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Chronic Hepatitis C and people with a history of injecting drugs in Spain: population assessment, challenges for effective treatment

Hepatitis C Crónica y usuarios con un historial de inyección de drogas en España: evaluación de la población, retos para un tratamiento efectivo

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Chronic hepatitis C (CHC) is a discriminatory disease that disproportionately affects people neglected by public health services. People with a history of opioid use or parenteral drug use (PDU) face inequality and stigma. A history of drug injecting is a behavior which increases the risk of contracting the hepatitis C virus (HCV). There is a high incidence of HCV among people injecting drugs. There are over 300,000 people in Spain with a current or former history of injecting drug use (Ministry of Health, Social Services and Equality, 2014). There are approximately 100,000 people in Spain with a history of opioid use disorder and the majority are PDU or ex-PDU (EMCDDA, 2016). Approximately 80,000 people make use of the services available to treat opioid use disorder each year (Torrens, Fonseca, Castillo, & Domingo-Salvany, 2013).

HCV affects 50-80% of this population (Muga et al., 2015), while 32% continue injecting drugs during their treatment in Spain (Roncero et al., 2011). However, substance users undergoing treatment have a lower risk of HCV infection because they are less likely to share needles than those not receiving treatment (Donmall, Jones, Davies, & Barnard, 2009).

Only a very limited number of PDUs with HCV have been treated in Spain (Muga et al., 2015). The tolerability and effectiveness of HCV treatment in the past has restricted successful interventions. However, there are currently new, efficient and accessible treatments (Grebely et al., 2015). In general, PDU are less likely to receive hepatitis C treatment than other patients (Mravčík et al., 2013). Many PDUs assume that they cannot access hepatitis C treatment because of their health problems and inequalities in the system; requesting screening and undergoing treatment is probably perceived as futile. In addition, the absence of new treatments and the fear of the side effects of the old medications used for the treatment of HCV, such as interferon, has limited access in the past (McGowan & Fried, 2012). Moreover, inadequate knowledge regarding HCV infection and its implications are limitations that must be taken into account. These problems must be solved with new and different forms of health education. For example, the use of peer support groups is likely to be of major importance. Facilitating peer- or self-diagnosis in certain contexts, including informal and non-clinical locations such as pharmacies, syringe exchange programs, and social service centers may also be a potential solution (Rose, Lutnick, & Kral, 2014).

The most important barrier to accessing HCV treatment for this population is the link between drug treatment centers and centers dealing with HCV (infectious disease and/or hepatology units or services). The separation of these services under the organization and infrastructure of the

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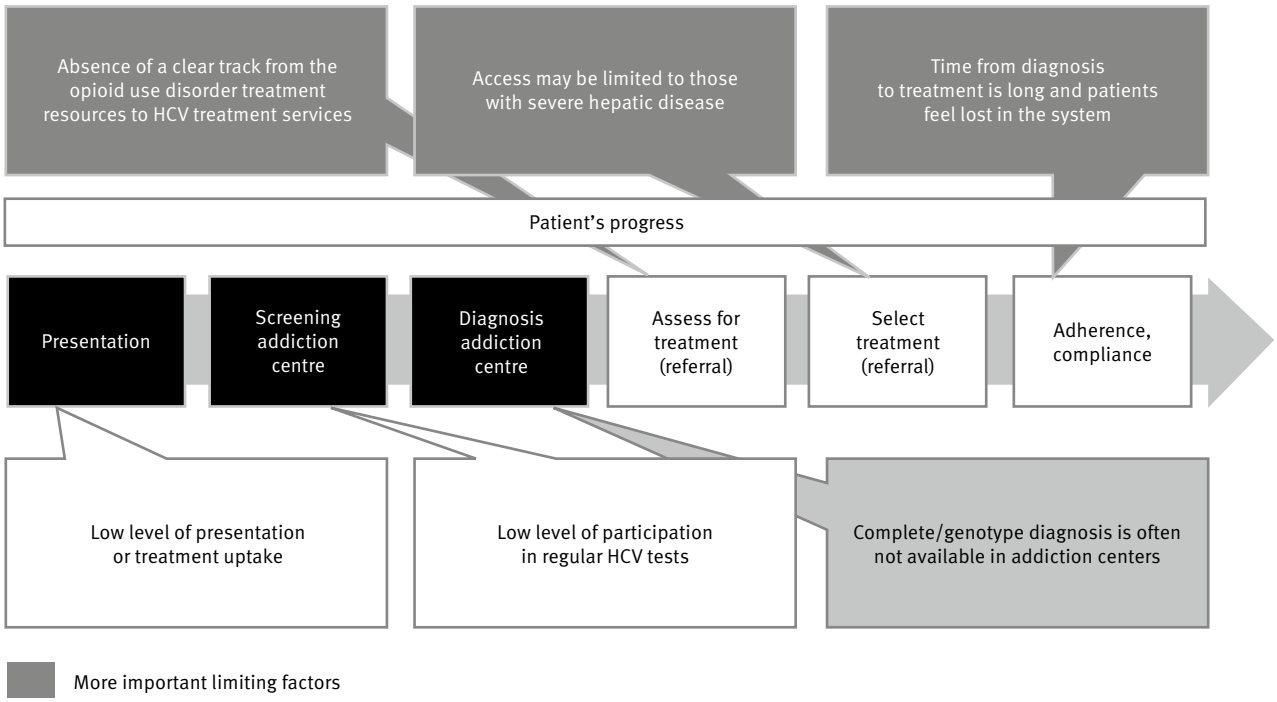

Fig. 1. Patient's progress

Spanish health system is the major limitation for the successful administration of treatment for patients with HCV. These limitations can be addressed by facilitating collaboration between units treating patients with addiction and services for infectious diseases and/or hepatology, including the development of a joint protocol for health professionals and patients.

It is very difficult to figure out how these groups can be effectively treated since many of them have no contact whatsoever with social and health services, or only with services for the treatment of opioid dependence. The following causes of limited access to treatment have been described: (1) low level of presentation of symptoms and treatment participation, (2) low participation in regular HCV tests, (3) conspicuous absence of a clear protocol from the resources for the treatment of opioid use disorder to HCV treatment services for many patients (Figure 1).

Conclusions

There are approximately 150,000 people in Spain with opiate use disorder and many of them also have a history of injecting drugs. Of this population, there are 80,000 people who are accessing services for the treatment of substance dependence, receiving opioid substitution treatment and other types of interventions. However, to date, few PDUs with HCV have been treated in Spain. The reasons behind the low number of PDUs treated suggest a series of strategies that can improve access to health services for these groups. This is an opportunity for policymakers, doctors and patients to make a significant change in the way HCV is treated in PDU.

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Conflict of interests

Dr Carlos Roncero has received fees to give talks for Janssen- Cilag, Ferrer-Brainfarma, Pfizer, Reckitt-Benckiser/Indivior, Lundbeck, Otsuka, Servier, Shire, Lilly, Shire, GSK, and Astra. He has received financial compensation for his participation as a member of the Janssen- Cilag, Indivior and Gilead board. He has carried out the PROTEUS project, which was funded by a grant from Reckitt-Benckisert/INDIVIOR. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Dr. Pablo Vega has received fees to give talks for Janssen- Cilag, Servier, Lundbeck, Indivior, Lilly

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Metacognitive abilities in adults with substance abuse treated in therapeutic community

Habilidades metacognitivas en adultos con abuso de sustancias bajo tratamiento en comunidad terapéutica

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Abstract

Background: The term metacognition reflects a spectrum of psychological activities that allows people to form and integrate representations about their own mental states and those of others. The main goal of this study was to examine whether people with substance abuse disorders (SUDs), and treated in therapeutic community regime, displayed specific patterns of metacognitive deficits on Self-reflectivity, Understanding others' mind, Decentration, and Mastery, comparing their scores with two clinical groups of patients with schizophrenia spectrum disorders (SSDs) and anxiety disorders.

Method: A mixed-methods (qualitative-quantitative) study was designed. Two hundred and sixteen adults aged 18-65 with principal diagnoses of SUDs (n = 52), SSDs (n = 49), and anxiety disorders (n = 115) were recruited. Qualitative data were obtained with the Metacognition Assessment Interview, which was then rated using a quantitative scale, the Metacognition Assessment Scale–Abbreviated (MAS–A).

Results: The anxiety disorders group had significantly higher MAS–A total scores than the SUDs group, and the SUDs group obtained significantly higher MAS–A total scores than the SSDs group. Concerning the MAS–A subscale scores, the SUDs group displayed significantly lower scores only on the Mastery subscale compared to the anxiety disorders group, with the SUDs and SSDs groups obtaining equivalent Mastery scores.

Conclusions: According to these findings, current interventions for addiction should focus more specifically on improving metacognitive Mastery.

Keywords: Addiction; Metacognition; Metacognition Assessment Scale–Abbreviated (MAS–A); Rehabilitation; mixed-methods.

Resumen

Antecedentes: El término de metacognición hace referencia al conjunto de procesos psicológicos que permiten a los individuos desarrollar e integrar representaciones sobre los estados mentales propios y de los demás. El objetivo principal de este estudio fue examinar si los pacientes bajo tratamiento por consumo de sustancias, en régimen de comunidad terapéutica, presentan un perfil específico de déficits metacognitivos en las áreas de Autorreflexividad, Diferenciación, Descentramiento y Dominio, comparando sus puntuaciones con las obtenidas por dos muestras clínicas de pacientes con trastornos del espectro esquizofrénico y trastornos de ansiedad.

Método: Se diseñó un estudio con metodología mixta (cualitativa-cuantitativa). Se seleccionaron un total de 216 participantes con diagnósticos principales por consumo de sustancias (n = 52), espectro esquizofrénico (n = 49) y trastornos de ansiedad (n = 115). Los datos cualitativos se obtuvieron con la Entrevista de Evaluación de la Metacognición (MAI) y, posteriormente, estos fueron cuantificados con la Escala Abreviada de Evaluación de la Metacognición (MAS-A).

Resultados: Las puntuaciones totales en la MAS–A del grupo con trastornos de ansiedad fueron estadísticamente superiores a las del grupo con trastornos por consumo de sustancias (TCS), y éstas, a su vez, fueron significativamente superiores a las del grupo con trastornos del espectro esquizofrénico. Por subescalas de la MAS-A, sólo hubo diferencias estadísticamente significativas entre las puntuaciones de Dominio del grupo con ansiedad y TCS, obteniendo el grupo con TCS puntuaciones estadísticamente equivalentes a las del grupo con trastornos del espectro esquizofrénico.

Conclusiones: De acuerdo con estos resultados, los programas actuales de intervención en drogadicción deberían orientarse más específicamente a mejorar las habilidades metacognitivas de Dominio.

Palabras clave: Drogadicción; Metacognición; Escala Abreviada de Evaluación de la Metacognición (MAS–A); Rehabilitación; metodología mixta.

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Originally, the term metacognition was used in the educational literature to refer the capacity to reflect on one's own thinking while learning (Flavell, 1979). Subsequently, the use of this concept has been extended to many fields of research, such as attachment, psychopathology, human development, or cognitive psychology (Bacon & Izaute, 2009; Dinsmore et al, 2008; Tarricone, 2011). Broadly speaking, this construct refers both to simple mental processes, for example, identifying one's own desires, thoughts, or emotions, and to complex processes that allow us to integrate intersubjective information to create broad representations about oneself, others, and the world (Semerari et al., 2003). Although this set of skills has received multiple denominations in the literature (e.g., social cognition, theory of mind, emotional intelligence or mentalizing), all of them indicate mental processes underlying interpersonal experience. In an attempt to unify the field, Lysaker et al. (2005) have proposed a general definition of metacognition that includes four large skills: (1) *Self-reflectivity* or the capacity to think about one's own mental states; (2) *Understanding others' mind* or the capacity to think about others' mental states; (3) *Decentration* or the capacity to understand that one is not the center of the world and that there are different ways of understanding reality; and (4) *Mastery* or the capacity to integrate intersubjective information in broad definitions of problems that allow one to respond adaptively.

In spite of the fact that there are numerous tests to assess low-order metacognitive skills (e.g., with tasks to measure the capacity to recognize and express specific emotions; Caletti et al., 2013), to date, there are few measurement instruments to appraise the higher order processes that involve addressing how individuals integrate and respond in interpersonal situations of high emotional content. In order to overcome this limitation, the *Metacognition Assessment Interview*, MAI; Semerari et al., 2012) was recently developed. The MAI is a semistructured interview that appraises individuals' metacognitive activity when faced by relevant autobiographical episodes of intersubjective nature. Specifically, the MAI requests interviewees to describe in detail the worst psychological event they experienced in the past months. The main goal is to provoke vivid narratives that allow identifying all the metacognitive processes deployed by the subject in that situation. Once the narration is obtained, the information of the responses is ordered and scored with the *Metacognition Assessment Scale–Abbreviated* (MAS–A; Lysaker et al., 2005). The MAS-A is a brief scale that was developed specifically to analyze qualitative data. As shown in Table 1, the MAS-A consists of four subscales measuring the four above-described metacognitive skills. High scores indicate a greater capacity to create broad representations about oneself, others, and the world, as well as to use these representations to respond appropriately to psychological and social challenges (Lysaker et al., 2005). Recent studies

Table 1. *Structure of the Metacognition Assessment Scale brief version (MAS–A; Lysaker et al., 2005).*

Level	Self-reflectivity (S)	Understanding others' mind (O)	Decentration (D)	Mastery (M)
0	Total lack of awareness of their own mental activity	Total lack of awareness of others' mental activity	Considering that one is the center of everything	Lack of awareness of problems
1	Slight awareness of own mental activity	Slight awareness of others' mental activity	Recognizing that others have independent lives	Awareness of problems as intractable
2	Awareness that thoughts are one's own	Awareness others have their own mental activity	Awareness that there are different ways to understand the same event	Awareness of problems as resolvable but with lack of response
3	Distinction of one's own different cognitive operations (thoughts, fantasies, memories…)	Distinction of others' different cognitive operations (thoughts, fantasies, memories…)	Awareness that facts are the result of multiple and complex factors	Passive responses
4	Distinction of different emotional states	Recognition of others' different emotional states	—	Responses of seeking help
5	Recognition that one's own thoughts are fallible	Plausible assumptions about others' mental state	—	Responses with specific actions
6	Recognition that desire is not reality	Complete descriptions of others' thinking over time	—	Responses with changes
7	Integration of one's own thoughts and emotions in a narration	Complete descriptions of others' thinking throughout their lives	—	Responses based on one's own knowledge
8	Integration of various narrations recognizing patterns over time	—	—	Responses based on others' knowledge
9	Recognition of thoughts and emotions connected throughout one's own life	—	—	Responses based on a broad comprehension of life

found that MAS-A scores correlate significantly with clinical variables such as symptom severity or the level of functioning in various mental disorders, including schizophrenia (McLeod et al., 2014), personality disorders (Semerari et al., 2014), or depression (Ladegaard, Lysaker, Larsen, & Videbech, 2014).

In the case of substance-use disorders (SUDs), it was observed that alexithymia, that is, the difficulty to name and express one's own emotions, correlates significantly with substance abuse (Thorberg, Young, Sullivan, & Lyvers, 2009). In this sense, Highland, Herschl, Klanecky, and McChargue (2013) concluded that the expression of certain genes increases the relationship between alexithymia and substance abuse. However, Lysaker et al. (2014) found that metacognitive skills related to the use of mental states to resolve social problems (or capacity of Mastery) moderate the effect of alexithymia on substance abuse. At the same time, Wasmuth et al. (2015) corroborated that people with SUDs present more pronounced deficits in Mastery skills compared with controls with HIV+ without a history of SUDs. Inasmuch as the type of substance is concerned, Roser et al. (2012) associated the consumption of cannabis with significant deficits in the capacity to infer mental states in others. Moreover, this study found that the chronic consumption of cannabis caused patterns of neuronal arousal very similar to those of people at risk for psychosis. In another study of Gizewski et al. (2013), it was observed that abusive alcohol consumption affected brain areas related to cognitive and affective empathy. There is empirical evidence showing that deficits in metacognition correlate with poorer results in drug dependency treatments (Saladin et al, 2012; Thorberg et al., 2011), the type of substance consumed, abstinence, risk of relapse (Toneatto, 1999), self-injuries (Verrocchio, Conti, & Fulcheri, 2010), emotional distress (de Rick, Vanheule, & Verhaeghe, 2009), and alcohol abuse in nonclinical samples (Lyvers, Onuoha, Thorberg, & Samios, 2012).

Ultimately, the results of the literature to date seem to underline the relevance and interest of studying this set of skills in people with substance abuse. The fact that it is not yet clear whether there are different metacognitive profiles depending on the type of disorder, or the effects of current interventions on metacognition requires further research of these issues in order to improve our comprehension of the psychological processes underlying drug addictions and their treatment. With regard to types of intervention, although there is evidence that drug addictions provoke important neuropathological changes, the capacity to act on them still is fairly limited (Bart, 2012). In this sense, an analysis in terms of metacognitive abilities can contribute new psychotherapeutic treatment options and/or help to optimize the existing ones. For example, it has been observed that people who score low on Self-reflectivity respond better to individual interventions (Lysaker et al., 2013). Conversely, it can be assumed that people with low scores on Decentration will benefit more from group interventions that allow them to improve their comprehension of others' mental states (Wasmuth et al., 2015). Low scores in all the metacognitive areas would justify the use of both intervention formats, as well as other multidisciplinary interventions to act on all the deficits and their functional implications.

Within this context of research, the purpose of this study was to examine the metacognitive skills of a group of patients with SUDs under treatment for drug addiction in therapeutic community regime. Specifically, we aimed to determine whether the patients with SUDs displayed differences in metacognitive skills assessed with the MAS-A, in comparison with patients with schizophrenia spectrum disorders and with mild anxiety disorders. These comparison groups were selected for the following reasons. Recent studies suggest that healthy controls—that is, individuals with no specific health problems—are not an adequate control group to compare the metacognitive capacity of patients with mental health problems, such as the case of the SUDs group (Wasmuth et al., 2015). Specifically, this proposal argues that the use of healthy controls could lead to underestimate the other group's metacognitive capacity simply because they present a health problem (e.g., Lysaker et al., 2012). Therefore, the inclusion of the group of patients with minor anxiety disorders sought to ensure that all the participants of the study had some health problem, and that, moreover, they received some kind of mental health treatment (psychotherapeutic and/or psychopharmacological), although of low intensity, at the time of the assessment. The patients with schizophrenia spectrum disorders is included as the group with more clearly established metacognitive deficits in the literature (e.g., see Bacon & Izaute, 2009), providing relevant data mainly from the lower levels of the construct. In line with these findings, the hypotheses of the study were as follows. Firstly, it was expected that the group of patients with schizophrenia spectrum disorders obtained the lowest scores on the subscales of the MAS–A. Secondly, based on the higher functioning level of patients with mild anxiety disorders compared with patients with SUDs, it was expected that the anxiety disorders group presented higher scores than the SUDs group on the MAS-A.

Method

Participants

The study included three groups of patients. The first group was comprised of a of total of 52 adults with SUDs treated in therapeutic community regime, and who were clinically stabilized (no hospitalizations or changes of medication in the last month). Within this group, 21 participants presented a primary diagnosis of polysubstance dependence, 13 of alcohol dependence, 10 of opiate dependence, and 8 of cocaine dependence.

A second group included 49 adults with schizophrenia spectrum disorders, specifically: schizophrenia (n = 33), schizoaffective disorder (n = 15), and delusional disorder (n = 1), according to ICD-10 criteria (WHO, 1992), under day-hospital regime and clinically stable (no changes in antipsychotic medication in the last 6 months).

The third group comprised 115 adults with mild anxiety disorders from two outpatient community mental health services and with principal diagnoses of, at least, an anxiety disorder, according to ICD-10 criteria. Within this third group, 42 participants presented a main diagnosis of panic disorder with agoraphobia, 24 of generalized anxiety, 19 of panic without agoraphobia, 18 of social phobia, and 12 of agoraphobia without panic. The sociodemographic characteristics of the participants are presented in Table 2.

All the diagnoses and clinical assessments were made by psychiatrists or clinical psychologists external to the investigation. The general exclusion criteria of the study were: suspected or diagnosis of intellectual disability or pervasive developmental disorders, presence neurological syndromes (dementia, epilepsy, multiple sclerosis, etc.), sensory problems (blindness, deafness, etc.), or comprehension difficulties (e.g., not speaking Spanish), and not signing or not having the capacity to consent to research participation. We also excluded participants with severe or extreme positive psychotic symptoms [scores ≥ 4 in any item of the Scale for the Assessment of Positive Symptoms (SAPS; Adrenasen, 1984)] and participants with moderate or severe anxiety disorders [total scores ≥ 30 in the Beck Anxiety Inventory (BAI; Sanz & Navarro, 2003)]. Lastly, the presence or suspicion of SUDs was an exclusion criterion in the schizophrenia spectrum and anxiety groups.

Instruments

Metacognition Assessment Interview (MAI; Semerari et al., 2012). The MAI is a 30-60 minutes semistructured interview. In the context of the interview, individuals are elicited to narrate the most unpleasant experience or event undergone in the last 6 months. The requirements are that the episode should be of an autobiographic nature, personally relevant, and should include interactions with other people. At first, the questions are intentionally open to allow free narrative; this leads to the spontaneous emergence of the metacognitive skills deployed by the interviewee. Then, concrete questions are asked in order to specifically appraise each metacognitive skill. All the interviews were audio-recorded for subsequent transcription and quantification with the MAS-A.

Metacognition Assessment Scale–Abbreviated (MAS–A; Lysaker et al., 2005). The MAS-A assesses the four types of metacognitive activity described above (Lysaker et al., 2005; Semerari et al., 2003). This instrument is a brief adaptation of the MAS (Semerari et al., 2003) that quantifies the implicit metacognitive skills in the verbal responses of the interview. It consists of four subscales: Self-reflectivity, which includes nine levels of the capacity to think and form increasingly plausible and integrated ideas about oneself; Mind of Others, which consists of seven levels of the capacity to think and form increasingly complex and plausible ideas about others; Decentration, consisting of three levels that measure the capacity to form integrated ideas about oneself and others; and, lastly, Mastery, which includes nine levels of the capacity to use one's own and others' mental states to respond to psychological and social problems (see Table 1). Higher scores on the subscales indicate higher capacity to integrate and effectively use intersubjective information. The data obtained to date with the North American version of the MAS-A indicate acceptable values of internal consistency and test-retest and inter-judge reliability, with intraclass coefficients between .71 and .91 (Lysaker et al, 2005; Lysaker, & Salyers, 2007). With regard to the evidence of the validity of the theoretical construct, the MAS-A scores correlate significantly with other tests measuring the awareness of disease, cognitive insight, complexity of social schemas, or the preference for active coping strategies in people with psychosis (Lysaker et al., 2015).

Given that neither the MAS-A nor the MAI are validated into Spanish, in this study, pilot versions of both instruments

Table 2. *Sociodemographic characteristics of the participants.*

	Group 1 Anxiety (n = 115)	**Group 2 Drug Addiction** (n = 52)	**Group 3 Schizophrenia** (n = 49)			
Variable	f or Mean (SD)	f or Mean (SD)	f or Mean (SD)	F	η^2_p	Post hoc analysis
Gender						
Male	32	41	26			
Female	83	11	23			
Age	43.07 (15.54)	36.86 (9.18)	37.69 (12.62)	4.94*	0.07	1 › 2. 3
Education in years	13.42 (1.97)	12.64 (1.92)	12.44 (2.73)	4.57*	0.05	1 › 2. 3

Note. f = frequency; η^2_p = partial eta-squared. *p < .05

were used (more information on the translations can be requested from the main author, F.I.). The Spanish translation and adaptation was performed following the International Test Commission guidelines (Muñiz, Elosua, & Hambleton, 2013). The quantification, with the MAS-A, of the qualitative data obtained in the MAI was conducted by two raters external to the research who were experts in the use of both instruments. The judges scored each participant according to the MAI transcripts, so they were blind to the hypotheses of the study and the participants' characteristics at all times. The inter-raters reliability of the MAS-A scores was .91.

