical problem scores and thereby resulted in a greater statistical power. Furthermore, the questionnaire may be oversensitive regarding internet abuse (Billieux, Schimmenti, Khazaal, Maurage, & Heeren, 2015), for which a high percentage of the sample scored above the risk threshold for clinical problems. However, the plausible prevalence rates found for the other non-drug-related SRPs still show substantial percentages of potentially clinical addictive behaviors among university students. This supports the relevance of early recognition and intervention, especially since people showing addictive behaviors often experience comorbid psychopathological symptoms and even suicidal ideation (Bousoño et al., 2017; Martín-Fernández et al., 2017). Correctly assessing individual profiles of potentially clinical problematic behaviors, including non-drug-related SCPs and LTPA practice patterns, helps the identification of people at risk, contributes to prevention, and helps to establish treatment plans adapted to the profile of a person (Martín-Fernández et al., 2017). The study has major strengths regarding eating-related SRPs. The possibility that we actually measured clinical eating-related self-regulation pathology is high, given multiple indicators. Negative urgency was associated with eating-related SRPs, and substantial evidence has shown that this impulsive personality trait is an indicator of clinical pathology (Billieux et al., 2007; Dick et al., 2010). Furthermore, Pedrero Pérez et al. (2007) found a diagnostic sensibility for the cut-off point of two or more affirmative answers indicating a clinical problem above 90% for substance abuse: In the present study, we used an even more conservative cut-off point of three or four affirmative answers to indicate clinical eating-related SRPs. Finally, the difference in eating-related SRPs between the Low–Normal Endurance LTPA and Excessive Endurance LTPA participants seemed to be especially true for the use of vomiting as a strategy to avoid weight gain: This MULTICAGE CAD-4 questionnaire item was previously found to be related to diagnosed anorexia and bulimia (Rodríguez Monje et al., 2009), and thus could be considered as a sign of clinical eating pathology.

Finally, the powerful outcomes of the endurance LTPA cluster comparisons strongly suggest that associations between LTPA and SRPs occur only on very high (that is, ex-

cessive or clinically significant) levels of both constructs. This may be an explanation for the small effects between the continuous variables when measured in the full range, and requires further examination.

Conclusions

In order to develop effective intervention and treatment plans for SRPs and behavioral addictions, the understanding of the at-risk population is imperative. The present study has aided in the identification of LTPA practice patterns and impulsive personality traits as risk and protective factors for non-drug-related SRPs, and is of added value due to explorations per LTPA modality. Main novel findings were an inverse relationship between Fitness and Bodybuilding LTPA and video gaming-related SRPs; a triangle of positive associations between Fitness and Bodybuilding LTPA, sex-related SRPs, and sensation seeking; and, most important, a positive relationship of running, fitness at home, hiking, and similar endurance LTPAs with eating-related SRPs, with the eating disorder symptom vomiting more often shown in people presenting very high participation in those activities. This result is of particular importance, since the use of vomiting as a weight loss strategy is highly indicative of eating pathology.

The results of our study suggest a substantial prevalence of potentially clinical non-drug-related SRPs and behavioral addictions among university students, supporting that possibilities to recognize, intervene on or prevent those are relevant to address. Therefore, it is recommended that well-designed future research extends the evidence for the role of LTPA as both a risk behavior and a non-pharmaceutical intervention strategy for self-regulation issues in various populations, and further detects psychological antecedents of those associations. This can aid in further elucidation of warning signs and treatment possibilities for risky and unhealthy behaviors regarding self-regulation.

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Conflicts of interest

None of the authors declare competing financial interests.

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Appendix A
Factor Analysis for Leisure Time Physical Activities

In order to boil down the number of LTPAs assessed with the CPAD-T questionnaire to a manageable set of dimensions, we extracted the combination of dimensions that best accounted for correlations among different LTPAs with a principal component analysis (PCA). Because scores on the variables of interest significantly differed depending on gender and faculty, we only included activities practiced by both female and male students, from the faculty of Sports Sciences as well as other faculties. These were running, soccer, bodybuilding, aerobics, fitness at home, cycling, fitness at gym, padel tennis, hiking, swimming, winter sports, basketball, tennis, athletics, and skating. The minimum amount of cases for factor analysis was satisfied (MacCallum, Widaman, Zhang, & Hong, 1999), with at least 15 respondents in each LTPA category. We analyzed the intercorrelations among the variables, showing that all items significantly correlated up to .14–.33 (one-tailed) with at least one other item. The only exception was basketball, although the data showed a trend to significance with aerobics, $r = -.07$, $p = .116$. This indicated reasonable factorability and the absence of multicollinearity. Bartlett's test of sphericity was significant, $\chi^2(105) = 283.17$, $p < .001$, and the communalities were all (except basketball, .43) above .50, with an average communality of .61. This confirmed that each item shared some variance with other variables, thus that the relations between the variables were sufficiently large for PCA. Given these indicators, we carried out the factor analysis with all 15 items.

The analysis resulted in seven components, with eigenvalues over Kaiser's criterion of 1. In combination, the components explained 60.7% of the variance. There was little difference between the Varimax and Oblimin solutions: For the final model we chose the Varimax rotation. Table 1 shows the factor loadings after rotation. Based on literature (Ford, 2007; García et al., 2011; Kondric et al., 2013; NIH, 2011) we identified the components as Opposition LTPA (Factor 1); Ski, Skate, and Board LTPA (Factor 2); Non-Intrusive Endurance LTPA (Factor 3); Fitness and Bodybuilding LTPA (Factor 4); Aerobics LTPA (Factor 5); Competitive Individual LTPA (Factor 6); and Swimming LTPA (Factor 7).

Appendix B
Cluster Analysis for Endurance LTPA

We carried out a k-means cluster analysis with Euclidean distance measure on the Non-Intrusive Endurance LTPA and Aerobics LTPA factors, in order to discriminate a group of participants who practiced endurance LTPA at very high levels compared to the rest of the sample. The Aerobics LTPA factor did not discriminate between the clusters, $F(2, 326) = .11$, $p = .738$, so we made the decision to carry out the cluster analysis only with the Non-Intrusive Endurance LTPA factor.

We labeled the clusters Low–Normal Endurance LTPA (Cluster 1; $n = 287$) and Excessive Endurance LTPA (Cluster 2; $n = 42$). The small size of the Excessive Endurance LTPA cluster is an indication of the statistical anomaly of this group: As aimed for, the clusters separated the individuals who practiced excessive levels of endurance LTPA from the rest of the sample. In Table 2, demographic characteristics per cluster are shown. There were no significant intercluster differences as examined using chi-square and *t* tests: The lowest *p*-value was $p = .320$. Table B.1 displays intercluster differences in participation in each LTPA.

Table B.1 *Practiced Leisure Time Physical Activity (LTPA) in Hours per Week per Cluster Distinguished on Endurance LTPA* (N = *329)*

	Cluster 1: Low–Normal Endurance LTPA (*n* = 287)				Cluster 2: Excessive Endurance LTPA (*n* = 42)			
LTPA	*n*	%	*Mdn*	*IQR*	*n*	%	*Mdn*	*IQR*
Running	90	31.4	1.50	2.00–1.00	30	71.4	4.00	6.00–2.00
Soccer	67	23.3	2.00	5.00–1.00	11	26.2	2.00	3.00–1.00
Bodybuilding	64	22.3	5.00	7.50–3.00	8	19.0	4.92	7.13–3.13
Aerobics	52	18.1	3.00	5.00–2.00	7	16.7	2.00	4.00–1.67
Fitness at home	33	11.5	1.00	1.50–0.58	25	59.5	3.00	4.75–2.67
Cycling	43	15.0	2.00	3.00–1.00	11	26.2	4.50	9.67–3.00
Fitness at gym	40	13.9	3.00	7.40–1.75	6	14.3	5.25	6.50–2.50
Padel tennis	38	13.2	1.50	2.50–1.00	7	16.7	1.00	1.50–1.00
Hiking	27	9.4	2.00	3.00–1.50	18	42.9	6.00	10.13–3.00
Swimming	24	8.4	2.00	4.50–1.13	4	9.5	3.00	4.00–0.64
Winter sports	19	6.6	3.50	8.00–2.00	6	14.3	5.38	9.00–2.19
Basketball	20	7.0	3.50	4.50–1.50	4	9.5	2.75	4.00–0.75
Tennis	20	7.0	2.00	3.75–1.00	3	7.1	1.50	––1.00[a]
Athletics	14	4.9	1.63	2.63–1.00	1	2.4	2.50	–––[a]
Skating	11	3.8	4.00	10.50–1.00	4	9.5	1.00	3.25–0.63

Note. [a]No upper and/or lower quartile exists due to small *n*.

Appendix C
Preliminary Analyses for Demographic Confounders

We used a correlation analysis to identify potential demographic confounders. Age significantly correlated with internet-related SRPs, r = -.15, p = .007. Years of education attendance presented significant associations with leisure time practice of soccer, r = -.12, p = .032, fitness at gym, r = .12, p = .028, as well as with eating-related SRPs, r = .11, p = .045. The education level completed by the mother was correlated with leisure time practice of cycling, r = .12, p = .029, and winter sports, r = .11, p = .048.

Variance analyses showed significant differences between students of the faculty of Sports Sciences (n = 125) and other faculties (n = 204). The students of the faculty of Sports Sciences showed higher means on leisure time practice of soccer, $F(1, 326) = 26.13$, $p < .001$, bodybuilding, $F(1, 326) = 29.45$, $p < .001$, padel tennis, $F(1, 326) = 27.23$, $p < .001$, swimming, $F(1, 326) = 6.68$, $p = .010$, basketball, $F(1, 326) = 7.43$, $p = .007$, tennis, $F(1, 326) = 15.30$, $p < .001$, athletics, $F(1, 326) = 3.93$, $p = .048$, and lower means on eating-related SRPs, $F(1, 326) = 5.72$, $p = .017$. We also found significant differences between male (n = 183) and female students (n = 146). Confirming previous reports, male students showed higher means on leisure time practice of soccer, $F(1, 326) = 30.40$, $p < .001$, bodybuilding, $F(1, 326) = 50.08$, $p < .001$, aerobics, $F(1, 326) = 11.43$, $p = .001$, padel tennis, $F(1, 326) = 12.49$, $p < .001$, basketball, $F(1, 326) = 5.43$, $p = .020$, winter sports, $F(1, 326) = 4.74$, $p = .030$, tennis, $F(1, 326) = 7.48$, $p = .007$, and skating, $F(1, 326) = 5.21$, $p = .023$, as well as in video gaming-, $F(1, 326) = 30.71$, $p < .001$, sex-, $F(1, 326) = 15.00$, $p < .001$, and gambling-related SRPs, $F(1, 326) = 4.58$, $p = .033$, and lower means on eating-related SRPs, $F(1, 326) = 8.01$, $p = .005$.

Based on these results, in the final analyses we set control measures for the variables age, gender, studying at the faculty of Sports Sciences or not, years of education attendance, and education level completed by the mother, but not for education level completed by the father.

The urban environment of alcohol: a study on the availability, promotion and visibility of its use in the neighborhoods of Barcelona

Entorno urbano de alcohol: un estudio sobre disponibilidad, promoción y visibilidad del consumo en barrios de Barcelona

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Abstract

Introduction. This paper describes the presence of alcohol in the public space, assessing establishments that offer it, its advertising, and signs of consumption, as factors that may influence its consumption.

Method. Descriptive observational study based on cluster sampling with two-step selection. Results are described, and the spatial association between variables is assessed.

Results. In the 20 census tracts studied, 306 premises were identified that offered alcoholic beverages: 204 were on-premises and 102 were off-premises, mainly supermarkets and food retail stores. Their spatial distribution was uneven, concentrated in two central districts. We identified 72 publicity items, mostly sponsorship of musical events. There were many promotional items linked to on- premises, especially in their terraces. Five people were detected promoting consumption or selling alcohol in the Old Town. In each time slot, between 39 and 51 signs of consumption on the public space were observed (mostly abandoned beer cans), more frequent at night and in the Old Town. There is an association between the presence of establishments that offer alcohol and advertising. There is no relationship between these variables and signs of consumption in the public space; these are concentrated in the Old Town, which has greater presence of tourism.

Conclusions. The urban environment is characterized by elements that stimulate alcohol use and its distribution is uneven, with a strong influence of tourism-related activities. Further regulation of alcohol promotion, availability and consumption in the public space may change its social image and decrease its use.

Keywords: Alcoholic beverages; Public policy; Evaluation; Observation; Social environment.

Resumen

Introducción. Se describe la presencia de alcohol en el espacio público, valorando los establecimientos que lo ofrecen, la publicidad, y los indicios de consumo, como factores que pueden inducir el consumo.

Método. Estudio observacional descriptivo basado en un muestreo por conglomerados con selección bietápica. Se describen los resultados, y se valora la asociación espacial entre variables.

Resultados. En las 20 secciones censales estudiadas se identificaron 306 establecimientos que ofrecían bebidas alcohólicas: 204 de venta y consumo y 102 de venta sin consumo, básicamente supermercados y comercio alimentario. Su distribución territorial fue desigual, concentrada en dos distritos céntricos. Se identificaron 72 elementos de promoción y publicidad destacando el patrocinio de actividades musicales. Se observan elementos promocionales vinculados a los locales de venta y consumo, sobre todo en sus terrazas. Se detectaron cinco personas realizando venta ambulante o promoción del consumo en el casco antiguo. En cada franja horaria se apreciaron entre 39 y 51 indicios de consumo en la vía pública (mayoritariamente envases de cerveza abandonados), más frecuentes de noche y en el casco antiguo. Hay una asociación entre la presencia de establecimientos que ofrecen alcohol y la de elementos de publicidad. No se aprecia relación entre estas variables y los indicios de consumo en el espacio público; éstos se concentran en el casco antiguo, con mayor presencia del turismo.

Conclusiones. El medio urbano se caracteriza por elementos que estimulan el consumo de alcohol y su distribución es desigual, muy influida por las actividades orientadas al turismo. Mejorar la regulación de su promoción, disponibilidad y consumo en el espacio público puede contribuir a cambiar su imagen social y disminuir su uso.

Palabras clave: Bebidas alcohólicas; Política pública; Evaluación; Observación; Entorno social.

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Introduction

Perceived social norms influence patterns of alcohol use (Sudhinaraset, Wigglesworth & Takeuchi, 2016). Given that alcohol advertising, availability and the visibility of consumption in public spaces contribute to the creation of an image of social acceptance and are linked to increased use, the regulation of alcohol consumption can have an important preventive value (Ahern, Margerison-Zilko, Hubbard & Galea, 2013; Campbell et al., 2009; de Bruijn et al., 2016). Indeed, European countries with the greatest restrictions on the advertising of alcoholic beverages are shown to have a lower occurrence of high-risk drinkers (Bosque-Prous et al., 2014). In the Catalan context, recent years have seen a documented increase in alcohol intoxication among adolescents and young people, and the health sector is increasingly interested in adopting preventive measures (Pulido et al., 2014; Sánchez-Queija, Moreno, Rivera & Ramos, 2015). However, resistance by groups with vested economic interests has blocked legislative attempts in recent years (Villalbi, Granero & Brugal, 2008).

Advertising and availability play an important role in the onset and maintenance of alcohol use (Anderson, de Bruijn, Angus, Gordon & Hastings, 2009). Some regulations, such as Law 20/1985, on the prevention and assistance regarding substances that may cause addiction in Catalonia, have limited the promotion of alcoholic beverages. The ban on advertising for highly alcoholic drinks on public thoroughfares was contested in the courts by the industry, but the European Court of Justice ruled in favor of the Government of Catalonia (Ford, 1993), and advertising disappeared from public spaces for a time. However, the industry has since managed to introduce new, more subtle promotional strategies based on sponsorship and indirect advertising (Villalbí & Benavides, 2014). Currently, advertising pressure is high, as it is in Spain as a whole (López-Sánchez, Garcia del Castillo & Gázquez-Pertusa, 2013; Sánchez-Pardo, 2012). Similarly, international studies suggest that there is an association between the availability of alcohol and the amount consumed, as well as the harm it causes. (Popova, Giesbrecht, Bekmuradov & Patra, 2009). The retailing of alcoholic beverages in Spain does not require a specific license, so that alcohol can be sold in the great majority of food outlets without being specifically registered. In recent years, the deregulation of opening hours appears to have led to a general increase in the availability of alcoholic beverages at low cost in the urban environment, especially at night and on weekends (Sureda, Villalbí, Espelt & Franco, 2017; Villalbí et al., 2015). Until now, we have lacked objective and empirical data in our context that would enable us to quantify how the exposure to urban factors influences alcohol use. That is why we have proposed the present study. Its aim was to quantify three aspects related to alcoholic beverages in the city of Barcelona: the establishments that sell them, the elements of advertising and visible promotion, and the evidence of consumption in public spaces, and to explore the possible relationship between them.

Methods

Design and sampling. A descriptive observational study was carried out in the city of Barcelona (Catalonia, Spain) in November 2015. Cluster sampling was used, taking as a sampling unit the census tract, a relatively homogeneous geographical unit in terms of the resident population (an estimated average of 1,600 inhabitants and 1,000 voters per tract) into which the city council divides the city. A two-stage selection process was applied. First, two neighborhoods were selected for each of the ten districts, chosen according to their population (the seven neighborhoods with fewer than five thousand residents were excluded) and their socioeconomic indicators (in each district the two neighborhoods with the highest and lowest number of registered unemployed were included), thus obtaining twenty neighborhoods reflecting the city's variability. Secondly, within each neighborhood, a census tract was randomly selected, and the observers walked all public roads within the limits of the tract, carrying out meticulous observations during each of the following periods from Monday to Friday: mornings (from 11 am to 2 pm), afternoon (from 5 pm to 9 pm), and night (after 11 pm). In this way, data from 60 observation episodes were obtained.

Data gathering instrument and process. The data were recorded in a standardized questionnaire in paper format, developed by the research team after a pilot test (Sureda et al., 2017) and subsequently validated with high percentages of inter and intra observer reliability (Ruiz-Pérez, 2016). Data collection was carried out by a single team of two previously trained observers, who worked simultaneously taking inverse routes in each area and resolving possible discrepancies *in situ*. The observers took photographs of elements they were unsure of how to classify in order to decide on the appropriate classification later with the person supervising data collection. The supervisor reviewed 10% of the 60 observations registered in order to verify accuracy. The final database thus comprises information gathered from three time periods in the 20 zones.

Variables. The independent variable is the district. The dependent variables are the establishments selling alcoholic beverages, the items advertising alcohol, and the indicators of consumption in public spaces. The time slot is treated as a contextual independent variable. The establishments were classified according to their type, grouped according to whether alcohol is sold and consumed there (on-premises) or merely sold but not consumed (off-premises), i.e. bars, cafeterias or restaurants vs. shops. The items found in the city streets referring to alcoholic beverages or commercial brands of alcoholic beverages were

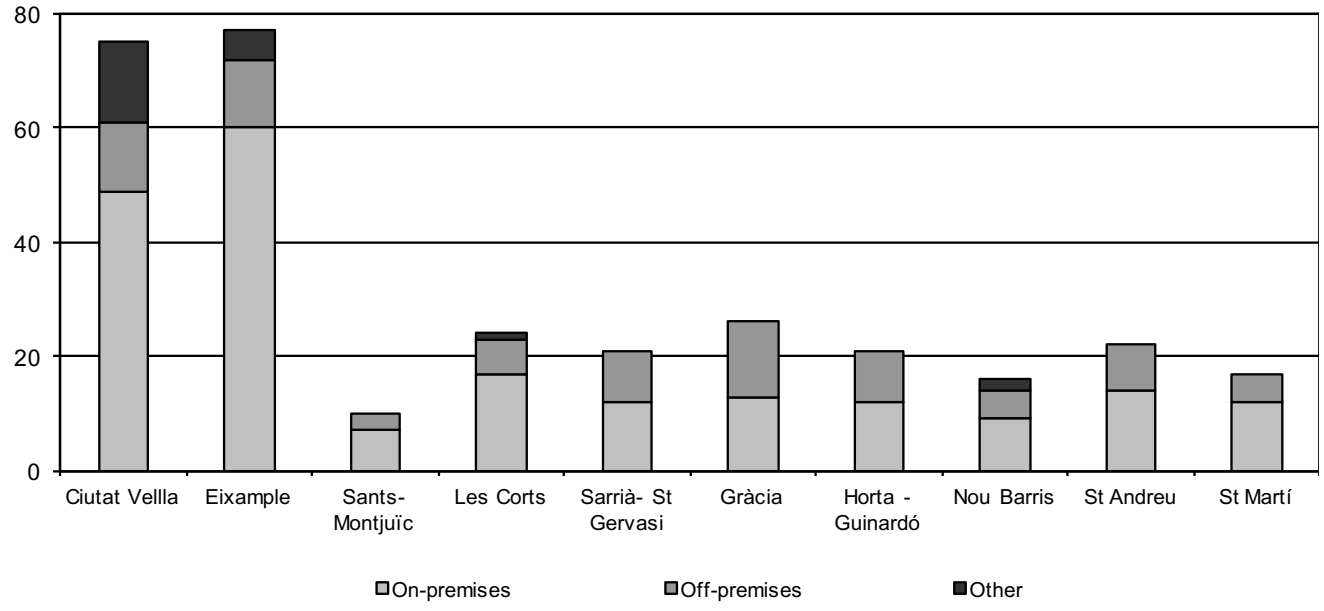
divided into advertising (direct or indirect advertising, and sponsorship), and other items of alcoholic drinks promotion (such as items naming drink brands in establishments selling alcohol or on their terraces). The signs of consumption were the elements seen in public spaces outside the terraces of the establishments where drinking is allowed, such as people drinking, discarded containers, or other signs of consumption (empty glasses, broken glass bottles, etc.). Subsequently, four synthetic variables were created to compare the territories. Synthetic variable 1 (SV1) combines the supply and availability of alcoholic beverages (combining establishments of any type selling drinks in the two census tracts observed in each district). Synthetic variable 2 (SV2) combines the promotional and advertising items observed in each district. Synthetic variable 3 (SV3) combines the values of SV1 and SV2 in order to reflect the total availability and advertising of alcohol in each neighborhood considered to be a stimulus to consumption. Synthetic variable 4 (SV4) tries to demonstrate the visibility of alcohol use in public spaces, combining the observations of signs of consumption which reflect socially inappropriate practices (people drinking in public spaces outside the on-premises terraces, abandoned containers, remains of glasses and bottles, etc.).

Analysis. Data were analyzed using SPSS 18.0. The unit of analysis was the geographical area (census tract, and neighborhood or district in which it is located). Results are presented descriptively. Two simple linear regressions are employed to analyze the relationships between availability and advertising (VS1 and VS2) with the values of the synthetic variables in the districts (n = 10), and then between the synthetic variable that combines them and the signs of consumption (VS3 and VS4).

Results

Supply and availability. In the 20 census tracts studied, a total of 306 establishments were identified that sold alcoholic beverages (an average of 15.3 per tract, ranging from 3 to 51). With an average of 1,600 residents per census tract in the city, this corresponds to 9.6 establishments selling alcoholic beverages per 1,000 inhabitants. On-premises establishments made up 67%, while 33% were off-premises; of these, 27% were supermarkets and food shops, and 7% were other establishments where drinks were sold as a marginal part of the business (such as tourist souvenir shops selling bottled sangria). On-premises establishments were open and busy more frequently in the mornings (85%) and afternoons (77%), but many were also open at night (47%). Of the retail-only outlets, 96% were open in the morning, 79% in the afternoon and 26% at night. Figure 1 shows their distribution by district. As can be seen, their spatial distribution is uneven: almost half (46%) are found in the census tracts of the two most central district neighborhoods (Ciutat Vella and Eixample), in which the density of establishments selling alcohol is as high as 23 and 24 establishments per 1,000 inhabitants.

Advertising and promotion. In the census tracts studied, 72 items of promotion and advertising of alcoholic beverages were identified in public thoroughfares. The sponsorship of music events by drinks companies stands out. On-premises establishments also feature numerous promotional



Note. The 'others' category includes off-premises establishments where the sale of alcohol plays a very minor role in the business (for example bottled sangria in tourist souvenir shops).

Figure 1. Establishments selling alcoholic drinks in the 20 census tracts analyzed, by type and district. Barcelona, 2015.

items. Thus, 61% of premises with terraces have alcohol marketing items (mainly furniture with logos or printed brand names). Additionally, 91% of the businesses that sell alcohol have items on view that can be considered stimuli for the sale or consumption of alcoholic beverages. There is a great deal more advertising and promotional material in Ciutat Vella and Eixample: between them, these two districts combine more than half of all promotional items found in the study. Five people were also seen selling drinks or promoting places to drink, directly approaching pedestrians in the street, all in Ciutat Vella. This information is summarized in Table 1.