Procedure

The protocol of the study was approved by the institutional ethics committee of the centers where the data were collected. After explaining the goals, benefits, and possible risks of the investigation to all the participants, those who voluntarily agreed to participate were requested to sign an informed consent prior to gathering the data. Participation in the study did not lead to any type of consideration or reward. The information obtained was stored ensuring the total confidentiality of the data. Data were collected in a single interview lasting approximately 30 to 60 minutes, within the context of the general assessment sessions or the clinical follow-up of the cases. All the interviews were conducted by two clinical psychologists trained in the use of the MAI.

Data Analysis

Data analysis was carried out in two stages using the SPSS statistical package version 21 (IBM Corp., 2012). Firstly, sociodemographic variables, age, and educational level of the participants of the three groups (SUDs, schizophrenia spectrum, and anxiety) were compared to determine whether it was necessary to use one of these variables as covariate in the subsequent analyses. Secondly, analysis of variance (ANOVA) or analysis of covariance (ANCOVA) were performed to compare the total mean score of the MAS-A in the target groups. If these differences were statistically significant ($p < .05$), the mean scores of the MAS-A subscales were compared. As estimator of the magnitude of the effects, the partial squared eta (η^2_p) statistic was used.

Results

Table 3 presents the means of the MAS-A total and subscales scores obtained by the participants of the SUDs, schizophrenia spectrum, and anxiety disorders groups. The ANOVAs indicated that the groups differed in age and educational level; specifically, the group with anxiety disorders scored higher, in avarage, on age and educational level than either group ($p < .05$). To control the possible effect of these two variables in the subsequent comparisons, age and educational level were included as covariates.

The participants of the anxiety group obtained significantly higher total scores in the MAS-A than the SUDs group, and this group scored significantly higher than the schizophrenia spectrum group ($p < .001$). By subscales, after controlling the effect of age and educational level, the participants of the anxiety disorders and SUDs groups obtained significantly higher scores on Self-reflectivity, Understanding others' thoughts, and Decentration than the group with schizophrenia spectrum disorders. The participants of the anxiety disorders group scored significantly higher on the Mastery subscale in comparison with the other two groups of participants. Lastly, equivalent scores on Mastery were found in the SUDs and schizophrenia spectrum groups (see Table 3).

Discussion

The main goal of this study was to examine the metacognitive skills assessed with the MAS-A in a group of patients with SUDs. This research also intended to determine whether their metacognitive skills differ from those observed in other patients with schizophrenia spectrum and mild anxiety disorders. For this purpose, a sample of 216 adults in treatment for SUDs, schizophrenic-spectrum disorders, or anxiety disorders were selected. All the participants were interviewed first with the MAI and subsequently, their responses were quantified by two blinded raters using the MAS-A. In the light of the results obtained, it can be stated that: (a) patients with SCD obtained scores on Mastery statistically equivalent to those of patients with schizophrenia spectrum disorders; and (b) participants with SUDs showed a poorer metacognitive performance on Self-reflectivity, Understanding others' thoughts, and Decentration than patients with mild anxiety disorders.

These findings are far from the conceptualization of drug addictions as impulsive or compulsive behaviors strongly associated with a poor capacity for self-awareness (Chambers & Potenza, 2003; O'Brien, 2008).) For example, many current addiction recovery programs, such as Alcoholics Anonymous (2001), are based on a model that characterizes this type of disorders as closely linked to lack of self-control and self-perception of one's mental states. The high prevalence of alexithymia (Lysaker et al., 2014), scarce cognitive flexibility (Luoma, Drake, Kohlenberg, & Hayes, 2011), difficulties in interpersonal relations (Greene et al., 1999), or poor self-concept (Chelton & Bonney, 1987) shown in SUDs could support this type of definitions of addictions. However, the results of this study point in the direction of other recent findings suggesting that the problem of people with SUDs would not be much in their difficulties to describe and understand their own and others' thoughts, emotions, or intentions, but in their poor capacity to regulate and integrate this information and to perform adaptive behaviors (Lysaker et al., 2014; Wasmuth et al., 2015).

Table 3. *ANCOVA, effect sizes and post hoc analysis of metacognition scores, controlling for age and educational level of the participants.*

	Group 1 Anxiety (*n* = 115)	**Group 2 Drug Addiction** (*n* = 52)	**Group 3 Schizophrenia** (*n* = 49)			
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	*F*	n^2_p	Post hoc analysis
MAS-A						
Self-reflectivity	6.05 (1.61)	6.00 (1.66)	4.08 (1.19)	32.74**	0.17	1. 2 › 3
Others	4.00 (1.26)	3.91 (1.01)	2.69 (0.98)	29.81**	0.15	1. 2 › 3
Decentration	1.52 (0.98)	1.14 (1.22)	0.99 (0.92)	6.06**	0.09	1. 2 › 3
Mastery	4.70 (1.71)	3.51 (1.34)	3.36 (1.56)	18.24**	0.14	1 › 2. 3
Total	16.26 (4.96)	14.56 (4.72)	11.12 (4.01)	26.95**	0.19	1 › 2 › 3

Note. MAS-A = Metacognition Assessment Scale brief version; η^2_p = partial eta-squared. ***p* < .001.

Likewise, the results of this study support the idea that substance abuse per se does not alter metacognitive functions (Wasmuth et al., 2015), offering an alternative hypothesis to understand the etiology of the functional deficits often associated with SUDs. This hypothesis is based on the fact that substance abuse can be explained as a compensatory behavior for deficits in the metacognitive skills of Mastery (Wasmuth et al., 2015). Substance consumption, as a known, controllable, and easily manageable activity, does not require important metacognitive efforts, in contrast to other social and occupational activities. As the underlying neurobiological circuits of rewarding and substance abuse are similar (Chambers, Bickel, & Potenza, 2007), it is reasonable to assume that addictions could compensate the difficulties to earn rewards in other more complex contexts. However, the alternative hypothesis—that deficits in Mastery skills are a partial or total consequence of chronic substance abuse (Lysaker et al., 2014)—should not be discarded.

Nonetheless, the similarities observed on Mastery in participants with schizophrenia spectrum disorders and with SUDs could lead to suspect the presence of underlying common neural mechanisms or, at least, of certain similarities in the way of processing information in both groups of disorders. Nevertheless, this may also be due to many other causes, such as attachment styles (Fonagy & Bateman, 2006), genetic variables (Highland et al., 2013), motivation (Bachiller et al., 2015), or the experience of traumatic events (Pec, Bob, & Lysaker, 2015). Future studies should clarify whether these types of deficits share similar neural mechanisms and/or whether they have a common etiology.

As main limitations of this study can be identified as follows. Firstly, the reduced size of the groups, especially the schizophrenia spectrum and SUDs groups, and the over-representation of women in the anxiety group and of men in the SUDs group that clearly affect the validity and extrapolation of these results to other samples of interest. Moreover, as consumption behaviors like, for example, alcohol or cannabis, are very widespread and deeply rooted in our society, these problems often go unnoticed and are not diagnosed. The risk that the data could be contaminated by the presence of participants with comorbid SUDs in the schizophrenia spectrum and anxiety groups is a potential limitation of the validity of the results. Secondly, the fact that the conclusions are supported by the scores obtained with pilot versions of the MAI interview and the MAS-A scale (neither instrument has been yet validated into Spanish) is a limitation that can affect the validity of the estimations of the metacognition construct. Likewise, the two assessment techniques used are based on verbal information provided by the individuals, so there may be discrepancies between real metacognitive skills and those described in the interview. Future studies should use other methods of convergent assessment, such as those based on the analysis of social interaction or individual non-verbal techniques that allow inferring the use of metacognitive strategies from repeated patterns in observed behavior while performing certain tasks. The current level of development in the field of metacognition indicates that no single technique is sufficient to assess these processes, but instead that various metacognitive markers should be used. Thirdly, and from a practical viewpoint, although this study shows how important it is for future studies to examine the effectiveness of treatments based on metacognition in SUDs, for example, metacognitive training (van Oosterhout et al., 2015) or metacognitive-oriented social skills trainning (Ottavi et al., 2014), this findings does not provide detailed information about the variables that could improve metacognition or the potential effects of metacognitive-focused interventions could have in concrete clinical populations. It should also be noted that, although substance abuse could be a compensatory behavior for metacognitive deficits, it is quite possible that these deficits emerge in an exaggerated manner as a consequence of neuropathological changes associated with chronic drug abuse (Chambers, 2013; Volkow, Fowler, Wang, Baler, & Telang, 2009). Lastly, although the selection of the groups was carried out to attenuate the possible effects of (mental) health problems and of the psychological and/or psychopharmacological treatment received,

none of these variables (specific diagnosis, treatment type and duration, medication, etc.) or their potential impact on participants' metacognitive capacity (López-Duran et al., 2006) were specifically controlled.

Future lines of research should explore more closely the relations between addictive behaviors, metacognitive skills, the level of personal, occupational, and social functioning, as well as the implicated neurobiological bases. It also seems relevant to analyze in more detail the role played by metacognition in general and Mastery in particular in the prediction of the maintenance of abstinence. In this line, it can be assumed that improvements in the Mastery skills would help to improve general coping strategies in the face of problems associated with drug abuse, risk situations, abstinence, or relapses, as suggested by Marlatt and Donovan (2005).

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Conflict of interests

The authors declare no conflict of interest

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Psychiatric comorbidity and plasma levels of 2-acyl-glycerols in outpatient treatment alcohol users. Analysis of gender differences

Comorbilidad psiquiátrica y valores plasmáticos de 2-acilgliceroles en consumidores de alcohol en tratamiento ambulatorio. Análisis de las diferencias de género

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Abstract

Alcohol addiction is associated with high psychiatric comorbidity. Objective stratification of patients is necessary to optimize care and improve prognosis. The present study is designed to gain insights into this challenge by addressing the following objectives: a) to estimate the prevalence of psychiatric comorbidities in a sample of outpatients seeking treatment for alcohol use disorder, b) to describe the existence of gender differences and c) to validate 2-acyl-glycerols as biomarkers of alcohol use disorder and/or psychiatric comorbidity. One hundred and sixty-two patients were recruited and evaluated with the semi-structured interview PRISM. The presence of psychopathology was associated with a greater number of criteria for alcohol abuse and dependence according to DSM-IV-TR. We found gender differences in psychiatric comorbidity, e.g., mood disorder, as well as in comorbid substance use disorders. The prevalence of lifetime psychiatric comorbidity was 68.5%, with mood disorders the most frequent (37%), followed by attention deficit disorder (24.7%) and anxiety disorders (17.9%). Substance-induced disorders were more frequent in mood and psychotic disorders, whereas the primary disorders were more prevalent in patients with comorbid anxiety disorders. We found that 2-acyl-glycerols were significantly decreased in comorbid anxiety disorders in alcohol dependent patients in the last year, which makes them a potential biomarker for this psychopathological condition.

Keywords: Psychiatric co-morbidity; Addiction; Alcohol; Outpatient; Gender; 2-acyl-glycerols.

Resumen

La adicción al alcohol se asocia con una elevada comorbilidad psiquiátrica que complica el tratamiento, siendo necesaria una fenotipación clínica objetiva de estos pacientes para optimizar la atención y mejorar el pronóstico. El presente estudio aborda este problema mediante los siguientes objetivos: a) estimar la prevalencia y tipos de comorbilidad psiquiátrica de una muestra de pacientes que buscan tratamiento por uso de alcohol, b) describir las diferencias de género en su presentación y c) analizar los valores plasmáticos de 2-acilgliceroles (incluyendo el endocannabinoide 2-araquidonilglicerol), estudiando su posible valor como biomarcador de alcoholismo y/o comorbilidad psiquiátrica. Para ello se reclutaron 162 pacientes evaluados con la entrevista semiestructurada PRISM, para evaluar la presencia de comorbilidad y su carácter primario o inducido. Los resultados obtenidos indican que la presencia de psicopatología se asoció a un mayor número de criterios de abuso y dependencia de alcohol Se encontraron diferencias de género tanto en la comorbilidad psiquiátrica, especialmente en trastornos del estado de ánimo. La prevalencia de comorbilidad psiquiátrica encontrada a lo largo de la vida fue del 68,5%, destacando los trastornos del estado ánimo (37%), y seguidos por el trastorno por déficit de atención (24,7%, monitorizado específicamente por la entrevista WURS) y los trastornos de ansiedad (17,9%). Entre los trastornos del estado de ánimo y psicóticos fueron más frecuentes los inducidos, mientras que en los trastornos de ansiedad los primarios fueron más prevalentes. Además, se encontraron concentraciones disminuidas significativamente de 2-acilgliceroles en pacientes con trastornos de ansiedad comórbidos diagnosticados en el último año.

Palabras clave: Comorbilidad psiquiátrica; Adicción; Alcohol; Ambulatorio; Género; 2-acilgliceroles.

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Alcohol is a psychoactive substance with addictive properties, the consumption of which can have powerful economic, social and health impacts on the individuals who consume it. The harmful use of this substance is an etiological factor in mortality at a global level, with 5.9% of deaths up to 2012 found to have a link to alcohol (World Health Organization, 2014). Although consumption trends have stabilised in Spain over the last 10 years, levels of alcohol use are still high. A 4.9% rate of problematic alcohol use is observed among the 15-65 year-old population, with 4.5% presenting high-risk consumption [1,600,000 people, 1,300,000 men and 300,000 women]. The average age of alcohol consumption onset is 16.7 years and alcohol is linked to a greater prevalence of the consumption of other drugs, since alcohol is present in 90% of polydrug consumption patterns (EDADES, 2013)

Given the frequency of alcohol use disorders (AUD), the association with other medical complications presents a challenge to health systems. Among these, psychiatric comorbidity in alcohol addiction, i.e. the co-existence in one person of AUD alongside another disorder distinct from the addiction, constitutes a serious health problem (Goldsmith, 1999) which demands a differential approach. Patients with psychiatric comorbidity are a risk group from a clinical and social perspective. They access hospital services more frequently (Ruffles, 2009), have higher suicide rates (Fiedler et al., 2012) and respond less well to treatment than patients with only AUD (Karila et al., 2012). Furthermore, from a social point of view, they provide a greater source of conflict at occupational, judicial and social inclusion levels (Karila et al., 2014).

AUD patients are 2 to 4 times more likely to suffer a depressive disorder during their lifetime than those who are not alcohol dependent (Hasin et al., 2005, 2007; Kessler et al., 1997; Ross, 1995). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) in North America reports rates of 39.5% in AUD populations compared to 14.8% in the general population, as well as a high psychopathological comorbidity of AUD with disorders of mood (MD), anxiety (AD) and personality (PD) (Grant et al., 2004). With regard to psychotic disorders, these are found within the general population at a rate of 0.4%, while among the AUD population this rises to 4.0% (Engelhard et al., 2015).

These data from North America are matched by research results in Europe. In Copenhague, AUD prevalence was 7,6% and half of them had a psychopathological comorbidity: 24% PD, 16,8% MD and 16,6% another SUD (Flensborg-Madsen et al., 2009). The prevalence of AUD in our country in 2010 was 2.3% in men and 1.3% among both sexes (WHO, 2014). Disorders associated with alcohol use, such as intoxication or withdrawal symptoms, impair the majority of social relations (Blanco et al., 2015). Patients with high severity of alcohol dependence disorder are very prone to emotional and anxiety disorders (Blanco et al., 2015). In one study carried out among hospitalised patients in Madrid, for example, 24.9% presented substance abuse, with the majority of them (78.1%) also suffering from AUD (Rodriguez-Jimenez et al., 2008).

The profile of patients needing treatment for AUD is different from that of patients with substance use disorders (SUD), given that the typical withdrawal symptoms of AUD have an effect on the search for and motivation to enter a treatment programme (Blanco et al., 2015). For all these reasons, subjects with AUD have a greater degree of comorbidity with other mental disorders than the general population, and this comorbidity leads to more severe forms of AUD, greater disability and a higher likelihood that they will seek treatment at mental health centres, which reinforces the need for accurate detection of AUD in patients attending these.

Both SUD psychiatric comorbidity as well as the presence of non-substance related psychiatric comorbidity are factors which contribute to the worsening of alcohol abuse to the point of dependence. In terms of AUD comorbidity and gender differences, it is known that women start drinking later and develop dependence more quickly than men (Keyes et al., 2010). Among AUD patients, men have a greater prevalence of personality disorders, while women are more frequently affected by other psychiatric disorders (Ávila Escribano et al., 2007). Given the gender differences we believe it is necessary to establish programmes and strategies to control the excessive consumption of alcohol and its growing use among the female population, while also describing the similarities and differences in the patterns of use and psychiatric comorbidity that might be found.

We can see that there are very few studies dealing with the phenomenon of psychiatric comorbidity in the AUD population in Spain. The present study may therefore serve as a reference in extending this field of knowledge, especially in the hospital outpatient context.

One of the basic problems of clinical practice in treating addictions is the lack of objective biological tests to determine the level of consumption, the severity of SUD, toxicity and the response to treatment of this type of patient. These objective tests, or biomarkers, are fundamental to the diagnosis, stratification, prognosis and treatment approach with regard to addictive disorders. One way of searching for biomarkers is to explore compartments of cell signalling in connection with the changing responses to addictive substances, as has been observed in patients who consume cocaine (Araos et al., 2014; Pavón et al., 2013; Pedraz et al., 2015). The present study is focused on signal molecules called acylglycerols, ethers formed from fatty acids. The best known molecules of this type include 2-araquidonil-glycerol (2-AG) and 2-linoleoyl-glycerol (2-LG). The 2-AG is the principal endogenous endocannabinoid and its activity is linked to the preference for alcohol as well as the development of

tolerance, as many studies have borne out in preclinical models (Basavarajappa et al., 2005; Caillés et al., 2007; Malinen et al., 2009; Serrano et al., 2012). These molecules are present in the central nervous system and more abundant than other lipid transmitters such as the N-acyl-ethanolamines, with which they share their endogenous endocannabinoid profile (Piomelli, 2003).

In sum, this study has been designed to assess the prevalence of psychiatric comorbidity among alcohol use disorder patients under outpatient treatment. We describe gender differences and determine the plasma levels of N-acyl-ethanolamines and their value as biomarkers.

Method

Study design and target population

In 1994, a specific programme was set up in Madrid's 12 de Octubre hospital with the aim of providing an integrated response for AUD patients in the shape of a mixed medical-psychiatric unit, bringing together patients from the psychiatry and internal and digestive medicine departments. This unit has proceeded to recruit patients to carry out an observational descriptive transversal study in order to determine the prevalence of psychiatric comorbidities among subjects seeking treatment at the hospital, and to obtain plasma samples for the validation of the 2-acylglycerols as biomarkers.

The study sample consisted of 262 participants divided into two groups. The first group included abstinent patients undergoing outpatient treatment for alcoholism in the programme for addictive behaviour disorders at the 12 de Octubre hospital in Madrid after being diagnosed with AUD. The second group was a control group of patients without any previous diagnosis of illegal substance abuse and/or dependence, and with no history of concomitant psychiatric diagnosis (both according to DSM-IV-TR diagnostic criteria). The clinical assessment study included 162 patients taking part in the above mentioned programme, of which 133 consented to provide a biological sample, and 100 control patients matched for age, sex and body mass index.

To calculate the sample size, the work of the Pérez-Gálvez team (Pérez-Gálvez et al., 2008) was used as a reference point. Here, psychiatric comorbidity in AUD patients is approximately 70%. In order to obtain an accuracy of 8% in the estimation of proportion with a normal asymptotic confidence interval of 95% bilaterally, assuming the proportion is 70%, a sample of approximately 160 subjects would be necessary. Given the aims of the study, a pragmatic attitude was taken in the selection of subjects for the sample. For this purpose, non-restrictive criteria were used in order to maximise the representativeness of the selected sample and the extrapolation of the study's results. Consecutive and non-random sampling was applied on patients as they arrived at the hospital outpatients unit after checking that they met the selection criteria.

These criteria were: being a patient on the programme and under treatment for AUD, with at least 30 days' abstinence, willing to participate and giving informed consent. The criteria for inclusion in the control group was not having a record of substance abuse or dependence, concomitant psychiatric comorbidity, and a signed letter of informed consent.

Reasons for exclusion from both study and control groups were the presence of cognitive disorders which would hamper the application of diagnostic assessment instruments, and the patient's refusal to participate in the study.

The ethical aspects of the study were approved by the ethics committee of the Clinical Research Department of the 12 de Octubre hospital in Madrid. All patients were informed and only those signing the letter of informed consent were approved by the committee. The study was part of the "Medical consequences of alcoholism" programme of the Carlos III Health Institute's Addictive Disorders Network (Red de Trastornos Adictivos).

The assessment process was carried out by a general health psychologist with special training and qualified in psychopathological assessment.

Procedure

The programme's psychiatrists and nurses collaborated in informing the patients during consultations and group therapy sessions about the existence of the study in the hospital, referring them to the research team if they met the inclusion criteria and agreed to take part. After arranging an appointment with the patient, once the informed consent letter had been signed, clinical assessment was carried out in the Oupatient Activity Centre (Centro de Actividades Ambulatorias) of Madrid's 12 de Octubre university hospital.

Psychopathological assessment was carried out in a single morning during an individual consultation lasting between one and two hours. The interviews took place between October 2013 and March 2015, and on completion of each interview the results were registered in the database designed for the purposes of this study.

Measurement instruments

PRISM. The PRISM diagnostic interview (*Psychiatric Research Interview for Substance and Mental Diseases*) is the first instrument to evaluate psychiatric and substance related disorders. It is a semi-structured clinical interview designed to solve the problems of diagnosing patients with level of alcohol and/or substance consumption, assessing the subject's consumption history in the first module and generating an abuse and dependence diagnosis covering both the previous year and before. In addition, it evaluates 20 Axis I disorders and the two most prevalent Axis II disorders in this population: borderline personality disorder and antiso-

cial personality disorder. The diagnoses focus on two time frames, with the interview assessing the current disorders, i.e. those present during the last year on the one hand, and those existing before the last year on the other. In general terms, the subject's lifetime diagnostic prevalence would include all diagnoses made previously in both periods, i.e. the most recent and those made earlier.

One of the most important festures of this instrument is that it makes it possible to differentiate between substance-induced disorders and the expected symptoms of the effects of intoxication and withdrawal. The PRISM criterion for whether a psychiatric disorder is substance induced is that it must occur within the context of pathological use of the substance, in either of the following two situations: a) chronic intoxication, i.e. substance use on four days or more per week over the course of a month; b) bingeing over three consecutive days. To differentiate the induced psychiatric symptoms from those expected during intoxication or withdrawal, a sudden change in consumption patterns needs to be detected (Hasin et al., 1996; Torrens et al., 2004).

This interview has good test-retest reliability, validity and inter rater reliability, with the Kappa coefficient ranging from 0.66 to 1.00 (Morguello et al., 2006).

WURS. As a result of the special interest surrounding the link between AUD and attention deficit and hyperactivity disorder (ADHD), it was decided to test for the the prevalence of ADHD using a further instrument, the WURS (*Wender-Utah Rating Scale*). This test is used for the restrospective assessment ADHD in adult patients. It is a self-administered questionnaire with 61 items, from which 25 were selected for their capacity to differentiate adult patients with a childhood history of ADHD from other populations such as patients with depression or in control groups. The WURS has shown internal reliability and stability over time in various studies. It includes questions regarding mood, relationship problems with family members, colleagues and figures of authority, as well as medical, school and academic problems. The Cronbach coefficient for the subscale was 0.94. The cut-off point of 32 optimised sensitivity (91.5%) and specificity (90.8%). The positive and negative predictive values were 81% and 96% respectively (Rodríguez-Jiménez et al., 2001).

CIDI. For the psychiatric assessment of the participants in the control group, the Spanish version of the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988) was applied. This structured interview has a section which assesses 22 diagnoses of different disorders in a screening for mood, anxiety and substance use disorders, early-onset disorders in childhood and others (such as personality and psychotic disorders) (Kessler and Ustün, 2004). In addition, for the assessment of substance use disorders in the control group, the history of substance use section of the PRISM interview was applied.

Processing blood samples and obtaining plasma samples

Peripheral blood samples were obtained from the 233 patients (133 in abstinence and 100 control subjects) in the morning, 8-12 hours after last eating or drinking and on the same day as the interview. Samples of 10ml of peripheral blood were taken using BD vacutainer® tubes with K2 EDTA by nursing staff participating on the project. To obtain the plasma, the samples were centrifuged at room temperature at 2200 xG for 15 minutes. Tests were immediately carried out on each sample to eliminate the presence of infectious diseases (AIDS-HIV, hepatitis B and C). Each plasma sample was registered and and recorded individually and those containing any kind of infection were rejected in accordance with safety protocols. Finally, all samples were frozen at -80°C for later analysis. The time between extraction and freezing at no point exceeded 30 munites.

Analysis of 2-acyglycerol plasma concentrations

The plasma samples were processed following standard techniques after organic extraction of plasma lipids (Pavón et al., 2013). Chromatic separation was carried out using a Zorbax 80 Å StableBond C8 column (2.1 x 100 mm, 1.8 µm particle size) maintained at 40° C, with a mobile phase of 0.4 ml/min flow. The composition of the mobile phase was A) 0.1% (v/v).

formic acid in water; B) 0.1% (v/v) formic acid in acetonitrile. The initial conditions were 40% B. The gradient was increased linearly to 100% B over 4 min, maintained at 100% B for 4 min, and returned to the initial conditions for a further 5.5 min, with a total run time of 13.5 min. The tandem quadrupole mass spectrometer operated on the positive electrospray mode. Desolvation gas temperature of 350°C and a gas flow rate of 10 l/min were used. The pressure of the nebulizer was set at 40 psi and the capillary voltage at 4,000 V. The fragmentor was set at 135 V and 20 ms for all analytes. The monitoring mode for multiple reactions was used for the analysis with the following precursors to product ion transitions: m / z 379.2 / 287 for 2-AG, m / z 384.3 / 287 for 2-AG-d5 and m / z 355.2 / 263 for 2-LG. An external calibration curve of 6 points in the mobile phase (10:90, A: B) was used with the addition of 0.8 at 50 ng of acylglycerols for quantification as has been described by our group in a previous study (Pavón et al., 2013).

Description of the study

The descriptive study aimed to research: the existence of gender differences in the socio-demographic characteristics and alcohol consumption patterns; the prevalence of psychiatric comorbidity among the participating patients with AUD and SUD (abuse or dependence); the frequency of psychiatric comorbidity among non-SUD patients; and finally, the analysis of 2-acyl-glycerol plasma levels in the population in comparison to the control population, while also

Table 1. *Socio-demographic variables by sex in a population of alcohol users under treatment.*

Variables		Total	Men	Women	Value p
Number of patients [N(%)]		162 (100)	122 (75,3)	40 (24,7)	-
Age [mean (SD)]		49,3 (8,1)	49,1 (8,5)	49,9 (6,9)	0,575 [1]
Body mass index [mean (SD)]		26,2 (4,5)	26,8 (4,5)	24,1 (3,9)	**‹0,001** [1]
Marital status [N(%)]	Single	47 (29,0)	34 (27,9)	13 (32,5)	**‹0,05** [2]
	Married	60 (37,0)	50 (41,0)	10 (25,0)	
	Separated/Divorced	51 (31,5)	37 (30,3)	14 (35,0)	
	Widow(er)	4 (2,5)	1 (0,8)	3 (7,5)	
Educational level [N(%)]	No school	4 (2,5)	3 (2,5)	1 (2,5)	0,200 [2]
	Primary	53 (32,7)	45 (36,9)	8 (20,0)	
	Secondary	83 (51,2)	60 (49,2)	23 (57,5)	
	University	22 (13,6)	14 (11,5)	8 (20,0)	
Work situation [N(%)]	Employed	46 (28,4)	36 (29,5)	10 (25,0)	0,466 [2]
	On sick leave	27 (16,7)	23 (18,9)	4 (10,0)	
	Unemplyed/Invalidity	68 (42,0)	49 (40,2)	19 (47,5)	
	Retired	17 (10,5)	14 (11,5)	3 (7,5)	
	Domestic	4 (2,5)	-	4 (10,0)	
Criminal record [N(%)]	Yes	40 (24,7)	37 (30,3)	3 (7,5)	**‹0,01** [2]
	No	122 (75,3)	85 (69,7)	37 (92,5)	
Other medical problems [N(%)]	No	89 (54,9)	65 (53,3)	24 (60,0)	0,215 [2]
	Endocrine	8 (4,9)	4 (3,3)	4 (10,0)	
	Circulatory	23 (14,2)	20 (16,4)	3 (7,5)	
	Digestive	33 (20,4)	27 (22,1)	6 (15,0)	
	Nervous system	9 (5,6)	6 (4,9)	3 (7,5)	
Patient referred by [N(%)]	Psychiatry	120 (74,1)	86 (70,5)	34 (85,0)	0,192 [2]
	Internal/digestive Medicine	35 (21,6)	4 (3,3)	1 (2,5)	
	Mental Health Centre	5 (3,1)	30 (24,6)	5 (12,5)	
	Other	2 (1,2)	2 (0,16)	-	
Initial psychiatric treatment [N(%)]	‹1 year	38 (23,5)	29 (23,8)	9 (22,5)	0,167 [2]
	1-5 years	46 (28,4)	36 (29,5)	10 (25,0)	
	5-10 years	16 (9,9)	15 (12,3)	1 (2,5)	
	›10 years	62 (38,3)	42 (34,4)	20 (50,0)	
Psychiatric medication [N(%)]	Yes	123 (75,9)	86 (70,5)	37 (92,5)	**‹0,01** [2]
	No	39 (24,1)	36 (29,5)	3 (7,5)	
Family history of addiction [N(%)]	Yes	100 (61,7)	45 (36,9)	17 (42,5)	0,576 [2]
	No	62 (38,3)	77 (63,1)	23 (57,5)	
Smoker [N(%)]	Yes	111 (68,5)	80 (65,6)	31 (77,5)	0,218 [2]
	Ex-fumador	26 (16,0)	23 (18,9)	3 (7,5)	
	No	25 (15,4)	19 (15,6)	6 (15,0)	
Substance use disorder (SUD) [N(%)]	Only AUD	98 (60,4)	68 (55,7)	30 (75,0)	**‹0,05** [2]
	AUD + other SUDs	64 (39,6)	54 (44,3)	10 (25,0)	
Other psychiatric comorbidity disorder* [N(%)]	Yes	111 (68,5)	78 (63,9)	33 (82,5)	**‹0,05** [2]
	No	51 (31,5)	44 (36,1)	7 (17,5)	

Note. Abbreviations: N=number of subjects; SD=standard deviation; AUD=alcohol use disorder; SUD= substance use disorder.
Value p is the level of significance calculated by: (1) Student's t test, and (2) Fisher's exact test or chi-square.
(*) Substance use disorders are excluded (SUD)

establishing the links that exist with the psychiatric comorbidity of the participating patients.

Statistical analysis

The data was expressed in numerical terms, percentage of subjects [n (%)], means and standard deviations (SD). The differences between categorical variables were determined using Fisher's exact test or the Chi-square test (χ^2), while continuous variables were measured with different statistical approaches depending on the number of comparisons and the distributions involved. For the two-group comparisons the Student's t-test was used for continuous variables with normal distributions and the Mann-Whitney test was applied as a non-parametric test. For comparisons of three groups or more, the Kruskal-Wallis test was used, with Dunn's post-test being used for non-parametric analyses. Normal distribu-

tions were tested for using the D'Agostino and Pearson tests for general normality. The lower *p*-value of 0.05 was considered statistically significant.

The statistical programmes SPSS version 19.0 (SPSS Inc., an IBM Company) and version 5.04 of Graph-Pad Prism (GraphPad Software, San Diego, CA, USA) were used for statistical analyses.

Results

Socio-demographic characteristics and gender differences

Table 1 shows the results of the socio-demographic analysis.

With regard to gender differences in the socio-demographic variables, we can say that 75.3% of the sample was made up of men, and 24.7% were women, without differences in terms of age [mean: 49.3 years (SD=8.1)]. The body mass index, however, did display very significant differences (*p<0.01) between sexes, being higher in women [mean: 24.1 (SD =3.9)] than men [mean: 26.8 (SD=4.5)]. Other very significantly different gender differences (*p<0.01) were found in criminal records and psychiatric medication. Men have more criminal records, while women take more psychiatric medication. Other significant differences (*p<0.05) were found in marital status, with 41% of men and 25% women being married, and substance use disorders (SUD), with 25% of women having AUD comorbidity as against 44.3% of men. Finally, there were significant differences (*p<0.05) in psychiatric comorbidity with other disorders unrelated to substance use, with 82.5% of women presenting such comorbidity compared to 63.9% of men in this variable.

Alcohol consumption patterns in terms of sex and psychiatric comorbidity

Table 2 shows the variables related to acohol consumption patterns, gender differences and psychiatric comorbidity with disorders not related to substance use.

Highly significant differences (*p<0.01) were found in the drinking onset age variable. There are very significant differences (*p<0.01) between the two comorbidity groups, with women starting to drink alcohol later [mean age 18.2 years (SD=3.2)] than men [mean age 15.92 (SD=3.6)]. There were also significant differences (*p<0.05) in the onset age for problematic drinking between sexes and psychiatric comorbidity. Here, there were also significant specific differences (*p<0.05) between men with psychiatric comorbidity [mean age 25.73 years (SD=9.8)] and women with psychiatric comorbidity [mean age 32.5 years (SD=12.9)]. These data tell us that women start drinking later than men and also begin problematic drinking later.

Highly significant differences (*p<0.001) are also found in number of years of problematic drinking, where we also see significant differences (*p<0.05) between the two psy-

Table 2. *Alcohol consumption patterns by sex and diagnosis of lifetime psychiatric comorbidity in a population of drinkers under treatment.*

Alcohol consumption patterns	**Total** N=162	**Men** N=122		**Women** N=40		**Value p**
		Without psychiatric comorbidity*	**With psychiatric comorbidity***	**Without psychiatric comorbidity***	**With psychiatric comorbidity***	
Onset age of alcohol use [mean (SD)]	16,8 (4,2)	17,30 (5,4)	15,92 (3,6)	16,2 (2,4)	18,2 (3,2) bb	‹0,01
Onset age of problematic alcohol use [mean (SD)]	28,5 (11,5)	29,32 (11,9)	25,73 (9,8)	34,4 (13,3)	32,5 (12,9) b	‹0,05
Duration of problematic consumption (years) [mean (SD)]	14,9 (7,8)	17,2 (9,1)	15,3 (6,9)	12,0 (8,2)	11,2 (6,3) b	‹0,01
Previous periods of abstinence ** [mean (SD)]	1,2 (1,1)	1,0 (0,9)	1,3 (1,2)	1,4 (1,3)	0,9 (1,0)	0,345
Duration of last period of abstinence (months) [mean (SD)])]	11,4 (17,5)	6,4 (7,2)	13,0 (20,0)	9,6 (11,7)	12,0 (19,6)	0,584
Addiciton criteria met in episode of maximum severity [mean (SD)]	7,1 (2,2)	6,4 (1,8)	8,0 (2,3) aaa	6,1 (1,1)	6,2 (1,9) bbb	‹0,001

Note. Abbreviations: N=number of subjects; SD=standard deviation
Value p is the level of significance calculated on the basis of the Kruskal-Wallis analysis of variance by ranks
([aaa]) p‹0.001 compared to the group "Men without comorbidity"; ([b, bb, bbb]) p‹0.05, p‹0.01 and p‹0.001 compared to the group"Men with comorbidity". Calculated with Dunn's post test.
(*) Substance use disorders are excluded (SUD)
(**) minimum of 6 months abstinence

Table 3. *Diagnoses of alcohol use and other substance use disorder (DSM-IV-TR) by sex and diagnosis of lifetime psychiatric comorbidityin a population of alcohol users under treatment .*

Variable		Total N=162	Men N=122		Women N=40		Value p Gender comorbidity
			Without psychiatric comorbidity*	With psychiatric comorbidity*	Without psychiatric comorbidity*	With psychiatric comorbidity*	
Alcohol [N (%)]	Abuse and/or Dependence	162 (100)	44 (36,1)	78 (63,9)	7 (17,5)	33 (82,5)	-
Cocaine [N (%)]	Abuse and/or Dependence	48 (29,6)	6 (14,3)	36 (85,7)	-	6 (100)	‹0,001
Cannabis [N (%)]	Abuse and/or Dependence	22 (13,6)	2 (11,1)	16 (88,9)	-	4 (100)	‹0,05
Sedatives [N (%)]	Abuse and/or Dependence	6 (3,7)	1 (25,0)	3 (75,0)	-	2 (100)	0,543
Other stimulants** [N (%)]	Abuse and/or Dependence	7 (4,3)	2 (33,3)	4 (66,7)	-	1 (100)	0,627

Note. Abbreviations: N=number of subjects; SD=standard deviation.
Value p is the level of significance calculated by Fisher's exact/chi-square test with patients grouped by sex and psychiatric comorbidity
(*) Excluding substance use disorders (SUD)
(**) Meta-amphetamines and derivatives.

Table 4. *Description of lifetime psychiatric comorbidity (DSM-IV-TR) in a population of alcohol users under treatment.*

Variable		Total N=162	Men N=122	Women N=40	Value p
Psychiatric comorbidity* [N (%)]	Some psychiatric disorder	111 (68,5)	78 (63,9)	33 (82,5)	‹0,05
	MD	74 (45,7)	47 (38,5)	27 (67,5)	‹0,05
	AD	32 (19,8)	23 (18,9)	9 (22,5)	0,650
	Psychotic disorders	15 (9,3)	10 (8,2)	5 (12,5)	0,529
	ED	2 (1,2)	-	2 (5,0)	0,060
	Personality disorders	39 (24,1)	28 (22,9)	11 (25,0)	0,670
	ADHD	46 (28,4)	37 (30,3)	9 (22,5)	0,421
Mood disorders (MD) [N (%)]	Primary Induced Primary+Induced	30 (18,5) 32 (19,8) 12 (7,4)	19 (15,6) 22 (18,0) 6 (4,9)	11 (27,5) 10 (25,0) 6 (15,0)	0,516
Anxiety disorders (AD) [N (%)]	Primary Induced Primary+Induced	19 (11,7) 11 (6,8) 2 (1,2)	12 (9,8) 9 (7,4) 2 (1,6)	7 (17,5) 2 (5,0) -	0,422
Psychotic disorders [N (%)]	Primary Induced Primary+Induced	5 (3,1) 9 (5,6) 1 (0,6)	4 (3,3) 6 (4,9) -	1 (2,5) 3 (7,5) 1 (2,5)	1,000
Eating disorders (ED) [N (%)]	Anorexia Bulimia	- 2 (1,2)	- -	- 2 (5,0)	0,060
Childhood conduct disorder (CCD) [N (%)]		14 (8,6)	13 (10,7)	1 (2,5)	0,192
Personality disorders [N (%)]	Antisocial disorder Bordeline personality disorder	7 (4,3) 24 (14,8)	7 (5,7) 15 (12,3)	- 9 (22,5)	0,152
Attention deficit and hyperactivity disorder (ADHD)** [N (%)]		24 (14,8)	19 (15,6)	5 (12,5)	0,799

Note. Abbreviations: N=number of subjects; SD=standard deviation.
Value p is the level of significance calculated by Fisher's exact/chi-square test with patients grouped by sex.
(*) Axis I=Clinical disorders [substance use disorders are excluded (SUD)]; Axis II=Personality disorders.
(**)ADHD diagnosis (WURS).

Table 5. *Description of lifetime psychiatric comorbidity (DSM-IV-TR) in a population of alcohol users under treatment, by sex and diagnosis of alcohol use and other substance use disorders.*

Variables	Total	Men N=122		Women N=40		Value p
		AUD + other SUD	AUD	AUD + other SUD	AUD	
Number of patients [N (%)]	162 (100)	53 (43,4)	69 (56,6)	10 (25,0)	30 (75,0)	‹0,05
Psychiatric comorbidity * [N (%)]	111 (68,5)	46 (37,7)	32 (26,2)	10 (25,0)	23 (57,5)	‹0,01
Psychiatric comorbidity (≥ two diagnoses) * [N (%)]	63 (38,9)	31 (25,4)	14 (11,5)	8 (20,0)	10 (25,0)	0,087
Mood disorders (MD) [N (%)]	74 (45,7)	24 (19,7)	23(18,9)	8 (20,0)	19 (47,5)	‹0,001
Anxiety disorders (AD) [N (%)]	32 (19,8)	15 (12,3)	8 (6,5)	2 (5,0)	7 (17,5)	‹0,05
Psychotic disorders [N (%)]	15 (9,3)	5 (4,1)	5 (4,1)	2 (5,0)	3 (7,5)	1,000
Eating disorders (ED) [N (%)]	2 (1,2)	-	-	2 (5,0)	-	-
Antisocial personalilty disorder [N (%)]	11 (6,8)	9 (7,4)	1 (0,8)	1 (2,5)	-	-
Borderline personality disorder [N (%)]	28 (17,3)	13 (10,6)	5 (4,1)	7 (17,5)	3 (7,5)	1,000
Attention deficit hyperactivity disorder (ADHD) ** [N (%)]	46 (28,4)	28 (22,9)	9 (7,4)	4 (10)	5 (12,5)	0,106

Note. Abbreviations: N=number of subjects; TUA=trastornos por uso de alcohol; TUS=trastornos por uso de otras sustancias.
Value p is the level of significance calculated by Fisher's exact/chi-square test with patients grouped by sex and AUD and SUD diagnosis
(*) Axis I= Clinical disorders [substance use disorders are excluded (SUD)]; Axis II=Personality disorders
(**)ADHD diagnosis (WURS)

chiatric comorbidity groups with non-substance related disorders. Men with other psychiatric comorbidity are affected for longer by the condition [mean 15.3 years (SD=6.9)] than women [mean 11.2 years (SD=6.3)] before seeking treatment for AUD. Finally, there are very significant differences (*p<0.001) in the number addiction criteria in the most severe episode. Specifically, we found very significant differences (*p<0.001) between the group of men with psychiatric comorbidity and those without comorbidity in terms of the number of criteria in the severest episode. The differences are also highly significant (*p<0.001) with regard to gender when comorbidity is present, with men meeting more criteria [mean 8.0 criteria (SD=2.3)] than women when comparing the two psychiatric comorbidity groups.

In addition, gender differences are reported when severe physical dependence symptoms are present, convulsions and/or *delirium tremens*, with a prevalence of 7.4% among men alone, irrespective of the presence of non-AUD psychiatric comorbidity or not.

SUD psychiatric comorbidity. Substance abuse and dependence

Table 3 shows the SUD comorbidity of the population under scrutiny in relation to psychiatric comorbidity and gender. Significant differences can be seen (*p<0.05) in cocaine SUD linked to gender, with men being affected more. Very significant differences (*p<0.001) were found in the prevalence of comorbid disorders in patients with cocaine SUD compared to those without cocaine SUD. Significant differences (*p<0.05) were also discovered in relation to cannabis consumption, with a high prevalence of cannabis SUD in other psychiatric comorbidity disorders, but without gender differences. Patients with AUD and cannabis and cocaine SUD comorbidity are more likely to be comorbid with other, non-substance related disorders than those patients without SUD.

We must point out that with regard to the remaining other substances studied, no statistically significant differences were found between groups throughout patients' lives.

Psychiatric comorbidity of disorders not related to substance use

Table 4 shows the different diagnoses, excluding the disorders related to the use of substances presented by the patients and gathered with the assessment instruments (PRISM and WURS), differentiated by gender. We found statistically significant differences (*p<0.05) in the prevalence of psychiatric disorders, with 82.5% of women as opposed to 63.9% of men diagnosed with non-addictive mental disorders. Very significant differences (*p<0.01) are also present in the prevalence of MD among women (67.5%) versus men (38.5%). No significant gender diffences were found in the other disorders.

Gender differences in SUD psychiatric comorbidity.

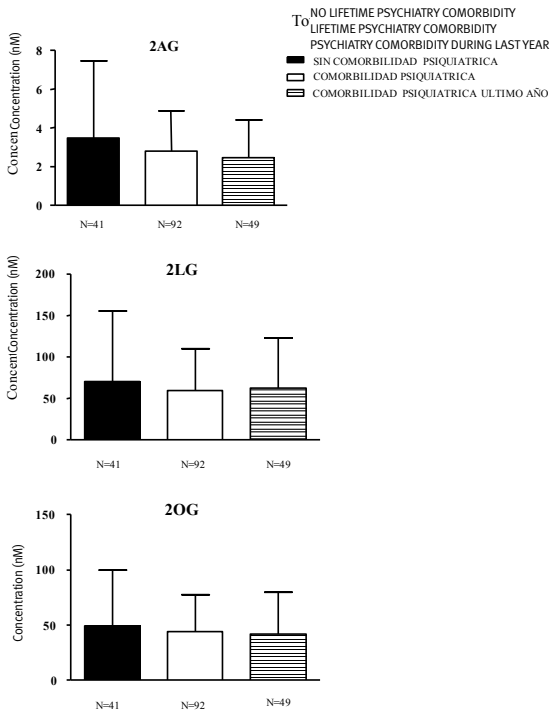
This section (see Table 5) will describe in detail the distribution of psychiatric disorders across the differences arising from gender and the type of SUD diagnosed. It can be said that when differentiating according to substance, psychiatric comorbidity varies among those who have just one (AUD) compared to those who have a SUD as well as an AUD. In the case of women with SUD comorbidity, we can see that 100% are also affected by other psychiatric disorders during their lifetime, most frequent among them MD and borderline personality disorder. Men without SUD comorbidity (AUD only) are less likely to suffer from other psychiatric disorders if we compare them to those who have SUD comorbidity, and although these differences are not noticeable in MD diagnoses, they are very pronounced in personality disorders.

It is worth looking at the attention deficit and hyperactivity disorder, given its close link to depressant drugs and its high prevalence in SUD (Daigre et al., 2013; Polanczyk et al., 2014), and also in AUD, as is also the case in our patients (Ponce et al., 2000).