Indicators of consumption. In each time slot, between 39 and 51 items considered as signs of drinking in public spaces (excluding the terraces of on-premises establishments) were recorded in the 20 areas studied, totaling 133 signs, as can be seen in Figure 2. Most of these items were discarded containers (80), especially beer cans. Signs of consumption were more frequently seen during the night observation periods and in the tracts of the Ciutat Vella neighborhood studied: of the 27 observations of people consuming in public spaces (outside the terraces), 21 were in this district.

Table 2 shows the distribution by district of the synthetic variables. Ciutat Vella and Eixample districts feature prominently, combining the bulk of both drink availability and advertising and promotional items, and there is a high correlation between SV1 (reflecting the availability of alcoholic beverages) and SV2 (reflecting alcohol advertising), with a correlation coefficient r of 0.96 ($R^2 = 0.92$). Conversely, SV4 (which reflects inappropriate consumption) is high in only one district Ciutat Vella, whereas there are hardly any signs of inappropriate consumption in Eixample. While in Ciutat Vella there were 50 indications of drinking in public spaces, in most districts this value fluctuates between 9 and 18. There does not seem to be a correlation between VS4 and VS3, which combines the visible stimuli observed ($r = 0.35$, $R^2 = 0.12$).

Discussion

The results of this empirical study show that our urban environment is characterized by high availability of alcohol, even at night, and particularly in the most central neighborhoods. Promotional and advertising elements are ubiquitous. Signs of inappropriate consumption in public spaces are highly noticeable and especially concentrated in certain areas. Many of these reflect violations of the city Ordinance on measures to encourage and guarantee the

Table 1. *Advertising and promotional items on public thoroughfares relating to alcoholic drinks. Barcelona, 2015.*

District	Advertising on public thoroughfares (*)	Promotional items in drinking establishments			Promotional elements in off-premises establishments		Total promotional elements	
		Terraces with promotional items	Other promotional items	Total drinking establishments	Elements in establishments	Total off-premises establishments	Elements	%
Ciutat Vella	13	8	18	49	12	75	51	19.8%
Eixample	26	14	15	60	10	76	65	25.2%
Sants- Montjuïc	3	3	2	7	3	10	11	4.3%
Les Corts	13	4	6	17	6	24	29	11.2%
Sarrià- St Gervasi	1	2	4	12	9	21	16	6.2%
Gràcia	3	4	0	13	8	25	15	5.8%
Horta- Guinardó	4	3	1	12	9	21	17	6.6%
Nou Barris	3	5	5	9	5	15	18	7.0%
Sant Andreu	4	5	4	14	8	22	21	8.1%
Sant Martí	2	6	3	12	4	17	15	5.8%
Barcelona	72	54	58	205	74	306	258	100%

Note. *Includes direct and indirect advertising and sponsorship.

Note. Terraces and other on-premises establishments are excluded. The 'other waste' category includes elements such as broken glass bottles, discarded plastic cups and other signs of drinking.

Figure 2. Visible signs of alcohol consumption in public spaces in the census tracts analyzed, by time slot. Barcelona, 2015.

Table 2. *Distribution of synthetic variables (SV) linked to the presence of alcohol in public spaces, by district. Barcelona, 2015.*

District	Establishments selling drinks (SV1)	Promotional items (SV2)	Total stimuli (SV3)	Stimuli / 1000 pop.	Signs of consumption (SV4)	Signs of consumption/ 1000 pop.
Ciutat Vella	75	51	126	39.37	50	15.63
Eixample	76	65	141	44.06	1	0.31
Sants- Montjuïc	10	11	21	6.56	15	4.69
Les Corts	24	29	53	16.56	15	4.69
Sarrià- St Gervasi	21	16	37	11.56	0	0
Gràcia	25	15	40	12.5	9	2.81
Horta- Guinardó	21	17	38	11.87	5	1.56
Nou Barris	15	18	33	10.31	18	5.62
Sant Andreu	22	21	43	13.44	11	3.44
Sant Martí	17	15	32	10	14	4.37
Barcelona	306	258	564	17.63	138	4.31

coexistence of citizens, prohibiting drinking from cans or glass containers in public spaces, as well as the discarding of drink containers on public thoroughfares (Ordenanza de medidas para fomentar y garantizar la convivencia ciudadana en el espacio público de Barcelona, 2005). Both the availability of alcohol and the exposure to promotional items have been linked to alcohol use in studies carried out in other media (Ahern et al., 2013; Bryden, Roberts, McKee & Petticrew, 2012; Ellickson, Collins, Hambarsoomians & McCaffrey, 2005; Hurtz, Henriksen, Wang, Feighery & Fortmann, 2007). We believe that quantifying the presence and distribution of alcohol in our urban context provides elements which may improve its control.

Among the study's limitations, the fact that it is based on a relatively small sample of areas stands out, although having two census tracts per district ensures some variability. It must also be borne in mind that the observations were made at one particular time (autumn 2015) and could be different at another time. In the summer of 2015 some aspects of the municipal Ordinance governing the city's terraces began to be applied, which reduced the advertising elements linked to these (Castan, 2014). Additionally, the weather plays a seasonal role in outdoor activities and may have influenced some of the phenomena studied. The autumn of 2015 featured particularly mild weather without rain. Among the strengths of the study, the careful creation of the standard form must be highlighted, as the precautions to optimize the validity of data collection, and the realization of observations in three time periods in each zone.

The results suggest a strong concentration of both the availability of alcoholic beverages and their promotion in the center of the city, with a strong association between the two. Other neighborhoods have far more limited availability, and fewer visible items of alcohol promotion. Nevertheless, the signs of inappropriate consumption seem to be much more common in a specific part of the city center, since they are concentrated in the center but they do not affect the Eixample district, nor other districts associated in the public imagination with young people's leisure activities (such as the Gracia district). Perhaps this is due to the sampling limitations, although it could also be that tourism and related night-time leisure activities, relatively concentrated in the historic center (Ciutat Vella), are the biggest drivers of visible inappropriate consumption. Other studies have shown that a greater density of premises and longer opening hours are associated with greater alcohol consumption and greater impact (Popova et al., 2009).

There are estimates of the density of establishments by population in the Nordic and Baltic countries (although territorially greater in scope than the municipal level) that show far lower availability than in our study of the city (Orro, Martens, Lepane, Josing & Reiman, 2015). The findings in the city of Barcelona cannot be compared with other cities in our environment because comparative data are lacking, so we do not know if this situation is better or worse in other major cities. Certain legal aspects (such as the current municipal Ordinances governing terraces and citizen coexistence, or the Catalan legislation on the sale of alcohol) (Villalbí et al., 2015), may have some influence in the city, where massive binge events (*botellón*) like those described in other Spanish regional capitals have never been reported. Currently, the regional diversity in Spain of regulations covering this area is remarkable (Martín, Simó & García, 2009). We believe that after this pilot study in a single city it should be possible to undertake more ambitious studies which allow the comparison of several places subject to different public policies governing alcohol. Furthermore, we propose to analyze the relationship between these variables and the alcohol consumption of adolescents, for which we have self-reported data through representative surveys (Santamariña-Rubio, Serral-Cano & Ariza, 2017). This has not been studied before in our context. More rigorous regulation of the promotion, availability and consumption of alcohol, and actions that guarantee compliance, could reduce the number of visual stimuli associated with alcoholic beverages. This could change the current social image of alcohol, which seems to favor greater consumption by the population as a whole, and especially by young people and minors (Babor, 2010; Bryden et al., 2012; Luty, 2016). In this connection, local policies have demonstrated important potential for reducing the harm caused by alcohol, especially among young people (de Goeij et al., 2016).

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Conflicts of interest

The authors declare no conflicts of interest.

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Individual and contextual factors related to binge drinking among adolescents in Spain: a multilevel approach

Factores individuales y contextuales relacionados con el binge drinking *en adolescentes españoles: un enfoque multinivel*

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Abstract

The aim of this study was to estimate the prevalence of binge drinking by regions in Spain and assess the effect of individual and contextual factors related to this drinking pattern in adolescents. A cross-sectional study was performed with data from the 2014 Spanish School Survey on Drug Use (ESTUDES) in students aged 14-18 years (N = 34,259). The outcome was binge drinking in adolescents during the last 30 days. Individual independent variables were socioeconomic variables and variables related to access to alcohol and its availability. Contextual variables consisted of adult alcohol consumption, public policies on alcohol, and socioeconomic factors. Multilevel Poisson regression models with robust variance were estimated, obtaining prevalence ratios (PR) and their 95% confidence intervals.

The results showed that the prevalence of youth binge drinking by region of residence was similar for both sexes (r = 0.72). At the individual level, binge drinking was mainly associated with the perception of easy access to alcohol (PR: 1.38; 95% CI: 1.23-1.55), consumption in open areas [(PR: 3.82; 95% CI: 3.44-4.24) < once a month and (PR: 6.57; 95% CI: 5.85-7.37) ≥ once a month], at least one parent allowing alcohol consumption (PR: 1.42; 95% CI: 1.37-1.47), and receiving >30 euros weekly (PR :1.51; 95% CI: 1.37-1.67). Contextual variables were not associated with youth binge drinking when individual variables were considered. In conclusion, youth binge drinking was associated with individual variables related to high alcohol accessibility and availability, regardless of contextual variables. These variables explained the variability in binge drinking among Spanish regions.

Keywords: Alcohol; Underage drinking; Binge drinking; Adolescents; Alcohol accessibility.

Resumen

El objetivo de este estudio era estimar la prevalencia de *binge drinking* por provincias en España y estimar el efecto de variables individuales y contextuales relacionadas con dicho consumo en adolescentes españoles. Se realizó un estudio transversal con datos de la Encuesta sobre uso de drogas en Enseñanzas Secundarias en España (ESTUDES 2014) a estudiantes de 14 a 18 años (N = 34.259). La variable dependiente fue *binge drinking* en adolescentes durante los últimos 30 días. Las variables independientes individuales fueron variables socioeconómicas y variables relacionadas con el acceso y la disponibilidad de alcohol. Las variables contextuales fueron el consumo de alcohol en adultos, políticas públicas relacionadas con el alcohol y factores socioeconómicos. Se ajustaron modelos de regresión de Poisson multinivel con variancia robusta, obteniendo razones de prevalencia (RP) y sus intervalos de confianza al 95%.

Los resultados muestran que la prevalencia de *binge drinking* en estudiantes españoles en función de la provincia era similar para ambos sexos (r = 0,72). A nivel individual, el *binge drinking* se asociaba principalmente a una percepción de acceso fácil al alcohol (RP: 1,38; IC 95%: 1,23-1,55), a su consumo en zonas abiertas [(RP: 3,82; IC 95%: 3,44-4,24) < una vez al mes y (RP: 6,57; IC 95%: 5,85-7,37) ≥ una vez al mes], a tener uno de los dos padres que permite beber (RP: 1,42; IC 95%: 1,37-1,47), y a disponer de más de 30 euros semanales (RP: 1,51; IC 95%: 1,37-1,67). Las variables contextuales no se asociaban al *binge drinking* cuando se consideraban las variables individuales. En conclusión, el *binge drinking* se asociaba con variables individuales relacionadas con una alta accesibilidad y disponibilidad de alcohol independientemente de las variables contextuales. Estas variables explicaban la variabilidad de el *binge drinking* entre las provincias.

Palabras clave: Alcohol; Consumo intensivo; Adolescentes; Accesibilidad al alcohol.

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Alcohol consumption is one of the leading risk factors for mortality and disease worldwide (Rehm et al., 2009; Shield et al., 2013; WHO, 2014). Although it can affect all age groups, adolescents and young people are especially vulnerable (CNAPA, 2014; Zeigler et al., 2005). Adolescence is a period in which many risk behaviors, including alcohol intake, are initiated (Pitkänen, Lyyra, & Pulkkinen, 2005; Plan Nacional Sobre Drogas, 2016). The most common risky drinking pattern among adolescents is binge drinking. Binge drinking can be defined as drinking at least 60 grams or more of pure alcohol on at least one occasion in the past 30 days (CNAPA, 2014) or to drink 5 or more alcoholic drinks on a single occasion, i.e. an approximate interval of two hours (Plan Nacional Sobre Drogas, 2016). Prevalence rates of monthly binge drinking among European adolescents vary from 13% to 56% (in Spain 32.2%) (Hibell et al., 2012; Plan Nacional Sobre Drogas, 2016). At this age, binge drinking is associated with other risky behaviors, such as alcohol-impaired driving, risky sexual or violent behaviors (CNAPA, 2014; Font-Ribera et al., 2013; Kuntsche et al., 2013). There is also evidence that alcohol use in adolescence seems to be a risk factor for high alcohol consumption and problem drinking in adulthood (Pitkänen, et al, 2005; Pitkänen, Kokko, Lyyra, & Pulkkinen, 2008).

Several studies have reported that binge drinking in adolescence is associated with individual variables such as age, gender, family socioeconomic position, family structure, family and friends' habits and attitudes related to alcohol, parental permissiveness, parental supervision or control, and the amount of money for personal needs (Heimisdottir, Vilhjalmsson, Kristjansdottir, & Meyrowitsch, 2010; Llorens, Barrio, Sánchez, Suelves, & ESTUDES Working Group, 2011). Adult influence could be another factor as adults are a model for young people (Bendtsen et al., 2014; Heimisdottir et al., 2010). Adults can tolerate or promote family or environmental conditions that facilitate youth drinking (Foley, Altman, Durant, & Wolfson, 2004; Heimisdottir et al., 2010; Reimuller, Shadur, & Hussong, 2011; van der Vorst, Engels, Meeus, Deković, & Van Leeuwe, 2005) or even directly offer or provide alcohol to young people (Foley et al., 2004; Jones-Webb et al., 1997; Pettigrew, Pescud, Jarvis, & Webb, 2013). In Spain, the phenomenon called "botellón", consisting of groups drinking in open-air public spaces such as squares or parks, has become a widespread practice among adolescents in many regions and has also been associated with binge drinking (Cortés, Espejo, Martín del Río, & Gómez, 2010; Romo-Avilés, Marcos-Marcos, Marquina-Márquez, & Gil-García, 2016). However, alcohol use and alcohol-related problems in adolescents can be explained by other contextual variables: (1) public alcohol policies, such as alcohol access restriction, alcohol tax, traffic safety policies, or alcohol advertising regulation (Bendtsen et al., 2014; Nelson et al., 2013, 2005; Paschall, Grube, & Kypri, 2009; WHO, 2014; Xuan et al., 2013, 2015); (2) socioeconomic and demographic factors such as changes in per capita income or the unemployment rate (Krieg & Kuhl, 2016; Pedersen, Bakken, & von Soest, 2015); and (3) adult drinking at the population level (Bendtsen et al., 2014; Nelson, Naimi, Brewer, & Nelson, 2009; Nelson, Naimi, Brewer, & Wechsler, 2005; Xuan et al., 2013).

Although both individual and contextual variables have been associated with alcohol consumption, most studies on youth drinking have focused on individual adolescent characteristics (Nelson et al., 2005) or have explored the relationship between youth and adult consumption at the family level (Rossow, Keating, Felix, & McCambridge, 2015). Studies exploring adolescent drinking that include individual and contextual variables related to socioeconomic or demographic factors and to the accessibility and availability of alcohol, are lacking. Given this background, it is important to assess the effect of some contextual variables on binge drinking in a country like Spain, where this phenomenon has increased significantly in recent years (Galán, González, & Valencia-Martín, 2014) and which has also been immersed in a deep economic crisis since 2008 accompanied by high unemployment levels.

Thus, the aim of this study was to estimate the prevalence of binge drinking and assess the effect of individual and contextual factors on this drinking pattern in Spanish adolescents.

Methods

Data sources

Cross-sectional study with individual data drawn from the 2014 Spanish ESTUDES survey (Spanish acronym for School Survey on Drug Use), carried out within the framework of the National Plan on Drugs. The sample consisted of 34,259 students aged 14–18 years (17,498 girls; 16,761 boys) who attended secondary school in all regions of Spain, including urban and rural, public and private schools. The student sample represented approximately 70% of all youths of this age range in Spain. Two-stage cluster sampling was used, by randomly selecting schools as first-stage units and classrooms as second-stage units. A detailed description of the sample has been published elsewhere (Plan Nacional Sobre Drogas, 2016). Students with missing values for country of birth (0.1%), alcohol consumption in open public spaces (4.7%), parental behavioral control (3%) or binge drinking occurrence (1.2%) were excluded. Conversely, missing values for the parents' educational attainment (14.7%), pocket money received weekly (8.2%), parental permissiveness toward drinking alcohol (16.9%), and perceived access to alcohol

(13.8%) were included in an "unknown" category because of their high percentage. For all other independent variables, no missing values were found. Contextual or aggregated data measured at the Spanish region level were drawn from various sources, such as the 2011 and 2013 Spanish EDADES surveys (Spanish acronym for "Household Survey on Alcohol and Drugs"), which gathers information on adult per capita alcohol consumption and policies limiting outdoor alcohol consumption; ESTUDES survey, which collects data on policies preventing alcohol sales to minors; and the 2011 Spanish EPA survey (Spanish acronym for "Labor Force Survey"), which provides information on the unemployment rate.

Variables

Dependent variable

The outcome was the occurrence of current binge drinking in students aged 14-18 years, defined as drinking five or more standard drink units in a 2-hour interval at least once in the last 30 days for both sexes. Students' binge drinking was considered when it occurred at least once in the last 30 days, not being possible to know if it was a maintained pattern over time.

Socioeconomic variables at the individual level

Individual socioeconomic variables were socioeconomic position, age (entered as continuous variable), sex, country of birth (immigrants being defined as individuals born outside Spain) and Spanish region of residence (52 regions; Palencia being the region with the lowest number of students [n=50] and Madrid with the highest number [n=4,634]). Socioeconomic position was measured by educational attainment (highest degree of education completed by father or mother) (Krieger, Williams, & Moss, 1997).

Alcohol access and availability variables at the individual level

Independent variables related to individual access to alcohol and its availability were perceived access to alcohol, alcohol consumption in open areas, weekly pocket money, parental permissiveness toward drinking alcohol, and parental behavioral control. Youth perceived access to alcohol was obtained through the question "What difficulty do you think you would have to get alcoholic drinks?, collapsing the four possible response options into two categories (difficult, easy). Information on alcohol consumption in open areas, known in Spain as "botellón", was obtained through the question "How often have you participated in "botellón" in the last 12 months?", with the seven possible response options being collapsed into three categories (≥once/month, < once/month, never). Weekly pocket money was gathered through an open question and it was classified into 4 categories (0 euros, <10 euros, between 10-30 euros and >30 euros). Parental permissiveness toward drinking alcohol was obtained through the question "If you want to drink alcoholic beverages, would your parents allow you?", considering parental permissiveness when at least one parent allowed drinking alcohol inside or outside home. Parental behavioral control referred to how often the parents knew with whom and where the student went out in the evenings, with the five possible response options being collapsed into three categories (often, sometimes, rarely).

Socioeconomic and alcohol-related variables at the contextual level

Contextual independent variables measured at the Spanish region level were adult per capita alcohol consumption, indicators of regional public alcohol policies, and socioeconomic factors. Adult per capita alcohol consumption was estimated as the average grams of pure alcohol consumed daily in the population aged 25-64 years living in each region, from quantity-frequency questions in EDADES, which refer to the last 30 days. Grams of pure alcohol were obtained by multiplying the intake of alcoholic beverages in volume by the proportion alcohol-by-volume for each beverage category and by 0.79 (or alcohol density in g/ml). Regarding regional public alcohol policies, the prevalence of students who perceived easy access to alcohol, adding individualized results in ESTUDES in each region, was entered as a proxy of the effectiveness of regional policies on regulations and interventions preventing alcohol sales to minors. The prevalence of alcohol consumption in open areas, "botellón", was entered as a proxy of the effectiveness of regional policies on regulations and interventions limiting outdoor alcohol consumption. It was considered any episode of "botellón" among the Spanish population aged 15-30 years in the last 12 months in EDADES survey. The selected socioeconomic factor was the unemployment rate among the economically active population aged 16-64 years, as an average of the four quarters of 2011 in each region, in 2011 Spanish EPA survey.

Statistical analysis

The results of the survey were weighted by region, school ownership, and type of studies to correct the imbalance of the sample with respect to the sampling frame. Firstly, a description of the sample was performed, separately for girls and boys, to estimate the prevalence of binge drinking according to the individualized covariates with their respective 95% confidence intervals (95%CI). To determine the binge drinking distribution in the different Spanish regions, two maps based on sex were constructed, allowing the different regions to be classified according to the quartile to which they belonged. To explore the

association between youth binge drinking and contextual factors, simple linear correlations according to region were performed with their respective scatter charts. Finally, to identify the effect of both individual and contextual factors on adolescent binge drinking, Poisson multilevel regression models with robust variance were fitted, obtaining prevalence ratios (PR) with 95%CI (Espelt, Mari-Dell'Olmo, Penelo, & Bosque-Prous, 2017). The first model (model 0) included only youth binge drinking to calculate its variability between the different Spanish regions. Next, the association of individual or contextual variables with binge drinking was estimated, building a multilevel model with the individual socioeconomic variables (model 1), another with the individual alcohol access and availability variables (model 2), another with all the individual variables together (model 3), and another model including all the contextual variables only (model 4). Finally, a last multivariate model was fitted (model 5) to estimate the conjoint effect of individual and contextual factors on youth binge drinking, assuming that the intersection had a random effect. All the models were constructed jointly for girls and boys because of the limited sample size in some regions and the similarity of binge drinking distribution by the independent variables for both sexes. Analyses were performed using STATA software version 14.

Results

In the study sample, 89% of girls and 90% of boys were born in Spain and around half had parents with secondary education or less (53% of girls; 49% of boys) and more than 90% were younger than 18 years. The total prevalence of youth binge drinking in the last month was around 33%. For both girls and boys, the prevalence of binge drinking increased with age, and although the prevalence was generally higher in boys, sex differences were only significant from 17 years and above. For both sexes, the prevalence of binge drinking was higher among natives than immigrants (32% vs 28% in girls and 34% vs 32% in boys), among those whose parents had secondary education or less compared to university education (34% vs 30% in girls and 37% vs 33% in boys) and among those with at least one parent who allowed drinking in contrast to those whose parents did not allow drinking (49% vs 19% in girls and 53% vs 19% in boys). Regarding parental behavioral control, when parents knew with whom and where their adolescents went out in the evening, the prevalence of binge drinking was lower in both sexes. Moreover, binge drinking in the last 30 days was reported by more than 40% of adolescents who had more than 30 euros of weekly pocket money, more than 35% of those who perceived easy alcohol access and more than 65% of those who had drunk alcohol in open public areas during the last month (Table 1).

Figure 1 shows the distribution of binge drinking, separately for girls and boys, by region of residence. A between-sex correlation coefficient of 0.72 was obtained. Regions in central Spain showed a higher prevalence of binge drinking, the exception being Madrid, because it was placed in the lowest quartile for both girls and boys.

All individual variables showed a significant effect on the risk of binge drinking among adolescents, regardless of whether their effects were measured alone or together with those of contextual variables. In relation to individual socioeconomic variables, being a girl (PR 0.95; 95%CI 0.91-0.99) and having parents with university studies vs. secondary or less (PR 0.95; 95%CI 0.91-0.99) had a negative effect, while being older had a positive effect (PR 1.35; 95%CI 1.31-1.40). On the other hand, when individual socioeconomic variables were analyzed alone, country of birth was negatively associated with binge drinking (PR 0.88; 95%CI 0.82-0.95), but when other variables were added to the model, whether they were individual or contextual, this association became positive (PR 1.13; 95%CI 1.08-1.18). Regarding individual alcohol-related variables, a positive effect (increased risk) was found on binge drinking for easy alcohol access (PR 1.40; 95%CI 1.25-1.58), alcohol consumption in open areas (PR 6.77; 95%CI 6.01-7.63 at least once a month), parental permissiveness (PR 1.52; 95%CI 1.45-1.59), parental behavioral control (PR 1.17; 95%CI 1.12-1.22 when parents rarely knew with whom the student went out in the evenings and PR 1.14; 95%CI 1.07-1.20 when parents rarely knew where the student went out in the evenings), and weekly pocket money (PR 1.56; 95%CI 1.42-1.73 of more than 30 euros). Moreover, there was a gradient in the strength of the association in the latter three variables (Table 2).