Plasma levels of 2-acyl-glycerols

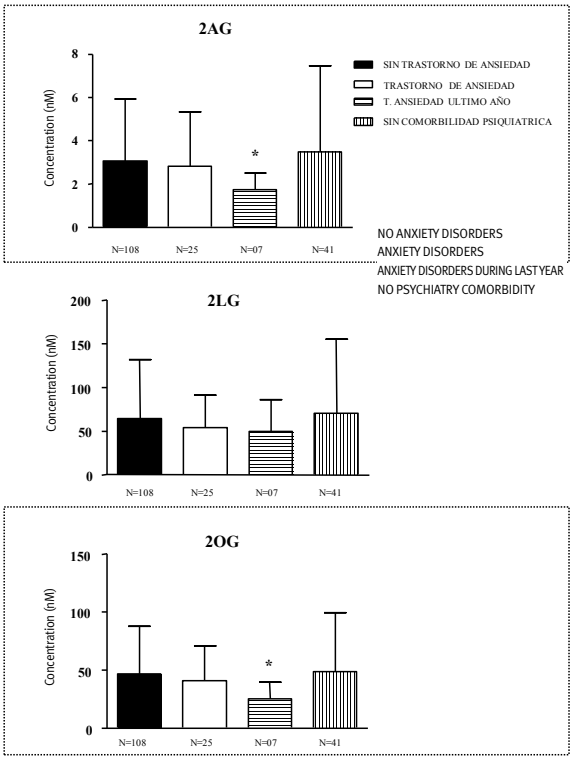
Plasma levels of 2-acyl-glycerols are lower in patients with psychiatric comorbidity (excluding SUDs), but there are no significant differences between the groups with regard to psychiatric comorbidity. We have made a distinction in time frames among patients with psychiatric comorbidity (lifetime versus last year) and a comparison with patients without psychiatric comorbidity (Figure 1).

The 2-AG and 2-OG plasma levels are significantly lower in (*p<0.05) in patients diagnosed with anxiety disorders in



(#) Substance use disorders (SUD) were excluded.

Figure 1. Plasma levels of 2-acy-glycerol (2-AG, 2-linoleil glycerol (2-LG) and 2-oleoylglycerol (2-OG) in alcohol dependence patients grouped by psychiatric comorbidity (#).



(*) p<0.05 indicate significant differences from no anxiety disorders group.

Figure 2. Plasma levels of 2-acy-glycerol (2-AG, 2-linoleil glycerol (2-LG) and 2-oleoylglycerol (2-OG) in alcohol dependence patients grouped by anxiety disorders (DSM-IV-TR)].

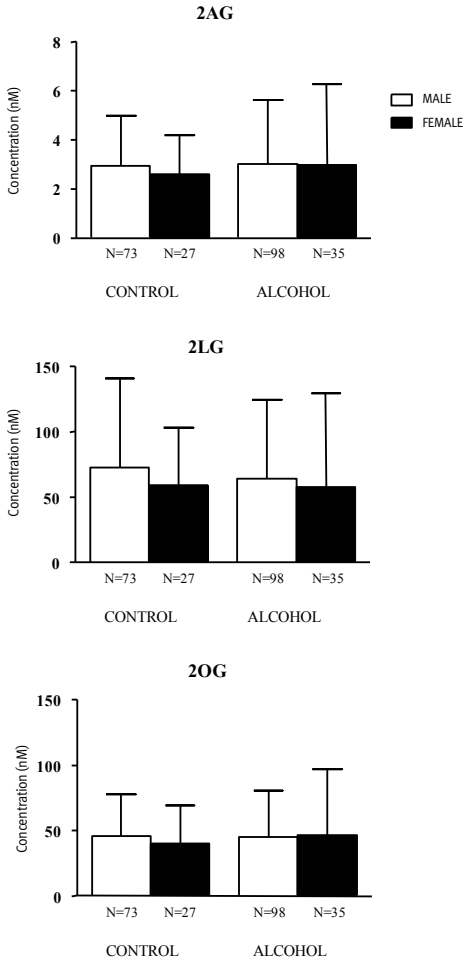


Figure 3. Plasma levels of 2-acy-glycerol (2-AG, 2-linoleil glycerol (2-LG) and 2-oleoylglycerol (2-OG) in alcohol dependence patients and control subjects grouped by sex.

the last year when comparing their levels to patients having anxiety disorders throughout their lives, those free of anxiety disorders and patients without psychiatric comorbidity (Figure 2).

Levels of 2-acyl-glycerols show no significant gender differences when comparing the sample of AUD patients with a control group (Figure 3).

Discussion

The results of the present study indicate that patients needing treatment for alcohol use disorders are more frequently affected by psychiatric comorbidity, and in some cases, especially in connection with anxiety disorders, this is reflected in altered 2-acyl-glycerol levels. The prevalence of lifetime psychiatric comorbidity was found to be high (68.5%) in this study, in line with results of some studies carried out on different types of AUD and other pathologies, which reported 60-70% psychiatric comorbidity (Pérez-Gálvez et al., 2008; Driessen et al., 1998). The outpatient profile is mainly masculine, of a low-middle educational background, with a mean age of 49.27 years and a high level of unemployment. Cases with a diagnosis of severe mental disorder have been excluded from this population, but not organic pathologies. These characteristics may lead to a series of biases which need to be taken into account when comparing our data with other AUD populations.

There are important gender differences within AUD, most notably that although women start drinking later than men, they take less time to develop dependence symptoms and meet fewer severity criteria than men. These data match those found in the bibliography, where women have intense drinking patterns, with a faster development from onset to dependence. This pattern could be the reason why they are more likely to suffer concomintant medical problems in comparison to men with AUD (Ávila Escribano et al., 2007; Keyes et al., 2010). Gender differences are also found in disorders not related to substance use, where men are more likely to suffer personality disorders. Antisocial personality disorder, for example, is diagnosed three times more frequently among men than women (Alegría et al., 2013). Women, on the other hand, have a greater likelihood of being affected by depressive disorders (Ávila Escribano et al., 2007). The lack of social support among women and the interpersonal problems in family contexts are risk factors and possible causes of the gender differences in non-SUD psychiatric comorbidity (Alegría et al., 2013).

In the analysis of the population with respect to SUD comorbidity, we found that polydrug use may be related to psychiatric comorbidity, especially when AUD is accompanied by other SUDs involving cocaine and cannabis. It is known that cocaine SUD is linked to a high prevalence of psychiatric comorbidity (Araos et al., 2014), and the literature also reports high polydrug use in patients receiving treatment, mostly young men who have never been married, with a low onset age and psychiatric comorbidity (Blanco et al., 2015). An analysis of psychiatric comorbidity in our sample reveals firstly that primary and substance-induced mood disorders are equally frequent over a lifetime. We know that depression beginning before the onset of SUD reduces the probability of remission from dependence, as does severe induced depression (Samet et al., 2013). Some studies claim that the severity of SUD is a good predictor of depressive disorders arising during patient follow-up (Boschloo et al., 2012), and this is makes sense in our sample when we see the connection between the presence of psychiatric comorbidity and the severity of AUD addiction symptoms. Secondly, with repect to anxiety disorders (AD), primary were more prevalent than induced disorders in terms of lifetime diagnoses. Thirdly, psychotic disorders (PD) in our sample are mostly induced, although they are less far frequent than those found in other populations with substance use disorders, where the prevalence was high (15.5%) (Araos et al., 2014). Although primary mood and anxiety disorders are

generally more frequent than substance-induced disorders (Torrens et al., 2011), our results are in line with those of other studies carried out with PRISM for mood and psychotic disorders in cocaine SUD populations, where induced disorders were more common than primary disorders, and anxiety disorders were more frequently primary than induced (Araos et al., 2014; Vergara-Moragues et al., 2012). Finally, with regard to personality disorders, our population has a 6.8% prevalence of antisocial personality disorders and a 17.4% rate of borderline personality disorder. These figures are lower than those found in other SUD populations involving substances such as cocaine (Araos et al., 2014). There is some evidence suggesting that personality disorders are more frequently associated with other SUDs because the consumption of the substances involved increases behavioural problems, clinical severity and social difficulties (Salom et al., 2014).

With regard to ADHD, this is diagnosed in 7% of children with approximately 4% continuing to be affected as adults (Kessler et al., 2006). In our population an above average prevalence of this disorder was detected, and this result may have been influenced by the use of a specific measurement instrument in the diagnosis. Nevertheless, symptoms in adults may give rise to errors such as, for example, restlessness being interpreted as anxiety or distractibility as lack of interest or motivation (Quintero et al., 2013). Having SUD comorbidity increases the psychiatric comorbidity of the sample (Tómasson y Vaglum, 1995). In our sample, when we eliminate other SUDs in AUD patients, the prevalence of other psychiatric comorbidity is reduced (from 82.5% to 57.5% among women, and from 63.9% to 26.2% in men). Mood and anxiety disorders are the most prevalent among AUD patients. The frequency of personality disorders also went down because antisocial disorder among men without SUD comorbidity fell to 0.8% and borderline personality disorder in women dropped to 7.5%. Our figures are in line with those obtainaed in studies of similar populations (only AUD) in Spain, where antisocial disorder appears in around 2% of cases and borderline personality in about 6% (Fernández-Montalvo et al., 2006). These patients have both internal and external behavioural problems in comparison to those only suffering AUD (Salom et al., 2014).

The results regarding psychiatric comorbidity described above support the need to find objective biological evidence which could serve as specific biomarkers for AUD subgroups with specific psychiatric comorbidities psiquiátricas. In this regard, our research contributes a description of the 2-acyl-glycerol plasma values in these patients for the first time. Our data suggests that 2-AG and 2-OG are affected by anxiety disorders diagnosed during the last year. Endocannabinoid signaling has been involved in anxiety modulation and emotional response (Navarro et al., 1997). An increase in the liberation of endocannabinoids is associated with the anxiolytic effect, which has driven the development of many pharmaceuticals, especially those linked to the blockade of endocannabinoid degrading enzymes FAAH and MAGL (Gaetani et al., 2003; Kinsey et al., 2011). We have found studies linking the deregulation of acylglycerols with difficulties in adapting to stressful and adverse stimuli, with an increase in stress, anxiety and fear responses (Guggenhuber et al., 2015; Jenniches et al., 2015). Our further findings of a relationship between changes in 2-acyl-glycerols and the diagnoses of anxiety disorders places our research closer to potential stress and anxiety therapy targets.

Among the limitations of our study we have to point out that the retrospective assessment of clinical and withdrawal symptomatology was not ideal, and the same must be said of the abstention periods as reported by the patients. In addition, sample size was small from a statistical point of view, although adequate from a clinical perspective, and the percentage of women included in the study was also modest.

Continuing research in this area of phenotypic characterization should be carried out with larger and more representative samples. A longitudinal study which would enable testing for psychopathological symptoms and addiction severity while increasing the female population meeting the inclusion criteria would be welcome. In this way, more accurate comparisons can be made between the sexes and more specialised treatments can be designed. Furthermore, there is a need to incorporate and increase the samples of the different biomarkers to diagnose consumption, severity and comorbidity in an effort to improve prognoses and optimise treatments adapted to the needs of each type of patient.

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Conflict of interests

None.

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Substance use or abuse, internet use, psychopathology and suicidal ideation in adolescents?

Uso y abuso de sustancias psicotrópicas e internet, psicopatología e ideación suicida en adolescentes

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Abstract

Substance and Internet use or abuse, psychopathology and suicidal ideation appear to be related. The aim of this study is to investigate the association between use of psychotropic substances, inadequate Internet use, suicidal ideation and other psychopathological symptoms within the adolescent population. The present study was carried out as part of the Saving and Empowering Young Lives in Europe (SEYLE) project, funded by the European Union. The sample is composed of 1026 adolescents aged between 14 and 16 years from 12 state schools in Asturias (530 men and 496 women). This study adds to the possibility of knowing whether the SEYLE data is confirmed in a relatively isolated and recession hit province of Spain.

In the present study the following consumption rates were obtained: a) alcohol 11.89% in males and 7.86% in females; b) tobacco: 4.15% and 5.44 % in males and females respectively; c) other drugs: 6.98% in males and 4.44% in females; d) maladaptive or pathological Internet use: 14.53% and 20.77% in males and females respectively.

The variables that predict suicide ideation in the logistic regression model were: previous suicide attempts, depression, maladaptive or pathological Internet use, peer problems and alcohol consumption.

Keywords: Suicide; Substances; Internet; Psychopathology; Teenagers.

Resumen

El uso o abuso de sustancias o internet, la psicopatología y la ideación suicida parecen estar relacionadas. El objetivo del presente estudio es investigar la asociación en población adolescente entre consumo de sustancias potencialmente adictivas, uso inadecuado de internet, psicopatología e ideación suicida. El estudio forma parte del proyecto europeo *Saving and Empowering Young Lives in Europe* (SEYLE). La muestra está compuesta por 1026 adolescentes con edades comprendidas entre 14 y 16 años procedentes de 12 centros escolares públicos del Principado de Asturias (530 varones y 496 mujeres). El presente trabajo aporta la posibilidad de conocer si los datos generales del proyecto SEYLE varían en una zona relativamente aislada y socioeconómicamente en recesión.

Las tasas obtenidas de consumo de las distintas sustancias y de uso de internet fueron: a) alcohol: 11,89% en varones y 7,86% en mujeres; b) tabaco: 4,15% y 5,44% en varones y mujeres respectivamente; c) otras drogas: 6,98% en varones y un 4,44% en mujeres; d) uso de internet desadaptativo o patológico: 14,53% y 20,77% en varones y mujeres respectivamente.

Se ha observado que las variables con capacidad predictiva sobre las conductas suicidas fueron: tentativas suicidas previas, síntomas depresivos, uso desadaptativo o patológico de internet, problemas con los compañeros y consumo de alcohol.

Palabras clave: Suicidio; Sustancias; Internet; Psicopatología; Adolescentes.

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Suicidal behaviors and the use of potentially addictive psychoactive substances are two of the problems with the greatest impact on global public health, particularly among young people. Suicide is the second leading cause of death in people aged 15-29 (World Health Organization, 2012), and the proportion of psychotropic substance consumption among young people is high. The percentage of young people using psychoactive substances in 2014 was: alcohol 76.8%; tobacco 31.4%; cannabis 25.4%; cocaine 2.8% and other types of illegal drugs less than 1% (ESTUDES 2014). Under the heading of behaviors that may be considered non-substance related addictions (behavioral addictions), the excessive use of the Internet is a growing phenomenon of our time that occurs especially among groups of young people (Fioravanti, Dettore & Casale, 2012; Seybert, 2012; Smahel, Blinka & Ledabyl, 2008).

The pathological use of the Internet has in recent years transcended the category of impulse control disorder (Young, 1999) to be considered as a behavioral addiction (Griffiths, 2000), given that it shares common characteristics with other addictive behaviors (Brezing, Derevensky & Potenza, 2010; Goldstein & Volkow, 2011; Grant, Potenza, Weinstein & Gorelick, 2010; Kormas, Critselis, Janikian, Kafetzis & Tsitsika, 2011; Montag, Kirsch, Sauer, Markett & Reuter, 2012; Zhou et al., 2011). Pathological gambling is included in DSM-5 (APA, 2013) under addictive disorders and Internet gaming disorder is listed in the section headed Conditions for Further Study (Section III). However, despite their importance, the handbook does not include addiction to the Internet or new virtual technologies as a whole (Carbonell, 2014).

Among people who inject drugs, the use of substances such as alcohol, sedative-hypnotics and cannabis seems to be associated with a higher likelihood of subsequent attempted suicide (Artenie et al., 2015). People with substance dependence and a history of depression are at increased risk of suicide attempts, regardless of whether depression occurred before or during substance abuse (Aharonovich, Liu, Nunes & Hasin, 2002). Other types of mood disorders show the same trend, for example patients with bipolar disorder and alcohol abuse are at higher risk of suicide (Dalton, Cate-Carter, Mundo, Parikh & Kennedy, 2003; Hawton, Sutton, Haw, Sinclair & Harriss, 2005; Oquendo et al., 2010; Potash et al., 2000).

In adolescents, Internet addiction is associated with attention-deficit hyperactivity disorder (Gundogar, Bakim, Ozer & Karamustafalioglu, 2012; Yoo et al., 2004), depressive disorders (Andreou & Svoli, 2013; Sasmaz et al., 2014), anxiety disorders (Lee & Stapinski, 2012; Zboralski et al., 2009), and with suicidal behaviors (Fernández-Villa et al., 2015; Hakala, Rimpela, Saarni & Salminen, 2006; Kim, 2012; Kim et al., 2016; Shapira, Goldsmith, Keck, Khosla & McElroy, 2000).

The study of the relationship between substance use, Internet use and abuse, and suicide ideation and behaviors, and psychopathology (Al-Asadi, Klein & Meyer, 2015) is justified because it could improve the chances of reaching a better understanding of the psychopathological substrates underlying these phenomena (Kaess et al., 2014).

The aim of the present study is to assess the situation of a young population in relation to the consumption of psychotropic substances, suicidal ideation and other psychopathological symptoms, and to explore the possible associations between these aspects. The research is limited to the Autonomous Community of the Principality of Asturias, one of the areas of Spain with the lowest economic growth in the period 2000-2009, during which it has suffered a strong socioeconomic recession (INE, 2010), and has the added interest of enabling us to assess whether the unique socio-economic situation can produce differential data. It also provides an assessment of inappropriate Internet use as an emergent behavioral addiction with an influence on suicidal ideation.

Method

This is an observational, descriptive and cross-sectional epidemiological study analyzing Spanish data from the Saving and Empowering Young Lives in Europe (SEYLE) (Wasserman et al., 2012) project and using the same methodology (Kaess et al., 2014).

Participants

The sample (Spanish sub-sample) is composed of 1026 individuals, from 12 state schools in Oviedo, Gijón and Avilés randomly selected from among the schools in the Autonomous Community of Asturias, in accordance with the inclusion and exclusion criteria of the SEYLE project (Wasserman et al., 2010).

Procedure

Prior to the start of the study and in compliance with the rules governing research on young people, the authorization of the juvenile prosecutor was obtained as well as the approval of the Ethics and Clinical Research Committee of the Principality of Asturias. Local school authorities granted permission to visit the randomly selected schools and participating individuals gave their approval and informed consent when requested.

Instruments

A structured self-report questionnaire was used, administered in the classroom during school hours to collect data on lifestyles, behaviors, values, mental health and suicidality.

Suicidal ideation and behavior were measured using the Paykel Suicide Scale (PSS) (Paykel, Myers, Lindenthal &

Tanner, 1974). The PSS comprises the following five questions: During the last two weeks: (i) Have you felt that life is not worth it?; (ii) Did you wish to be dead?; (iii) Have you thought about taking your life even though you were not really going to do it?; (iv) Have you reached the point where you have really considered taking your life or making plans about how you would do it?; and (v) Have you ever tried to take your life? The person was considered to have suicidal thoughts if they answered "yes" to questions (iii) or (iv) of the PSS. Suicide attempts were defined by the "yes" response to the last question (v) of the PSS.

In order to assess levels of substance use, the Global School-based Student Health Survey (GSHS) (World Health Organization, 2015) was used, with the following cut-off points: drinking any amount of alcohol on two or more occasions per week was considered alcohol consumption; regarding substance use, the cut-off was set at having used illicit drugs at least three times during their lifetimes and smoking more than ten cigarettes a day.

Pathological Internet use was evaluated using the Young's Diagnostic Questionnaire (YDQ) (Young, 1998). The score on the eight items reflects eight of the nine criteria for Internet gambling disorder in DSM-5. Based on the responses to the questionnaire, subjects were divided into three categories of Internet use. With one point for each affirmative answer, individuals scoring between 0 and 2 were considered to have adaptive Internet use (AIU), while scores of 3 and 4 signaled maladaptive Internet use (MIU). A score of 5 or above corresponded to pathological Internet use (PIU) (Kaess et al., 2014).

The Beck Depression Inventory (BDI-II) was used to evaluate depressive symptoms (Beck, Steer, Ball & Ranieri, 1996), with a score equal to or greater than 20 signaling a risk of depression. For the present study a modified version, the BDI-II, was used. The item "loss of libido" was removed from the scale as it was considered to be 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 degrees of psychopathology, the Strengths and Difficulties Questionnaire (SDQ) (Goodman, Meltzer & Bailey, 2003) was used. This evaluates emotional symptoms, behavior problems, hyperactivity/inattention, problems with peer relationship and pro-social behavior. The cut-off points were set as follows: a score equal to or greater than 7 for emotional symptoms, a score equal to or greater than 5 for behavior problems and a score equal to or greater than 7 for hyperactivity. In the case of peer problems, the cut-off was set at a score of 6 or higher, while the lack of pro-social behavior was defined as a score 4 or less (Carli et al., 2013).

To evaluate global subjective well-being, the WHO-5 Wellness Questionnaire (Topp, Ostergaard, Sondergaard & Bech, 2015) was employed.

Data analysis

A study of the global and sex disaggregated sample was conducted. The values of the categorical variables were expressed in frequencies and percentages, and those of the continuous variables in means and standard deviations. In the categorical variables, the comparison between groups was performed using the Chi-square test, or Fisher's exact test in those cases in which a group was smaller than five. For quantitative variables, Student's t-test was applied for the comparison of means.

The analysis of the relationship between suicidal ideation, risk behaviors and the psychopathological characteristics of the subjects of the sample was carried out using a logistic regression model with forward selection, including as dependent variables all those that were significant in the univariate analysis (Tables 3 and 4), age and sex. Statistical significance was set at an alpha level of 5%.

Results

We studied 1026 schoolchildren, 530 (51.66%) of which were males and 496 (48.34%) females, aged between 14 and 16. The mean age of the sample studied was 14.52 years (SD = 0.70), with no differences between the sexes.

Table 1 shows the rate of substance use and Internet usage patterns according to sex, with significantly higher alcohol consumption in men and a significantly higher maladaptive or pathological Internet use in women.

With regard to psychopathological characteristics (Table 2), women showed more emotional symptoms and previous suicide attempts, while men scored higher on hyperactivity and lack of pro-social behavior on the SDQ scale. Likewise, there were statistically significant differences in the perception of quality of life according to the WHO-5 questionnaire (higher among males).

Table 1. *Risk behaviors by sex. Substance use (alcohol, drugs and tobacco) and Internet use.*

	Males (n=530)	Females (n=496)	X^2	p-value
Consumption of alcohol	63 (11.89%)	39 (7.86%)	4.20	0.040
Consumption of drugs	37 (6.98%)	22 (4.44%)	2.61	0.132
Consumption of tobacco	22 (4.15%)	27 (5.44%)	0.68	0.410
Internet use			4.91	0.027
AIU	453 (85.47%)	393 (79.23%)		
MIU	58 (10.94%)	78 (15.73%)		
PIU	19 (3.59%)	25 (5.04%)		

Note. AIU: adaptive Internet use, MIU: maladaptive Internet use, PIU: pathological Internet use.