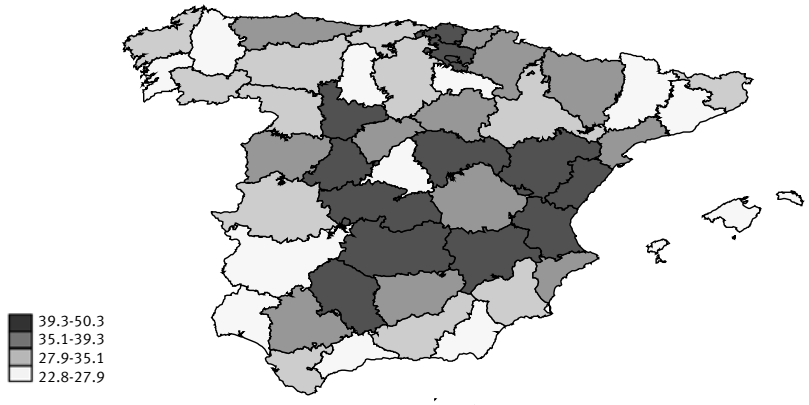
Regarding contextual variables, as shown in Figure 2, adult per capita alcohol consumption and the prevalence of adolescents perceiving easy access to alcohol showed the strongest positive correlations with youth binge drinking for both sexes ($r(girls)=0.304$; p-value=0.03; $r(boys)=0.230$; p-value=0.10; and $r(girls)=0.603$; p-value<0.001; $r(boys)=0.585$; p-value<0.001), respectively), while the unemployment rate showed a negative correlation, especially in boys ($r(boys)= -0.305$; p-value=0.03). However, in the multilevel models (Table 2), only easy access to alcohol was significantly associated with binge drinking and only when contextual variables were considered isolated from the individual (PR 1.03; 95%CI 1.02-1.04). In fact, the empty model determined that variability in youth binge drinking between the different regions was around 3.6%. When all the individual variables were considered (model 3), they explained 75% of this variability in youth binge drinking. Despite this, model 2, which contained only alcohol-related individual variables, explained 78%. When contextual variables were considered alone, 46% of the variability in youth binge drinking was explained

Table1. *Prevalence of binge drinking in the last 30 days and 95% confidence interval (95% CI) by sex and other individual variables among students aged 14-18 years. Spain, 2014.*

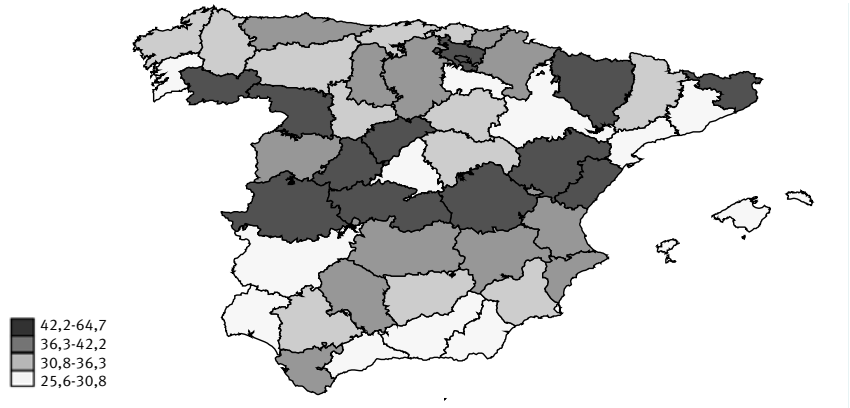
	Girls		Binge drinking		Boys		Binge drinking	
N total = 34,259	**n**	**%**	**%**	**95% CI**	**n**	**%**	**%**	**95% CI**
Total	17,498	51.1	31.6	(30.9-32.3)	16,761	48.9	34.0	(33.3-34.7)
Age								
14 years	3,517	20.1	14.8	(13.7-16.0)	3,143	18.8	13.6	(12.5-14.9)
15 years	4,423	25.3	25.4	(24.1-26.7)	4,130	24.6	24.3	(23.0-25.7)
16 years	4,221	24.1	37.3	(35.9-38.8)	3,928	23.4	38.2	(36.7-39.8)
17 years	4,080	23.3	41.9	(40.4-43.4)	4,039	24.1	47.6	(46.0-49.1)
18 years	1,258	7.2	47.9	(45.2-50.7)	1,521	9.1	55.3	(52.8-57.8)
Country of birth								
Spain	15,533	88.8	32.0	(31.3-32.8)	15,062	89.9	34.2	(33.5-35.0)
Outside Spain	1,965	11.2	28.1	(26.1-30.1)	1,700	10.1	32.1	(29.9-34.3)
Parents' educational attainment								
Secondary education or less	9,327	53.3	34.0	(33.0-34.9)	8,143	48.6	36.6	(35.6-37.7)
University	5,874	33.6	29.5	(28.3-30.6)	5,991	35.7	32.9	(31.7-34.1)
Unknown	2,297	13.1	27.4	(25.6-29.3)	2,627	15.7	28.4	(26.7-30.2)
Perceived access to alcohol								
Difficult	1,269	7.3	10.0	(8.4-11.8)	1,233	7.4	13.2	(11.5-15.3)
Easy	14,453	82.6	35.5	(34.8-36.3)	13,377	79.8	38.7	(37.9-39.5)
Unknown	1,775	10.1	14.9	(13.3-16.6)	2,151	12.8	16.5	(15.0-18.2)
Alcohol consumption in open public areas								
No	7,604	43.5	7.7	(7.1-8.3)	7,858	46.9	8.1	(7.6-8.8)
< once/month	5,312	30.4	34.9	(33.7-36.2)	4,808	28.7	40.9	(39.5-42.3)
≥ once/month	4,582	26.2	67.3	(66.0-68.7)	4,096	24.4	75.5	(74.1-76.8)
Parental Permissiveness								
Neither parent allows drinking	7,815	44.7	19.1	(18.2-19.9)	7,010	41.8	18.6	(17.7-19.5)
At least one parent allows drinking	7,067	40.4	48.8	(47.6-50.0)	6,916	41.3	52.9	(51.7-54.0)
Unknown	2,616	15.0	22.6	(21.1-24.3)	2,835	16.9	26.1	(24.6-27.8)
Parents know with whom he/she goes out in the evenings								
Often	14,769	84.4	28.9	(28.1-29.6)	12,742	76.0	31.5	(30.7-32.3)
Sometimes	1,633	9.3	44.6	(42.2-47.0)	2,104	12.6	41.2	(39.1-43.3)
Rarely	1,096	6.3	48.9	(46.0-51.9)	1,915	11.4	42.8	(40.6-45.1)
Parents know where he/she goes out in the evenings								
Often	14,156	80.9	28.5	(27.8-29.3)	12,015	71.7	30.53	(29.7-31.4)
Sometimes	1,930	11.0	42.6	(40.4-44.8)	2,412	14.4	41.52	(39.6-43.5)
Rarely	1,412	8.1	47.5	(44.9-50.1)	2,334	13.9	44.03	(42.0-46.0)
Weekly pocket money								
0 euros	1,869	10.7	17.9	(16.2-19.7)	1,948	11.6	16.9	(15.3-18.6)
Less than 10 euros	3,742	21.4	25.0	(23.6-26.4)	3,098	18.5	24.4	(23.0-26.0)
Between 10-30 euros	9,401	53.7	36.9	(36.0-37.9)	8,871	52.9	40.0	(39.0-41.0)
More than 30 euros	1,093	6.3	43.8	(40.9-46.8)	1,525	9.1	48.1	(45.6-50.6)
Unknown	1,393	8.0	22.4	(20.3-24.7)	1,319	7.9	25.1	(22.8-27.5)

Note. *Excluding people with missing information on country of birth, alcohol consumption in open public areas or binge drinking occurrence. ESTUDES: Spanish School Survey on Drug use.

(a) Prevalence of binge drinking in girls



(b) Prevalence of binge drinking in boys



Note. *The map excluded Las Palmas, Santa Cruz de Tenerife, Ceuta and Melilla. The prevalence of binge drinking in these regions was: 21.4% (girls) and 20.8% (boys) in Las Palmas; 28.7% (girls) and 30.4% (boys) in Santa Cruz de Tenerife; 5.5% (girls) and 11.9% (boys) in Ceuta; and 10.8% (girls) and 16.4% (boys) in Melilla.
** Correlation coefficient between the prevalence of binge drinking in boys and girls in different regions.
***Variance of the prevalence of binge drinking among regions: girls = 3.3%; boys = 3.1%.

Figure 1. Prevalence of binge drinking in the last 30 days by Spanish region and sex among students aged 14-18 years. Spain, 2014.

(model 4). Finally, when both individual and contextual variables were taken into account, the explanatory power of the model was 77%.

Discussion

Main findings

The prevalence of binge drinking in the last 30 days among Spanish students aged 14-18 years was 32% in girls and 34% boys, varying by region of residence. Although the prevalence was higher in boys than in girls, there was a high between-sex correlation in this prevalence in different Spanish regions of residence. At the individual level, the main variables associated with a higher risk of binge drinking among adolescents were perception of easy access to alcohol, participating in "botellón"–especially in the last month–, more parental permissiveness, less parental behavioral control, and having plenty of pocket money. Regions with a higher proportion of adolescents who perceived easy access to alcohol had a higher prevalence of youth binge drinking. However, this association disappeared when individual variables were considered.

In our study, the overall prevalence of binge drinking in the last 30 days in Spanish students aged 14-18 years was 33%. This result is similar to those observed in other studies in Europe and the USA, with youth binge drinking prevalences ranging 26%-47% (CNAPA, 2014; Hibell et al., 2012; Llorens et al., 2011; Nelson et al., 2009; Nelson et al., 2005; Xuan et al., 2013). However, the prevalence of binge drinking seems to have decreased compared with that reported in the 2012 ESTUDES survey, which indicated a binge drinking prevalence of 42% (Plan Nacional Sobre Drogas, 2016). According to the National Plan on Drugs, this decrease can be explained by the reduction in alcohol drinking among students aged 14-15 years and coincides with an increase in the percentage of students who are aware of the risks of alcohol drinking in comparison to the 2012 survey.

Table 2. *Effect of individual and contextual factors on binge drinking in the last 30 days among adolescents aged 14-18 years. Spain, 2014*

BINGE DRINKING	**Model 1** (socioeconomic variables)		**Model 2** (alcohol-related variables)		**Model 3** (all individual variables)		**Model 4** (contextual variables)		**Model 5** (multivariate)	
Individual factors among adolescents			PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI
Age	1.35	(1.31-1.40)			1.09	(1.06-1.12)			1.09	(1.06-1.12)
Sex										
Boys	1				1				1	
Girls	0.95	(0.91-0.99)			0.93	(0.90-0.96)			0.93	(0.90-0.97)
Country of birth										
Spain	1				1				1	
Outside Spain	0.88	(0.82-0.95)			1.13	(1.08-1.19)			1.13	(1.08-1.18)
Parent's educational attainment										
Secondary education or less	1				1				1	
University	0.95	(0.91-0.99)			0.96	(0.92-0.99)			0.95	(0.92-0.99)
Adolescents' perceived access to alcohol										
Difficult			1		1				1	
Easy			1.40	(1.25-1.58)	1.38	(1.23-1.54)			1.38	(1.23-1.55)
Alcohol consumption in open areas										
No			1		1				1	
‹ once/month			3.90	(3.50-4.34)	3.82	(3.44-4.24)			3.82	(3.44-4.24)
≥ once/month			6.77	(6.01-7.63)	6.56	(5.85-7.36)			6.57	(5.85-7.37)
Parental permissiveness										
Neither parent allows drinking			1		1				1	
At least one parent allows drinking			1.52	(1.45-1.59)	1.42	(1.37-1.47)			1.42	(1.37-1.47)
Parents know with whom he/she goes out in the evenings										
Often			1		1				1	
Sometimes			1.10	(1.04-1.16)	1.09	(1.04-1.15)			1.10	(1.04-1.16)
Rarely			1.17	(1.12-1.22)	1.16	(1.10-1.22)			1.16	(1.10-1.22)
Parents know where he/she goes out in the evenings										
Often			1		1				1	
Sometimes			1.07	(1.03-1.12)	1.07	(1.03-1.12)			1.07	(1.03-1.12)
Rarely			1.14	(1.07-1.20)	1.15	(1.09-1.22)			1.15	(1.09-1.22)
Weekly pocket money										
0 euros			1		1				1	
Less than de 10 euros			1.10	(1.00-1.22)	1.13	(1.02-1.25)			1.13	(1.02-1.25)
Between 10-30 euros			1.30	(1.19-1.43)	1.29	(1.18-1.42)			1.29	(1.18-1.41)
More than 30 euros			1.56	(1.42-1.73)	1.52	(1.38-1.67)			1.51	(1.37-1.67)
Socioeconomic factors										
Unemployment rate							1.01	(0.97-1.05)	0.98	(0.95-1.01)
Proxies of effectiveness of alcohol control policies										
Prevalence of adolescents perceiving easy access to alcohol							1.03	(1.02-1.04)	1.00	(0.99-1.01)
Prevalence of adolescents drinking in open public areas							1.00	(1.00-1.01)	1.00	(1.00-1.00)
Adult per capita alcohol consumption										
Grams of pure alcohol/day							1.00	(0.99-1.02)	1.00	(0.99-1.01)
Variance	0.0370		0.0080		0.0083		0.0196		0.0081	

Note. The variance of the empty model (model 0) was 0.0360. Model 1 was adjusted by age, sex, country of birth, and parent's educational attainment; model 2 was adjusted by adolescents' perceived access to alcohol, alcohol consumption in open areas, parental permissiveness, parents' knowledge about where and with whom the adolescent went out in the evenings, and weekly pocket money; model 3 was adjusted by all the variables included in models 1 and 2; model 4 was adjusted by socioeconomic factors, proxies of alcohol control policies, and adult per capita alcohol consumption; model 5 was adjusted by all the variables.

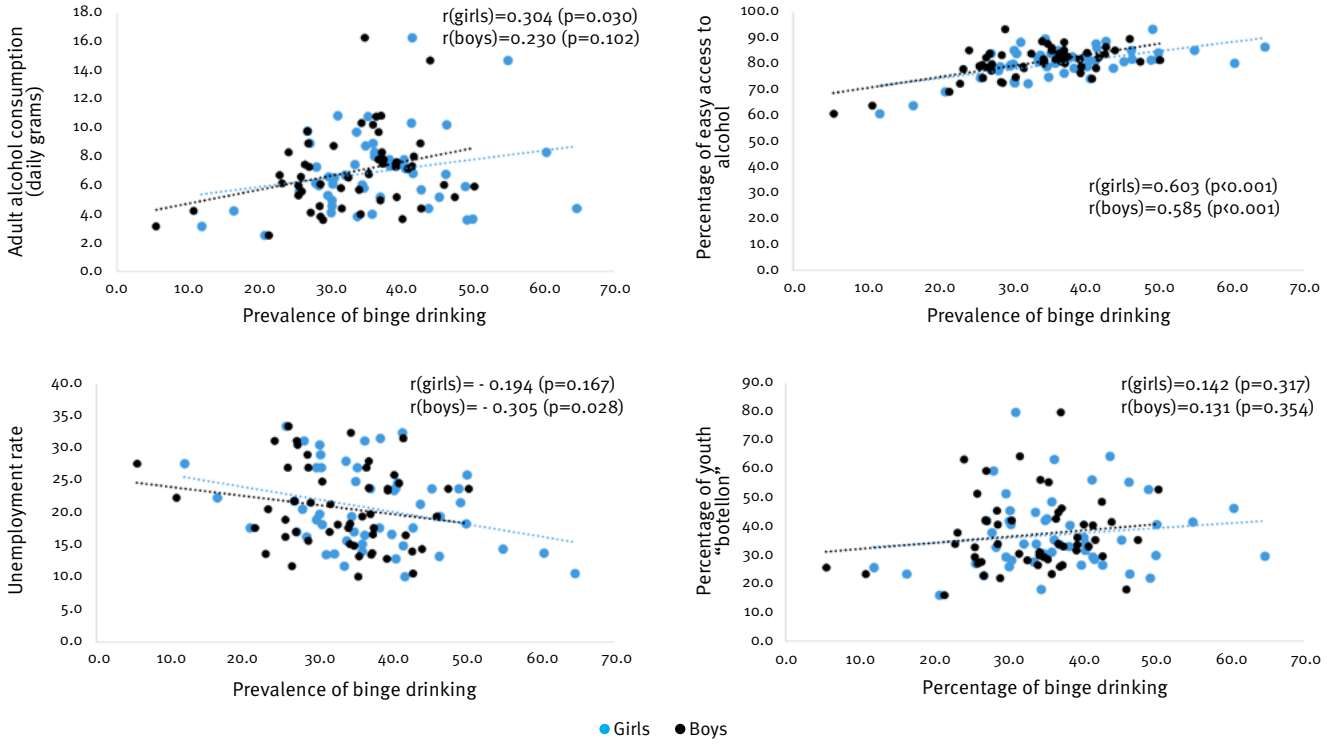


Figure 2. Correlations of region-level youth binge drinking with adult per capita alcohol consumption, unemployment rate and indicators of regional public alcohol policies.

Individual variables related to alcohol were the best predictors of the observed differences in adolescent binge drinking between Spanish regions. Thus, independently of contextual variables, a higher prevalence of binge drinking was found in adolescents who perceived easy access to alcohol, had participated in "botellón" during the last month, had at least one parent allowing alcohol consumption, whose parents rarely knew where and with whom they went out in the evenings, and who had pocket money for their expenses. Previous studies have already suggested that the availability of pocket money and easy access to alcohol in adolescents increases the probability of alcohol consumption and binge drinking (Jones & Magee, 2014; Llorens et al., 2011). There is also evidence that parental permissiveness and control could be associated with adolescents' drinking (Abar, Abar, & Turrisi, 2009; Foley et al., 2004; Heimisdottir et al., 2010; Llorens et al., 2011; Nash, McQueen, & Bray, 2005; van der Vorst et al., 2005). Specifically, it seems that that establishing strict rules and complete disapproval of youth drinking prevents heavy alcohol use and negative alcohol-related consequences (Abar et al., 2009; van der Vorst et al., 2005). In this regard, one study found that adolescents who reported greater parental disapproval of alcohol use also reported a positive family environment, such as greater parental monitoring or better communication, which could attenuate the potentially negative impact of peers on adolescents' drinking behavior and increase self-efficacy in refusing alcohol (Nash et al., 2005). Like other Spanish studies, our study found an association between "botellón" and youth binge drinking (Cortés et al., 2010; Romo-Avilés et al., 2016). Reasons that may explain high alcohol consumption during "botellón" include the focus on the positive effects of alcohol drinking (such as having fun or facilitating social relationships), peer pressure to drink alcohol, greater access to alcohol, and adolescents' expectation that they will be cared for and looked after by their friends if they drink large amounts of alcohol (Espejo, Cortés, del Río, Giménez, & Gómez, 2012; Gómez, Fernández, Romero, & Luengo, 2008; Romo-Avilés et al., 2016).

Notwithstanding the above, almost half of the observed variability between Spanish regions was explained by contextual variables. Specifically, the greater the proportion of young people perceiving easy access to alcohol at the regional level, the higher the risk of binge drinking in that region. This result is consistent with evidence showing a relationship between more restrictive alcohol control policies and less youth binge drinking (Nelson et al., 2005; Xuan et al., 2015). However, when individual variables were taken into account, this association disappeared. This result can be explained by several reasons. Firstly, as reported in the ESPAD report (Hibell et al., 2012), most European students perceived easy access to alcohol (81% of students in both the ESPAD report and the present study)

even though many countries have laws restricting access for young people. Therefore, it is possible that although the laws in the different Spanish regions are very similar, compliance with these laws varies greatly. Secondly, in our study, this contextual variable may be strongly related to individual access to alcohol and its availability, because it is an aggregated individual variable. Finally, another possibility is that the variability of the contextual variables measured in our study between regions was quite small, and therefore, the most influential factor in youth binge drinking was the individual access of each adolescent to alcohol.

Surprisingly, in this study, adult per capita alcohol consumption was not associated with youth binge drinking. However, other studies have shown an influence of adult alcohol consumption at a population level on youth drinking (Bendtsen et al., 2014; Nelson et al., 2009; Nelson et al., 2005; Xuan et al., 2013, 2015). One possible explanation for this lack of significance in the association between adult and youth alcohol use could be that the variable used in this study to measure alcohol consumption in adults came from a population survey and may not have adequately captured the distribution of alcohol consumption in different regions.

Strengths and limitations

To our knowledge, this is the first study in Spain that analyzes the influence of several individual and contextual variables on youth binge drinking at the regional level. One of the main strengths of this study is the use of multilevel methodology to analyze the phenomenon of binge drinking in adolescents, simultaneously taking into account individual and contextual factors. In addition, a population-based survey that is representative of Spanish students aged 14-18 years was used. However, this survey excludes those young people outside the formal education system. For this reason, a sensitivity analysis was performed including only students aged 14-16 years and the results showed no statistically significant differences compared to those from the entire study sample.

The main limitation of the study is its cross-sectional nature, which does not allow causal relationships to be established. In addition, both adolescents' and adults' alcohol consumption was self-reported. However, there is evidence that self-reported questionnaires are a feasible method for measuring alcohol consumption in adolescents (Engs & Hanson, 1990). Moreover, the individual and anonymous nature of both questionnaires (EDADES and ESTUDES) could reduce social desirability bias in self-reporting. Another limitation is the use of proxies to measure public alcohol policies that are individual aggregate variables. Even so, such measures may be more effective in determining the degree of enforcement of regulations than the existence or absence of alcohol control policies in each region.

Conclusion

This study shows that youth binge drinking in Spain is associated with individual variables related to alcohol, regardless of contextual variables. In addition, these individual variables explained the variability in binge drinking among regions. Therefore, to be effective, alcohol control policies must be accompanied by interventions that take into account these individual variables, paying special attention to parental behavioral control and permissiveness toward drinking control and youth accessibility and availability to alcohol.

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Conflicts of interest

The authors have no conflicts of interest to report, financial or otherwise.

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Predictive factors of alcohol consumption in adolescents: data from 1-year follow-up prospective study

Factores predictores del consumo de alcohol en adolescentes: datos de un estudio prospectivo de 1 año de seguimiento

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Abstract

Alcohol use/abuse is a health problem in adolescents. The last Survey on use of drugs in Secondary Schoolers carried out in Spain (ESTUDES 2014-2015), reveals that 76.8% of adolescents aged 14 to 18 years consumed alcohol in the previous year and 68.2% in the last month. The aim of this study is to determine the medium-term factors associated with alcohol consumption in a sample of Spanish adolescents. The present study was carried out as a part of the Saving and Empowering Young Lives project in Europe (SEYLE) project. The final sample was composed of 708 students, assessed at two times [basal (T_0) and one year later (T_1)] [males: 51.98%, basal mean age (SD)=4.43 (0.67)]. Univariate and multivariate regression analyses were performed in order to investigate relationships between possible predictive variables found at time T_0 and alcohol consumption at time T_1. At basal time (T_0) the prevalence of alcohol abuse was 25.56%, whereas the prevalence one year later was 49.72% (T_1). Variables that significantly predict alcohol abuse within a year are: previous alcohol abuse at T_0 (p<0.001), previous abuse of drugs (p=0.011), parents attending their sporting events (p=0.005), peer problems (p=0.019), and lack of prosocial behaviour (p=0.043). In the light of our results, it can be concluded that, in adolescents, externalizing disorders seem to be determining factors of medium-term alcohol consumption.

Keywords: Adolescents; Alcohol Consumption; Predictive factors; Follow-up study.

Resumen

El uso/abuso de alcohol es un problema de salud en los adolescentes. La última Encuesta sobre uso de drogas en Enseñanzas Secundarias realizada en España (ESTUDES 2014-2015), pone de manifiesto que 76,8% de los adolescentes entre 14 y 18 años consumieron alcohol en el último año y 68,2% en el último mes. El principal objetivo es determinar los factores que se asocian con el consumo de alcohol a medio plazo en una muestra de adolescentes españoles. El estudio forma parte del proyecto Saving and Empowering Young Lives in Europe (SEYLE). La muestra final estuvo compuesta por 708 estudiantes, evaluados en dos momentos temporales [basal (T_0) y al año (T_1)] [varones: 51,98%, edad media basal (DE)=4,43 (0,67)]. Se realizaron análisis de regresión univariante y multivariante, con el fin de investigar las relaciones entre posibles variables predictoras descritas en el momento temporal T_0 y el consumo de alcohol en el momento T_1.En el momento basal (T_0) la prevalencia de abuso de alcohol fue del 25,56%, mientras que la prevalencia al año fue del 49,72% (T_1). Las variables que predicen de forma significativa el abuso de alcohol al cabo de un año son: abuso previo del alcohol en el momento T_0 (p< 0,001), abuso previo de drogas (p=0,011), padres que asisten a sus competiciones deportivas (p=0,005), problemas de relación con compañeros (p=0,019) y ausencia de comportamiento prosocial (p=0,043). A la vista de nuestros resultados se puede concluir que, en adolescentes, los trastornos externalizantes parecen ser factores determinantes de consumo de alcohol a medio plazo.