Table 2. *Psychopathological characteristics by sex.*

	Males (n=530)	Females (n=496)	X^2/T	p-value
Depression (BDI)	29 (5.47%)	40 (8.06%)	3.25	0.126
Emotional symptoms (SDQ)	9 (1.70%)	56 (11.29%)	38.13	‹0.001
Behavioral problems (SDQ)	32 (6.04%)	19 (3.83%)	2.20	0.138
Hyperactivity (SDQ)	106 (20.00%)	57 (11.49%)	13.25	‹0.001
Problems with peers (SDQ)	15 (2.83%)	14 (2.82%)	0.03	0.863
Lack of pro-social behavior (SDQ)	17 (3.21%)	1 (0.20%)		‹0.001
Suicidal ideation	37 (6.98%)	40 (8.06%)	0.43	0.510
Prior suicide attempts	11 (2.08%)	21 (4.23%)	3.9503	0.046
Quality of life (WHO-5)	68.21 (DE=19.16)	64.40 (DE=18.15)	3.27	‹0.001

Table 3. *Risk behaviors in the presence of suicidal ideation. Substance use (alcohol, drugs and tobacco) and Internet use among males and females.*

	Suicidal ideation (n=77)	No suicidal ideation (n=949)	X^2	p-value
Consumption of alcohol	25 (32.47%)	77 (8.11%)	44.50	‹0.001
Consumption of drugs	15 (19.48%)	44 (4.64%)	26.28	‹0.001
Consumption of tobacco	9 (11.69%)	40 (4.21%)	7.18	0.007
Internet use			590.11	‹0.001
AIU	37 (48.05%)	809 (85.25%)		
MIU	25 (32.47%)	111 (11.69%)		
PIU	15 (19.48%)	29 (3.06%)		

Note. AIU: adaptive Internet use, MIU: maladaptive Internet use, PIU: pathological Internet use.

Table 4. *Psychopathological characteristics of individuals sampled according to presence of suicidal ideation.*

	Suicidal ideation (n=77)	No suicidal ideation (n=949)	X^2/T	p- value
Depression (BDI)	37 (48.05%)	32 (3.37%)	219.59	‹0.001
Emotional symptoms (SDQ)	22 (28.57%)	43 (4.53%)	65.37	‹0.001
Behavioral problems (SDQ)	16 (20.78%)	35 (3.69%)	40.50	‹0.001
Hyperactivity (SDQ)	20 (25.97%)	143 (15.07%)	55.49	0.018
Problems with peers (SDQ)	10 (12.99%)	19 (2.00%)	27.42	‹0.001
Lack of pro-social behavior (SDQ)	5 (6.49%)	13 (1.37%)	8.08	0.004
Prior suicide attempts	18 (23.38%)	14 (1.48%)	105.93	‹0.001
Quality of life (WHO-5)	46.03 (19.43)	68.02 (17.73)	9.61	‹0.001

Table 5. *Logistic regression model of suicidal ideation.*

Variable	B	OR	CI 95%	p
Constant	-2.03	0.13	(0.05; 0.38)	‹0.001
Internet use				‹0.001
MIU vs AIU	1.09	2.37	(1.19; 4.76)	
PIU vs MIU	1.37	2.56	(0.95; 6.92)	
Consumption of alcohol	1.47	3.44	(1.67; 7.07)	‹0.001
Depression (BDI)	2.45	9.26	(4.60; 18.64)	‹0.001
Problems with peers (SDQ)	1.92	3.88	(1.22; 12.37)	0.029
Prior suicide attempts	2.52	8.45	(3.31; 21.55)	‹0.001
Quality of life (WHO-5)	-0.03	0.97	(0.95; 0.99)	‹0.001

Dividing the subjects of the study according to the presence of suicidal ideation (Table 3), a significant link was found between substance use (alcohol, illicit drugs and tobacco) and maladaptive or pathological use of the Internet with suicidal ideation. Table 4 shows the positive association between all psychopathological characteristics studied and suicidal ideation.

Table 5 shows the results of the logistic regression model for the likelihood of occurrence of suicidal ideation events. The presence of depressive symptoms and the existence of previous suicide attempts were found to have great predictive capacity with regard to suicidal behavior. This was lower in the case of problems with peers, alcohol consumption and maladaptive use of the Internet. Some variables that emerged as significant when performing univariate analysis included drug use, the significance of which disappears when it is studied in conjunction with the effect of the other variables.

Discussion

The present study, conducted with adolescents of both sexes with a mean age of 14.52 years, has revealed high rates of substance use and maladaptive or pathological Internet, which is worrying given the negative consequences for physical and psychological health of young people (Fernández-Villa et al., 2013).

There are differences in the substance use profile, which is congruent with the data from the SEYLE project as a whole (Carli et al., 2014) but lower than data from other Spanish studies on older populations. The ESTUDES (ESTUDES 2014) survey of high school students aged 14-18 and a study of university students (Hernández-Serrano, Font-Mayolas & Gras, 2015) found far higher consumption rates of all substances; in addition, in the case of older res-

pondents (university students), tobacco was the most heavily consumed substance, followed by cannabis. Mean age is an important element to take into consideration (14 in the present study), since the onset of alcohol or tobacco use at an early age is associated with subsequent regular intakes and increases the risk of developing other substance use disorders or dependence, and is also associated with problem gambling (Míguez & Becoña, 2015; Motos, Cortés, Giménez & Cadaveira, 2015). As for Internet use, the data are similar to the European sample, except in the case of PIU, which is more frequent in males (5.2% in males and 3.8% in females) in the European sample. Socioeconomic conditions and lack of social and family support may be the cause of variations in PIU risk (Durkee et al., 2012, 2016).

The rates of psychopathological symptoms are high considering the age of the population studied. It is remarkable that the prevalence of hyperactive disorders in males (20%) doubles the European sample rate (about 10%), although not among females. The prevalence figures for Attention Deficit Disorder and Hyperactivity obtained in other studies hover around 5% (Polanczyk, de Lima, Horta, Biederman & Rohde, 2007; Schlack, Mauz, Hebebrand & Holling, 2014; Willcutt, 2012). This rather notable difference could raise doubts regarding the validity of the scale used (SDQ).

In the case of suicidal ideation, the European sample returned rates (21.2% in men and 35.4% in women) almost four times higher than those of the Spanish sample. Despite the difficulty in ascertaining the determinants of ideation and suicidal behavior, this divergence is likely, at least in part, to be justified by the socio-cultural differences between Spain and the rest of the European Union. The culture of suicide has penetrated more deeply in other societies and although an increase has been observed in Spain in recent years, the suicide figures are lower than those of neighboring countries (Alvaro-Meca, Kneib, Gil-Prieto & Gil de, 2013; Kolves & De Leo, 2016).

Overall, the data of the present study confirm the association between consumption of potentially addictive psychotropic substances, inappropriate use of Internet, psychopathology and suicidal ideation, which could be based on common personality elements or neurobiological mechanisms (Albert, Rosso, Maina & Bogetto, 2008; Schoevers, Deeg, Van & Beekman, 2005; Sher, 2006). However, there are some differences, especially in the lack of a significant association between suicidal ideation and consumption of substances other than alcohol, or in the almost nonexistent effect of quality of life on suicidality.

The effect of Internet use on suicidality is confusing. On the one hand, it is believed to increase the risk of suicidal behavior since it facilitates interaction with other people with suicidal intentions, and it has been shown that exposure to such behaviors through the Internet is associated with the use of more dangerous methods of self-harm. Moreover, the Internet can also be used for cyberbullying (Collings, Fortune, Steers, Currey & Hawton, 2011). On the other hand, the Internet could protect against suicidal ideation if used as a source of emotional support or as an instrument for improving coping strategies (Daine et al., 2013). In any case, in the discussion regarding inappropriate Internet use, the balance appears to be tipping towards negative effects and its use in general is associated with an increased risk of self-harm, suicidal ideation and depression (Madge et al., 2011; O'Connor, Rasmussen & Hawton, 2012).

The present study presents some limitations, among which is sample size, which despite being large, does not allow associations between infrequent variables such as drug use to be established nor analysis disaggregated by age groups to be performed.

Conclusions

The present study has found a relatively high prevalence of psychotropic substance use, maladaptive or pathological use of the Internet, suicidal ideation and psychopathological symptoms in a sample of young adolescents.

The variables that predict suicidal ideation with a relevant effect are: prior suicide attempts, presence of depressive symptoms, maladaptive or pathological use of the Internet, alcohol consumption and problems with peers.

Conflict of interests

The authors state that there is no conflict of interest.

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Applied Prevalence Ratio estimation with different Regression models: An example from a cross-national study on substance use research

Estimación de la Razón de Prevalencia con distintos modelos de Regresión: Ejemplo de un estudio internacional en investigación de las adicciones

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Abstract

Objective: To examine the differences between Prevalence Ratio (PR) and Odds Ratio (OR) in a cross-sectional study and to provide tools to calculate PR using two statistical packages widely used in substance use research (STATA and R). *Methods:* We used cross-sectional data from 41,263 participants of 16 European countries participating in the Survey on Health, Ageing and Retirement in Europe (SHARE). The dependent variable, hazardous drinking, was calculated using the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C). The main independent variable was gender. Other variables used were: age, educational level and country of residence. PR of hazardous drinking in men with relation to women was estimated using Mantel-Haenszel method, log-binomial regression models and poisson regression models with robust variance. These estimations were compared to the OR calculated using logistic regression models. *Results:* Prevalence of hazardous drinkers varied among countries. Generally, men have higher prevalence of hazardous drinking than women [PR=1.43 (1.38-1.47)]. Estimated PR was identical independently of the method and the statistical package used. However, OR overestimated PR, depending on the prevalence of hazardous drinking in the country. *Conclusions:* In cross-sectional studies, where comparisons between countries with differences in the prevalence of the disease or condition are made, it is advisable to use PR instead of OR.

Keywords: Poisson regression; Log-binomial regression; Prevalence Ratio; Odds Ratio; Cross-sectional studies.

Resumen

Objetivo: Examinar las diferencias entre la Razón de Prevalencia (RP) y la Odds Ratio (OR) en un estudio transversal y proporcionar herramientas para calcular la RP usando dos paquetes estadísticos ampliamente utilizados en la investigación de adicciones (STATA y R). *Métodos:* Se utilizaron los datos de un estudio transversal de 41.263 participantes de 16 países de Europa que participaron en la Encuesta sobre Salud y Envejecimiento en Europa (SHARE). La variable dependiente, consumo de riesgo de alcohol, se calculó a partir del Alcohol Use Disorders Identification Test – Consumption (AUDIT-C). Como principal variable independiente se utilizó el género. Otras variables fueron la edad, el nivel de estudios y el país de residencia. Las RP de consumo de riesgo de alcohol entre hombres y mujeres se estimaron a partir del método de Mantel Haenzel, de modelos de regresión log-binomial y de modelos de regresión de Poisson con varianza robusta. Estas estimaciones fueron comparadas con las OR obtenidas a partir de modelos de regresión logística. *Resultados:* La prevalencia de consumidores de riesgo de alcohol varía según país. En general los hombres tienen un mayor consumo de riesgo que las mujeres [RP=1.43 (1.38-1.47)]. La RP estimada no varía, independientemente del método o paquete estadístico utilizado. Sin embargo, dependiendo de la prevalencia del consumo de riesgo del país, la OR entre los consumidores de riesgo y el género sobrestima la RP. *Conclusiones:* En estudios transversales en los que se comparan distintos países con diferente prevalencia de una determinada enfermedad o condición es recomendable utilizar la RP en lugar de la OR.

Palabras clave: Regresión de Poisson; Regresión Log-binomial; Razón de Prevalencia; Odds Ratio; Estudios transversales.

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Cross-sectional designs are used extensively in substance use research. Substance use researchers usually use this type of design to estimate the association between a dichotomous dependent variable and one or more independent variables. Although the Odds Ratio (OR) or the Prevalence Ratio (PR) could be good estimators of this association, traditionally most studies have used OR, calculated with logistic regression, to estimate the association (Barros & Hirakata, 2003). The PR is defined as the prevalence in exposed population divided by the prevalence in non-exposed, while OR is the odds of disease or condition among exposed individuals divided by the odds of disease or condition among unexposed. In this sense, in cross-sectional designs, when the dependent variable is dichotomous, we usually obtain the prevalence in the descriptive analysis and therefore, PR is more intuitive and easy to understand than OR. Although OR is a good estimator of PR when the prevalence is low, it is known that OR overestimates PR when the prevalence is moderate or high (e.g. prevalence rates above 10%) (Szklo & Nieto, 2012). This could be a problem because OR has usually been treated and interpreted as a PR, independently of the prevalence of the illness (e.g in a paper about predictors of driving under the influence of alcohol among Spanish adolescents, the authors treated the OR as probabilities although the prevalence rate was above 10% in some categories) (Barlés-Arizón, Escario & Sánchez-Ventura, 2014). For those reasons, several studies have come up with alternative methods to estimate associations between a dichotomous dependent variable and several independent variables in cross-sectional designs, which yielded PR (Barros et al., 2003; Coutinho, Scazufca & Menezes, 2008; Deddens & Petersen, 2008; Schiaffino et al., 2003; Thompson, Myers & Kriebel, 1998). One of the simplest methods consists in using the following formula to calculate PR from a given OR (Schiaffino et al., 2003):

$$PR = \frac{OR}{(1 + p_1 * [OR - 1])},$$

where p_1 is the prevalence of the illness or condition in the reference group (non-exposed).

In this case, although point-estimates are correct, there could be a problem when estimating confidence intervals, especially if the models have been adjusted for many variables. The intuitive method to calculate PR would be to use log-binomial regression. However, log-binomial regression often has convergence problems when any of the independent variables is continuous (Cummings, 2009; Deddens et al., 2008). As a result, alternative methods of modelling have been studied (e.g. cox regression models or Poisson regression models) (Barros et al., 2003; Deddens et al., 2008). In addition, although there is evidence supporting the use of Poisson regression models with robust variance to estimate PR in cross-sectional studies (Barros et al., 2003; Coutinho et al., 2008; Deddens et al., 2008), the optimal solution would be to use a log-binomial regression model (Deddens et al., 2008), if it converged. But, if we only take into account one decimal, the results using different regression models do not vary regardless of prevalence of the illness or condition (Cummings, 2009). In this sense, the estimation of PR using Poisson regression models with robust variance, based on the Huber sandwich estimate, has proved to be correct and robust in different experimental situations, such as using different prevalence values (low, moderate or high prevalence) or fitting several models (crude and adjusted) (Barros et al., 2003; Coutinho et al., 2008; Deddens et al., 2008).

Although there appears to be a tendency in recent years to use PR instead of OR in cross-sectional studies (Bosque-Prous et al., 2014; Espelt et al., 2013; Palencia et al., 2010), knowledge among substance use researchers about how to perform these analyses tends to be scarce. For this reason, the objectives of this brief report are to examine the differences between PR and OR in a cross-national study and to provide the tools to calculate PR using log-binomial and Poisson regression models with robust variance with two statistical packages commonly used in substance use research [STATA and R (free software)].

Methods

Design and participants

We used the database of the Survey of Health, Ageing and Retirement in Europe project (SHARE) (Börsch-Supan et al., 2013). The study population consisted of people over 50 years from 16 European countries who participated in wave 4 (2010-2012) of SHARE (n=41,263). Although the database contained sampling weights, they were not used in this study as it was not intended to do a population study. Moreover, participants with missing values in any of the variables were excluded.

Variables

The dependent variable was the prevalence of hazardous drinking, which was constructed using an adaptation of the Alcohol Use Disorders Identification Test Consumption (AUDIT-C test) (Meneses-Gaya et al., 2010). It was constructed based on three questions: two assessing regular drinking in terms of frequency and quantity and one assessing binge drinking (six or more alcoholic drinks in a single occasion, at least once a month in the preceding 3 months). Each answer was ranked from 0 to 4 points, and a final score was calculated as the sum of scores from each question. Hazardous drinking was built as a dichotomous variable (hazardous/non-hazardous drinking), considering drinking to be hazardous when the score was 5 or more among men, and 4 or more among women (Gual, Segura, Contel, Heather & Colom, 2002) [variable name: *auditc*]. The independent

Table 1. *Explanation of the steps to estimate PR using log-binomial regression models or Poisson regression models with robust variance in two statistical packages (STATA and R), using the tool bar or the specific syntax*

Package	Tool Bar (step by step)	Syntax unadjusted	Syntax adjusted
Log-Binomial regression Model			
STATA	Menu tools→Statistics→Generalized Linear Models→Generalized Lineal Models (GLM)→Model [(dependent variable: auditc; independent variable: sex)/ (family: binomial; link choices: log)] →Reporting [report exponentiated coefficients.	glm auditc sex, family(binomial 1) link(log) eform	glm auditc sex educ age, family(binomial 1) link(log) eform
R		install.packages(pkgs = c("Epi", "foreign")) library(Epi) library(foreign) data←read.dta("C:/BBDD.dta", convert.factors=F) model←glm(auditc ~ sex, data=data, family=binomial(link=log)) summary(model) round(ci.lin(model, Exp=T),2)	install.packages(pkgs = c("Epi", "foreign")) library(Epi) library(foreign) data←read.dta("C:/BBDD.dta", convert.factors=F) model←glm(auditc ~ sex + educ + age, data=data, family=binomial(link=log)) summary(model) round(ci.lin(model, Exp=T),2)
Poisson regression model with robust variance			
STATA	Menu tools→Statistics→Generalized Linear Models→Generalized Lineal Models (GLM)→Model [(dependent variable: auditc; independent variable: sex)/ (family: poisson; link choices: log)] →SE/Robust [standard error type: Robust]→Reporting [report exponentiated coefficients.	glm auditc sex, family(poisson) link(log) robust eform	glm auditc sex educ age, family(poisson) link(log) robust eform

R		install.packages(pkgs = c("Epi", "foreign", "sandwich", "lmtest"))
		library(Epi)
		library(foreign)
		library(sandwich) # to get robust estimators
		library(lmtest) # to test coefficients
		
		data←read.dta("C:/BBDD.dta", convert.factors=F)
		
		model←glm(auditc ~ sex, data=data, family=poisson(link=log))
		summary(model)
		coef←coeftest(model, vcov = sandwich)
		## Sex Coefficient
		B←coef["sex","Estimate"]
		## Sex coefficient Standard Error
		SE←coef["sex","Std. Error"]
		## PR point estimation
		exp(B)
		## PR 95% Confidence Interval
		# upper 95% CI
		exp(B + qnorm(0.05 / 2) * SE)
		# lower 95% CI
		exp(B + qnorm(1 - 0.05 / 2) * SE)exp(B + qnorm(0.05 / 2) * SE)
		# lower 95% CI
		exp(B + qnorm(1 - 0.05 / 2) * SE)
			install.packages(pkgs = c("Epi", "foreign", "sandwich", "lmtest"))
			library(Epi)
			library(foreign)
			library(sandwich) # to get robust estimators
			library(lmtest) # to test coefficients
			
			data←read.dta("C:/BBDD.dta", convert.factors=F)
			
			model←glm(auditc ~ sex + educ + age, data=data,
			family=poisson(link=log))
			summary(model)
			coef←coeftest(model, vcov = sandwich)
			## Sex Coefficient
			B←coef["sex","Estimate"]
			## Sex coefficient Standard Error
			SE←coef["sex","Std. Error"]
			## PR point estimation
			exp(B)
			## PR 95% Confidence Interval
			# upper 95% CI
			exp(B + qnorm(0.05 / 2) * SE)
			# lower 95% CI
			exp(B + qnorm(1 - 0.05 / 2) * SE)

variable used was gender [variable name: *sex*] and two different covariables were used to adjust: age, as a continuous variable [variable name: *age*], and educational level (less than secondary studies or secondary or tertiary studies), as a categorical variable [variable name: *educ*]. Finally, we took into account the country of residence, as a stratification variable.

Analysis

We calculated the prevalence of hazardous drinking by gender in each country, using STATA. PR of being a hazardous drinker in men with respect to women was estimated with Mantel-Haenszel method in STATA [syntax: cs *auditc sex*], and with log-binomial regression models and Poisson regression models with robust variance, stratified by country, in STATA and R (table 1). To estimate Poisson regression models, it is necessary to have individual data and to satisfy the following two conditions in order to obtain a realistic point-estimate and confidence intervals of reasonable width (Barros et al., 2003). First, the dependent variable has to be dichotomous with values 0 and 1 (other values cannot be used) when estimating the Poisson models. Value 1 is assigned to the individuals with the disease or condition (hazardous drinkers in our example) and 0 to the remaining participants. And second, the variance of the estimations has to be robust. All the models were performed using Generalized Linear Models with Poisson or binomial families with log link function.

Finally, we also calculated the association between gender and hazardous drinking for each country using logistic regression models in STATA [logit *auditc sex*, or], which yielded OR. Overestimations of OR with respect to PR for each country were calculated, using the following formula: [Overestimation=(OR-PR)/(OR-1)] (Brotman, 2006; Espelt et al., 2013; Shishehbor, Litaker, Lauer, 2006). To perform all the analyses, we used STATA13.0 and R 3.0.2.

Results

Table 1 shows the steps to calculate PR by fitting log-binomial regression models and Poisson regression models with robust variance through the toolbar and the specific syntax, using STATA and R. Data to perform all the analyses are available in STATA format (supplementary data). To get these data and to execute all the analyses properly with R statistical package, the user needs to have previously installed "foreign", "Epi" and "sandwich" libraries (table 1). To read STATA data in R the instruction is data<- read.dta("C:/Users_directori/bbdd.dta", convert.factors=F).

Table 2 shows hazardous drinking prevalence in men and women for each country and the associations between variables calculated using STATA. Hazardous drinking prevalence varied from one country to another. For example, hazardous drinking prevalence in Slovenia was low in both men and women (14% and 11%, respectively), while it was high in both genders in Denmark (39% in men and 35% in women) and in Estonia it was moderate in men (17%) but low in women (4%). PR estimates and their 95% confidence intervals (95%CI) calculated using STATA and R were the same as those calculated using the Mantel-Haenszel method. However, OR overestimated PR in almost all analyses. For example, PR of being a hazardous drinker in men with respect to women in Austria was 1.49 (95%CI: 1.34-1.66) while the corresponding OR was 1.66 (95%CI: 1.45-1.90). Moreover, PR was 1.33 (95%CI: 1.22-1.46) in France, while OR was 1.47 (95%CI: 1.30-1.66). If OR was interpreted as a PR, the overestimation of OR was high in some countries (e.g. 40% in Denmark or 33% in Belgium). The degree of this overestimation depended on the prevalence of hazardous drinking among men and women in each country. However, when the prevalence was similar for men and women, no differences between PR and OR were observed in Netherlands and Switzerland but 33% of overestimation was found in Italy (table 3).

In general, PR calculated using log-binomial or Poisson regression models with robust variance do not vary among them in the unadjusted analysis. However, in the adjusted analysis controlling for educational level and age, some differences in the second decimal were found. PR obtained using different packages were not statistically different.

Discussion

The results show that there is no reason to systematically use OR instead of PR in cross-sectional studies, especially if the prevalence of the disease or condition is moderate or high, since PR are calculated easily and there are methods to obtain robust estimations of PR and their 95%CI. Moreover, our findings are in line with other published articles (Barros et al., 2003; Coutinho et al., 2008; Deddens et al., 2008; Schiaffino et al., 2003; Thompson et al., 1998). As stated in this methodological study, statistical packages used in most epidemiological studies allow researchers to calculate PR easily. However, if we use Poisson regression models we have to be sure that we have used robust methods to estimate their variance, otherwise the Poisson regression would produce wider confidence intervals compared to a log-binomial regression model (McNutt, Wu, Xue, & Hafner, 2003).