Palabras clave: Adolescentes; Consumo de Alcohol; Factores predictores; Estudio prospectivo.

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The World Health Organization (WHO) has described the abuse of alcohol as a worldwide public health problem and has warned of the damage it causes to physical and psychological health. In 2012, around 3.3 million deaths worldwide were caused by alcohol (World Health Organization, 2014). It is also a significant among the younger population. According to the latest national survey of drug use in secondary schools (ESTUDES 2014-2015), 76.8% of adolescents aged between 14 and 18 in Spain had consumed alcohol within the previous year and 68.2% during the previous month (Plan Nacional sobre Drogas, 2016). At the European level, the data are similar, with 79% of students aged between 15 and 16 years having consumed alcohol in the previous 12 months and 57% in the previous month (Hibell et al., 2012) .

There are data that reveal a link between different characteristics of the adolescent population group and the use of alcohol and other drugs. For example, high school students (Patrick, Yeomans-Maldonado & Griffin, 2016) have a higher prevalence of alcohol consumption during school years than non-students, who use marijuana more (Johnston, O'Malley, Miech, Bachman & Schulenberg, 2012; O'Malley & Johnston, 2002). However, in the long term, people who did not attend high school tend to use alcohol more and have more problems involving the use of other substances in adulthood, compared to those who did study. (Lanza & Collins, 2006; Patrick et al., 2016; White, Labouvie & Papadaratsakis, 2005).

Sex is also a factor associated with alcohol use. At younger ages (8th grade), the rate of alcohol use in the previous 30 days is slightly higher among girls (13%) than boys (12%). However, this proportion is inverted in older students (12th grade), with rates of 38 and 42% respectively, and remains so in adulthood, with higher rates of use among men than women (Johnston et al., 2012; Wilsnack et al., 2000).

Alcohol use among adolescents has furthermore been associated with behavioral and neuropsychological problems, where an association has been observed between alcohol consumption and executive function deficit that manifests itself in greater difficulty in decision making, the severity of which correlates inversely with the age when alcohol was first drunk (Deckel, Bauer & Hesselbrock, 1995; Kim, Kim & Kwon, 2001; Sobeck, Abbey, Agius, Clinton & Harrison, 2000).

There are also other factors that have been associated with alcohol use in adolescents. The following have presented a negative correlation with alcohol consumption: parental supervision (Dever et al., 2012; Pilgrim, Schulenberg, O'Malley, Bachman & Johnston, 2006); religiosity (Brown, Schulenberg, Bachman, O'Malley & Johnston, 2001; Wallace et al., 2007; Wray-Lake et al., 2012); links to the community (Wray-Lake et al., 2012); levels of self-esteem (Maslowsky & Schulenberg, 2013); as well as a negative attitude towards alcohol, which turns out to be one of the most powerful prevention factors against abusive consumption. Conversely, these factors correlate positively with alcohol use: externalized conflict behavior (Bachman et al., 2008; Maslowsky & Schulenberg, 2013); sensation seeking and risk taking (Dever et al., 2012; Patrick et al., 2010; Pilgrim et al., 2006; Schulenberg et al., 1996); and a depressive affective state (Maslowsky & Schulenberg, 2013; Patrick et al., 2010; Schulenberg et al., 1996). Exercise and sports have a complex effect: while doing exercise negatively correlates with the alcohol use during adolescence, participating in team sports correlates positively, especially among males (Dever et al., 2012; Terry-McElrath, O'Malley & Johnston, 2011).

Of all the variables studied, the one with the strongest link to using alcohol and other drugs is having friends who get drunk (Patrick & Schulenberg, 2010); and the one that most influences the prognosis is the onset age: young alcohol abusers respond worse to treatments and have worse prognoses (Gueorguieva et al., 2014).

Earlier onset of alcohol use worsens the long-term prognosis. People who later develop alcohol dependence, typically begin intensive use at an early age (Schulenberg et al., 1996; White, Johnson & Buyske, 2000). The consumption of alcohol early in adolescence, especially when it involves individuals with low socioeconomic levels, appears to be associated with more rapidly growing dependence (Ehlers, Slutske, Gilder, Lau & Wilhelmsen, 2006) and increased risk of persistent alcohol abuse (Yaogo, Fombonne, Lert & Melchior, 2015). Another negative prognostic factor, as pointed out by Jessor (1991), is that the use and abuse of alcohol does not usually occur in isolation, but tends to be associated with other problems of adolescent behavior such as the use of illicit drugs, antisocial behavior, early sexual behavior and poor academic performance.

The objective of the present study is to determine the factors associated with alcohol consumption among a sample of Spanish adolescents.

Method

A prospective longitudinal observational epidemiological study was carried out which analyzed the Spanish data of the *Saving and Empowering Young Lives in Europe* (SEYLE) project (Wasserman et al., 2012) at two points of the study: baseline (T_0) and one-year (T_1).

Participants

The sample (Spanish sub-sample) at baseline (T_0) consisted of 1026 subjects who were recruited from twelve randomly selected public schools in the Autonomous Community of the Principality of Asturias, taking into account the inclusion and exclusion criteria of the SEYLE project listed below (Bousoño et al., 2017; Wasserman et al., 2010).

To participate in the study, schools and adolescents had to meet the following inclusion criteria: the local education authority agrees to participate; the school is a non-specialized public school; there are at least forty 15-year-old students at the school; the school has students of both sexes; the school has more than two teachers for 15-year-old students; no more than 60% of students at the age of 15 are of the same sex; parents and students provide informed consent.

At baseline (T_0), 1026 adolescents were included in the study (mean age 14.52 years, standard deviation 0.702, 51.66% male and 48.34% female). Of these, 708 students (51.84% male and 48.16% female) participated in the follow-up one year after the start of the study (T_1), which corresponds to 69.01% of the baseline sample. At T_0 and T_1, adolescents completed pencil and paper questionnaires.

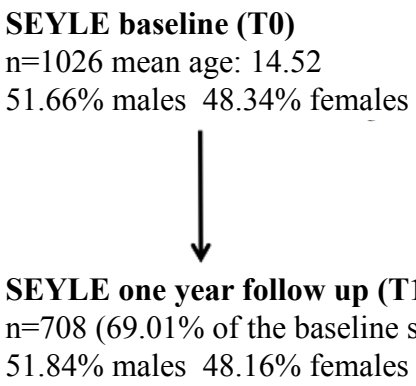

Figure 1. Flow chart of the number of students participating in each of the phases of the investigation (To-T1).

Procedure

In compliance with the rules governing research with young subjects, authorization was obtained from the juvenile prosecutor prior to the start of the study, as was the approval of the Clinical Research Ethics Committee of the Principality of Asturias. The local education authority granted permission to approach the selected schools, and the subjects of the study agreed to take part and provided informed consent, as required. A structured self-report questionnaire was given to the participants at the two different time periods (T_0 = baseline and T_1 = 1 year), each student recruited was assigned a unique code so that the follow-up could be carried out at the individual rather than merely the group level. The coding of the data protects the privacy of the study subjects, and the database was anonymous, making it impossible to identify the people involved. The key matching the anonymous codes to the study subjects was kept confidentially in an independent location which was set up for this purpose and properly secured in the Psychiatry Department at the University of Oviedo, with the principal investigator of the project in charge of the data. All aspects regarding quality control, homogenization of procedure, ethical aspects and the validity of the scales used are described in detail in the work of Carli et al. (2013).

Study assessment

Assessments was conducted during school hours and data such as age, the country of birth of the adolescent and their parents, the work situation of the parents, lifestyles, family, coexistence, mental health and suicidality were collected.

Alcohol abuse was investigated with the item (*"Throughout your life, how many times have you drunk so much alcohol that you were really drunk?"*), where 'never' contrasted with the other answer categories (1 or 2 times, 3 to 9 times, 10 or more times) at the two moments considered, T_0 and T_1.

Suicidal ideation and behavior were measured by the Paykel suicide scale (PSS) (Paykel, Myers, Lindenthal & Tanner, 1974). The PSS asks the following five questions: during the last 2 weeks, (i) Have you felt that life is not worth living? (ii) Have you wished you were dead? (iii) Have you thought about taking your life even though you would not really do it? (iv) Have you reached the point where you have seriously considered taking your life or perhaps made plans about how you would go about doing it?; and (v) Have you ever tried to take your life? People answering "yes" to the third (iii) or the fourth (iv) question of the PSS were considered to have suicidal thoughts, while suicide attempts were defined by the "yes" answer to the last question (v).

For the assessment of substance use, the Global School-based Student Health Survey questionnaire, GSHS, (World Health Organization, 2015) was used, and the following cut-off points established: in terms of alcohol use, the cut-off point was considered to be consuming any amount of alcohol twice or more a week; in terms of drugs, to have used illegal drugs at least three times during one's lifetime, and in terms of tobacco, smoking more than ten cigarettes a day. The same questionnaire was used to assess variables such as eating behaviors, protective factors, physical activity, mental health, etc. The GSHS questionnaire items were recoded to identify these areas of behavior by considering reduced sleep as sleeping 6 hours a night or less, being overweight as having a body mass index BMI above percentile 95, being underweight with a BMI below percentile 5, sedentary behavior as doing physical activity less than once a week, media use as using internet, TV and video games for reasons unrelated to school or work for 5 hours or more per day, absenteeism as skipping school at least once a week without being sick or having another legitimate excuse (Carli et al., 2014).

The Beck inventory (BDI-II) was used to evaluate depressive symptoms (Beck, Steer, Ball & Ranieri, 1996), and anyone with a score equal to or greater than 20 was considered to be at risk of depression. The BDI-II is normally

a 21-item questionnaire used to measure depressive symptoms, but for the present study a modified version was used from which the item "loss of libido" was removed since it was considered an inappropriate question for the adolescent population. Evidence shows that the omission of this question does not affect the reliability or validity of the instrument (Byrne, Stewart & Lee, 2004).

To assess psychopathology, the Strengths and Difficulties Questionnaire was used (SDQ) (Goodman, Meltzer & Bailey, 2003), which measures emotional symptoms, behavior problems, hyperactivity/lack of attention, relationship problems among couples and pro-social behavior. The chosen cut-off points were: a score greater than or equal to 7 for emotional symptoms, a score greater than or equal to 5 for behavioral problems and a score greater than or equal to 7 for hyperactivity. In the case of problems with peers, the cut-off point was set at a score greater than or equal to 6, while the lack of prosocial behavior was defined with a score less than or equal to 4 (Carli et al., 2013).

For the assessment of anxiety, the Zung Anxiety Questionnaire (Zung, 1971) was used, consisting of 20 items. Each has a response scale from 1 to 4 points, providing total score range from 20 to 80 points, with the cut-off point being 30 points or more.

Statistical analysis

Descriptive statistics were used to determine the prevalence of alcohol consumption at the different time points, as well as the frequencies for the different psychosocial variables (e.g., parental employment, caring parents, suicidal behavior, etc.). Means and standard deviations of the scale variables were also calculated (e.g., SDQ scale dimensions, BDI depression scale score, Zung anxiety scale, etc.).

Univariate and multivariate regression analyses were carried out in order to investigate the relationships between the predictors previously described at T_0 and alcohol consumption at T_1. Stepwise methodology was used for the multiple regression analysis, minimizing the value of the Bayesian information criterion (BIC). All statistical analyses were performed with version 24 of the SPSS software. An alpha significance level of 5% was chosen.

Results

The following results correspond to a cohort of 708 students, of which 367 were male (51.98%) and 339 female (48.02%), and who were assessed at the two moments of the study. At baseline (T_0), the mean age was 14.43 years with a standard deviation (SD) of 0.67 and an age range between 13 and 17. The prevalence of alcohol abuse at T_0 was 25.56%, rising to 49.72% at one year (T_1). Table 1 shows the proportion of students with alcohol abuse at the time points studied.

The results of the separate regressions of each of the characteristics studied at T_0 in relation to alcohol abuse at T_1 are presented in Table 2. This regression analysis, carried out variable by variable for all the independent variables considered, revealed significant results for the following: alcohol abuse and drug abuse in T_0, behavior problems (SDQ questionnaire), BDI depression scale and suicidal behavior. The results of the multiple regression analysis are presented in Table 3. After applying the stepwise regression procedure, the following variables turned out to be significant predictors of alcohol abuse in T_1: alcohol abuse at T_0 ($b = 0.34$, $p < 0.001$), drug abuse at T_0 ($b = 0.106$, $p = 0.011$), and parents who watched a sports performance or competition at T_0 ($b = 0.113$, $p = 0.005$), SDQ peer relationship problems at T_0 ($b = 0.092$, $p = 0.019$), prosocial behavior in T_0 ($b = -0.079$, $p = 0.043$). The adjusted R^2 of the final model was 0.287 with an F value for the model of 2129.78, which allows us to reject the null hypothesis that in this regression model all the coefficients of the independent variables are equal to zero. The other variables considered were not included in the final prediction model of alcohol abuse at T_1.

Table 1. *Alcohol abuse (baseline and one year)*

Baseline	1 year	N	(%)
no	no	356	50,28%
no	yes	171	24,16%
yes	yes	181	25,56%

Table 2. *Models of separate regressions of alcohol abuse after one year for each of the demographic, social and psychological factors considered at T_o.*

Demographic, social and psychological factors	Alcohol abuse at T_1		
	T_o		R^2
	β (IC 95%)	P	
Alcohol abuse	0.186 (0.163; 0.203)	‹0.001	0.345
Drug abuse	0.278 (0.189; 0.367)	‹0.001	0.076
Household composition			
Students live with a biological parent or relative	-0.060 (-0.160; 0.400)	0.109	0.04
Parental involvement			
Parents check you have done your homework	-0.087 (-0.177 ; 0.003)	0.066	0.029
Parents understand your problems or worries	0.014 (-0.006; 0.034)	0.766	0.054
Parents know what you really do in your free time	-0.066 (-0.616; 0.484)	0.172	0.073
Parents help you make decisions	-0.059 (-0.509; 0.391)	0.201	0.019
Parents try to find time to talk to you about things that happen to you	-0.051 (-0.147; 0.045)	0.263	0.028
Parents come to see you when you do something special, like play in a match or perform	0.005 (-0.325; 0.335)	0.917	0.01
Parents listen to your opinions or to what you say	-0.043 (-0.721; 0.635)	0.359	0.02
Parental unemployment			
Parents or tutors of the student are unemployed	0.059 (-0.513; 0.631)	0.141	0.003
Strengths and difficulties questionnaire (SDQ)			
Emotional symptoms (SDQ)	0.088 (-0.003; 0.179)	0.098	0.017
Conduct problems (SDQ)	0.141 (0.131; 0.151)	0.002	0.077
Hyperactivity / attention deficit (SDQ)	-0.027 (-0.116; 0.062)	0.557	0.014
Peer problems (SDQ)	0.041 (-0.205; 0.287)	0.357	0.001
Prosocial behavior (SDQ)	-0.051 (-0.113; 0.011)	0.313	0.024
Depression (BDI scale)	0.193 (0.161; 0.225)	‹0.001	0.097
Anxiety(Zung scale)	-0.001 (0.693; 0.691)	0.972	0.071
Suicidal behavior	0.12 (0.114; 0.126)	0.04	0.057

Tabla 3. *Multiple regression model of the alcohol abuse variable after one year for each of the demographic, social and psychological factors considered at T_0.*

Factores demográficos, sociales y psicológicos	**Alcohol abuse at T_1**	
	T_0	
	β (CI 95%)	**p**
Alcohol abuse	0.340 (0.16; 0.52)	‹0.001
Drug abuse	0.106 (0.021;0.191)	0.011
Household composition		
Students live with a biological parent or relative	-0.030 (-0.260; 0.200)	0.446
Parental involvement		
Parents check you have done your homework	-0.018 (-0.208; 0.172)	0.663
Parents understand your problems or worries	0.051 (-0.009; 0.111)	0.25
Parents know what you really do in your free time	0.039 (-0.511; 0.589)	0.444
Parents help you make decisions	0.043 (-0.327; 0.413)	0.323
Parents try to find time to talk to you about things that happen to you	-0.002 (-0.085; 0.089)	0.954
Parents come to see you when you do something special, like play in a match or perform	0.113 (0.015; 0.211)	0.005
Parents listen to your opinions or to what you say	0.048 (-0.630; 0.726)	0.265
Parental unemployment		
Parents or tutors of the student are unemployed	0 (-0.472; 0.472)	0.995
Strengths and difficulties questionnaire (SDQ)		
Emotional symptoms (SDQ)	0.046 (-0.864; 0.956)	0.372
Conduct problems (SDQ)	0.059 (-0.141; 0.259)	0.155
Hyperactivity / attention deficit (SDQ)	-0.007 (-0.587; 0.573)	0.857
Peer problems (SDQ)	0.092 (0.064; 0.120)	0.019
Prosocial behavior (SDQ)	-0.079 (-0.135; -0.023)	0.043
Depression (BDI scale)	0.088 (-0.001; 0.177)	0.058
Anxiety (Zung scale)	0.042 (-0.009; 0.093)	0.315
Suicidal behavior	0.029 (-0.008; 0.066)	0.478

Discussion

These results are in general similar to those brought to light by other authors researching the adolescent population, although with some differences worth highlighting. The alcohol abuse rate obtained in the baseline assessment of the present study (25.56%) is higher than the rates of alcohol consumption in European adolescents, which range from 6% to 23% (Green, Leyland, Sweeting & Benzeval, 2013; Richter, Kuntsche, de Looze & Pförtner, 2013), and triples the rates obtained by two previous studies carried out with similar methodology to ours. In the first, performed on a sample with an average age of 14.9 years (Rüütel et al., 2014), alcohol abuse (consuming alcohol 2 or more times a week) stood at 8.2%, and in the second (Carli et al., 2014), the rates of alcohol abuse in adolescents aged 14 and 15, were 5.2% and 7.3% respectively. In our case, the significant increase in the rate of consumption observed one year after the baseline observation (49.72%) may mean that a very relevant period has been identified for the beginning of alcohol use is the population studied.

It is understood that individual patterns of alcohol consumption are influenced by the neurological, cognitive and social changes that typically occur in adolescence and, furthermore, that alcohol consumption influences the emergence of neurological damage and social deterioration during adolescence (Brown et al., 2008). Nevertheless, the high frequency of alcohol consumption among young people has led to the phenomenon being trivialized, despite the recurrence of data from Spain (ESTUDES 2014-2015), Europe and the USA, which show that at age 16 almost two thirds of young people have tried alcohol at least once in their lives, and more than two fifths have reported having been drunk at least once. At 18, more than three-quarters of young people have tried alcohol at least once in their lives and more than three-fifths have reported being drunk at least once (Johnston, Bachman & Schulenberg, 2012). Our data confirm this phenomenon while adding a further negative element: alcohol use starts at a very early age (at T_0, at an average age of 14.4 years, around a quarter of the adolescents had already abused alcohol, and among those who had not yet started drinking at T_0, a significant percentage used alcohol during the year of the study's observation period).

The notably wide variability between different countries in the rate of alcohol use among adolescents could be due to socioeconomic, educational, legal and cultural factors (Kuntsche et al., 2014). It should be noted that the Spanish population involved in this study belongs to a single autonomous community (Asturias), whose sociodemographic characteristics (a declining and aging population, high rate of unemployment and economic impoverishment), may explain greater alcohol use as an escape route for adolescents in poor social circumstances with negative future perspectives.

In any case, the detection of a high rate of alcohol use at such an early age is very important fact which must not be ignored, since early alcohol onset is associated with an increased risk of developing an alcohol use disorder (DeWit, Adlaf, Offord & Ogborne, 2000; Pitkänen, Lyyra & Pulkkinen, 2005).

A key element in the contact minors have with alcohol has been shown to be the family situation. A study conducted in Spain shows that increased alcohol use within the family environment, especially by siblings (Golpe, Isorna, Barreiro, Braña & Rial, 2017), is a possible precedent. Other recent research reveals how teenagers' patterns of alcohol use are linked to their family structure. Living in a family with biological parents, for example, is a protective factor, in contrast to single-parent families or families with a biological parent and a step-parent (Rüütel et al., 2014).

Our work reveals data that seem counterintuitive. There is a correlation between the presence of parents at their children's sports activities and adolescent alcohol use at T_1. In principle, parents accompanying their children to sports activities is a form of parental monitoring, and monitoring represents a protective factor against alcohol and drug abuse (Fletcher, Steinberg & Williams-Wheeler, 2004; Tilton-Weaver, Burk, Kerr & Stattin, 2013) by delaying onset and reducing the risk of misuse (DeVore & Ginsburg, 2005). Conversely, alcohol use tends to increase with parental separation and a decrease in parental monitoring (Barnes, Reifman, Farrell & Dintcheff, 2000).

This paradox may in part be explained by the bias inherent in age, since alcohol consumption increases with age (Johnston, O'Malley, Miech, Bachman & Schulenberg, 2016). However, the association between sporting events and alcohol use could be due to the fact that victory celebrations involving alcohol are frequent; or because participation in competitions sometimes entails traveling away from the family home, which may increase the likelihood of alcohol use (Tahiraj et al., 2016). In any case, the link between alcohol use and sports among young people is not clear, with some studies finding that hazardous drinking is more frequent in boys who have spent more time participating in sports (OR = 1.49) (Sajber, Tahiraj, Zenic, Peric & Sekulic, 2016), and others showing that sport can have a positive effect on young people, resulting in less alcohol use (Lopez, Rodriguez, Garcia & Perez, 2016).

Disruptive behaviors among young people are associated with alcohol or drug use disorders. A model for the development of disorders has been described in which parental problems and experiences of abuse or abandonment during childhood are combined with problems at school and with peers during adolescence, thereby increasing the risk of substance abuse at the young adult stage (Abrantes, Brown & Tomlinson, 2003; Bifulco, Schimmenti, Jacobs, Bunn & Rusu, 2014). A study recently conducted in Spain has found a statistically significant association between vic-

timization and the use of psychoactive substances (Caravaca, Navarro-Zaragoza, Luna, Falcón & Luna, 2017).

There are studies showing that children and adolescents who experience rejection by their peer group because of their disturbed behavior tend to relate to one another (Coie, Terry, Lenox, Lochman & Hyman, 1995; Laird, Jordan, Dodge, Pettit & Bates, 2001) and this association with peer groups with behavioral disturbances mediates the association between depressive symptoms experienced at 14 and high-risk alcohol use at 16 years of age (Pesola et al., 2015). It has also been observed that the early use of alcohol is associated with antisocial behavior (Brown, 1993; Hill, White, Chung, Hawkins & Catalano, 2000), and it is believed that the use of alcohol in adolescence increases the probability of other problematic behaviors given that exposure to alcohol affects the course of adolescent development (Kandel et al., 1999). For other authors, however, (Vanyukov et al., 2003), comorbidity is the product of a general predisposition to contravene social norms. According to this theory, the use of alcohol and the appearance of other problematic behaviors is a result of character structure. A recent study provides empirical evidence to link the use of alcohol and other drugs to problematic Internet use among adolescents (Golpe, Gómez, Braña, Varela & Rial, 2017).

In studies conducted with community samples of adolescents, the presence of alcohol or substance use multiplies the rates of comorbid mental health disorders by three compared to non-consumers (Kandel et al., 1999). It is known that alcohol use tends to increase during late adolescence (McCambridge, McAlaney & Rowe, 2011) and that the problems related to alcohol at this stage correlate strongly with greater morbidity and mortality (Hingson, Zha & Weitzman, 2009).

There appears to be a bidirectional relationship between depression and alcohol use in adolescence. Early use of alcohol has been associated with depression (Brook, Brook, Zhang, Cohen & Whiteman, 2002; Wells, Horwood & Fergusson, 2004), and the depression experienced in adolescence has been identified as a risk factor for greater alcohol use at this age (Marmorstein, Iacono & Malone, 2010; Saraceno, Heron, Munafo, Craddock & Van den Bree, 2012). A recent study by Pesola et al. (2015) found that the presence of depressive symptoms at age 14 is positively associated with hazardous drinking at 19 years of age.