One advantage of using PR is that the results are much more intuitive. For example, prevalence of hazardous drinkers in men and women in Austria is 25.6% and 17.2%, respectively. When dividing the prevalence in men by prevalence in women we obtain a PR of 1.49, which is the same PR that was estimated using the various statistical packages. Moreover, we found that the degree of overestimation of PR (using OR) varied among countries and depended on the prevalence of the disease or condition (i.e. hazardous drinking) in exposed and non-exposed participants (in

Table 2. *Unadjusted Prevalence, prevalence ratio, odds ratio and overestimation of OR with respect to PR estimates of being hazardous drinker between men and women in several European countries.*

	Men	**Women**	**Hazardous drinking prevalence**		**$PR_{Men/Women}$ Mantel-Haenszel**		**$PR_{Men/Women}$ log-binomial**		**$PR_{Men/Women}$ robust Poisson**		**$OR_{Men/Women}$ logistic regression**		**Overestimation***
	N	N	Men	Women	PR	95%CI	PR	95%CI	PR	95%CI	OR	95%CI	%
Austria	2,159	2,945	25.61	17.18	1.49	(1.34-1.66)	1.49	(1.34-1.66)	1.49	(1.34-1.66)	1.66	(1.45-1.90)	25.8%
Belgium	2,256	2,789	33.73	30.62	1.10	(1.02-1.19)	1.10	(1.02-1.19)	1.10	(1.02-1.19)	1.15	(1.02-1.30)	33.3%
Czech Republic	2,482	3,420	32.96	15.67	2.10	(1.91-2.31)	2.10	(1.91-2.31)	2.10	(1.91-2.31)	2.65	(2.34-3.00)	33.3%
Denmark	1,006	1,191	38.97	34.76	1.12	(1.00-1.25)	1.12	(1.00-1.25)	1.12	(1.00-1.25)	1.20	(1.01-1.43)	40.0%
Estonia	2,692	4,030	16.75	4.24	3.95	(3.33-4.68)	3.95	(3.33-4.68)	3.95	(3.33-4.68)	4.54	(3.78-5.46)	16.7%
France	2,380	3,164	28.91	21.68	1.33	(1.22-1.46)	1.33	(1.22-1.46)	1.33	(1.22-1.46)	1.47	(1.30-1.66)	29.8%
Germany	697	796	22.53	17.09	1.32	(1.07-1.62)	1.32	(1.07-1.62)	1.32	(1.07-1.62)	1.41	(1.09-1.82)	22.0%
Hungary	1,302	1,730	25.04	8.21	3.05	(2.54-3.66)	3.05	(2.54-3.66)	3.05	(2.54-3.66)	3.74	(3.02-4.62)	25.2%
Italy	1,577	1,940	25.94	25.31	1.02	(0.92-1.15)	1.02	(0.92-1.15)	1.02	(0.92-1.15)	1.03	(0.89-1.20)	33.3%
Netherlands	1,148	1,469	32.32	32.81	0.98	(0.88-1.10)	0.98	(0.88-1.10)	0.98	(0.88-1.10)	0.98	(0.83-1.15)	0.0%
Poland	651	874	14.59	2.75	5.31	(3.44-8.22)	5.31	(3.44-8.22)	5.31	(3.44-8.22)	6.05	(3.82-9.59)	14.7%
Portugal	857	1,129	31.74	20.99	1.51	(1.30-1.76)	1.51	(1.30-1.76)	1.51	(1.30-1.76)	1.75	(1.43-2.14)	32.0%
Slovenia	1,181	1,549	14.31	11.17	1.28	(1.05-1.56)	1.28	(1.05-1.56)	1.28	(1.05-1.56)	1.33	(1.06-1.67)	15.2%
Spain	1,510	1,878	18.34	12.51	1.47	(1.25-1.72)	1.47	(1.25-1.72)	1.47	(1.25-1.72)	1.57	(1.30-1.90)	17.5%
Sweden	848	1,002	12.85	14.57	0.88	(0.70-1.11)	0.88	(0.70-1.11)	0.88	(0.70-1.11)	0.86	(0.66-1.13)	14.3%
Switzerland	1,634	1,987	28.21	27.98	1.01	(0.91-1.12)	1.01	(0.91-1.12)	1.01	(0.91-1.12)	1.01	(0.87-1.17)	0.0%
Total	24,380	31,893	25.88	18.15	1.43	(1.38-1.47)	1.43	(1.38-1.47)	1.43	(1.38-1.48)	1.57	(1.51-1.64)	24.6%

Note. *Overestimation of OR with respect to PR was calculated using the formula: [Overestimation = (OR-PR)/(OR-1)] (Brotman, 2006; Espelt et al., 2013; Shishehbor, Litaker, Lauer, 2006)

Table 3. *Comparison of adjusted prevalence ratio, adjusted odds ratio and overestimation of adjusted OR with respect to adjusted PR estimates of being hazardous drinker between men and women in several European countries.*

	$PR_{Men/Women}$ log-binomial[1]		**$PR_{Men/Women}$ robust Poisson[1]**		**$OR_{Men/Women}$ logistic regression[1]**		**Overestimation***
	PR	95%CI	PR	95%CI	OR	95%CI	%
Austria	1.48	(1.33-1.65)	1.48	(1.32-1.64)	1.64	(1.43-1.88)	25.0%
Belgium	1.11	(1.02-1.20)	1.10	(1.01-1.19)	1.15	(1.02-1.30)	33.3%
Czech Republic	2.08	(1.89-2.29)	2.08	(1.89-2.30)	2.65	(2.33-3.01)	34.5%
Denmark	1.11	(0.99-1.24)	1.10	(0.99-1.23)	1.17	(0.98-1.39)	41.2%
Estonia	3.87	(3.27-4.57)	3.87	(3.28-4.58)	4.67	(3.87-5.63)	21.8%
France	1.30	(1.19-1.43)	1.31	(1.19-1.44)	1.44	(1.27-1.62)	29.5%
Germany	1.39	(1.13-1.71)	1.38	(1.12-1.70)	1.49	(1.15-1.94)	22.4%
Hungary	3.07	(2.56-3.69)	3.07	(2.55-3.68)	3.78	(3.05-4.68)	25.5%
Italy	1.05	(0.93-1.18)	1.05	(0.93-1.17)	1.06	(0.91-1.24)	16.7%
Netherlands	1.01	(0.91-1.13)	1.01	(0.90-1.12)	1.01	(0.85-1.19)	0.0%
Poland	5.77	(3.73-8.94)	5.77	(3.73-8.93)	6.91	(4.31-11.07)	19.3%
Portugal	1.60	(1.38-1.85)	1.59	(1.36-1.84)	1.88	(1.53-2.32)	33.0%
Slovenia	1.28	(1.05-1.57)	1.28	(1.05-1.56)	1.33	(1.06-1.67)	15.2%
Spain	1.52	(1.30-1.78)	1.51	(1.28-1.77)	1.63	(1.35-1.98)	19.0%
Sweden	0.92	(0.73-1.15)	0.91	(0.72-1.15)	0.90	(0.69-1.18)	10.0%
Switzerland	1.02	(0.91-1.13)	1.02	(0.91-1.13)	1.02	(0.88-1.18)	0.0%
Total	1.44	(1.40-1.49)	1.43	(1.38-1.49)	1.59	(1.53-1.66)	27.1%

Note. *Overestimation of OR with respect to PR was calculated using the formula: [Overestimation = (OR-PR)/(OR-1)](Espelt et al., 2013). [1] Adjusted by age and educational level.

this study, men were considered as exposed and women as non-exposed). For that reason, if we interpret OR as an estimation of PR, we could be misinterpreting the results, as we have seen in the results section. The fact that OR could overestimate PR depending on the prevalence of the condition or disease analysed in each country leads OR to be similar to PR in some countries, while in others the estimations of OR and PR are quite different. As a result, when OR are used to make comparisons among countries, the interpretation of the results could be a problem for researchers that intuitively interpret OR as PR. For those reasons, in cross-national studies, where comparisons between countries with large differences in the prevalence of the disease or condition are made, it is advisable to use PR instead of OR. It is especially relevant because, as we said, people usually read the OR estimate as a PR. The overestimation may inappropriately affect clinical decisions-making or policy development and therefore may lead to unintentional errors in the economic analysis of potential intervention programs or treatments (McNutt et al., 2003).

Nowadays, some substance use studies are starting to use regression models to obtain PR as estimators of the association between a dichotomous dependent variable and several independent variables. In this sense, in substance abuse research some studies have calculated PR to estimate which factors could be associated to illicit drug consumption (Jamieson et al., 2010; Sarasa-Renedo et al., 2014) or to licit drug use (Bosque-Prous et al., 2014; Font-Ribera et al., 2013; Jamieson et al., 2010). However, the use of regression methods to estimate PR is still scarce. For example, if we compare the studies published in Pubmed in 2013 that have used PR or OR using the following strategies: PR = (["cross-sectional"] and ["prevalence ratio" or "log-binomial" or "poisson regression model with robust variance"]); OR = (["cross-sectional"] and ["odds ratio" or "logistic regression"]), we found 132 papers that used PR and 4886 that used OR.

One of the main strengths of our study is that we explain how to calculate PR using different regression models and also two different statistical packages (one of which is free software available to all researchers). However, this study could suffer some limitations. Its main limitation is that it was not designed as a simulation study, using different conditions to analyse the changes in PR with respect to OR. However, this was not the aim of this article. Nevertheless, relying on a cross-national study with substance use real data will be easier to understand. In fact, almost all scenarios are found in the different countries participating in the study (i.e. high prevalence in both sexes, low prevalence in both sexes, combinations of high and low prevalence), strengthening our results. Another limitation is that we only show the models most frequently used to calculate PR, using two different packages, but there are other methods that could also be used (Barros et al., 2003; Cummings, 2009) and other software. However, how to perform these analyses with other packages, as SAS, have been explained elsewhere (Deddens et al., 2008). In addition, given that R is free software, anyone could use the syntax that is provided to estimate associations using PR in their own studies.

Conclusion

In conclusion, although logistic regression is highly used in cross-sectional studies to estimate associations between variables, it is possible and easy to use other models in the analysis of cross-sectional data with binary dependent variables, which yield PR. One of the important advantages of these alternative methods is that PR, as a measure of association, is easier to interpret and communicate, especially to non-epidemiologists (Barros et al., 2003).

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Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

A. Espelt, M. Bosque-Prous, M. Marí-Dell'Olmo contributed to the conception and design of the study. M. Bosque-Prous contributed to data management. A. Espelt, M. Marí-Dell'Olmo, M. Bosque-Prous and E. Penelo discussed

and contributed to interpretation of the results. A. Espelt wrote the first draft of the paper, which was revised with contributions by all authors.

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Profiles of drug addicts in relation to personality variables and disorders

Perfiles de drogodependientes en relación con variables y trastornos de personalidad

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Abstract

In recent decades, research has identified a set of impulsive/disinhibited personality variables closely associated with drug addiction. As well as this, disorders linked with these variables, such as ADHD and personality disorders, are being closely studied in the field of drug addiction. Although much knowledge has been accumulated about the relation of these variables and disorders taken separately, less is known about how these constructs allow identify-specific profiles within the drug dependent population to be identified. This work, on the basis of data collected on a sample of drug addicts in treatment, analyzes how impulsiveness, sensation seeking, self-control, ADHD and personality disorders contribute to identifying specific profiles of addicts. Cluster analysis allowed two profiles to be outlined according to these personality and psychopathology characteristics. Self-control, impulsiveness, impulsive and antisocial personality disorders, as well as scores in ADHD, emerge as the variables that contribute more to profile differentiation. One of these profiles (56.1% of participants) with a high disinhibition pattern, is associated with severe indicators of consumption and criminal career patterns. These results allow us to emphasize the role of personality and impulsiveness-related disorders in the identification of distinctive profiles within the addict population, and suggest the need to generate treatment strategies adapted to personal/psychopathology configurations of drug addicts.
Keywords: Personality; Impulsivity; ADHD; Personality Disorders; Addiction.

Resumen

En las últimas décadas, la investigación ha permitido identificar un conjunto de variables de personalidad impulsiva/desinhibida estrechamente asociadas a la adicción a drogas. Así mismo trastornos vinculados a estas variables, como el TDAH y los trastornos de personalidad, están siendo objeto de vigorosas líneas de trabajo en el ámbito de las drogodependencias. A pesar de que se ha acumulado mucho conocimiento sobre la relación de estas variables y trastornos, tomados aisladamente, se sabe menos acerca de cómo estos constructos permiten identificar perfiles específicos dentro de la población de drogodependientes. Este trabajo, partiendo de los datos recogidos en una muestra de drogodependientes a tratamiento, analiza cómo la impulsividad, la búsqueda de sensaciones, el autocontrol, el TDAH y los trastornos de personalidad permiten identificar tipos específicos de adictos. El análisis *cluster* permitió delimitar dos perfiles atendiendo a estas características de personalidad y psicopatológicas, destacando como variables que contribuyen a esta diferencia el autocontrol y la impulsividad, los trastornos de personalidad impulsivo y disocial, así como las puntuaciones en TDAH. Uno de esos perfiles (un 56.1% de los participantes) con un patrón personal de alta desinhibición, se asocia con indicadores de consumo y criminológicos de especial severidad. Estos resultados permiten subrayar el papel de la personalidad y de los trastornos asociados a la impulsividad en la identificación de perfiles distintivos dentro de la población de adictos, y sugieren la necesidad de generar estrategias de tratamiento ajustadas a las configuraciones personales/psicopatológicas de los drogodependientes.
Palabras clave: Personalidad; Impulsividad; TDAH; Trastornos de la Personalidad; Adicción.

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The growth in recent years of research within the area of psychobiological processes underlying the addictive process have highlighted the importance of personality variables of a temperamental character such as impulsiveness or sensation-seeking.

Impulsiveness has been linked to drug use and other problematic behaviours in many studies, with a diminished response inhibition capacity, difficulties for reflection and planning, and a tendency to choose minor reinforcers that are closer to hand in tasks involving delayed gratification being observed in addicts (Olmstead, 2006), as well as violent behaviours, poor behavioural regulation, and lower empathy (Romero-Martínez & Moya-Albiol, 2015). The relationship between impulsiveness and substance abuse has been shown to be a robust one in many studies, being identified as one of the variables that is most consistently linked to both early contact with substances and progression in addiction (Belin, Mar, Dalley, Robbins & Everitt, 2008; Gullo, Loxton & Dawe, 2014; Motos-Sellés, Cortés-Tomás, Giménez-Costa, & Cadaveira-Mahía, 2015; Stauzt & Cooper, 2013).

Within the action-oriented personality style of drug addicts, another relevant variable is that of sensation-seeking (Zuckerman, 1979). Sensation-seeking is considered an important predictor in the onset of drug consumption in adolescence (Luengo, Otero-López, Romero & Gómez, 1996), and, like impulsiveness, has been related to difficulties in inhibitory control (Fillmore, Ostling, Martin & Kelly, 2009) and with greater sensitivity to the effects of drugs (Nadal-Alemany, 2008).

Self-control is a construct that brings together different variables such as delayed gratification or risk-taking, among others (Romero, Gómez-Fraguela, Luengo & Sobral, 2003). Self-control has taken on special relevance in recent years in the field of deviant behaviour and the consumption of drugs, starting from Gottfredson and Hirschi's approach (1994), and stands out as one of the most consistent correlates of rule-breaking behaviors (Romero, Sobral, & Luengo, 1999), including drug-related problems (Gallupe & Baron, 2014; Romero et al., 2003) and substance use chronicity (López-Torrecillas, Peralta, Muñoz-Rivas & Godoy, 2003).

In the same way that dimensions such as impulsiveness, sensation-seeking or self-control are implicated in drug use, studies of personality and disorders have provided a body of knowledge of undoubtable value for the understanding of addictions. In recent years, much attention has been given to psychopathological entities that are closely related to these personality traits, specifically, Attention Deficit Hyperactivity Disorder (ADHD) and Personality Disorders (PD), which are now an active centre of interest within the field of addictions.

Thus, closely related to impulsiveness and the ambit of the uninhibited personality, ADHD is receiving ever more attention in the study of drug use (e.g., Wilens, 2007). Although ADHD is mainly diagnosed in children, its relevance in the case of adults is being studied increasingly (e.g., Grogan & Bramham, 2016); in some studies, it has been shown that the symptoms related to hyperactivity tend to lessen with age, with attention deficit and impulsiveness becoming more stable, and persistent symptoms after adolescence being associated with clinical and psychosocial difficulties (Romero & Alonso, 2015), including disorders related to aggressiveness, antisocial behaviours, risk-taking, traffic accidents and difficulties in carrying out day-to-day tasks, as well as psychiatric comorbidity (Ramos, Bosch, Castells, Nogueira, García & Casas, 2006). As for drug use, it has been reported that, among addicts, the prevalence of ADHD is high (Kalbag & Levin, 2005), aggravating the severity of both disorders: ADHD and addiction. Other studies have focused on addiction rates among groups of adults both with and without ADHD, and the results show a significantly higher percentage among those affected by ADHD (Biederman, Wilens, Mick, Milberger, Spencer & Faraone, 1995). It has been noted that ADHD can affect the course of substance abuse, predicting an earlier age of onset in consumption, a longer duration of the addiction, progression in the addiction and treatment failure (Schubiner et al, 2000).

PDs are also a field in which research in relation to addictions has grown exponentially in recent years (Magnavita, 2004). Thus, for example, in a meta-analysis of 16 studies of psychiatric disorder comorbidity in opiate addicts, a prevalence level of 42% is found (Frei & Rehm, 2002) among this population. Among cocaine addicts, between 47% and 97% have been found to have PDs (López & Becoña, 2006). Other studies have shown that, in general, among addicts in treatment, the prevalence of PDs varies between 44.3% (Echeburúa, de Medina & Aizpiri, 2007) and 35-73% (Verheul, 2001). Specifically, the research has shown that among substance users, the antisocial personality disorder (with figures of between 18 and 30%) and the borderline personality disorder (7-22%) are the most frequent (Verheul, van der Brink & Hartgers 1995). It has also been shown that the presence of PDs is related to greater severity in the addiction and to a higher probability of treatment interruptions (González, 2014).

In general, these different lines of research point to the importance of impulsiveness, and of the dimensions and disorders associated with it, in the understanding of drug use. Earlier research allows us to conclude that both the impulsive personality and the disorders related to lack of inhibition and self-control are key ingredients in the psychological characterisation of addicts.

Another area of interest in the study of addictions, and one that deserves to be taken further, is the development of typologies within the addict population that would allow for a better understanding of the processes that lead to addiction and therefore to improved tailoring of treatment strategies.

Employing cluster analysis techniques, Cloninger (1987) identifies two sub-types of alcohol users that are differentiated in terms of the of their onset in consumption, the heritability of addiction, risk factors in childhood, the level of severity of the dependence and psychosocial maladjustment. These typologies would correspond to others found by Babor et al. (1992) and Ball (1995). In this country, in a study of polydrug users who were in treatment (Muñoz, Nava, Graña & Martínez, 2006), two groups are identified which show significant differences in terms of sociodemographic variables, consumption variables and severity of addiction: one group of functioning users (type A), made up of cocaine users, with fewer medical, psychosocial and psychopathological problems; and a group of chronic users (type B), comprising heroin users and multiple drug users, who show a greater degree of functional and social deterioration and a tendency to infringe laws. Starting from this classification into two groups of consumers, in a later study (Graña, Muñoz & Navas, 2009) the differences between the variables and personality disorders were examined; the results showed that, while the functioning users scored significantly higher in extroversion and cordiality, the chronic users had higher scores in schizoid and dissocial PDs.

Bearing these results in mind, in this study the aim is to further the differentiation of the profiles of drug addicts starting from variables and personality disorders that seem to be relevant in the addictive process in research. In an earlier study (Carou, Romero, & Luengo, 2013) in which personality variables and consumption patterns of drug addicts who were in treatment were analyzed, the need arose to take into consideration a special group of addicts denominated "coca-heroin addicts", made up of patients who were rehabilitated heroin addicts but who later developed an addiction to cocaine. This group showed a profile that indicated a greater severity of addiction and marginalisation and certain peculiarities in the personality variables analyzed.

In this work, with an approach that is more focused on the person (Bergman & Magnusson, 1997) than on the variables, the intention is to understand the heterogeneity of addicts and analyze whether distinctive profiles may be identified by looking specifically at personality variables and those disorders which, as has been analyzed before, seem to be relevant to drug use. The analysis of addict profiles based on their personality traits allows us to go more deeply into the processes that lead to addiction and to develop treatments that are tailored to the personal and functional peculiarities of drug addicts. The need to identify specific types of addicts has been highlighted in earlier literature, and the broad body of research that has been generated over the last decade around personality and its disorders, as well as ADHD, suggests that it is useful to look at these constructs in order to define specific user profiles.

The main objective proposed by this study, therefore, is to identify specific addict profiles related to their personality and disorder profiles (PDs and ADHD). As specific objectives, the aims are a) to determine which variables and disorders have a greater weight in differentiating addict profiles, b) to examine how these profiles are associated with belonging to different user groups, and, c) to analyze whether these profiles are related to indicators of severity in use and criminological traits.

As has been pointed out, several earlier research projects suggest that two differentiated profiles may be specified, and for that reason it is now to be expected that, taking into account variables and personality disorders, these two profiles may be identified in a sample of addicts who are in treatment.

Method

Participants

In order to carry out this study, 176 adult addicts undergoing treatment at a Drug Addiction Treatment Centre (DATC, or UAD in its Spanish initials) belonging to the Galician public health network were evaluated. Of them, some 47.2% were diagnosed as heroin addicts, and 52.8% were addicted to cocaine. Of the cocaine addicts, 16 of the participants had previously been addicted to heroin. Given that the earlier studies (Carou et al., 2013) indicated that these coca-heroin addicts showed significant personal and psychosocial peculiarities, in the current study, all three types of users, cocaine, heroin and coca-heroin, are taken into account.

The principal criteria for being included in the sample were: addiction to cocaine or heroin according to CIE-10 criteria, being over 18 years of age, and signing the informed consent form. Patients undergoing treatment for addiction to another substance and those who show problematic consumption without being addicted were ruled out.

Instruments

Treatment Centre Management (**GECEAS** in its Spanish initials). This is a computer application by means of which a database of information recorded during interviews with the patient is built up. Apart from its information-gathering and evaluation functions, it also serves as a clinical management application for drug centres across Galicia and allows for all the processes that take place at a DATC to be handled, covering the clinical, assistance and management aspects. This study uses its Clinical History Module, which allows for several sociodemographic variables relating to use (such as age of onset, frequency), treatment (such as previous courses of treatment) and criminological (such as the number of arrests, time spent in prison) to be codified.

The **Barratt Impulsiveness Scale**, version 11 (BIS-11; Patton, Stanford & Barratt, 1995; Spanish adaptation by Oquendo et al., 2001). This is a self-administered scale for evaluating impulsiveness, composed of 30 items that are answered on a four-point Likert-type scale, providing scores in three

factors for impulsiveness (attentional, motor and non-planning), whose sum gives a measure of overall impulsiveness. For this study, the total score, with an internal consistency (Cronbach's alpha) of .79, was used. Suitable psychometric properties, regarding reliability and validity, were found in earlier studies with this scale (Carrillo-de-la-Peña, Otero & Romero, 1993; Oquendo et al., 2001).

Sensation Seeking Scale, form V, or SSS-V (Zuckerman, Eysenck & Eysenck, 1978; Spanish adaptation by Pérez & Torrubia, 1986). It comprises 40 forced-choice items which give scores in four subscales (thrill and adventure seeking, experience seeking, disinhibition and boredom susceptibility) and also an overall score resulting from the sum of the four subscales; this overall score was used in our study. The reliability of this scale in this study (Cronbach's alpha) was .76, and similar indices have been found in other research (Romero, Luengo & Sobral, 2001).

Grasmick, Title, Bursik and Arneklev's **Self-control Scale** (1993; Spanish adaptation by Romero et al., 2003). This scale consists of 24 items, with dichotomous response options, which allow for an overall self-control score to be obtained in accordance with Gottfredson and Hirschi's model (1990). The scale has shown its psychometric usefulness for evaluating the self-control construct in previous studies (e.g., Romero et al., 2003); in this study the overall measure showed, in a way that is similar to the earlier Spanish adaptation, internal consistency (Cronbach's alpha) of .89.