Adolescent girls are at greater risk than boys of being victims of abuse (Champion et al., 2004) and of suffering from depression or anxiety (Poulin, Hand, Boudreau & Santor, 2005). While in boys this is more likely to produce externalizing behaviors such as behavior disorders and impulsivity (Caspi, Moffitt, Newman & Silva, 1996), in girls this could result in alcohol use. Structured psychological interventions to treat early behavior problems have been effective; treated patients show less favorable attitudes toward drugs, lower intention to use, less frequent use of tobacco and lower alcohol use intensity (Romero, Rodríguez, Villar & Gómez-Fraguela, 2016).

The present study has some limitations, is part of a Europe-wide study, and the sample size does not allow relationships between infrequent variables, such as drug use, to be established, or for an age group segregated study to be conducted.

Conclusions

Our study confirms the widespread use of alcohol among the adolescent population. In addition, it shows that variables such as previous alcohol and/or drug abuse, relationship problems with classmates, and the absence of prosocial behavior are predictors of alcohol abuse in the medium term. Moreover, there seems to be a clearly established link between alcohol consumption and affective disorders, although our results do not allow us to infer causality. We believe that all these factors should be taken into account when designing and implementing preventive strategies.

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Conflict of interest

The authors declare no conflict of interest.

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Cannabis use among adolescents: Risk pattern, implications and possible explanatory variables

Consumo de cannabis entre adolescentes: patrón de riesgo, implicaciones y posibles variables explicativas

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Abstract

In contrast to the achievements with other substances, it has not yet been possible to reduce the levels of cannabis use, the most used illegal substance among Spanish adolescents. The objective of this paper consists of updating levels of use (incorporating ages 12 and 13), estimating high-risk use and analyzing possible associated variables. For this purpose, a correlational method was used consisting of the administration of a survey to compulsory secondary school and high school students from the autonomous community of Galicia (Spain) in 2016. Results obtained from a sample of 3,882 Galician adolescents aged 12 to 18 (M = 14.52; SD = 1.72) reveal that the percentage of adolescents currently using tobacco and cannabis is higher than that of those using tobacco alone (12.7% vs 10.5%). This implies not only a higher probability of using other illegal substances, but also of developing rather high-risk use pattern, binge drinking or even experiencing problematic Internet use or cyberbullying. From a preventive perspective, the results reveal that personal variables such as self-esteem, assertiveness, social skills or impulsiveness have really weak explanatory power compared with other variables related to the setting of rules and limits by parents. One of the main conclusions of this paper is the need to adopt a comprehensive prevention approach.

Key words: Adolescents; Cannabis; Consumption; Tobacco; Related variables.

Resumen

Contrariamente a lo que ocurre con el resto de sustancias todavía no se han logrado disminuir los niveles de consumo de cannabis, que sigue siendo la droga ilegal más consumida entre los adolescentes españoles. El objetivo de este estudio consiste en actualizar los niveles de consumo (incorporando la franja de edad de 12-13 años), estimar los consumos propiamente de riesgo y analizar las posibles variables asociadas. Para ello se ha utilizado una metodología correlacional consistente en la realización de una encuesta a estudiantes de ESO y Bachillerato de la comunidad autónoma de Galicia (España) en el año 2016. La muestra final estuvo compuesta por 3.882 adolescentes gallegos de entre 12 y 18 años (M = 14,52 y DT = 1,72). Los resultados obtenidos revelan que a día de hoy es ya mayor el porcentaje de adolescentes que consumen tabaco y cannabis que únicamente tabaco (12,7% vs 10,5%) y que ello no sólo implica una mayor probabilidad de consumir otras sustancias ilegales, sino también de desarrollar un patrón consumo de alcohol de riesgo, de *Binge Drinking* o incluso de experimentar un Uso Problemático de Internet o de ciberacoso. Las variables personales como la autoestima, la asertividad, las habilidades sociales o la impulsividad tienen una capacidad explicativa realmente débil, en comparación con otras variables vinculadas al establecimiento de normas y límites por parte de los padres. Una de las principales conclusiones de este trabajo es la necesidad de adoptar un enfoque de prevención integral.

Palabras clave: Adolescentes; Cannabis; Consumo; Tabaco; Variables asociadas.

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The data from the latest Spanish national survey on the use of drugs among secondary school students (ESTUDES 2014/15) (Plan Nacional sobre Drogas, 2016) show that, unlike what has been the case with other substances, the figures for cannabis use have hardly declined in comparison to the previous year, with this still the most used illegal drug among adolescents between 14 and 18 years of age. Looking beyond the levels of consumption, the 2014/15 ESTUDES report also reveals that 2.5% of Spanish adolescents have a high-risk pattern of use, with a positive score in the Cannabis Abuse Screening Instrument (CAST) (Legleye, Piontek & Kraus, 2011).

Moreover, other studies have warned of a decrease in the onset ages for different substances, among them cannabis (Golpe, Barreiro, Isorna, Gómez & Varela, 2016), and emphasize the consequences that an early start in use can lead to (Brook, Stimmel, Zhang & Brook, 2008; Hérnandez, Roldán, Jiménez, Mora, Escarpa & Pérez, 2009; Kokkevi, Gabhainn & Spyropoulou, 2006). According to the official data available (Nacional sobre Drogas, 2014) the onset age for cannabis is 14.9 years, although given the sampling frame used (14-18 years of age) this data may not accurately represent reality.

While some authors maintain that an increasing number of adolescents already begin using in cannabis before tobacco (Álvarez et al., 2016; Rolle et al., 2015), classical theories postulate that alcohol and tobacco use precede cannabis onset and this, in turn, the beginning of other illicit drug use (Kandel, 2003). Authors such as Morral, McCaffrey and Paddock (2002) or Swift et al. (2011) argue for example that starting to use cannabis represents a qualitative leap that would increase the risk of "progressing" towards other illegal drugs, and this makes it a matter of great importance. Nor should it be forgotten that when adolescents start using cannabis, they usually maintain their smoking habits (Álvarez et al., 2016; Ariza et al., 2014), so much so that the most common form of cannabis use among most European consumers is to mix it with tobacco for smoking (Font-Mayolas et al., 2013; Pirona, Noor & Burkhart, 2015). This combined use not only strengthens the habit maintenance of these two substances, but also increases its addictive potential (Hindocha et al., 2016; Tullis, Dupont, Frost & Gold, 2003), with severe implications at the neurobiological level, the study of which should, according to Pirona et al. (2015), receive more attention than it has had to date.

In addition to the above, there are a number of socio-health aspects that justify the need for continued progress in the study of cannabis (Isorna, 2017). Numerous studies have emphasized the implications that the use of this substance have at the brain development level, both from a structural and functional point of view (Jacobus & Tapert, 2014). There have also been adverse effects on health at the respiratory and cardiovascular levels (Bechtold, Simpson, White & Pardini, 2015). It has been associated with a higher prevalence of psychotic symptoms (Arseneault et al., 2002; Henquet et al., 2005), anxiety, depression or an increased risk of suicide (Feingold, Weiser, Rehm & Lev-Ran, 2016; Silins et al., 2014). From a psychosocial point of view it has been found that adolescents who use cannabis present greater difficulties in studying or working, perform worse at school and get involved in more conflicts or discussions, as well as in fights or physical aggression (Guerrero et al., 2015; Morales, Ariza, Nebot, Pérez & Sánchez, 2008; Plan Nacional sobre Drogas, 2014) and risky sexual practices (Harper, Dittus & Ethier, 2016). Furthermore, cannabis use in adolescence has been linked to a greater likelihood of developing potential dependence in adulthood (George & Vaccarino, 2015) and to the use of other drugs (Fergusson & Boden 2008; Michaelides, Miller & Jutras-Aswad, 2014). It has also been shown that driving under the influence of this drug increases the risk of car accidents (Asbridge, Hayden & Cartwright, 2012; Gerberich et al., 2003; Hartman & Huestis, 2013). Finally, no less important are the studies that have linked cannabis to the problematic use of the Internet (Golpe, Gómez, Braña, Varela & Rial, 2017; Rücker, Akré, Berchtold & Suris, 2015) and different risky on line practices, such as sexting (Benotsch, Snipes, Martin & Bull, 2013), cyberbullying (Halbohn, 2016) or the problematic use of online videogames (Van Rooij et al., 2014).

The potential implications at different levels of cannabis use justifies the need to develop specific lines of action at the level of prevention, duly supported by scientific evidence. This is precisely what has led different researchers to try to identify possible associated variables in an attempt to determine the relative weight of each one as prognostic factors. Some of the most studied have been those to do with personality characteristics, especially impulsivity (Barkus, 2008; Moreno et al., 2012) and sensation seeking (González, Sáiz, Quirós & López, 2000; Malmberg et al., 2010). Other studies have focused on analyzing the role of social skills (Griffith-Lendering et al., 2011). However, in recent years, models based on an environmental prevention approach have become increasingly important (Burkhart, 2011). Such models assume that people do not get involved in using substances only for personal or cognitive reasons, but are influenced by environmental factors. Research by Guxens, Nebot, Ariza and Ochoa (2007) or Thompson and Auslander (2007), for example, emphasizes the importance of cannabis use within the circle of adolescent friends. Terzic, Santric, Sbutega and Vasic (2013), on the other hand, warn that dysfunctional family contexts or bad relationships with parents are also associated with cannabis use, while Vázquez et al. (2014) emphasize the time at which the adolescents come home at night and Varela, Marsillas, Isorna & Rial (2013) focus on the money available.

Taking all of these considerations into account, this study has a triple objective: (1) to establish current figures for the number of adolescents users of both cannabis and other psychoactive substances, as well as onset ages high-risk consumption, incorporating adolescents aged 12 and 13 into the sample frame; (2) notwithstanding the impossibility of establishing cause-effect relationships, to analyze the relationship between the polydrug use of tobacco and cannabis and other behaviors in order to explore possible implications such as the consumption of other substances, high-risk alcohol use and binge drinking, problematic use of the Internet or certain risky practices on the Internet; (3) to analyze the role of possible prognostic factors, both of a personal (such as self-esteem, impulsivity, social skills or assertiveness), and of a family nature (essentially the money available and coming-home time at night).

Method

Participants

In order realize the above-mentioned objectives, a selective methodology was used consisting of a survey among students in compulsory secondary education (ESO) and those studying for the high school certificate (Baccalaureate) in the provinces of A Coruña and Pontevedra. In particular, we applied a correlational transversal model, using two-stage sampling; by clusters for the selection of the first-level units (school) - establishing quotas a priori by type of school - and intentional sampling for the selection of second-level units (individuals). Despite the non-probabilistic nature of the sampling used, it was found that the final sample quotas matched the population quotas in terms of sex, age, school year and school. Fifteen schools in different municipalities agreed to participate, both public and private, including charter, both urban and rural. Initially, 4063 questionnaires were collected, although 62 were discarded on review, either due to an excessive number of missing values (n = 32) or incoherent response patterns (n = 30). A further 119 cases were subsequently eliminated for being outside the age range under study (12-18 years), resulting in a final sample of 3882 adolescents (49.9% male and 50.1% female) between the ages of 12 and 18 (M = 14.52, SD = 1.72). Of these, 2669 attended public schools and 1213 attended private or charter schools. ESO pupils accounted for 74.8% (38% in the first phase and 36.8% in the second) and 25.2% were studying for the Baccalaureate.

Instrument

The data were collected through a questionnaire prepared expressly for the present study, in which questions were grouped into five blocks. A first block was taken from ESTUDES 2014/15 (Plan Nacional sobre Drogas, 2016) containing questions on habits of alcohol use, getting drunk and binge drinking (defined as "the intake of 6 or more alcoholic drinks per occasion", by studies such as Parada et al., 2011 or Golpe et al., 2017), as well as the use of tobacco, cannabis, cocaine, ecstasy, amphetamines and hallucinogens, both in the previous year and the previous month. A second block included three specific screening tools. The Cannabis Abuse Screening Test (CAST, Legleye et al., 2011), which identifies adolescents with high-risk cannabis use. Although CAST has three categories based on the total score obtained ("no risk" = 0-1 points, "low risk" = 2-3 points, "high risk" = 4 or more points), in accordance with ESTUDES 2014/15, only the latter cut-off point was used, thus distinguishing adolescents making abusive or problematic use of cannabis from non-users and those whose use does not put them at high risk. A version of the Alcohol Use Disorders Identification Test (AUDIT) recently validated with Spanish adolescents by Rial, Golpe, Araujo, Braña and Varela (2017) was used to identify alcohol users, with the cut-off point also being a score of ≥ 4. Finally, to identify problematic Internet users, the Problematic Internet Use Scale for adolescents was applied (PIUS-a) (Rial, Gómez, Isorna, Araujo & Varela, 2015), with a cut-off score ≥16, as recommended by the authors. A third block aimed at assessing different risky behaviors on the Internet, such as sexting, participation in online gambling and online betting, cyberbullying, contact with strangers, etc. The fourth block included questions referring to possible variables associated with cannabis use. Among them, personal variables such as self-esteem were explored (through the Rosenberg Self-esteem Scale, adapted by Martín, Núñez, Navarro and Grijalvo, 2007); assertiveness (through the Assertiveness Scale included in the Evaluation Instruments Bank of the European Monitoring Centre for Drugs and Drug Addiction [EMCDDA]), impulsivity (through the Barrat Impulsivity Scale, adapted by Martínez, Fernández, Fernández, Carballo and García, 2015), and social skills (through the Social Skills Scale of Oliva et al., 2011). To find out coming-home time and money available, two questions taken from Varela et al. (2013) were used. Finally, a fifth block collected sociodemographic data such as sex, age and school type.

Procedure

Data were collected directly in the school classrooms in small groups (between 15 and 20 individuals) using a questionnaire completed individually by each adolescent. This took place in the first quarter of 2016 and was carried out by a team of psychologists with proven experience in carrying out this type of task. Each subject was informed of the purpose of the study, and confidentiality and anonymity of their responses was guaranteed. In all cases, school managements and the respective parent and student associations consented to take part. Participation was totally voluntary

Tabla 1. *Use of various substances among secondary school adolescents by sex and age groups, according to substance. Eastern Galicia, 2016.*

LAST YEAR	GLOBAL		SEX			AGE GROUP			
	12-18 years % (n)	14-18 years % (n)	male % (n)	female % (n)	*p**	12-13 years % (n)	14-15 years % (n)	16-18 years % (n)	*p**
Cannabis	14.8 (575)	19.8 (509)	15.3 (295)	14.3 (277)	.42	4.5 (57)	12.6 (171)	27.9 (338)	‹ .001
Alcohol	52.1 (2021)	64.3 (1655)	50.7 (980)	53.4 (1035)	.10	27 (344)	54.5 (741)	75.4 (914)	‹ .001
drunkenness	26.3 (1017)	34.4 (882)	25.4 (490)	27 (522)	.28	9.4 (120)	21.6 (293)	48.6 (589)	‹ .001
6 or more alcoholic drinks	18.1 (697)	23.8 (608)	18.7 (361)	17.2 (332)	.25	6 (76)	14.3 (193)	34.4 (415)	‹ .001
Tobacco	23.4 (905)	30 (768)	21.2 (410)	25.4 (491)	.002	9.7 (124)	21.3 (289)	39.6 (479)	‹ .001
Cocaine	0.9 (34)	1 (26)	1.1 (21)	0.6 (12)	.16	0.5 (7)	1 (13)	1.1 (13)	.32
Ecstasy/ amphetamines/ hallucinogens	1.1 (42)	1.4 (35)	1.2 (24)	0.9 (17)	.34	0.5 (6)	0.9 (12)	1.9 (23)	.002
CAST (cut point ≥ 4)	**3.8**	**4.9**	**4.2 (80)**	**3.4 (66)**	**.23**	**1.3 (16)**	**3.7 (50)**	**6.3 (76)**	**‹ .001****
LAST MONTH	**GLOBAL**		**SEX**			**AGE GROUP**			
	12-18 years % (n)	14-18 years % (n)	male % (n)	female % (n)	*p**	12-13 years % (n)	14-15 years % (n)	16-18 years % (n)	*p**
Cannabis	8.5 (330)	11.4 (294)	8.6 (166)	8.4 (162)	.84	2.6 (33)	6.6 (90)	16.8 (204)	‹ .001
Alcohol	32.3 (1253)	41.3 (1062)	30 (580)	34.5 (669)	.003	13.6 (174)	29.1 (394)	55.1 (668)	‹ .001
drunkenness	12.9 (499)	17.2 (442)	11.7 (225)	14 (272)	.03	3.8 (49)	9.3 (126)	26.1 (316)	‹ .001
6 or more alcoholic drinks	8.6 (334)	11.4 (293)	8.9 (171)	8.3 (161)	0.57	2.6 (33)	6.6 (89)	16.8 (204)	‹ .001
Tobacco	16.1 (623)	20.7 (532)	14.3 (276)	17.8 (345)	.003	6.7 (85)	14.1 (191)	28.2 (341)	‹ .001
Cocaine	0.4 (15)	0.3 (8)	0.4 (7)	0.4 (7)	1	0.5 (6)	0.4 (6)	0.2 (2)	.38
Ecstasy/ amphetamines/ hallucinogens	0.4 (16)	0.4 (11)	0.3 (6)	0.5 (9)	.61	0.3 (4)	0.5 (7)	0.3 (4)	.65

Note. * *p*-values for Chi-square test.

and the time required to complete the questionnaire was approximately 20 minutes. The study was also approved by the Bioethics Committee of the University of Santiago de Compostela.

Data analysis

After an initial descriptive analysis and a bivariate tabulation, three comparison groups were established, with the first formed by adolescents who did not use tobacco or cannabis in the previous year, the second made up of those who only used tobacco, and the third with those who used both substances. Adolescents who used only cannabis, making up 2.1%, were excluded from the analysis. The differences between the groups were analyzed using parametric and non-parametric contrasts, depending on the nature of the variables. In the case of quantitative variables, unifactorial Anova with post-hoc Tukey contrasts and the partial eta squared coefficient (η2p) were used to estimate the effect size. In the case of qualitative variables, contrasts of independence $\chi 2$ and contingency coefficients (CC) were applied. The analyses were performed using the statistical package IBM SPSS Statistics 20.

Results

Levels of use and onset ages

As can be seen in Table 1, alcohol is the substance most frequently used by adolescents aged 12-18 years, followed by tobacco and cannabis. More specifically, over half the adolescents in the sample (52.1%) drank alcohol in the previous year, 1 in 4 got drunk and 18.1% consumed 6 or more alcoholic drinks in the same occasion or drinking episode. Tobacco was smoked by 23.4% , and 14.8% used cannabis. A slight increase is observed for all substances when analyzing levels of use with a reduced sample of adolescents aged 14 to 18. With regard to the youngest age group (12-13 years), which was not included in ESTUDES, the results reveal that 27% drank alcohol in the previous year (13.6% in the previous month), 9.4% used tobacco (6.7% in the previous month) and 4.5% cannabis (2.6% in the previous month). By sex, results reveal little difference between boys and girls in the use of the different substances, and when such differences do exist (tobacco use in the previous year and alcohol, drunkenness and tobacco in the previous month), the prevalence figures are higher for

girls. In terms of age group, the differences are more than evident, with the percentage of users being significantly higher among adolescents aged 16 to 18.

Onset ages for tobacco and cannabis use are 14.08 and 14.8 respectively, with the onset of other substances such as alcohol at 13.6 years, the age of first drunkenness 14.6, cocaine 15.08 and consumption of ecstasy, amphetamines or hallucinogens at 14.9. It should also be added that 56.3% of those who have tried tobacco at some time in their lives, and 38.8% of those trying cannabis did so first aged 14 or younger.

High-risk use

The data collected in Table 1 reveal that 3.8% of the adolescents in the sample exceeded the cut-off point established by the original authors of CAST (≥ 4) or, put another way, one in four (25.4%) of those who used cannabis in the previous year and slightly more than one in three (37.5%) of those who used it in the previous month were using the substance with high risk. To this percentage we should add the 2.1% of adolescents with low-risk use (2-3 points in CAST). In comparison, 94.1% do not present any risk.

Table 2. *Use of various substances and high-risk use of alcohol among secondary school students, by sex and age group. Eastern Galicia, 2016.*

SUBSTANCES USED AND HIGH-RISK USE (last year)	**GLOBAL**				
	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	CC
Alcohol	36.9 (1064)	93.9 (383)	98.6 (486)	‹ .001	.46
Drunkenness	10.4 (299)	53.7 (219)	87.1 (429)	‹ .001	.54
6 or more alcoholic drinks	6.3(180)	31.8 (128)	69.3 (339)	‹ .001	.50
AUDIT cut point ≥ 4	13.3 (371)	41.5 (158)	67 (310)	‹ .001	.41
Cocaine	0 (0)	0 (0)	5.9 (29)	‹ .001	.22
Ecstasy/amphetamines/ hallucinogens	0.1 (3)	0.5 (2)	6.3 (31)	‹ .001	.21

SEX	**Male**				**Mujer**			
	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**
Alcohol	36.8 (540)	90.9 (149)	98 (239)	‹ .001	37 (522)	95.9 (233)	99.2 (244)	‹ .001
Drunkenness	10.3 (151)	54.9 (90)	85.2 (207)	‹ .001	10.4 (146)	53.1 (129)	89 (219)	‹ .001
6 or more alcoholic drinks	6.6 (97)	36.3 (59)	71.6 (174)	‹ .001	5.8 (82)	29 (69)	66.7 (162)	‹ .001
AUDIT cut point ≥ 4	13.8 (195)	36.8 (56)	64.3 (146)	‹ .001	12.8 (175)	44.7 (102)	69.5 (162)	‹ .001
Cocaine	0 (0)	0 (0)	7 (17)	‹ .001	0 (0)	0 (0)	4.5 (11)	‹ .001
Ecstasy/amphetamines/ hallucinogens	0.1 (1)	0.6 (1)	8.2 (20)	‹ .001	0.1 (2)	0.4 (1)	4.1 (10)	‹ .001

AGE GROUP	**12-13 years**				**14-15 years**				**16-18 years**			
	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**
Alcohol	19.1 (217)	92.1 (70)	97.9 (46)	‹ .001	42.3 (438)	91.9 (136)	97.2 (137)	‹ .001	58.2 (402)	96.1 (172)	99.3 (296)	‹ .001
Drunkenness	3.2 (37)	43.4 (33)	85.1 (40)	‹ .001	9.2 (95)	45.3 (67)	77.9 (109)	‹ .001	23.7 (163)	65.4 (117)	91.6 (273)	‹ .001
6 or more alcoholic drinks	1.8 (20)	28.9 (22)	60.9 (28)	‹ .001	5.2 (54)	22.4 (32)	66.4 (93)	‹ .001	15 (103)	40.4 (72)	71.6 (212)	‹ .001
AUDIT cut point ≥ 4	2.7 (30)	13.5 (10)	13.3 (6)	‹ .001	11.1 (110)	35.6 (48)	63.6 (82)	‹ .001	34.4 (229)	59.3 (99)	77.7 (219)	‹ .001
Cocaine	0 (0)	0 (0)	14.9 (7)	‹ .001	0 (0)	0 (0)	6.4 (9)	‹ .001	0 (0)	0 (0)	4 (12)	‹ .001
Ecstasy/ amphetamines/ hallucinogens	0 (0)	0 (0)	8.5 (4)	‹ .001	0 (0)	0 (0)	8.8 (11)	‹ .001	0.4 (3)	1.1 (2)	5.1 (15)	‹ .001

Note. * *p*-values for Chi-square test.

No significant differences were found according to sex, but by age there was a 5-times greater high-risk use rate among 16-18 year olds (6.3%) than among 12-13 year olds (1.3%) ($\chi 2 = 44.52$; $p < 0.001$).

Link between tobacco and cannabis use

If we analyze what happens specifically in the case of tobacco and cannabis, a first point of interest is that the majority of adolescents (74.7%) do not use either substance. On the other hand, it was found that there are more adolescents who smoke both substances (12.7%) than tobacco only (10.5%), with the difference being significant ($\chi 2 = 8.02$, $p < 0.01$). The percentage of adolescents who use only cannabis turned out to be very low (2.1%). It has also been found that 54.7% of those who smoked tobacco in the previous year also used cannabis, while 86% of those who used cannabis also smoked tobacco (Figure 1).

Other risky practices

As can be seen in Table 2, the number of users of other substances is significantly higher among those adolescents who use tobacco and cannabis compared to the other two

Table 3. *Use of tobacco and cannabis by risky online practices and problematic Internet use among secondary school adolescents by sex and age group. Eastern Galicia, 2016.*

RISKY ONLINE PRACTICES AND PROBLEMATIC INTERNET USE	GLOBAL				
	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	CC
Cyberbullying victim	5 (145)	9.3 (38)	8.9 (44)	‹ .001	.08
Cyberbullying perpetrator	3.3 (95)	5.1 (21)	11 (54)	‹ .001	.12
Sexting	3.2 (91)	8.4 (34)	14.4 (71)	‹ .001	.17
Online betting	5.4 (156)	8.1 (33)	12.2 (60)	‹ .001	.10
Erotic websites	26.2 (754)	31.9 (130)	47.9 (236)	‹ .001	.17
Contact with strangers	28.4 (818)	40.2 (164)	44.6 (219)	‹ .001	.13
Problematic Internet use	15 (422)	26.1 (103)	30.3 (144)	‹ .001	.15

SEX	Male				Female			
	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**
Cyberbullying victim	3.9 (57)	9.1 (15)	5.3 (13)	‹ .001	6.2 (88)	9.5 (23)	12.6 (31)	‹ .001
Cyberbullying perpetrator	4.4 (65)	6.1 (10)	14.3 (35)	‹ .001	2.1 (30)	4.5 (11)	7 (17)	‹ .001
Sexting	2.9 (42)	7.4 (12)	13.1 (32)	‹ .001	3.4 (48)	9.1 (22)	15.4 (38)	‹ .001
Online betting	9.6 (141)	17.1 (28)	20.7 (50)	‹ .001	1.1 (15)	2.1 (5)	3.7 (9)	‹ .001
Erotic websites	43.8 (641)	60.4 (99)	74.2 (181)	‹ .001	7.9 (112)	12.8 (31)	21.5 (53)	‹ .001
Contact with strangers	30.6 (449)	42.1 (69)	49 (119)	‹ .001	26.1 (368)	39.1 (95)	40.4 (99)	‹ .001
Problematic Internet use	13.1 (187)	22.9 (36)	30.2 (71)	‹ .001	17.1 (235)	28.3 (67)	30.7 (73)	‹ .001

AGE GROUP	12-13 years				14-15 years				16-18 years			
	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**	None % (n)	Only tobacco % (n)	Tobacco and cannabis % (n)	*p**
Cyberbullying victim	3.9 (44)	11.8 (9)	14.9 (7)	‹ .001	6.2 (64)	9.5 (14)	12.1 (17)	.04	5.2 (36)	8.4 (15)	6.7 (20)	.15
Cyberbullying perpetrator	2.4 (27)	5.3 (4)	6.4 (3)	.17	3.9 (40)	6.1 (9)	13.7 (19)	‹ .001	3.8 (26)	4.5 (8)	9.7 (29)	.002
Sexting	1 (11)	3.9 (3)	0 (0)	.01	3.4 (35)	8.9 (13)	15.6 (22)	‹ .001	6.4 (44)	10.1 (18)	16.1 (48)	‹ .001
Online betting	2.9 (33)	6.6 (5)	8.5 (4)	.06	6 (62)	8.8 (13)	8.6 (12)	.20	8.7 (60)	7.8 (14)	13.8 (41)	.04
Erotic websites	12.6 (144)	10.5 (8)	10.6 (5)	.06	28.8 (297)	38.8 (57)	44.7 (63)	‹ .001	44.1 (305)	35.8 (64)	55 (164)	‹ .001
Contact with strangers	19.1 (217)	23.7 (18)	17.4 (8)	.61	33.8 (350)	38.5 (57)	51.8 (73)	‹ .001	35.5 (244)	48 (86)	45.5 (135)	.001
Problematic Internet use	10.7 (118)	22.2 (16)	15.6 (7)	.02	16.8 (171)	27.3 (39)	32.4 (44)	‹ .001	19.3 (129)	26.9 (47)	31.6 (91)	‹ .001

Note. * *p*-values for Chi-square test.

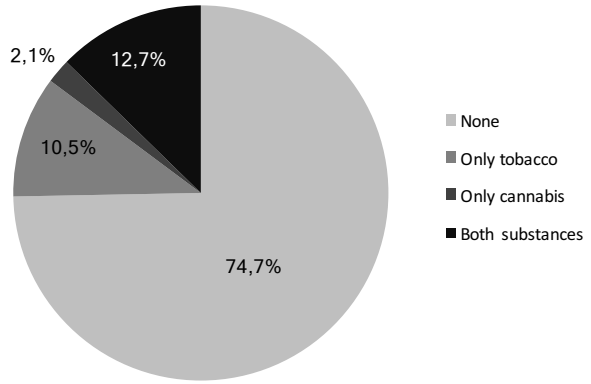

Figure 1. Use of tobacco, cannabis and both combined by secondary school students. Eastern Galicia, 2016.

groups, especially in terms of intensive alcohol use. For example, it can be observed that the percentage of adolescents who admitted to having been drunk in the previous year went from 10.4% among those who did not use either of the two substances, to 87.1% among those who used tobacco and cannabis ($\chi2 = 1591.02$; $p < 0.001$; CC = .54). The same is true for drinking 6 or more alcoholic beverages per occasion, which goes from 6.3% to 69.3% ($\chi2 = 1269.17$, $p < 0.001$, CC = .50). Similarly, the rates of use for cocaine, ecstasy, amphetamines and hallucinogens are also significantly higher, although effect sizes are more moderate. Furthermore, it has been possible to confirm that the incorporation of cannabis into the repertoire of substance use is also associated with greater high-risk consumption. So much so that the number of high-risk alcohol users, as detected by AUDIT, is 5 times higher in the case of adolescents who smoke tobacco and cannabis (13.3% vs. 67%) ($\chi2 = 764.26$; $p < 0.001$, CC = .41). The analyses by sex and age group reveal that these differences are maintained among both boys and girls as well as all age groups.

With regard to online behavior by adolescents (Table 3), it was found that users of tobacco and cannabis have a significantly higher probability of engaging in a variety of risky behaviors. In particular, the magnitude of effect size reveals that sexting ($\chi2 = 117.61$; $p < 0.001$; CC = .17) and accessing websites with erotic content ($\chi2 = 112.61$; $p < 0.001$; CC = .17) are the risky practices most closely associated with this pattern of simultaneous use. Likewise, it has been observed that the percentage of problematic Internet users goes from 26.1% among those who consume tobacco to 30.3% among those who consume tobacco and cannabis, a figure doubling that found for adolescents who do not consume any substance (15%) ($\chi2 = 84.34$; $p < 0.001$; CC = .15). The differences found between the different comparison groups are maintained regardless of sex, with the highest percentages found among the users of both substances, except in the case of victims of cyberbullying. While boys using tobacco are the ones with the highest prevalence figures (9.1%) ($\chi2 = 10.75$, $p < 0.001$), in the case of girls, the highest percentages are among those who consume both substances (12.6%) ($\chi2 = 16.49$; $p < 0.001$). Depending on the age group, it is worth mentioning the absence of statistically significant differences between the majority of risk practices among adolescents aged 12-13 years, except for being victims of cyberbullying (predominant risky behavior among users of both substances), sexting and problematic Internet use (predominant among tobacco users). After the age of 14, the observed trend is the same as that registered globally.

Associated variables

Firstly, with regard to personal variables (Table 4), it should be noted that although statistically significant differences have been found in all of them (self-esteem, impulsivity, assertiveness and social skills), the small estimated effect sizes show that these are not variables that can really explain cannabis use by themselves. In fact, only impulsivity and assertiveness present a clear pattern, with tobacco and cannabis users having the highest impulsivity scores and the lowest assertiveness scores. The analysis of the results by sex reveals statistically significant differences in three of the four personal variables in question (self-esteem, impulsivity and assertiveness), although the only one that continues to present a clear pattern is impulsivity. Both boys and girls who use tobacco and cannabis have the highest impulsivity scores ($M_{boys} = 67.21$, $F = 14.83$, $p < 0.001$ vs $M_{girls} = 68.31$, $F = 23.05$; $p < 0.001$). In terms of age group, impulsivity is again the most consistent variable, although in the group of 12 to 13-year olds tobacco users have higher scores in this variable, while in those older than 14 the highest impulsivity scores correspond to tobacco and cannabis users.

In addition to these variables, others were analyzed relating to the establishment of norms and limits in the family environment. Regarding coming-home time, the results collected in Table 5 reveal that the probability of belonging to the risk group increases significantly the later the adolescents arrive home, especially after 4 in the morning. ($\chi2 = 529.47$; $p < 0.001$). This same trend is maintained when the results are analyzed both by sex and by age group. Finally, it has also been possible to observe statistically significant differences depending on money available (Table 6), with the likelihood of tobacco and cannabis use increasing with the amount of money adolescents have available, especially above €20 ($\chi2 = 126.80$, $p < 0.001$). As in the case of coming-home time, this pattern is maintained regardless of sex and age group, although it is true that among12 to 13-year-old adolescents, the availability of more money seems to increase the probability of tobacco use more than the likelihood of using both substances (Table 6).

Finally, in an attempt to model the data, a logistic regression analysis was carried out, with the aim of exploring to

Table 4. *Use of tobacco and cannabis by mean scores for personal variables among secondary school adolescents by sex and age group. Eastern Galicia, 2016.*

	GLOBAL				
	None (M)	Only tobacco (M)	Tobacco and cannabis (M)	*p**	η^2p
Self-esteem	31.26	29.47	30.46	‹ .001	.06
Impulsivity	62.63	65.95	67.78	‹ .001	.05
Social skills	53.14	52.98	54.61	.04	.05
Assertiveness	19.50	18.88	18.64	‹ .001	.03

SEX	**Male**				**Female**			
	None (M)	Only tobacco (M)	Tobacco and cannabis (M)	*p**	None (M)	Only tobacco (M)	Tobacco and cannabis (M)	*p**
Self-esteem	32.14	30.33	31.30	‹ .001	30.31	28.88	29.55	.004
Impulsivity	63.09	66.51	67.21	‹ .001	62.16	65.55	68.31	‹ .001
Social skills	53.01	53.05	54.72	.15	53.25	52.99	54.50	.24
Assertiveness	18.65	17.49	18.10	‹ .001	20.37	19.84	20.89	.02

AGE GROUP	**12-13 años**				**14-15 años**				**16-18 años**			
	None (M)	Only tobacco (M)	Tobacco and cannabis (M)	*p**	None (M)	Only tobacco (M)	Tobacco and cannabis (M)	*p**	None (M)	Only tobacco (M)	Tobacco and cannabis (M)	*p**
Self-esteem	31.60	30.90	30.82	.58	31.10	28.58	29.96	‹ .001	30.94	29.56	30.68	.002
Impulsivity	61.96	64.91	62.38	.003	62.82	67.98	69.29	‹ .001	63.27	64.60	67.81	‹ .001
Social skills	53.33	52.88	53.79	.78	52.88	52.19	53.10	.88	53.07	53.66	55.97	.001
Assertiveness	19.50	18.26	19.16	.01	19.32	18.42	18.24	‹ .001	19.74	19.53	19.10	.05

Note. * *p*-values for *F* test.

what extent personal and family variables could jointly explain the fact that adolescents use cannabis in addition to tobacco. The results obtained, both for the global sample and stratified by sex and age group, reveal a rather poor explanatory power of the model, with Nagelkerke R^2 values never exceeding 10%.

Discussion

The present study has made it possible to confirm that the current social alarm regarding the use of cannabis among adolescents is not unfounded, insofar as the use of this substance (and in particular high-risk use) is at worrying levels. It has also been shown that adolescents who "make the leap" to cannabis use are more likely to develop a risk pattern, characterized by a more damaging repertoire of substance use and a greater likelihood of being involved in numerous risky practices online.

The results obtained reveal that the levels of consumption found in the sample of Galician adolescents aged 14 to 18 are below those recorded in ESTUDES 2014/15 for the whole of Spain and slightly higher than those obtained for Galicia (Plan Nacional sobre Drogas, 2016). Despite the fact that once the 12-13 age range is incorporated the figures decrease markedly, the fact is that cannabis use remains at worrying levels: in Galicia more than 10,000 adolescents aged between 12 and 18 will have used cannabis in the last month; for the first time at a really very early age (14.8 years) and coinciding with getting drunk for the first time. In the case of 12 to 13-year-old adolescents, despite the fact that the percentage of those using cannabis in the previous month is "only" 2.6%, we are talking about more than 1000 children, not a negligible figure in any way, especially when taking into account the consequences that cannabis use at such early ages can lead to both physically, cognitively, emotionally and behaviorally (Brook, et al., 2008; Fergusson, Lynskey & Horwood, 1996; Filbey, McQueeny, DeWitt & Mishra, 2015). Analyzing the results by sex and age group highlights some issues that should be taken into account from a preventive point of view: a) it is necessary to start paying special attention to girls, since for some substances (for example, tobacco) the prevalence figures are already higher than among boys, and b) efforts should be initiated at a preventive level at younger ages, given the worrying levels of use among adolescents as young as 12 or 13 years.

Regarding high-risk use, the results reveal that, overall, 3.8% of adolescents aged between 12 and 18 had problematic cannabis use (positive in CAST), which means that in 1 out of 4 cases use is not occasional or anecdotal. In the 14 to 18 age range, the percentage of consumers at risk stands at 4.9%, twice the national level (Plan Nacional sobre Drogas, 2016). The fact that levels of high-risk use are higher than those obtained at national level while global levels of consumption are lower could be warning us about worsening patterns of use, compatible according to some authors with a stagnation in the use of this substance in absolute terms (Isorna, 2017).

The analysis of the relationship between tobacco and cannabis use, on the other hand, reveals that the simultaneous consumption of both substances is much more frequent than one might think. Currently, there are more adolescents who smoke tobacco and cannabis than just tobacco. In the present study, it has also been found that adolescents who consume both substances not only show greater use of alcohol (binge drinking) and more drunkenness, but also greater high-risk use, specifically detected by AUDIT. Higher rates of use of other substances have also been observed, as well as greater comorbidity with other problem behaviors such as the problematic use of Internet, sexting, cyberbullying or online betting. All this coincides with the findings of previous studies that have shown the implications of simultaneous consumption of both substances at different levels. (Agrawal et al., 2009; Belánger, Akre, Kuntsche, Gmel & Suris, 2011; Hublet et al., 2015; Schauer, Rosenberry & Peters, 2017; Subramanian, McGlade & Yurgelun-Todd, 2016). In fact, Pinora et al. (2015) found that the endocannabinoid system plays an important role in the gratifying and motivational effects of nicotine. In addition, a recent study by Golpe et al. (2017) warned about the relationship they found with the problematic use of Internet and certain potentially risky behaviors on the Internet, and suggests, as proposed by Problem Behavior Theory (Jessor, 1991), that the different problem behaviors that often emerge jointly in adolescence may have a common etiological basis. The results obtained by sex have also served to show that the possible implications of the simultaneous use of tobacco and cannabis affect both girls and boys, with

Table 5. *Use of tobacco and cannabis by coming-home time among secondary school adolescents by sex and age group. Eastern Galicia, 2016.*

	GLOBAL				
	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**	CC
Before midnight	49.1 (1385)	23.3 (95)	13.8 (68)	‹ .001	.35
Between midnight and 2 a.m.	21 (592)	20.9 (85)	13.2 (65)		
Between 2 and 4 a.m.	19.1 (539)	32.2 (131)	30.1 (148)		
After 4 a.m.	10.8 (305)	23.6 (96)	42.8 (210)		

SEX	**Male**				**Female**			
	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**
Before midnight	47.4 (676)	27.6 (45)	16.5 (40)	‹ .001	50.7 (705)	20.6 (50)	11.4 (28)	‹ .001
Between midnight and 2 a.m.	22 (313)	23.3 (38)	13.2 (32)		20.1 (279)	18.9 (46)	13.1 (32)	
Between 2 and 4 a.m.	19.2 (274)	27 (44)	26.3 (64)		19 (264)	35.8 (87)	34.3 (84)	
After 4 a.m.	11.4 (162)	22.1 (36)	44 (107)		10.3 (143)	24.7 (60)	41.2 (101)	

AGE GROUP	**12-13 años**				**14-15 años**				**16-18 años**			
	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p*	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p*	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p*
Before midnight	77.5 (845)	53.9 (41)	62.2 (28)	‹ .001	43.6 (446)	26.4 (39)	19.1 (27)	‹ .001	12.6 (87)	8.4 (15)	3.4 (10)	‹ .001
Between midnight and 2 a.m.	14.8 (162)	23.7 (18)	15.6 (7)		28.1 (288)	29.7 (44)	26.2 (37)		20.1 (138)	11.7 (21)	7 (21)	
Between 2 and 4 a.m.	6 (66)	18.4 (14)	15.6 (7)		21.6 (221)	31.1 (46)	32.6 (46)		36.3 (249)	39.7 (71)	31.5 (94)	
After 4 a.m.	1.6 (18)	3.9 (3)	6.7 (3)		6.7 (69)	12.8 (19)	22 (31)		31.1 (214)	40.2 (72)	58.1 (173)	

Note. * *p*-values for Chi-square test.

Table 6. *Use of tobacco and cannabis by money available among secondary school adolescents by sex and age group. Eastern Galicia, 2016.*

	GLOBAL				
	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**	CC
Under €10	50.3 (1436)	34.8 (142)	28.9 (142)	‹ .001	.18
Between €11-20	34.6 (988)	43.6 (178)	42.1 (207)		
Between €21-30	10.6 (303)	16.2 (66)	19.3 (95)		
Over €30	4.4 (126)	5.4 (22)	9.8 (48)		

SEX	**Male**				**Female**			
	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**
Under €10	47.1 (682)	32.3 (53)	26.7 (65)	‹ .001	53.5 (750)	36.6 (89)	31.3 (77)	‹ .001
Between €11-20	35.2 (509)	41.5 (68)	38.3 (93)		34.1 (478)	44.9 (109)	45.5 (112)	
Between €21-30	12 (173)	22 (36)	21.8 (53)		9.3 (130)	12.3 (30)	17.1 (42)	
Over €30	5.7 (83)	4.3 (7)	13.2 (32)		3.1 (43)	6.2 (15)	6.1 (15)	

AGE GROUP	**12-13 years**				**14-15 years**				**16-18 years**			
	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**	None %(n)	Only tobacco %(n)	Tobacco and cannabis %(n)	*p**
Under €10	67.6 (753)	47.4 (36)	54.3 (25)	‹ .001	46 (475)	37.2 (55)	34.8 (49)	.02	28.9 (199)	27.9 (50)	22.1 (66)	.13
Between €11-20	23.8 (265)	31.6 (24)	28.3 (13)		38.2 (394)	43.9 (65)	39 (55)		46.9 (323)	48.6 (87)	46 (137)	
Between €21-30	5.9 (66)	15.8 (12)	10.9 (5)		10.8 (111)	11.5 (17)	16.3 (23)		18 (124)	19.6 (35)	21.8 (65)	
Over €30	2.7 (30)	5.3 (4)	6.5 (3)		5 (52)	7.4 (11)	9.9 (14)		6.2 (43)	3.9 (7)	10.1 (30)	

Note. * *p*-values for Chi-square test.

girls in some cases registering even higher rates than boys (as is the case, for example, in high-risk alcohol use or in cyberbullying). In terms of age group, it seems that those adolescents using both tobacco and cannabis are the ones who are more likely to consume other types of substances, regardless of age group, as well as to engage in risky behavior on the Internet, although in the latter case it becomes especially visible after the age of 14.

The present work was a good opportunity to explore some of the variables that may explain the simultaneous use of cannabis and tobacco. This was of interest, given that most studies have tended to address the possible risk and protective factors associated either with each of the substances independently, or with tobacco and alcohol together, but not with cannabis and tobacco simultaneously (Álvarez et al., 2016). The results obtained reveal that the use of both substances can hardly be explained by "classical" personal variables such as self-esteem, assertiveness, impulsivity or social skills, and relate more to other variables linked to the role of parents, such as coming-home time or money available, a fact that the studies by Becoña et al. (2013), Llorens, Barrio, Sánchez, Suelves and the ESTUDES Working Group (2011) and Varela et al. (2013) had already warned of. As a consequence, from a preventive point of view the results obtained emphasize the importance of reinforcing family prevention in general and the role of parents in particular; as suggested in the work of Burkhart (2011), it is essential to train them in monitoring their children (knowing where they are and with whom), as well as in the setting of a series of rules and limits, taking into account the repercussion that this has not only on the use of psychoactive substances, but also on their socialization in general. Finally, from an institutional point of view, it would be advisable to continue strengthening tobacco and cannabis control policies, and also to support continuous monitoring of the problem and an environmental prevention model that takes into account not only the personal characteristics of the individual, but also their cultural, social, physical and economic context (Burkhart, 2011).

Regarding the possible limitations of this work, it is important, first of all, to highlight the sample used. Despite working with data from 4000 adolescents, there is no doubt that the choice of non-probabilistic sampling and selecting exclusively from the provinces of A Coruña and Pontevedra means that the results should be interpreted with some caution. Future research will make it possible to verify to

what extent the estimated prevalence data can be generalizable to the rest of the Galician community or even to the whole of Spain. Secondly, it is possible that this study underestimates the prevalence of cannabis users among adolescents aged 17 to 18 because the two years of Baccalaureate study at high school are not compulsory and, therefore, the sample does not include adolescents of these ages who have left school or continued their education elsewhere, for example on vocational training courses. Similarly, it is important to point out the transversal nature of the study, which makes it impossible to establish causal relationships between the variables in question. Moreover, it is worth noting the limited number of variables included in the study as possible variables associated with cannabis use, although this was not the main objective of the study. Finally, we should also mention the fact that all the variables have been self-reported, so it is impossible to know definitively to what extent adolescents may have underestimated or overestimated their levels of use. Nevertheless, as previously noted by different experts in the field of addictive behaviors, self-report measures have proven to be reliable and even better than other methods when assessing the levels of alcohol and other drug use (Babor, Kranzler & Lauerman, 1989; Winters, Stinchfield, Henly & Schwartz, 1990).

Future lines of research should consider the possibility of exploring and incorporating new variables and focus their efforts on elaborating parsimonious explanatory models capable of guiding prevention effectively. Similarly, it would be of great interest to set up longitudinal studies to clarify cause and effect relationships between the variables.

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Conflict of interests

The authors declare no conflict of interests

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Mortality rate in patients on methadone treatment and infected with the human immunodeficiency virus and/or the hepatitis C virus

Mortalidad entre los pacientes en tratamiento con metadona e infectados con el virus de la inmunodeficiencia humana y/o hepatitis C

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Dear Director,

Heroin addiction is a chronic, relapsing disease with serious consequences, particularly in terms of premature and high mortality (Hser, Hoffman, Grella & Anglin, 2001). Methadone maintenance treatment programs (MMT's) have shown to be effective in reducing illicit opioid use and the risk of infection with human immunodeficiency virus (HIV) and/or Hepatitis C virus (HCV), among other (Kleber, 2008; Pedrero-Pérez & MethaQoL, 2017).

Nevertheless, the approximately 1% annual mortality among MMT patients is more than 10 times that of the general population (Zanis &y Woody, 1998); and overdose, HIV infection (VIH), and other viruses transmitted by blood (e.g., HCV infection) constitute the most common causes of death (Roncero, Vega, Martinez-Raga & Torrens, 2017).

In fact, among HIV-infected patients, HIV–HCV co-infection is observed in 50–95% of cases (Muga, Roca, Egea, Tor, Sirera & Rey-Joly, 2000); this simultaneous HIV infection can cause an increased viral load of HCV and a more rapid evolution to liver cirrhosis and its complications (Santos & Sanz, 2004; Elizalde, Iñarrairaegui, Rodríguez & Zozaya, 2004).

Therefore, the objective of this paper was to analyze the influence of HIV and HCV infection on the survival of patients included in MMT`s programs.

For this, an observational retrospective study was conducted of mortality over a ten-year period (2005–2014) in a cohort of heroin-dependent patients included in the MMT program of a care unit specializing in the outpatient treatment of addiction and *substance abuse* disorders at the Hospital Real de Nuestra Señora de Gracia in Zaragoza, Spain.

The sample comprised 299 patients at baseline (2004) and 253 patients at the end of the study period (2014). Data concerning gender, age, body mass index, methadone dose, age of inclusion in the MMT, year of diagnosis of HIV and/or HCV infections, and mortality were obtained from electronic and manual clinical records.

The patients were divided into four groups based on the presence or absence of HIV and HCV infections (non-infected, group 1; VIH-infected, group 2; VIH and VHC co-infected, grupo 3; VHC-infected, group 4); then, overall mortality from all causes, as well as the crude mortality rate (CMR) were calculated, the later for each patient group and expressed as the number of deaths per 100 patient-years of follow-up.

Finally, the influence of HIV and/or HCV infections on overall mortality was assessed by comparing the CMR data from groups 2 to 4 (those infected with HIV and/or HCV) versus group 1 (non-infected patients).

By the end of the study period (10 years), there had been 46 deaths (15.4%) and a calculated CMR of 0.9%, 2.2%, 2.6%, and 1.7% corresponding to groups 1 to 4, respectively.