The **Adult ADHD Self-Report Scale Screened Questionnaire**, ASRS-VI.1, developed by the WHO in conjunction with Adler, Kessler, Spencer in 2005 (Kessler et al., 2005), follows DSM-IV criteria and focuses on the current symptomatology of ADHD in adults. In this study the abbreviated 6-item version of the screener (Spanish adaptation by Daigre et al., 2009) was used, which is the only screening test validated in Spanish and that offers psychometric guarantees for measuring ADHD in adults. Although the scale allows for a dichotomous categorisation between "probable" and "not probable", it also allows for dimensional scores (0 to 24), resulting from adding together the scores (0 to 4; from "never" to "very often") for each item to be used (Kessler, Adler, Gruber, Sarawate, Spencer & Van Brunt, 2007). This dimensional scoring was used in this study, with a Cronbach alpha reliability of .65.

International Personality Disorder Examination Screening Questionnaire (IPDE, Loranger, 1994), adapted in Spain by López-Ibor, Pérez-Urdaniz, and Rubio-Larrosa (1996). The IPDE is a widely-used instrument for obtaining scores in nine PDs identified by the WHO. It consists of 59 items to which the patient responds True or False, describing his behaviour over the last five years. In this research, the screening questionnaire was employed and, for the statistical analysis, the dimensional scores obtained corresponding to each of the disorders were used, with Cronbach alphas of between .43 (paranoid disorder) and .63 (anxiety disorder), similar to those reported in earlier studies (Slade and Forrester, 2013).

Procedure

On being admitted or readmitted for treatment, patients who attend a DATC voluntarily seeking treatment for their drug addiction enter the orientation and care program. The details necessary to fill in their computerized Clinical History are noted and they are diagnosed by specialists in clinical psychology and psychiatry by means of a clinical interview. For the purposes of this study, in addition, the above-mentioned self-administered tools were used. Completion of the forms took on average 60 minutes and was carried out on the premises, individually, thus guaranteeing the confidentiality of the data provided, under the supervision of the first author of this study. The management of the centre gave their approval for the study to be carried out, and its compliance with pertinent ethical principles was guaranteed; the project upheld the guidelines laid down by the Declaration of Helsinki, scrupulously respecting the rights of the participants throughout the study, from beginning to end.

Statistical Analysis

Firstly, the principal descriptive statistics of the sample (sociodemographic, use, criminological) were calculated, as well as the Pearson correlations between the scales (personality and disorder) applied in this study. In order to identify profiles that address the personality and disorder variables, a cluster analysis with a two-step algorithm was used, which performs pre-grouping (pre-clustering) and then a later hierarchical grouping. The mean distance considered was the Euclidian and, to determine the optimal number of clusters, the Schwarz Bayesian Criterion (SBC) was taken into account. For the characterisation of the resulting clusters and, in order to analyze their relationship with use and criminological variables, contingency tables with the Chi-square as the test statistic, and multivariate analysis of variance (MANOVA), incorporating the Bonferroni correction in order to minimize type I errors, were all used. For each of the analyses carried out in this study, those participants who provided valid data in all of the variables considered in the analysis were included. The analyses were carried out by means of the IBM SPSS 20 software package.

Results

Preliminary analysis: descriptives and correlations between variables

First of all, and with regard to the descriptive data of the sample (see Table 1), men made up 76.1% of the sample and women 23.3%, with a mean age of 32.1 years. The majority (55.7%) lived at home with their family of origin, were single (74.4) and did not have children (71%). In terms of income in the six months prior to the start of treatment,

around half of the sample were working while the other half received help from their family or were on benefits, or subsisted by means of marginal activities.

Regarding the characteristics of consumption, the mean onset age of the main drug for which patients sought treatment was 19.4 years. At the start of treatment, the majority (60.2%) were using the drug on a daily basis. The main combination drug, found in 44.3% of cases, was alcohol, followed by cocaine (among heroin addicts) and cannabis, at 22.2% each. Other substances were also habitually consumed. Among these, tobacco, used by almost the whole sample (94.3%), alcohol (77.8%) and cannabis (62.5%) stand out. It is worth noting that there were 0.8 visits to the emergency room (E.R.) due to consumption, although 62.5% of the sample have not had any. For 59.7% this was not the first course of treatment for a problem of substance abuse, and 48.3% have had previous psychiatric treatment.

In terms of the criminological variables under study, 34.7% of the participants have had legal problems, the mean age of their first arrest was 23.3 years, they were arrested 3.1 times on average, spent 3.7 months in jail and complied with 1.1 legal orders.

Secondly, in order to determine the relationship between the personality measures and the disorders under investigation, a Pearson correlation analysis was carried out (see Table 2).

An examination of how the personality variables are connected yields significant correlations for all of them. The disorders also present significant associations, with the highest correlations being those between impulsive PD with dissocial PD and ADHD, and between dependent PD with anxiety and borderline PD.

With regard to the correlations between personality dimensions and disorders, the highest correlations for impulsiveness were found in ADHD and impulsive PD. Sensation seeking is most strongly correlated with impulsive PD, while self-control correlates most strongly with impulsive TD, ADHD and dissocial PD.

Patient profiles linked to personality dimensions

In the search for homogeneous profiles of substance abuse, the personality/psychopathological variables mentioned in the introduction, and which in previous research had been consistently linked to the severity of drug use, i.e. impulsiveness, sensation seeking, self-control, ADHD and PD, were introduced into the cluster analyses. As a result, two well-differentiated clusters emerged, with a BIC of 1623.18 (BIC for three clusters = 1645.00; BIC for four clusters = 1719.10). Since previous research has also tended to identify two subtypes, the two-cluster solution was also preferred for this study, by virtue of both empirical (BIC) and conceptual criteria. Figure 1 shows the composition of the two clusters: a first cluster of 77 participants (43.8%) and a second with 99 participants (56.1%).

Table 1. *Sociodemographic, use and criminological profile of the sample.*

	% (N)	M (DT)
Sociodemographic variables		
Sex		
Male	76.7% (135)	
Female	23.3% (41)	
Age		32.16 (7.1)
Cohabitation		
Single	10.8% (19)	
Partner	10.8% (19)	
Single with children	1.7% (3)	
Partner with children	17% (30)	
Parents	55.7% (98)	
Friends	1.1% (2)	
Other	2.8% (5)	
Marital status		
Single	74.4% (131)	
Married	10.2% (18)	
Widowed	1.1% (2)	
Divorced/separated	14.2% (25)	
No children	71% (125)	
Source of income		
Employed	50% (88)	
Supported by family	23.8% (42)	
Social benefits	17% (30)	
Marginal activities	7.4% (13)	
Consumption characteristics		
Onset age		19.43 (4.69)
Frequency		
Every day	60.2% (106)	
4-6 per week	14.8% (26)	
2-3 per week	19.3% (34)	
1 per week	2.8 % (5)	
Less than 1	2.8% (5)	
Main combination drug		
Cocaine	22.2% (39)	
Alcohol	44.3% (78)	
Cannabis	22.2% (39)	
Benzodiazepine	2.8% (5)	
Tobacco	5.7% (10)	
Other habitually used drugs		
Heroin	18.2(16)	
Cocaine	35.8% (63)	
Alcohol	77.8% (137)	
Cannabis	62.5% (110)	
Benzodiazepine	28.4% (50)	
Synthetic drugs	14.8% (26)	
Tobacco	94.3% (166)	
No. E.R.		.82 (1.65)
Previous treatment	59.7% (105)	
Psychiatric treatment	48.3% (85)	
Criminological variables	34.7% (61)	
Age of first arrest		23.33 (7.02)
No. arrests		3.10 (5.25)
No. months in prison		3.70 (10.40)
Criminal proceedings		1.15 (1.86)

Table 2. *Correlations between disorders and personality variables.*

	Impulsiveness	Sensation seeking	Self-control	ADHD	Paranoid PD	Schizoid PD	Dissocial PD	Impulsive PD	Borderline PD	Histrionic PD	Anankastic PD	Anxious PD	Dependent PD
Impulsiveness		366***	.581***	.547***	.259**	.203**	.319***	.417***	.334***	.343***	-.222**	.244**	.312***
Sensation seeking			.512***	.290***	.371***	.045	.349***	.431***	.236**	.315***	-.007	.089	.077
Self-control				.458***	.349***	.199**	.436***	.610***	.325***	.272***	.013	.276***	319***
ADHD					.283***	.146	.339***	.462***	.304***	.140	-.069	.283***	.321***
Paranoid PD						.100	.338***	.383***	.270***	.274***	.264***	.269***	.177*
Schizoid PD							.249**	.234***	268***	.069	.186*	.308***	.341***
Dissocial PD								.494***	.222**	.195*	.057	.141	.127
Impulsive PD									.323***	.274***	.155*	.298***	.272***
Borderline PD										.293***	.098	.336***	.409***
Histrionic PD											.037	.106	.225**
Anankastic PD												.215**	.175*
Anxious PD													.471***
Dependent PD													

Note: In accordance with the coding instructions for the Grasmick et al. (1993) scale, a low score on this scale indicates low self-control.
Note: * p < .05, ** p < .01, *** p < .001

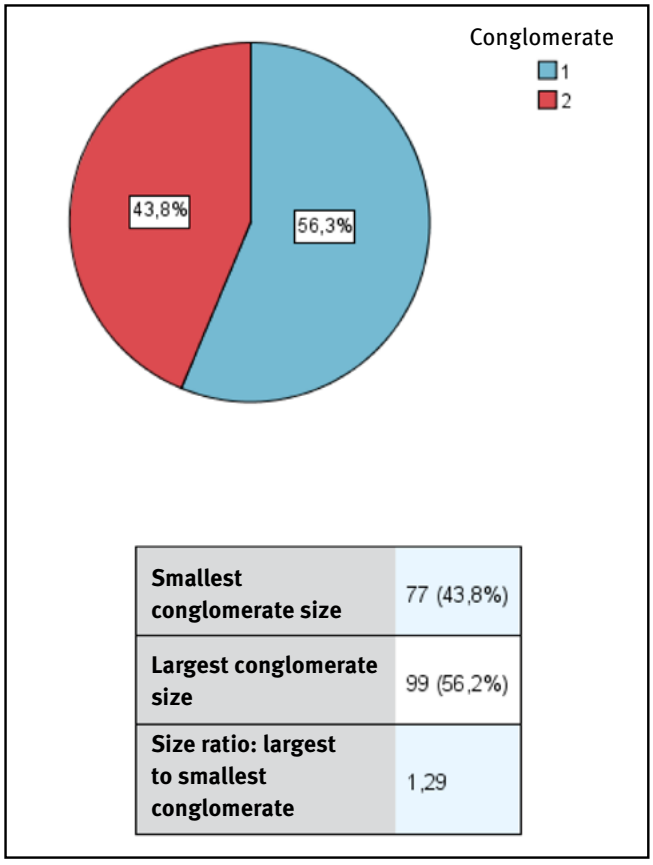

Figure 1. Size of the conglomerates identified in the cluster analysis.

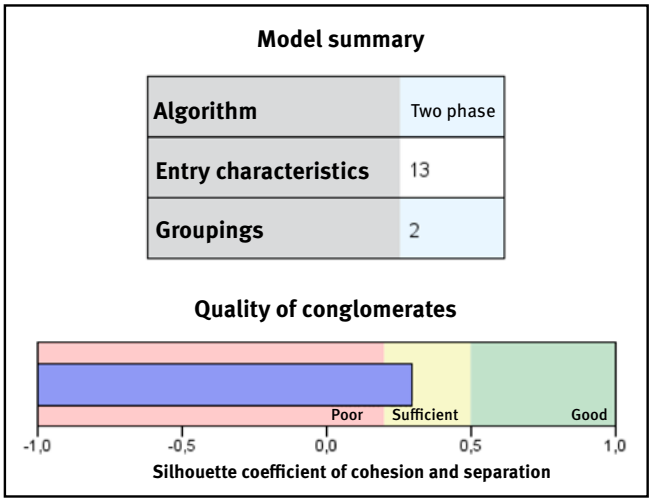

Figure 2. Summary of the model and quality indicator of the solution identified in the cluster analysis.

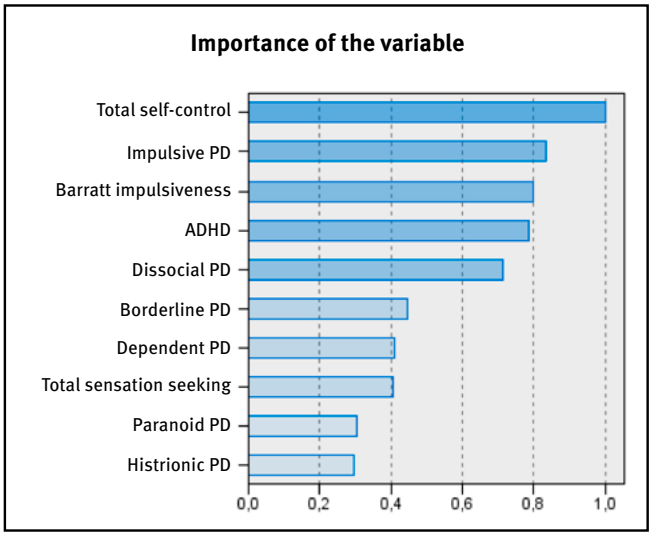

Figure 3. Importance of the variables in differentiating the two clusters.

Figures 2 and 3 present the quality of conglomerates test and the variables with the greatest weight in the cluster grouping, respectively.

The variables which contributed most strongly to group definition were: self-control, impulsive PD, impulsiveness, ADHD and dissocial PD, as shown in Figure 3.

Differences in the profiles regarding personality variables and disorders

With the aim of establishing a more accurate characterisation of the clusters on the basis of the variables introduced for their definition, the groups were compared by personality variables and disorders. This will make it possible to detail which personality profiles emerge for each of the groups. Given the multiple comparisons between the variables related to one another, a MANOVA was used, with results presented in Table 3.

As can be seen in the table, cluster 2 participants score significantly higher in all the variables ($p < .003$, using the Bonferroni adjustment to control for type I error), except for anankastic PD. Those individuals found in cluster 2 appear to have a more severe profile in terms of low self-control, high impulsiveness, high sensation seeking and greater scores for ADHD and for the majority of PDs.

Links between profiles and substance-user groups

In addition, a contingency tables analysis (see Table 4) was carried out in order to reveal how the three user groups (heroin, cocaine and coca-heroin addicts) are distributed across the two clusters.

As can be seen in the table, the chi-square was statistically significant, indicating an unequal distribution of the subjects across the groups. In particular, it can be noted that that a high proportion of the coca-heroin addicts are concentrated in the more severe personality cluster (cluster 2). This cluster contains 75% of the coca-heroin addicts, as opposed to 25% in cluster 1. Cluster 2 also has 41.7% of the cocaine addicts and 39.8% of the heroin addicts.

Both groups were also compared by sex and age. While no differences were found in terms of sex, with a chi-square (1) = 2.13, $p = .155$, there were differences in age, $F(1.174) = 12.44$, $p < .001$, with older subjects in cluster 1 ($M = 33.78$, $SD = 7.06$) compared to those in cluster 2 ($M = 30.09$, $SD = 6.63$).

Profiles in relation to indicators of substance use severity and criminality

Finally, we examined how the clusters were linked to severity of substance use and the criminological indicators assessed in this study. Given the differences in age across the

Table 3. *Results of the multivariable analysis of variance for the comparison of the two clusters regarding personality variables and disorders.*

	Group 1		Group 2					
	M	**SD**	**M**	**SD**	Λ	**F (gl)**	**Sig.**	η²
					.35	22.61 (13,161)	‹.001	.65
Impulsiveness	54.34	12.58	73.22	13.52		81.21 (1,173)	‹.001	.31
Sensation seeking	20.63	5.31	25.77	5.45		31.53 (1,173)	‹.001	.15
Self-control	10.65	3.78	16.88	3.60		112.91 (1,173)	‹.001	.39
ADHD	10.05	3.06	14.72	3.50		75.71 (1,173)	‹.001	.30
Paranoid PD	3.31	1.35	4.36	1.25		22.60 (1.173)	‹.001	.11
Schizoid PD	2.85	1.67	4.00	1.77		20.10 (1,173)	‹.001	.10
Dissocial PD	1.57	1.19	3.23	1.26		69.19 (1,173)	‹.001	.28
Impulsive PD	1.83	1.26	3.53	0.94		79.14 (1,173)	‹.001	.31
Borderline PD	2.32	1.20	3.46	1.03		39.06 (1,173)	‹.001	.18
Histrionic PD	2.07	1.29	3.07	1.25		20.97 (1,173)	‹.001	.18
Anankastic PD	2.98	1.65	3.10	1.58		.82 (1,173)	.351	.01
Anxious PD	3.33	1.40	4.28	1.21		18.94 (1,173)	‹.001	.09
Dependent PD	2.14	1.34	3.41	1.30		38.01 (1,173)	‹.001	.18

Table 4. *Results of the chi-square between the two clusters and the three user groups.*

	Cocaine	**Heroin**	**Coca-heroin**	**Total**	**Chi²**	**Sign.**
Group 1	58.3% (42)	60.2% (50)	25.0% (4)	56.1% (96)	7.00	‹.05
Group 2	41.7% (30)	39.8% (33)	75.0% (12)	43.9% (75)		

Table 5. *Results of the multivariable analysis of variance for the comparison of the two clusters regarding severity of use and criminological indicators.*

	Group 1		Group 2					
	M	**SD**	**M**	**SD**	Λ	**F (gl)**	**Sig.**	η²
Severity of use indicators					.42	4.78 (1,167)	‹.001	.19
Onset age	20.55	5.16	17.99	3.55		7.41 (1,173)	‹.05	.10
Frequency of use	1.68	1.03	1.81	1.06		.05 (1,173)	.82	.00
No. E.R.	.59	1.16	1.10	2.10		6.23 (1,173)	‹.001	.10
Previous treatments	.59	.49	.61	.49		3.30 (1,173)	‹.05	.03
Criminological indicators					.38	4.49 (4,56)	‹.01	.16
No. arrests	.65	1.30	1.67	4.93		3.21 (1,59)	‹.05	.07
Age of first arrest	24.73	7.40	21.97	6.45		2.42 (1,59)	.12	.03
Months of prison	1.62	7.97	.92	3.35		1.16 (1,59)	.28	.02
Criminal proceedings	.51	.97	1.13	2.44		5.23 (1,59)	‹.01	.10

groups and that this could be a spurious variable affecting the results of the comparisons, the age variable was controlled for in the MANOVAs. The results are shown in Table 5.

As can be seen in the table, onset age is significantly lower in cluster 2, although the significance becomes marginal when the Bonferroni correction is applied ($p < .012$). On applying the correction, however, the difference in terms of emergencies, greater in cluster 2, remains significant. A tendency towards more previous treatment in cluster 2 can be observed ($p = .05$), but this is not significant once the Bonferroni correction is applied.

With regard to criminological indicators, the number of criminal prosecutions in which participants have been involved is higher in cluster 2, and the difference remains significant on application of the Bonferroni correction ($p < .012$); the number of arrests also tends to be higher in cluster 2, although significance is marginal.

Discussion

The present study aims to investigate the heterogeneity of the substance dependent population by examining whether differentiated personal profiles can be identified. The results of cluster analysis revealed interesting data regarding the typology of substance dependence, delimiting two groups differentiated in particular in terms of self-control, impulsive PD, total impulsiveness, ADHD and dissocial PD. The second group contains those who score significantly higher in practically all variables and is characterised by a personal profile which suggests greater disinhibition, and thus a greater risk of severity, demonstrates lower self-control, high levels of impulsiveness and sensation seeking, higher scores in the disorders, of both personality and ADHD. This cluster also includes those patients with indicators of severity and criminality which in general, based on the MANOVA, are more extreme, particularly in connection with emergencies for substance abuse and more criminal prosecutions, which corroborates the psychosocial difficulties suggested by their personality profile.

These results are comparable to the alcohol addiction subtypes found by Cloninger (1987): type I with low scores in novelty seeking, type II with high scores in novelty seeking, early onset of problems with alcohol and consumption continued for longer, among other characteristics; or those referred to by Babor et al. (1992) as type A and B. Profile I or A would be less serious, with later onset, less heritability and fewer risk factors in infancy, and lower dependence. Type II or B, on the other hand is characterised by greater severity, dependence, heritability, novelty and sensation seeking, impulsive and antisocial behaviour. Ball (1995) discovered similar results in an analysis of cocaine users, with those in group B presenting more comorbid risk factors, greater cocaine and alcohol abuse severity, more associated psychosocial problems, antisocial PDs, psychiatric problems, criminality and drug and psychiatric treatments, as well as higher scores for sensation seeking. Our differentiated profiles thus correspond with those previous studies mentioned, with type II or B being more severe than I or A. Similarly, a certain parallelism can be found with those typologies labelled functional and chronic by Muñoz et al. (2006), the latter being the more severe, reflecting longer years of use and psychosocial problems associated with drugs. The differences we find in our study could also correspond to the types identified by Echeburúa, Bravo de Medina and Aizpiri (2008) in a study of alcoholics. They found that apart from greater impulsiveness and sensation seeking, those in type II also had a greater number of personality disorders (in particular obsessive, narcissistic, paranoid and antisocial disorders), more dramatic/erratic disorders (antisocial, borderline, histrionic and narcissistic PDs); furthermore, the

appearance in type II alcoholics of a profile with greater psychopathological symptomatology (impulsiveness and hostility) suggest that multicomponent treatment programmes would be beneficial. Our results are also congruent with the finding of Graña et al. (2006) in the sense that higher scores in dissocial personality disorder are characteristic of chronic substance abusers.

The clusters found are thus similar to those in preceding studies, both for alcoholism and illegal substances, of a type 2 with a more severe profile, mainly corresponding to coca-heroin addicts, as revealed in previous research (Carou et al., 2013) with a profile of greater severity, marginalization, and also legal problems, an earlier onset age, greater impulsiveness and boredom susceptibility. These results also endorse the definition of coca-heroin addicts as a special category of cocaine users with its own profile and which should be considered separately within the field of substance dependence. Indeed, other studies have observed that among drug users, those who are dependent on more than one substance are more impulsive that those addicted to only one (McCown, 1988; O´Boyle & Barratt, 1993). Farrington (1992), for example, has pointed out the existence of a general antisocial predisposition made up of a series of risk factors among which impulsiveness, hyperactivity, sensation seeking, risk taking and the inability to defer gratification stand out.

Furthermore, our research confirms the results of other studies which have associated high sensation seeking and impulsiveness with addiction (Ball, 2004; Hittner & Swickert, 2006), and also the severity of the addiction (Dom, De Wilde, Hulstijn, Van Den Brink, & Sabbe, 2006; Horvath, Milich, Lynam, Leukefeld, & Clayton, 2004). There seems to be an association between disorders which have impulsiveness in common, in particular disorders of impulse control, personality, those related to substance use, and ADHD, giving rise to comorbidity and what is beginning to be termed tri-morbidity (Tiffon, 2008). The appearance of PDs (in particular dissocial, impulsive, and borderline personality disorders), as well as ADHD are linked in the literature to the presence of addiction, and serving to indicate the severity of substance use (Ball, 1995), both in terms of earlier onset age and the presence of more emergencies or treatment failures (Verheul et al., 1995, Biederman, Wilens, Mick, Faraone, & Spencer, 1998). This is also borne out in our study.