Regarding the influence of HIV or HCV infection, the greatest difference in CMR was between the co-infected group 3 and the control group 1 (0.9% *vs* .2.6%; p = .0113*). Comparisons among the rest of the groups were smaller and not statistically significant. However, when considering HIV patients in Groups 2 and 3 and HCV pa-

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Table 1. *Patient characteristics and results.*

Variable	Group 1 Non-infect.	Group 2 VIH-infect.	Group 3 VIH-VHC co-infect.	Group 4 VHC-infect.
Patient characteristics				
Age, years	47(7.7)	48 (7.5)	47 (8)	46 (6.6)
Female, No. (%)	26 (28)	20 (43)	16 (19)	22 (32)
BMI, kg/m^2	25.6 (3.4)	24 (4)	23 (4)	26 (6)
Years on TMM	15 (7.7)	16 (7.6)	15.3 (8)	13.8 (6.6)
MTD dose, mg	56(32)	61 (41)	65 (35)	55 (31)
Results				
Patients, No. (%)	92 (30.8)	54 (18.1)	85 (28.4)	68 (22.7)
Exitus, No. (%)	9 (9.8)	10 (18.5)	18 (21.2)	9 (13.2)
Patient-years	87	45	69	53
CMR, (%)	0.9	2.2	2.6	1.7
Fisher's test (*p*)	comparator	.0734	.0113*	.092

Note. All data are expressed as mean (± SD), unless otherwise indicated.
* $p \leq .05$; DS = standard deviation; BMI = body mass index; MTD = methadone, No. = number, CMR= crude mortality rate; MMT = methadone maintenance treatment.

tients in Groups 3 and 4, the differences in CMR were also more than double and statistically significant, when compared to the control group: 28 deaths (114 patient-years) vs 9 deaths (87 patient-years, p=.0104*) and 27 deaths (122 patient-years) vs 9 deaths (87 patient-years, p = .0271*) for HIV and HCV, respectively.

The obtained data seem to indicate that HIV and HCV infection, and especially co-infection, along with factors directly related to the treatment of co-morbidities, such as antiretrovirals, tuberculostatic drugs, and psychotropic drugs, which can often be hepatotoxic, play a key role in morbidity and mortality in this cohort of patients.

Therefore, the introduction of new antiretroviral and therapeutic regimens and pharmacotherapeutic follow-up of both adherence to treatment and its side effects for patients with *acquired immune deficiency syndrome;* as well as the adoption of new antivirals for the treatment of hepatitis C, would be key factors to increase survival in this type of patient.

Finally, it should be noted, as the most important limitations of this analysis of mortality, due to sample size and absence of data, that it could not assess the influence of other factors, such as gender, age, or concomitant treatments for infectious and psychiatric co-morbidities.

Conflict of interests

The authors declare no conflict of interest.

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Is this the end for Cronbach's alpha?

¿Es el final del alfa de Cronbach?

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In 1951, Lee Cronbach proposed the alpha coefficient (α) as an estimate of the proportion of variance of a measurement instrument caused by the common factor among items. The impact of his proposal has been such that a recent search in Google Scholar® confirms it has been cited 35,915 times. Tentative explanations for the ubiquity of α include the ease with which it can be calculated using popular statistical programs; the absence of postgraduate courses that delve into different ways of analyzing reliability (Aiken, West & Millsap, 2008) and that thesis supervisors or magazine editors are not yet familiar with other reliability estimates (Cho & Kim, 2015).

Adicciones recognizes the importance of incorporating sophisticated methodological advances in its studies, specifically with regard to three aspects: design, measurement of variables and data analysis (Fonseca, 2017). Following the incorporation of the omega coefficient (ω, Merino-Soto & Blas, 2017) and estimation of its confidence intervals (Ventura -León, 2017) in contributions to the journal, the present letter to the editor aims to provide a reflection on the use of the Cronbach's alpha coefficient.

A variety of reliability estimates are currently used in Classical Test Theory. These include ordinal alpha, Armor's theta, coefficient β, coefficient H and the GLB coefficient, and in Item Response Theory the test information function and standard error of measurement are used as reliability estimates (Muñiz, 2010). In this context, the question needs to be asked: Is this the end for Cronbach's alpha? Is this estimate finished? The debate has been taking place at an international level, and has generated detractors of Cronbach's alpha with expressions such as: "A fatally flawed estimate of [...] reliability" (Peters, 2014, p 56).

However, the problems attributed to α are not intrinsic to it, but are based on the misinterpretations and the indiscriminate use by some researchers who do not check the basic assumptions that must be fulfilled for the use of this coefficient such as: tau-equivalence, which requires items measuring the same trait to have the same or a similar degree of precision (Cho, 2016); non-correlation of errors, since it is assumed that they are completely independent of each other (Cortina, 1993); one-dimensionality, that is, that all the items measure a single latent trait and that continuous measurement is required (Elosua & Zumbo, 2008).

Thus, to overcome the violation of some of its assumptions, modifications to α have been developed such as: α for correlated errors (Raykov, 1998), ordinal α based on polychoric matrices (Elosua y Zumbo, 2008), methods to test for tau-equivalence (Zhang & Yuan, 2016) and confidence intervals with certain levels of significance.

The tau-equivalent measurement model is essential in this regard because if it is violated, other estimates based on structural equation models may represent a better choice (Cho & Kim, 2015), with the omega coefficient (ω) being one example. This line of argument has recently been corroborated by a data simulation which indicated that if tau-equivalence is assumed, α and ω converge (Trizano-Hermosilla & Alvarado, 2016).

What follows is a data simulation using program R, specifically with the *psych* library (Revelle, 2017). First, a

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tau-equivalent measurement model is set up using the following code:

```
library(psych)
set.seed(42)
tau <- sim.congeneric(loads=c(0.7,0.7,0.7,0.7),N=500,
categorical = TRUE, short = TRUE, low=-3, high=3)
```

Second, Cronbach's alpha and omega are calculated:

```
alpha(tau)
omega(tau)
```

This yields quite similar alpha and omega values (α = .75; ω = .76).

In a second step, a congeneric measurement model is generated with the following code:

```
library(psych)
set.seed(42)
cong <- sim.congeneric(c(0.9,0.8,0.7,0.5),N=500,
categorical = TRUE, short = TRUE, low=-3, high=3)
```

The alpha and omega coefficients are then calculated using the congeneric measurement model:

```
alpha(cong)
omega(cong)
```

This yields results with a clearer difference between alpha and omega coefficients (α = .77; ω = .80).

In sum, it must be said that it is not α *per se* that is reaching the end, but rather the practices associated with its indiscriminate use. It seems to be seen as the "reliability coefficient par excellence", even though tau-equivalence has not been established or it has not been considered whether the variables in question are continuous (Elosua & Zumbo, 2008). For this reason, it is important to emphasize that there is no single best reliability coefficient, but that it all depends on the characteristics of the data being analyzed. Recognition of this fact will ensure that data analysis provides methodologically sound results for researchers in future instrumental studies for *Adicciones*.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1. NOMBRE DEL MEDICAMENTO. Xeplion 25 mg suspensión inyectable de liberación prolongada. Xeplion 50 mg suspensión inyectable de liberación prolongada. Xeplion 75 mg suspensión inyectable de liberación prolongada. Xeplion 100 mg suspensión inyectable de liberación prolongada. Xeplion 150 mg suspensión inyectable de liberación prolongada. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** 25 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 39 mg de palmitato de paliperidona equivalentes a 25 mg de paliperidona. 50 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 78 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. 75 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 117 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. 100 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 156 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. 150 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 234 mg de palmitato de paliperidona equivalentes a 150 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). **4. DATOS CLÍNICOS. 4.1. Indicaciones terapéuticas.** Xeplion está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos estabilizados con paliperidona o risperidona. En determinados pacientes adultos con esquizofrenia y respuesta previa a paliperidona o risperidona oral, Xeplion puede ser utilizado sin necesidad de estabilización previa con tratamiento oral si los síntomas psicóticos son leves o moderados y es necesario un tratamiento con un inyectable de acción prolongada. **4.2. Posología y forma de administración.** Posología. Se recomienda iniciar Xeplion con una dosis de 150 mg en el día 1 de tratamiento y 100 mg una semana después (día 8), ambos administrados en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). La 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 de liberación prolongada o risperidona oral a Xeplion.* El tratamiento con Xeplion se debe iniciar según se describe al comienzo de esta sección 4.2 . Durante el tratamiento de mantenimiento mensual con Xeplion, los pacientes previamente estabilizados con diferentes dosis de paliperidona comprimidos de liberación prolongada, pueden alcanzar una exposición similar a paliperidona en estado estacionario por vía inyectable. La dosis de mantenimiento de Xeplion necesaria para alcanzar una exposición similar en el estado estacionario se muestra a continuación:

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

El tratamiento recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con Xeplion. Algunos pacientes se pueden beneficiar de una retirada gradual. Algunos pacientes que cambian de dosis orales más altas de paliperidona (p. ej., 9-12 mg diarios) a inyecciones en el glúteo con Xeplion pueden tener una exposición plasmática menor durante los primeros 6 meses después del cambio. Por lo tanto, alternativamente, se puede considerar administrar inyecciones en el deltoides durante los primeros 6 meses. *Cambio desde Risperidona inyectable de acción prolongada a Xeplion.* 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 los 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 (ver sección 5.2). *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. No se debe administrar por ninguna otra vía. Se debe inyectar lentamente, profundamente en el músculo deltoides o en el glúteo. Cada inyección debe ser administrada por un profesional sanitario. La administración debe realizarse en una sola inyección. La dosis no se debe administrar en inyecciones divididas. Las dosis de iniciación del día 1 y del día 8 se deben administrar ambas en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. Se debe cambiar del glúteo al deltoides (y viceversa) en caso de dolor en el lugar de inyección si no se tolera bien el malestar en el lugar de inyección (ver sección 4.8). También se recomienda alternar entre los lados izquierdo y derecho (ver más adelante). Para consultar las instrucciones de uso y manipulación de 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 determinada 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 paliperidona. Discinesia tardía/síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos <1x10⁹/l) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. 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 que incluye coma diabético y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con 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. Uso en pacientes con tumores dependientes de prolactina. Los estudios de cultivo de tejidos sugieren que la prolactina puede estimular el crecimiento de células en los tumores de mama humanos. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona se debe utilizar con precaución en pacientes con un tumor preexistente que pueda ser dependiente de prolactina. 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 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. Excipientes. Este medicamento contiene menos de 1 mmol (23 mg) de sodio por dosis; esto es, esencialmente "exento de sodio". **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 2.000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xeplion y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a Xeplion. Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vitro* ni *in vivo* de que esas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{max} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad del principio activo inalterado excretado en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP o en la biodisponibilidad de paliperidona. Con dosis más altas de carbamazepina, podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al inicio del tratamiento con carbamazepina, se debe reevaluar y aumentar la dosis de Xeplion, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xeplion, si es necesario. La administración concomitante de una sola dosis de un comprimido de paliperidona oral de liberación prolongada de 12 mg con comprimidos de divalproex sódico de liberación prolongada (dos comprimidos de 500 mg una vez al día) tuvo como resultado un aumento de aproximadamente el 50% en la C_{max} y el AUC de paliperidona, probablemente como resultado de un aumento de la absorción oral. Dado que no se observó ningún efecto sobre el aclaramiento sistémico, no se espera que se produzca una interacción clínicamente significativa entre los comprimidos de divalproex sódico de liberación prolongada y la inyección intramuscular de Xeplion. Esta interacción no se ha estudiado con Xeplion. Uso concomitante de Xeplion y risperidona 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 períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. Uso concomitante de Xeplion y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron 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 excreto 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 distonia. 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 palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *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); 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[a]
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonia, bronquitis, infección del tracto respiratorio, sinusitis, cistitis, infección de oídos, amigdalitis, onicomicosis, celulitis	infección de ojos, acarodermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, recuento de eosinófilos aumentado	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia[b]		secreción inapropiada de la hormona antidiurética, presencia de glucosa en orina	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, disminución de peso, apetito disminuido	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, aumento de los triglicéridos en sangre, aumento del colesterol en sangre	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio[a]	agitación, depresión, ansiedad	trastorno del sueño, manía, disminución de la libido, nerviosismo, pesadillas	catatonía, estado confusional, somnambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[a], acatisia[a], sedación/somnolencia, distonía[a], mareos, discinesia[a], temblor, cefalea	discinesia tardía, 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, convulsión[a], trastorno del equilibrio, coordinación anormal	coma diabético, temblor cefálico en reposo
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma, trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		

Trastornos cardiacos		taquicardia	bloqueo auriculoventricular, trastorno de conducción, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringeolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, disfagia, sequedad de boca, flatulencia	pancreatitis, hinchazón de la lengua, incontinencia fecal, fecaloma, queilitis	obstrucción del intestino, íleo
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas		ictericia
Trastornos de la piel y del tejido subcutáneo			urticaria, prurito, erupción cutánea, alopecia, eccema, sequedad de la piel, eritema, acné	erupción debida al medicamento, hiperqueratosis, caspa	angioedema, decoloración de la piel, dermatitis seborreica
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda, artralgia	aumento de la creatina fosfoquinasa en sangre, espasmos musculares, rigidez en las articulaciones, debilidad muscular, dolor de cuello	rabdomiólisis, inflamación de las articulaciones	anomalía postural
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria	retención urinaria	
Embarazo, puerperio y enfermedades perinatales					síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea, galactorrea	disfunción eréctil, trastorno de la eyaculación, trastornos menstruales[c], ginecomastia, disfunción sexual, dolor de mamas	malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción vaginal	priapismo
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[a], aumento de la temperatura corporal, alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, escalofríos, sed, síndrome de abstinencia a medicamentos, absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección, hematoma en el lugar de la inyección	disminución de la temperatura corporal, necrosis en el lugar de la inyección, úlcera en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

[a]La frecuencia de estas reacciones adversas se clasifica como "no conocidas" porque no fueron observadas en los ensayos clínicos con palmitato de paliperidona. Proceden de notificaciones espontáneas poscomercialización y la frecuencia no se puede determinar, o proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral y/o de informes poscomercialización. [b]Referido a "Hiperprolactinemia" a continuación. [c]Referido a "Síntomas extrapiramidales" a continuación. [d]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 0,65% en todos los pacientes tratados con palmitato de paliperidona. **Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** retraso en la menstruación, menstruación irregular, oligomenorrea.

Reacciones adversas notificadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de risperidona, por lo tanto, los perfiles de las reacciones adversas de estos compuestos (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica.* Durante la experiencia post-comercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de Xeplion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (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 con Xeplion. Las inyecciones en el músculo deltoides se perciben como un poco más dolorosas que las correspondientes inyecciones en el glúteo. Otras reacciones en el lugar de la inyección fueron en su mayoría de intensidad leve e incluyeron induración (frecuente), prurito (poco frecuente) y nódulos (raro). *Síntomas extrapiramidales (SEP).* SEP incluye un análisis agrupado de los siguientes términos: parkinsonismo (incluye hipersecreción salival, rigidez musculoesquelética, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tensión muscular, acinesia, rigidez de la nuca, rigidez muscular, modo de andar parkinsoniano, reflejo de la glabella anormal y temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreatetosis, atetosis y mioclonía), distonía (incluye distonía, hipertonía, tortícolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo orofaríngeo, pleurotótonos, espasmo lingual y trismo) y temblor. Hay que destacar que se incluye un espectro más amplio de síntomas que no tienen forzosamente su origen en el trastorno extrapiramidal. *Aumento de peso.* En el estudio de 13 semanas de duración que incluyó un régimen de dosificación inicial de 150 mg, la proporción de sujetos con un aumento anormal de peso ≥7% mostró una tendencia relacionada con la dosis, con una tasa de incidencia del 5% en el grupo placebo, en comparación con tasas del 6%, 8%, y 13% en los grupos tratados con 25 mg, 100 mg y 150 mg de Xeplion, respectivamente. Durante el periodo 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 ciega hasta el final del estudio); la media (DE) del cambio de peso desde el nivel basal del periodo abierto fue de +0,7 (4,79) kg. *Hiperprolactinemia.* En ensayos clínicos, se observaron medianas de aumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un aumento de los niveles de prolactina (p. ej., amenorrea, galactorrea, alteraciones de la menstruación, ginecomastia) se notificaron en <1% de los sujetos. Efectos de clase. Con antipsicóticos puede aparecer prolongación del QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicable, parada cardíaca y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, incluidos casos de embolismo pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** 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).

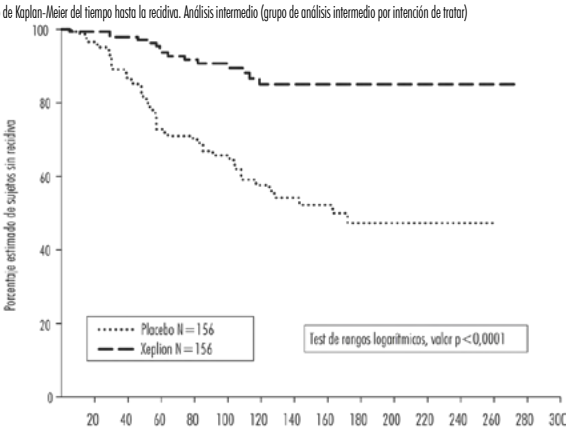
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración 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 los primeros 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 o una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radioactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y 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 (día 8 y día 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_{inf}) de 1,5; 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de los simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. El análisis de la farmacocinética poblacional demostró que no había evidencia de diferencias en la farmacocinética relacionada con la edad. Índice de masa corporal (IMC)/Peso corporal. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. 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. No se ha estudiado con Xeplion el efecto del consumo de tabaco en la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) 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 mayoritariamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30ºC. **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: 168,18 €; PVP: 214,09 €; PVP (IVA): 222,65 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 218,62 €; PVP: 269,53 €; PVP (IVA): 280,31 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 269,10 €; PVP: 320,01 €; PVP (IVA): 332,81 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 403,64 €; PVP: 454,55 €; PVP (IVA): 472,73 €. **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.** 25 mg: EU/1/11/672/001. 50 mg: EU/1/11/672/002. 75 mg: EU/1/11/672/003. 100 mg: EU/1/11/672/004. 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

1. NOMBRE DEL MEDICAMENTO. TREVICTA 175 mg suspensión inyectable de liberación prolongada. TREVICTA 263 mg suspensión inyectable de liberación prolongada. TREVICTA 350 mg suspensión inyectable de liberación prolongada. TREVICTA 525 mg suspensión inyectable de liberación prolongada. **2. COMPOSICION CUALITATIVA Y CUANTITATIVA.** 175 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 273 mg de palmitato de paliperidona equivalentes a 175 mg de paliperidona. 263 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 410 mg de palmitato de paliperidona equivalentes a 263 mg de paliperidona. 350 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 546 mg de palmitato de paliperidona equivalentes a 350 mg de paliperidona. 525 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 819 mg de palmitato de paliperidona equivalentes a 525 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). 4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a TREVICTA. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de paliperidona inyectable mensual (±7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de paliperidona inyectable mensual, utilizando una dosis 3,5 veces más alta como se indica en la tabla siguiente:

Dosis de TREVICTA en pacientes tratados adecuadamente con palmitato de paliperidona inyectable mensual

Si la última dosis de palmitato de paliperidona inyectable mensual es de	TREVICTA se iniciará en la dosis siguiente
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

No se ha estudiado la dosis de TREVICTA equivalente a la dosis de 25 mg de palmitato de paliperidona inyectable mensual. Después de la dosis inicial de TREVICTA, este medicamento se administrará mediante inyección intramuscular una vez cada 3 meses (± 2 semanas, ver también la sección Dosis omitidas). Si es necesario, se puede ajustar la dosis de TREVICTA cada 3 meses en incrementos dentro del intervalo de 175 a 525 mg en función de la tolerabilidad del paciente y/o de la eficacia. Debido a la acción prolongada de TREVICTA, la respuesta del paciente al ajuste de la dosis puede no ser evidente hasta que han transcurrido varios meses (ver sección 5.2). Si el paciente sigue presentando síntomas, se le tratará conforme a la práctica clínica. *Cambio desde otros medicamentos antipsicóticos.* TREVICTA se debe usar solo después de que el paciente haya sido tratado adecuadamente con la formulación inyectable mensual de palmitato de paliperidona preferiblemente durante cuatro meses o más. *Cambio desde TREVICTA a otros medicamentos antipsicóticos.* Si se suspende la administración de TREVICTA, se deben tener en cuenta sus características de liberación prolongada. *Cambio desde TREVICTA a palmitato de paliperidona inyectable mensual.* Para cambiar desde TREVICTA a palmitato de paliperidona inyectable mensual, este se administrará en el momento en que se debe administrar la dosis siguiente de TREVICTA, dividiendo la dosis por 3,5 según se indica en la tabla siguiente. No es necesaria la dosis de inicio según se describe en la ficha técnica de palmitato de paliperidona inyectable mensual. El palmitato de paliperidona inyectable mensual se seguirá administrando una vez al mes tal como se describe en su ficha técnica.

Dosis de palmitato de paliperidona inyectable mensual en los pacientes que cambian desde TREVICTA

Si la última dosis de TREVICTA es de	Iniciar palmitato de paliperidona inyectable mensual 3 meses después en la dosis siguiente
175 mg	50 mg
263 mg	75 mg
350 mg	100 mg
525 mg	150 mg

Cambio desde TREVICTA a los comprimidos diarios de liberación prolongada de paliperidona oral. Para cambiar desde TREVICTA a los comprimidos de palmitato de paliperidona de liberación prolongada, se debe iniciar la administración diaria de los comprimidos 3 meses después de la última dosis de TREVICTA y continuar el tratamiento con los comprimidos de paliperidona de liberación prolongada según se describe en la tabla siguiente. La tabla siguiente indica las pautas recomendadas de conversión de las dosis para que los pacientes previamente estabilizadas con diferentes dosis de TREVICTA obtengan una exposición a paliperidona similar con los comprimidos de paliperidona de liberación prolongada.

Dosis de los comprimidos de paliperidona de liberación prolongada para los pacientes que cambian desde TREVICTA*

	Tiempo transcurrido desde la última dosis de TREVICTA		
	de la semana 12 a 18, incluida	de la semana 19 a la 24, incluida	desde la semana 25 y en adelante
Última dosis de TREVICTA (semana 0)	Dosis diaria de los comprimidos de paliperidona de liberación prolongada		
175 mg	3 mg	3 mg	3 mg
263 mg	3 mg	3 mg	6 mg
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

*Todas las dosis de los comprimidos de paliperidona de liberación prolongada diarios se debe adaptar siempre al paciente individual, teniendo en cuenta variables como los motivos del cambio, la respuesta al tratamiento previo con paliperidona, la gravedad de los síntomas psicóticos y/o la tendencia a presentar efectos adversos.

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

Dosis omitidas

Si se ha omitido la dosis programada y el tiempo transcurrido desde la última inyección es de	Medida
> 3 meses y medio a 4 meses	Se administrará la inyección lo antes posible y a continuación se reanudará el calendario de inyecciones trimestrales.
de 4 meses a 9 meses	Se seguirá la pauta de reanudación recomendada que se indica en la tabla siguiente.
> 9 meses	Se reanudará el tratamiento con palmitato de paliperidona inyectable mensual según se describe en la ficha técnica del producto. Se podrá reanudar la administración de TREVICTA después de que el paciente haya sido tratado adecuadamente con la formulación inyectable mensual de palmitato de paliperidona preferiblemente durante cuatro meses o más.

Pauta recomendada de reanudación del tratamiento después de 4 a 9 meses de interrupción de TREVICTA

Si la última dosis de TREVICTA fue de	Se administrarán dos dosis de palmitato de paliperidona inyectable mensual con un intervalo de una semana (en el deltoides)		A continuación se administrará TREVICTA (en el deltoides[a] o el glúteo)
	Día 1	Día 8	1 mes después del día 8
175 mg	50 mg	50 mg	175 mg
263 mg	75 mg	75 mg	263 mg
350 mg	100 mg	100 mg	350 mg
525 mg	100 mg	100 mg	525 mg

[a] Ver también la *Información reservada para médicos y profesionales sanitarios* donde se describe la selección de la aguja para inyección en el deltoides en función del peso corporal.

Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia ni la seguridad en la población mayor de 65 años. En general, la dosis de TREVICTA recomendada en pacientes de edad avanzada con función renal normal es la misma que para los adultos más jóvenes con función renal normal. Dado que los pacientes de edad avanzada pueden presentar una reducción de la función renal, ver debajo en Insuficiencia renal las recomendaciones de dosificación para pacientes con insuficiencia renal. *Insuficiencia renal.* TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal (ver sección 5.2). En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se debe ajustar la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min). *Insuficiencia hepática.* No se ha estudiado el uso de TREVICTA en pacientes con insuficiencia hepática. Según la experiencia con paliperidona oral no es necesario ajustar la dosis en pacientes con insuficiencia hepática leve o moderada. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, por lo que se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y eficacia de TREVICTA en niños y adolescentes menores de 18 años. No se dispone de datos. Forma de administración. TREVICTA está indicado para administración intramuscular únicamente. No se debe administrar por ninguna otra vía. Cada inyección se administrará solo por un profesional sanitario, que administrará la dosis completa en una sola inyección. Se debe inyectar lenta y profundamente en el músculo deltoides o en el glúteo. Si aparecen molestias en el lugar de inyección, se considerará el cambio del glúteo al deltoides (y viceversa) en sucesivas inyecciones (ver sección 4.8). TREVICTA se debe administrar usando únicamente las agujas de pared fina que se faciliten en el envase de TREVICTA. Para la administración de TREVICTA no se utilizarán las agujas que se faciliten en el envase de la inyección mensual de palmitato de paliperidona ni otras agujas comercialmente disponibles (ver *Información reservada para médicos o profesionales sanitarios*). Se inspeccionará visualmente el contenido de la jeringa precargada para descartar la presencia de cuerpos extraños o decoloración antes de la administración. Es importante agitar enérgicamente la jeringa con la punta hacia arriba y la muñeca relajada durante al menos 15 segundos para garantizar una suspensión homogénea. TREVICTA debe ser administrado dentro de los 5 minutos siguientes a la agitación. Si transcurren más de 5 minutos antes de la inyección, agitar otra vez enérgicamente durante al menos 15 segundos para resuspender el medicamento (ver *Información reservada para médicos o profesionales*). *Administración en el deltoides.* El tamaño especificado de la aguja para administración de TREVICTA en el músculo deltoides está determinado por el peso del paciente. • En pacientes de peso ≥90 kg, se debe utilizar la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm). • En pacientes de peso <90 kg, se debe utilizar la aguja de pared fina de 22 G 1 (0,72 mm x 25,4 mm). Se debe administrar en el centro del músculo deltoides. Las inyecciones deltoideas se deben alternar entre los dos músculos deltoides. *Administración en el glúteo.* Para la administración de TREVICTA en el músculo glúteo, se utilizará la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm), sin tener en cuenta el peso corporal. La administración se debe hacer en el cuadrante superior externo del músculo glúteo. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. *Administración incompleta.* Para evitar la administración incompleta de TREVICTA, se debe agitar enérgicamente la jeringa precargada durante al menos 15 segundos en los 5 minutos que preceden a la administración para asegurar una suspensión homogénea (ver *Información reservada para médicos o profesionales sanitarios*). Sin embargo, si la dosis inyectada ha sido incompleta, la dosis restante de la jeringa no se debe reinyectar y no se debe administrar otra dosis dado la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará clínicamente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. **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 estados psicóticos graves o de agitación aguda. No se debe utilizar TREVICTA para controlar estados psicóticos graves o de agitación aguda en los que es necesario un control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se usa a la vez que otros medicamentos que se espera que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autónoma, alteración de la consciencia y elevación de la creatinfosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SMN, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía/Síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, que se caracteriza por movimientos rítmicos involuntarios, predominantemente de la lengua y/o de la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la posibilidad de suspender la administración de todos los antipsicóticos, incluido la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar una o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y agranulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo clínicamente relevante o de leucopenia/neutropenia inducida por medicamentos se deben someter a vigilancia estrecha durante los primeros meses de tratamiento y se considerará la suspensión de TREVICTA ante el primer signo de leucopenia clínicamente relevante sin que intervengan otros factores causantes. A los pacientes con neutropenia clínicamente relevante se les monitorizará estrechamente a fin de detectar la aparición de fiebre u otros síntomas o signos de infección y, si se presentan estos síntomas, se administrará un tratamiento rápido. A los pacientes con neutropenia grave (recuento total de neutrófilos <1 x 10^9/l) se les retirará la administración de TREVICTA y se les hará un seguimiento de los niveles de glóbulos blancos hasta su recuperación. Se tendrá en cuenta la acción prolongada de TREVICTA. Reacciones de hipersensibilidad. Se pueden producir reacciones de hipersensibilidad incluso en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.8). Hiperglucemia y diabetes mellitus. Se han notificado hiperglucemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso coma diabético y cetoacidosis con el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica antipsicótica habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polidipsia, poliuria, polifagia y astenia) y los pacientes con diabetes mellitus deben ser monitorizados regularmente de un empeoramiento del control de la glucosa. Aumento de peso. Se han notificado casos de aumento significativos de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipotensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o isquemia de miocardio, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipotensión (p. ej., deshidratación e hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se ajustará la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos de pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en estos pacientes. Pacientes de edad avanzada con demencia. TREVICTA no se ha estudiado en pacientes de edad avanzada con demencia. No se recomienda la administración de TREVICTA a pacientes de edad avanzada con demencia, debido al riesgo aumentado de mortalidad global y de reacciones adversas cerebrovasculares. La experiencia obtenida con risperidona que se describe a continuación se considera aplicable también a paliperidona. *Mortalidad global.* En un metaanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como risperidona, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con risperidona, la mortalidad fue del 4% en comparación con el 3,1% de los pacientes que recibieron placebo. *Reacciones adversas cerebrovasculares.* En ensayos clínicos aleatorizados y controlados con placebo en los que pacientes con demencia recibieron tratamiento con algunos antipsicóticos atípicos como risperidona, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplica por 3 aproximadamente. 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 beneficios de prescribir TREVICTA a pacientes con enfermedad de Parkinson o con demencia con cuerpos de Lewy (DCL), porque ambos grupos tienen un mayor riesgo de Síndrome Neuroléptico Maligno y una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, embotamiento, inestabilidad postural y caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Se indicará al paciente que solicite asistencia médica urgente si el priapismo no se ha resuelto en el trascurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de reducir la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescriba TREVICTA a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej., ejercicio intenso, exposición a calor extremo, tratamiento concomitante con medicamentos de actividad anticolinérgica o deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con el uso de antipsicóticos. Dado que los pacientes tratados con antipsicóticos presentan a menudo factores de riesgo añadido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transcurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto antiemético. En los estudios preclínicos con paliperidona se observó un efecto antiemético. Si se produce este efecto en los seres humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA 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 TREVICTA (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. Excipientes. Este medicamento contiene menos de 1 mmol de sodio (23 mg) por dosis; esto es, esencialmente "exento de sodio". **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir TREVICTA con medicamentos que prolongan el intervalo QT, como antiarrítmicos de la clase IA (por ejemplo, quinidina o disopiramida) y antiarrítmicos de la clase III (por ejemplo, amiodarona o sotalol), algunos antihistamínicos, antibióticos (por ejemplo, fluoroquinolonas), algunos antipsicóticos y algunos antipalúdicos (por ejemplo, mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que TREVICTA afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos metabolizados por las isoenzimas del citocromo P-450. Dado que paliperidona actúa principalmente sobre el sistema nervioso central (SNC) (ver sección 4.8), se debe usar con precaución la combinación de TREVICTA con otros medicamentos que actúan sobre el sistema nervioso central, como los ansiolíticos, la mayoría de los antipsicóticos, los hipnóticos, los opiáceos etc. o el alcohol. La paliperidona puede antagonizar el efecto de la levodopa y de otros agonistas de la dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se prescribirá la dosis mínima eficaz de cada tratamiento. Debido a su capacidad de inducir hipotensión ortostática (ver sección 4.4), es posible observar un efecto aditivo cuando se administra TREVICTA con otros medicamentos que tienen esta capacidad, como otros antipsicóticos o los antidepresivos tricíclicos. Se recomienda precaución al combinar la paliperidona con otros medicamentos que disminuyen el umbral convulsivo (por ejemplo, fenotiacinas o butirofenonas, antidepresivos tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de los comprimidos de liberación prolongada de paliperidona en el estado estacionario (12 mg una vez al día) con comprimidos de liberación prolongada de valproato sódico (de 500 mg a 2.000 mg una vez al día) no afectó a la farmacocinética en el estado estacionario del valproato. No se han llevado a cabo estudios de interacción entre TREVICTA y el litio, sin embargo, no es probable que se produzcan una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a TREVICTA. Los estudios in vitro indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios in vitro ni in vivo de que esas isoenzimas desempeñen un papel importante 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 conjunta de paliperidona oral de liberación prolongada una vez al día con carbamazepina 200 mg dos veces al día produjo una reducción de aproximadamente un 37% de los valores medios de C_{max} y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el adaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA 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 TREVICTA con otros antipsicóticos son limitados. Uso concomitante de TREVICTA y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellos síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición materna a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo incluso si la administración de TREVICTA es muy anterior a la lactancia. TREVICTA no se debe utilizar durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios 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 visión, como sedación, somnolencia, síncope o visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a TREVICTA. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas al medicamento observadas con mayor frecuencia notificadas en ≥5% de los pacientes en dos ensayos clínicos controlados a doble ciego de TREVICTA, fueron aumento de peso, infección de las vías respiratorias altas, ansiedad, cefalea, insomnio y reacción en el lugar de inyección. Tabla de reacciones adversas. A continuación se recogen todas las RAM notificadas con paliperidona en función de la frecuencia estimada en los ensayos clínicos realizados con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *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) y *frecuencia no conocida* (no se puede estimar a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	Frecuencia no conocida[a]
Infecciones e infestaciones		infección de vías respiratorias altas, infección urinaria, gripe	neumonía, bronquitis, infección de vías respiratorias, sinusitis, cistitis, otitis, amigdalitis, onicomicosis, celulitis	infección oftálmica, acaradermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, aumento del recuento de eosinófilos	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia[b]		secreción inadecuada de hormona antidiurética, glucosuria	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, pérdida de peso, apetito disminuido	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, triglicéridos en sangre elevados, colesterol en sangre elevado	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio[a]	agitación, depresión, ansiedad	trastornos del sueño, manía, disminución de la libido, nerviosismo, pesadillas	catatonía, estado de confusión, sonambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[a], acatisia[a], sedación[a], somnolencia, distonía[a], mareo, discinesias[a], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotriz, mareo postural, trastornos de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, falta de respuesta a los estímulos, pérdida del conocimiento, reducción del nivel de conciencia, convulsiones[a], trastornos del equilibrio, coordinación anormal	coma diabético, temblor de cabeza
Trastornos oculares			visión borrosa, conjuntivitis, ojo seco	glaucoma, trastornos de los movimientos oculares, rotación anormal de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oídos		
Trastornos cardíacos		taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolia pulmonar, isquemia

Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión respiratoria, sibilancias, dolor faringolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores		hiperventilación, neumonía por aspiración, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, odontalgia	molestias abdominales, gastroenteritis, distagia, sequedad de boca, flatulencia		pancreatitis, edema lingual, incontinencia fecal, fecaloma, queilitis	obstrucción intestinal, íleo
Trastornos hepatobiliares		niveles elevados de transaminasas	niveles elevados de gamma-glutamiltransferasa y de enzimas hepáticas			ictericia
Trastornos de la piel y del tejido subcutáneo			urticaria, prurito, erupción cutánea, alopecia, eccema, sequedad de la piel, eritema, acné	erupción farmacológica, hiperqueratosis, caspa		angioedema, trastornos de la pigmentación, dermatitis seborreica
Trastornos osteomusculares y del tejido conjuntivo		dolor osteomuscular, dolor lumbodorsal, artralgia	valores elevados de creatinfosfoquinasa en sangre, espasmos musculares, rigidez articular, debilidad muscular, dolor cervical		rabdomiólisis, hinchazón de las articulaciones	alteraciones posturales
Trastornos renales y urinarios			incontinencia urinaria, polaquiuria, disuria		retención urinaria	
Embarazo, puerperio y enfermedades perinatales						síndrome de abstinencia neonatal (ver sección 4.6)
Trastornos del aparato reproductor y de la mama		amenorrea, galactorrea	disfunción eréctil, trastornos de la eyaculación, trastornos menstruales[2], ginecomastia, disfunción sexual, dolor mamario	hinchazón o malestar mamario, aumento del tamaño de las mamas, flujo vaginal		priapismo
Trastornos generales y alteraciones en el lugar de administración		fiebre, astenia, fatiga, reacciones en el lugar de inyección	edema facial, edema[4], aumento de la temperatura corporal, alteraciones de la marcha, dolor torácico, molestias en el pecho, malestar general, induración	hipotermia, escalofríos, palidipsia, síndrome de abstinencia de fármacos/drogas, abscesos en el lugar de inyección, celulitis en el lugar de inyección, quistes en el lugar de inyección, hematomas en el lugar de inyección		descenso de la temperatura corporal, necrosis en el lugar de inyección, úlceras en el lugar de inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas			

[a] La frecuencia de estas reacciones adversas se clasifica como "no conocida" porque no se observaron en los ensayos clínicos con palmitato de paliperidona. Proceden de notificaciones espontáneas poscomercialización y la frecuencia no se puede determinar, o proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral y/o de informes poscomercialización. [2] Ver el apartado "Hiperprolactinemia" a continuación. [3] Ver el apartado "Síntomas extrapiramidales" a continuación. [4] En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con palmitato de paliperidona inyectable mensual comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,65% en todos los pacientes tratados con palmitato de paliperidona inyectable mensual. [a]

Insomnio incluye: Insomnio inicial e insomnio medio; **Convulsiones incluye:** convulsiones del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea; **Trastornos menstruales incluye:** retrasos de la menstruación, menstruación irregular, oligomenorrea.

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica*. Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección*. En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la clasificación realizada por los investigadores, síntomas como induración, rubefacción e hinchazón no se presentaron o fueron leves en ≥95% de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP)*. En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y mioclonía), distonía (incluye distonía, espasmo cervical, empujotónos, crisis oculógiras, distonía bucomandibular, risa sardónica, tetania, hipertonía, torticolis, contracciones musculares involuntarias, contractura muscular, blefaroespasmo, oculogiración, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurotótonos, espasmo lingual y trismus) y temblor. *Aumento de peso*. En el estudio a largo plazo de retirada aleatorizada, se notificaron aumentos anormales de ≥7% de peso corporal desde el momento inicial hasta el momento final del estudio, analizados a doble ciego, en el 10% de los pacientes del grupo de TREVICTA y el 1% de los pacientes del grupo de placebo. A la inversa, se notificaron reducciones anormales del peso corporal (≥7%) desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, en el 1% de los pacientes del grupo de TREVICTA y el 8% de los pacientes del grupo de placebo. Las variaciones medias del peso corporal desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, fueron de +0,94 kg y -1,28 kg en los grupos de TREVICTA y placebo, respectivamente. *Hiperprolactinemia*. Durante la fase de doble ciego del estudio a largo plazo de retirada aleatorizada, se observaron niveles de prolactina por encima del intervalo de referencia (>13,13 ng/ml en los varones y >26,72 ng/ml en las mujeres) en un porcentaje más elevado de varones y mujeres del grupo de TREVICTA que del grupo placebo (9% frente a 3% y 5% frente a 1%, respectivamente). En el grupo de TREVICTA, la variación media entre el momento inicial y el final en un estudio doble ciego controlado con placebo fue de +2,90 ng/ml para los varones (frente a -10,26 ng/ml en el grupo placebo) y de +7,48 ng/ml para las mujeres (frente a -32,93 ng/ml en el grupo placebo). Una mujer (2,4%) del grupo de TREVICTA tuvo una reacción adversa de amenorrea, mientras que no se observaron reacciones adversas potencialmente relacionadas con la prolactina en ninguna mujer del grupo placebo. No hubo reacciones adversas potencialmente relacionadas con la prolactina en ninguno de los grupos de varones. Efecto de clase. Con el uso de antipsicóticos pueden aparecer prolongación del intervalo QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicada, paro cardíaco y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, entre ellos de embolia pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de 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 QT y síntomas extrapiramidales. Se han descrito Torsades de pointes y fibrilación ventricular en un paciente expuesto a sobredosis de paliperidona oral. En caso de sobredosis aguda se debe tener en cuenta la posibilidad de que estén implicados varios fármacos. Tratamiento. Al evaluar las medidas terapéuticas y de recuperación, se tendrán en cuenta la naturaleza de liberación prolongada del medicamento, así como la prolongada vida media de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio se deben tratar con las medidas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales graves, se debe administrar medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos y continuos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros fármacos antipsicóticos, código ATC: N05AX13. TREVICTA contiene una mezcla racémica de paliperidona (+) y (–). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de los monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une estrechamente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D-2. Asimismo, paliperidona bloquea los receptores alfa 1adrenérgicos y, en menor medida, los receptores histaminérgicos H-1 y los receptores alfa 2 adrenérgicos. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque se trata de un potente antagonista de D2, motivo por el que se cree que alivia los síntomas de la esquizofrenia, produce menos catalepsia y menos reducción de las funciones motoras que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. La eficacia de TREVICTA para el tratamiento de mantenimiento de la esquizofrenia en pacientes que han sido tratados adecuadamente durante al menos 4 meses con la formulación inyectable mensual de palmitato de paliperidona y las últimas dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retirada aleatorizado, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizada, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual administradas en el músculo deltoides o glúteo (50-150 mg) durante 17 semanas (los ajustes de dosis fueron en las semanas 5 y 9). Un total de 379 pacientes recibieron una dosis única de TREVICTA en el músculo deltoides o glúteo durante la fase de estabilización abierta (la dosis era 3,5 veces la última dosis de palmitato de paliperidona mensual). Los pacientes que se consideraban clínicamente estabilizados al final de la fase de estabilización de 12 semanas se aleatorizaron en proporción 1:1 para recibir TREVICTA o un placebo en una fase doble ciego de duración variable (la dosis de TREVICTA fue la misma que la última dosis recibida durante la fase de estabilización; esta dosis se mantuvo fija durante toda la fase de doble ciego). En este periodo, 305 pacientes sintomáticamente estables fueron aleatorizados para continuar el tratamiento con TREVICTA (n=160) o placebo (n=145) hasta que se produjese la recaída, la retirada prematura o el final del estudio. La variable principal de eficacia fue el tiempo hasta la primera recaída. Se puso fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 283 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICTA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,81 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICTA en comparación con placebo. En la figura 1 se representa la gráfica de Kaplan Meier del tiempo hasta la recaída para cada grupo de tratamiento. Se observó una diferencia significativa (p<0,0001) entre los dos grupos de tratamiento en el tiempo hasta la recaída a favor de TREVICTA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICTA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

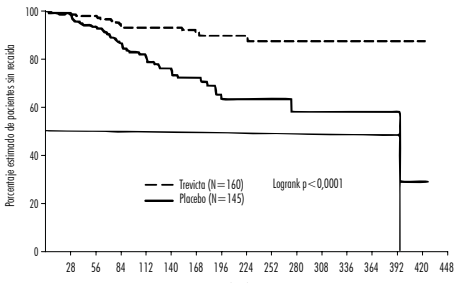


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída – Análisis final

En el estudio de no inferioridad, 1.429 pacientes con enfermedad aguda (puntuación PANSS total media en el momento inicial: 85,7) que cumplían los criterios DSM-IV de esquizofrenia se incorporaron a la fase abierta y recibieron tratamiento con palmitato de paliperidona inyectable mensual durante 17 semanas. Se permitía ajustar la dosis (esto es, 50 mg, 75 mg, 100 mg o 150 mg) después de 5 semanas y 9 inyecciones y el lugar de inyección podía ser el deltoides o el glúteo. De los pacientes que cumplían los criterios de aleatorización en las semanas 14 y 17, 1.016 fueron aleatorizados en proporción 1:1 para seguir recibiendo una vez al mes la inyección de palmitato de paliperidona mensual o bien cambiar a TREVICTA, multiplicando por 3,5 la dosis de las semanas 9 y 13 de palmitato de paliperidona inyectable mensual, durante un periodo de 48 semanas. Los pacientes recibieron TREVICTA una vez cada 3 meses y una medicación inyectable placebo durante los meses restantes para mantener el ciego. En este estudio, el criterio de valoración de la eficacia principal era el porcentaje de pacientes sin recaída al final de la fase doble ciego de 48 semanas, basado en la estimación de Kaplan-Meier de las 48 semanas (TREVICTA: 91,2%, palmitato de paliperidona inyectable mensual: 90,0%). No fue posible calcular la mediana de tiempo hasta la recaída en ninguno de los grupos, dado el escaso porcentaje de pacientes con recaídas. La diferencia (IC 95%) entre los grupos de tratamiento fue del 1,2% (-2,7%, 5,1%), lo que satisface el criterio de no inferioridad basado en un margen de -10%. Por tanto, el grupo de tratamiento con TREVICTA fue no inferior al grupo tratado con palmitato de paliperidona inyectable mensual. Las mejorías funcionales, determinadas según la Escala de Funcionamiento Personal y Social (PSP), que se observaron durante la fase de estabilización abierta se mantuvieron durante la fase de doble ciego en ambos de tratamiento.

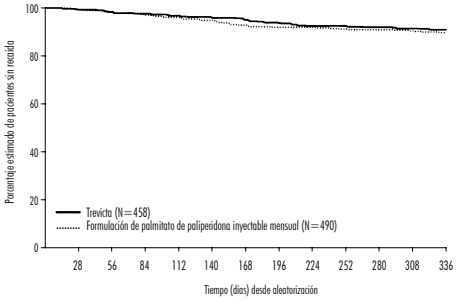


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{ss}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en 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 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios in vitro se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del 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. Estudios in vitro han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos in vivo y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona. TREVICTA está diseñado para liberar paliperidona durante un periodo de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{inf}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con personas sanas. Población de edad avanzada. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con la edad. Índice de masa corporal (IMC)/peso corporal. En los pacientes obesos y con sobrepeso se observaron valores de C_{max} más bajos. En el estado estacionario aparente de TREVICTA, las concentraciones valle eran similares en los pacientes normales, con sobrepeso y obesos. Raza. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el origen racial. Sexo. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el sexo. Tabaquismo. Según estudios in vitro realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no tiene un efecto en la farmacocinética de paliperidona. El efecto del consumo de tabaco sobre la farmacocinética de paliperidona no se ha estudiado en el caso de TREVICTA. Un análisis de farmacocinética poblacional basado en los datos obtenidos con comprimidos de liberación prolongada de paliperidona demostró una exposición a paliperidona ligeramente más baja en los fumadores que en los no fumadores. No es probable que esta diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) en inyección intramuscular y de paliperidona en administración oral a ratas y perros mostraron efectos fundamentalmente farmacológicos, como sedación y efectos mediados por la prolactina en glándulas mamarias y genitales. En animales tratados con palmitato de paliperidona se observó una reacción inflamatoria en el lugar de inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas con risperidona oral, que se convierte en gran medida en paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y en la supervivencia de las crías. No se han observado embriotoxicidad ni malformaciones después de la administración intramuscular de palmitato de paliperidona a ratas gestantes a dosis máximas (160 mg/kg/día), equivalentes a 2,2 veces el nivel de exposición de los humanos a la dosis máxima recomendada de 525 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la motricidad y del aprendizaje en las crías cuando se administraron a animales gestantes. Ni el palmitato de paliperidona ni la paliperidona han demostrado ser genotóxicos. En estudios sobre el potencial carcinogénico de la risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y de los adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico del palmitato de paliperidona administrado en inyección intramuscular a ratas. Se observó un incremento estadísticamente significativo de adenocarcinomas de las glándulas mamarias en ratas hembra a las que se administraron dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho experimentaron un incremento estadísticamente significativo de adenomas y carcinomas de las glándulas mamarias cuando se expusieron a dosis de 30 y 60 mg/kg/mes, que representan 0,6 y 1,2 veces el nivel de exposición humana a la dosis máxima recomendada de 525 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la relevancia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina cíclica) con émbolo, tope trasero y capuchón protector (goma bromobutílica), equipada con una aguja de seguridad de pared fina de 22 G 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 pulgadas (0,72 mm x 25,4 mm). Tamaño del envase: Envases con 1 jeringa precargada y 2 agujas. Presentaciones y precios. Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 489,25 €; PVP: 540,16 €; PVP (IVA): 561,77 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 636,50 €; PVP: 692,41 €; PVP (IVA): 720,11 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 782,80 €; PVP: 838,71 €; PVP (IVA): 872,26 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.174,20 €; PVP: 1.230,11 €; PVP (IVA): 1.279,31 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver Información reservada para médicos o profesionales sanitarios). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007. EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 5 de diciembre de 2014. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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