The present study has some limitations which should be taken into account. For example, the sample analysed has not been compared with a control group from the general population, nor was it possible to expand data gathering to different centres, which would have allowed us to include other groups of substance users; secondly, the evaluation of personality and disorder variables was carried out entirely on the basis of questionnaires and consequently subject to biases such as social desirability, as described in the literature; thirdly, other important substances which cause people to seek treatment were excluded, such as cannabis and alcohol, and results are therefore not generalisable to substance dependence in general but need to be contextualised with regard to the substances under study and among individuals who have sought help for them; finally, the cross-sectional nature of this study does not permit assumptions to be made as to the potential influence of personality characteristics and disorders on how patients adjust and respond to treatment. Nevertheless, it has been possible to establish the existence of specific profiles among different types of substance users associated with personality variables. The study has also allowed us to confirm the importance of PDs and ADHD in the delineation of a subtype with more severe characteristics of use. The disorders linked to impulsiveness and disinhibition appear to play a crucial role in the psychological characterisation of the most severe addiction patterns, and this should be borne in mind when assessing the treatment needs of substance dependent users

Conflict of interests

The authors declare that there is no conflict of interests in this study.

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Adolescents with Internet Gaming Disorder (IGD): profiles and treatment response

Adolescentes con Trastorno por juego en Internet (IGD): perfiles y respuesta al tratamiento

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Abstract

Demand for treatment for problems related to the use of video games have increased significantly in adolescents. Most cases have a comorbid mental disorder that jeopardises both pathologies. The aim of this study is to describe profiles of adolescents with Internet Gaming Disorder (IGD) according to comorbidity and analyze treatment response at 3 and 6 months. A sample of 86 patients which consulted in the Addictive Behavior Unit of a hospital was assessed with diagnostic criteria for IGD, the interview K-SADS-PL for mental disorders and the Clinical Global Impression (CGI) to treatment progress. Of the initial sample, 68,6% (n = 59) met diagnostic criteria for IGD. Of these, the 45,76% matched an internalizing profile, presenting comorbidity with Mood Disorders (44,4%), Anxiety Disorders (44,4%) and Personality Disorders (11,1%). The externalizing profile would comprise 52,54% of the sample presenting Disruptive Behavior Disorder (48,4%=, ADHD (29%) and Disruptive Behavior Disorders not otherwise specified (22,6%). Unlike externalizing, the internalizing patients had a family history of psychiatric problems (63%), difficulties in social relationships (77,8%) and seemed to use video games preferably to escape discomfort (66,7%). After 3 months the externalizing profile showed improvements. Comorbid disorders allow the discrimination of two IGD profiles in adolescents and these could influence treatment response. Therefore, it is important to assess comorbidities to design a more accurate intervention focused on the specificities of each profile.

Keywords: Adolescents; Video games; IGD; Comorbid disorders; Treatment.

Resumen

Las demandas de tratamiento de adolescentes con problemas relacionados con el uso de videojuegos han incrementado significativamente. La mayoría de casos presentan un trastorno mental comórbido que compromete ambas patologías. El objetivo del presente estudio es describir los perfiles de adolescentes con Trastorno por Juego en Internet (IGD) según la comorbilidad y analizar la respuesta al tratamiento a los 3 y 6 meses. Se ha valorado una muestra de 86 pacientes que han consultado en la Unidad de Conductas Adictivas de un hospitalmediante los criterios del IGD, la entrevista semiestructurada K-SADS-PL para los trastornos mentales y la Impresión Clínica Global (ICG) para la evolución del tratamiento. Del total de pacientes, un 68,6% (n = 59) cumplían criterios para el IGD. De estos, el 45,76% corresponderían a un perfil internalizante, presentando comorbilidades con Trastornos Afectivos (44,4%), Trastornos de Ansiedad (44,4%) y Trastornos de Personalidad (11,1%). El perfil externalizante englobaría al 52,54% de la muestra, presentando Trastorno del Comportamiento Perturbador (48,4%), TDAH (29%) y Trastorno del Comportamiento Perturbador no especificado (22,6%). A diferencia de los externalizantes, los pacientes internalizantes tienen más antecedentes psiquiátricos familiares (63%), dificultades con las relaciones sociales (77,8%) y parecen utilizar los videojuegos preferentemente para escapar del malestar (66,7%). A los 3 meses el perfil externalizante muestra mejorías. Se pueden discriminar dos perfiles de adolescentes con IGD en función de los trastornos comórbidos y esto puede influir en la respuesta al tratamiento. Por ello, resulta clave valorar las comorbilidades para realizar un planteamiento más eficaz del abordaje psicoterapéutico enfocado a las especificidades de cada perfil.

Palabras clave: Adolescentes; Videojuegos; IGD; Trastornos comórbidos; Tratamiento.

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Internet has become an essential tool in daily life, especially among the younger population (Buil, Solé & García, 2015; Ko, Yen, Chen, Chen & Yen, 2012; Yau & Potenza, 2014), where it is used to access a great range of content via multiple devices, principally for social relationships, entertainment, and learning (Cho et al., 2014; Marco & Chóliz, 2014). At the same time, it has been noted that inappropriate or excessive use of Internet impacts negatively on everyday life, family and interpersonal relationships, and emotional stability, which has given rise to a growing number of studies on Internet addiction (Griffiths & Meredith, 2009; Ko et al., 2012; Kuss, Van Rooij, Shorter, Griffiths & Van de Mheen, 2013; Vallejos & Capa, 2010; Yau & Potenza, 2014). These studies have revealed that the rates of Internet addiction among adolescents range from 1.7% to 10% (Kuss, et al., 2013; Matalí-Costa, Serrano-Troncoso, Pardo, Villar & San, 2014; Petry et al., 2014; Yau & Potenza, 2014). A review carried out by Ferguson et al. came to the conclusion that at around 3.1% the estimates of very problematic use appeared to be lower than those described in some studies (Ferguson, Coulson & Barnett, 2011; Van Rooij, Kuss, Griffiths, Shorter, Schoenmakers & Van de Mheen, 2014), with other authors reporting between 2% and 5% (Kuss et al., 2013; Rehbein, Kliem, Baier, Mößle & Petry, 2015). There is greater consensus regarding age, with the adolescent population presenting the most problematic Internet use and/or abuse (Carbonell, 2014; Buil, Solé & García, 2015; Ferguson et al., 2011; Kuss et al., 2013). Gender differences can be observed in terms of video game use, with men having a greater propensity to play than women (Fernández-Villa et al., 2015; Király, Nagygyörgy, Griffiths & Demetrovics, 2014; Kuss et al., 2013; Lemos, De Abreu & Sougey, 2014).

In its latest edition (DSM-5), the Diagnostic and Statistical Manual of Mental Disorders states that while Internet addiction is not sufficiently severe to warrant the label disorder, Internet gaming disorder (IGD) does exist, although it requires further research (American Psychiatric Association, 2013; Carbonell, 2014; Petry & O'Brien, 2013). A variety of subsequent studies (Lopez-Fernandez, Honrubia-Serrano, Baguley & Griffiths, 2014) has provided sufficient evidence that disproportionate use of video games is a potentially problematic activity. With regard to game type, the massively multiplayer online role-playing games (MMORGP) are those with the greatest repercussions and would appear to have a greater addictive capacity, given that they offer an activity lacking a previously established outcome and with numerous possibilities for action where players create their own avatars and advance by forming clans with other players. On completion of each mission, players receive a reward in the form of an ability or some information which puts them in a new position for continuing the game (Carbonell, 2014). These factors make it difficult to give up playing and to control one's time when taking part in a game (Griffiths & Meredith, 2009; Marco & Chóliz, 2014).

Patients with IGD have high comorbidity rates with other mental disorders (Yen, Ko, Yen, Wu & Yang, 2007), the most frequent of which are mood disorders, generalized anxiety disorder, panic disorder, social fear, obsessive-compulsive disorder, substance use disorder, attention deficit and hyperactivity disorder, behavioural disorders, personality disorders and psychotic disorders (Echeburúa & Corral Gargallo, 2010; Ko et al., 2012; Marco & Chóliz, 2014; Van Rooij et al., 2014; Yau & Potenza, 2014; Yen et al., 2007). The controversy or difficulty in differential diagnosis lies in the question whether the maladaptive use of video games is a disorder in itself or whether, given the high frequency of comorbidity (Echeburúa & Corral Gargallo, 2010; Yen et al., 2007), and as is the case with other addictions (Király et al., 2014; Matalí-Costa et al., 2014), it is a symptom of another mental disorder. A good assessment is essential in order to understand how the maladaptive pattern managed to establish itself and to determine the most suitable treatment for the patient (Yen et al., 2007).

In recent years, the demand for treatment for problems involving the use of video games among minors has grown, (Matalí-Costa et al., 2014). However, there is not a great deal of evidence about the best type of approach for IDG (Griffiths & Meredith, 2009; Marco & Chóliz, 2014). According to the literature, cognitive behavioural therapy is most effective in identifying the problems relating to video games, and modifying or substituting such behaviour with more adaptive patterns (Echeburúa & Corral Gargallo, 2010; Petry et al., 2014; Young, 2007). Some of the treatments which have been proposed for Internet addiction could be of great use in the treatment of IGD currently. There is a consensus in all studies in that the main aim of IDG treatment is to achieve the controlled and adaptive use of video games (Arias Rodríguez, Gallego Pañeda, Rodríguez Nistal, & Del Pozo López, 2012; Echeburúa & Corral Gargallo, 2010; King & Delfabbro, 2014; Yau & Potenza, 2014).

The literature shows that there are different Internet use profiles and therefore the response to treatment may be conditioned (Matalí-Costa et al., 2014). The present study suggests that, taking into account the different comorbidities found in IGD, profiles could be created in which the response to treatment is different. To test this proposition, a study was designed with two main objectives. First, profiles were established in a clinical sample of adolescent patients diagnosed with IGD according to the type of internalising and externalising comorbid disorders, and describing the clinical characteristics and the pattern of video games use in both profiles. Subsequently, the response to treatment was analysed by profile at three and six months, with an assessment of both the type and intensity of treatment applied.

Method

This study employed a transversal design.

Sample

The initial sample consisted of a total of 86 outpatients referred to the addictive behaviour unit of the department for child and adolescent psychiatry and psychology from 2009 to 2015 with problems relating to the use of Internet or video games.

Inclusion criteria were being under 18 years of age at the time of the first visit, presenting a maladaptive use of Internet or video games and meeting the DSM-5 criteria for IGD, applied retrospectively. A total of 27 patients were excluded for not meeting the above criteria, leaving a final sample of 59 adolescents.

Ethical aspects

The approval of the hospital ethics committee was obtained for the present research, taking into consideration internal ethics regulations as well as those of the World Medical Association and the 1995 Helsinki Declaration and its subsequent amendments. All participants gave their verbal consent after being informed about the study and its aims.

Procedure

This research was carried out entirely in the addictive behaviour unit attached to the department for child and adolescent psychiatry and psychology. The hospital's clinical records provided the data to be included in the study: sociodemographic and clinical data, data relating to the pattern of game playing, the treatment received and its progress at three and six months.

A clinical interview was carried out in the first assessment session with the young patients. The information was used to evaluate their potential problems related to Internet or video games, the presence of IGD (according to DSM-5), and whether an associated mental disorder was present. The following variables were recorded for all patients who met the inclusion criteria:

- *Sociodemographic data:* gender, age and current school year.
- *Clinical variables:* criteria proposed in DSM-5 were used in the diagnosis for IGD, and when checking for the existence of comorbid mental disorders the semi structured *Kiddie-sads-present & Lifetime* interview (Kaufman el al., 1997; Ulloa et al., 2006) was used. This is based on DSM-IV-TR criteria and was created to investigate psychopathologies in children and adolescents aged between 6 and 17. Reliability coefficients of the Spanish version of the scale range from .76 for the depression disorder to values close to 1 for antisocial disorder. In addition, they were asked about whether they had received previous treatment or more than one diagnosis, and whether there was any family history of psychiatric issues.
- *Psychosocial variables:* patients were asked about whether they were experiencing problems with their primary support group (family) or group of friends, whether they had experienced bullying at school or the loss of contact (prior to the current problem) with the group of friends due to a change of school or address, changes in academic performance and the consumption of drugs.
- *Variables related to the pattern of game playing:* we recorded when games were played, preferences for gaming in the afternoons or evenings, the type of applications used (online games, MMORPG and/or chats), the main reason for using video games and how patients felt when they were taken away (bored or helpless).
- *Treatment and progress:* information regarding treatment intensity (outpatient visits, full or partial hospitalization) and type (psychotherapeutic, pharmacological or combined) was registered. Progress was assessed at three and six months using the Global Clinical Impression scale (CGI-I). This scale has a scoring range of 0-7, with 1-3 representing an improvement in the patient's condition, 4 equivalent to no change and 5-7 indicating that symptoms have worsened.

All participants in the study received personalised treatment with a psychotherapeutic approach which followed the behavioural addiction model proposed by Echeburúa (Echeburúa & Corral Gargallo, 2010). Pharmacological treatment was applied where necessary.

In creating the profiles we followed the criteria used in the Matalí-Costa study (Matalí-Costa et al., 2014), in which the sample was divided into two groups differentiated according to the Achenbach classification of mental disorders: internalizing and externalizing (Achenbach & Edelbrock, 1984; Matalí-Costa et al., 2014). Thus, profiles were created according to the adolescents' comorbidity diagnosis. Members of the group with an externalizing profile suffered from an imbalance in their control of aggression, impulsivity, negativity or hyperactivity, and displayed disruptive behaviour disorders, ADHD and non-specific disruptive behaviour disorder. The problems or difficulties of the internalizing group, on the other hand, materialised through inhibition, unease, avoidance or timidity. These patients suffered from depressive, anxiety and personality (Cluster C) disorders (Achenbach & Edelbrock, 1984).

Statistical analysis

Descriptive analyses were carried out using frequencies and percentages for the categorical variables, and means and standard deviations for quantitative variables. To measure the differences between the proposed profiles we

used chi-square, Fisher's z and Student t tests as appropriate. SPSS 18.8 (IBM Corp.) was used to run the statistical analyses. The level of statistical significance for all tests was set at 5% probability or lower, with the exact SPSS figure always indicated.

Results

Of the 86 patients attending the Addictive Behaviours Unit with Internet or video game problems, 59 met the DSM-5 criteria for IGD. The ages of these 59 cases ranged between 12 and 17 (M = 14.83; SD = 1.45) and 96.6% were male (n = 57).

The 59 participants were grouped into the internalizing or externalizing group depending on their comorbid disorders. The internalizing profile was found in 45.76% of the sample (n = 27) with a mean age of 15.19 (SD = 1.62), while 52.54% of the sample made up the externalizing profile (n = 31), with a mean age of 14.48 (SD = 1.23). In the internalizing profile the main diagnoses were affective disorders (44.4%; n = 12), anxiety disorders (44.4%; n = 12), and to a lesser degree, cluster C personality disorders (11.1%; n = 3). The disorders found in the externalizing group were disruptive behaviour disorder, (48.4%; n = 15), ADHD (29%; n = 9) and adaptive disorder (22.6%; n = 7). No statistically significant differences were observed in age or gender across the two groups.

Tables 1 and 2 show a comparison between the participants' profiles, both for the clinical variables and those relating to the patterns of video game use.

Table 1. *Variables relating to clinical profile variables.*

	Internalizing (n=27)		**Externalizing** (n=31)		
	%	**n**	**%**	**n**	**p**
Diagnosis					
Affective Disorder	44.4	12	0	0	p < .001
Disruptive Behavior Disorder	0	0	48.4	15	
ADHD	0	0	29	9	
Anxiety Disorder	44.4	12	0	0	
Personality Disorder	11.1	3	0	0	
Non-specific Disruptive Behavior Disorder	0	0	22.6	7	
More than one diagnosis					
Yes	81.5	22	19.4	6	p < .001
No	18.5	5	80.6	25	
Previous treatments					
Yes	85.2	23	48.4	15	p = .003
No	14.8	4	51.6	16	
Family history of psychiatric problems					
Yes	63	17	12.9	4	p < .001
No	37	10	83.9	26	
Bullying / Previous loss of contact					
Yes	77.8	21	45.2	14	p = .011
No	22.2	6	54.8	17	
School level					
Maintaining level	11.1	3	22.6	7	p>.05
Repeating/Dropping levels	66.7	18	67.7	21	
Dropout	22.2	6	9.7	3	
Family exclusion					
Yes	59.3	16	80.6	25	p=.074
No	40.7	11	19.4	6	
Drug use					
Yes	11.1	3	12.9	4	p=.834
No	88.9	24	87.1	27	

Table 2. Variable relating to video game playing patterns.

	Internalizing (n=27)		**Externalizing** (n=31)		
	%	**n**	**%**	**n**	**p**
Group of friends maintained					
Yes	18.5	5	61.3	19	
No	81.5	22	38.7	12	p = .001
Complaints when Internet not available					
Boredom	25.9	7	61.3	19	
Failure	59.3	16	16.1	5	p = .003
Both	14.8	4	22.6	7	
Game playing period					
Afternoons	25.9	7	71	22	
afternoon / evenings	74.1	20	29	9	p < .001
Type of application					
Online game	0	0	38.7	12	
MMORPG	81.5	22	25.8	8	
Chat and MMORPG	11.1	3	29	9	
Chat	3.7	1	6.5	2	
Offline games	3.7	1	0	0	p < .001
Main reason for playing games					
Recreational	3.7	1	80.6	25	
Escape	66.7	18	6.5	2	
Both	29.6	8	6.5	2	
Unknown	18.5	5	9.7	3	p < .001

Note: MMORPG = Massively Multiplayer Online Role-Playing Games.

In terms of the clinical variables, it was found that among the internalizing adolescents 81.5% had been given more than one different diagnosis, and in 85.2% of cases had received earlier treatment. This was quite different to the findings in the externalizing group, at 19.4% and 48.4% respectively. Similarly, while 63% of patients in the internalizing group had a family history of psychiatric treatment, this figure was only 12.9% in the externalizing group. At a social level, 77.8% of internalizing participants reported an earlier loss of contact with the group of friends or to have suffered bullying at some point, as opposed to 45.2% of the externalizers. The academic performance, family exclusion and substance use variables did not display significant difference across the two groups.

With regard to the variables related to the use of video games, 80.6% of the externalizing group stated that they were mostly motivated to use them for leisure purposes. The internalizing patients, on the other hand, claimed that 66.7% of the time they used them in order to hide themselves away or avoid discomfort. When faced with the game being taken away from them or not being able to play it, 59.3% of the internalizing adolescents say they felt incapable of dealing with the situation, while externalizers in the same situation said that they were bored 61.3% of the time. Furthermore, it was observed that 74.1% of the internalizers had a preference for night-time game playing. In terms of the most frequently used applications, the externalizing group expressed a greater variety of preferences, using online games (38.7%), MMORPG (25.8%), MMORPG together with social networks (29%) and social networks on their own (6.5%). In contrast, the internalizing group had a clear propensity to play mainly MMORPG, doing so in 81.5% of cases. Alongside MMORPG, 11.1% also used social networks, while 3.7% used only social networks, and 3.7% played games offline. A majority of 81.5% of the internalizing adolescents did not maintain friendships.

With regard to the therapeutic approach, Table 2 shows a comparison of the internalizing and externalizing profiles in relation to the intensity of treatment, i.e. whether treatment was outpatient or required full or partial hospitalization. At the same time, the type of treatment employed (psychotherapeutic, pharmacological or combined) is compared as well as the assessment of progress at three and six months.

An analysis of the variables measuring treatment intensity yielded statistically significant differences in terms of full hospitalization, which was necessary for 25.9% of (n = 7) of the internalizing profile, as against 3.2% (n = 1) of the externalizers. Such differences are not apparent in outpatient treatment or partial hospitalization. Neither are

statistically significant differences found across the groups in terms of the treatment recommended.

With regard to the progress of the disorder under treatment at three months, 63% of internalizing patients said that their symptoms had not changed, while 14.8% claimed a worsening and 18.5% were beginning to show improvement. Among the externalizers, symptoms did not change in 41.9% of cases, 3.1% got worse and 48.4% registered an improvement. At six months, no statistically significant differences were found across the two groups.

Discussion

This study compares the profile of adolescents diagnosed with IGD based on their comorbid mental disorder (internalizing vs. externalizing), and highlights the importance of the type of comorbidity in their use of videogames as well as clinical presentation and progress. The aim of the present study is thus of particular relevance given the scarcity of research in this area and the clinical and psychotherapeutic implications which may arise from a correct evaluation of these adolescents.

Firstly, it is worth pointing out that all cases in our study had comorbid disorders alongside IGD. Previous studies have yielded similar results, where, while not in all cases, comorbidity was present in a high number (Chin, Shin & Kim, 2006; Ferguson et al., 2011). The most prevalent comorbidities were depression, social anxiety, ADHD and aggressive behaviours (Fernández-Villa et al., 2015; Ko et al., 2012).

If we focus on the motivation for playing video games, differences could be observed between the profiles depending on comorbidity group (internalizing vs. externalizing). The externalizers showed a tendency towards more recreational play despite the attendant consequences in terms of family and friendships (Ko et al., 2012), which can be partially explained by the fact that the defiant nature of these adolescents is one of the reasons why video game related problems are perpetuated (Holtz & Appel, 2011). The internalizers, on the other hand, used MMORPG, described in the literature as potentially addictive (Carbonell, 2014), as a coping strategy to reduce discomfort caused by their interpersonal problems (Carbonell,2014; Fernández-Villa et al., 2015; Ko et al., 2012; Matalí-Costa et al.,

Table 3. *Variables relating to therapeutic approach.*

	Internalizing (n=27)		Externalizing (n=31)		
	%	n	%	n	p
Outpatient					
Yes	100	27	100	27	p›.05
No	0	0	0	0	
Full hospitalization					
Yes	25.9	7	3.2	1	p=.012
No	74.1	20	96.8	30	
Partial hospitalization					
Yes	14.8	4	3.2	1	p=.117
No	85.2	23	96.8	30	
Treatment type					
Psychotherapeutic	48.1	13	64.5	20	
Pharmacological	0	0	0	0	p=.209
Combined	51.9	14	35.5	11	
Progress at 3 months					
Unchanged	63	17	41.9	13	
Worse	14.8	4	3.2	1	p = . 027
Better	18.5	5	48.4	15	
Unknown	3.7	1	6.5	2	
Progress at 6 months					
Unchanged	29.6	8	22.6	7	
Worse	11.1	3	6.5	2	p=.562
Better	44.4	12	58.1	18	
Unknown	14.8	4	12.9	4	

2014), while at the same time clearly being a socialization tool (Carbonell, 2014; Király et al., 2014). Studying and understanding the motivation behind video game use is a key aspect for the design of the therapeutic treatment (Matalí-Costa et al., 2014) given that the efficacy of the treatment depends on the specific features of each case.

As mentioned previously, those with an internalizing profile tended to use the game as a way of alleviating the discomfort arising from their problems with peer relationships, and frequently displayed high levels of loneliness (Fernández-Villa et al., 2015; Matalí-Costa et al., 2014). This led at times to physical confinement at home, which in turn worsened socio-familial functioning (Teo, 2013). This factor has been described the principal risk factor for the development of IGD (Ferguson et al., 2011; Fernández-Villa et al., 2015; Marco & Chóliz, 2014; Matalí-Costa et al., 2014).

Within both profiles, family issues were highly prevalent and there were also problems in the academic sphere. The literature indicates that family exclusion is a clear risk factor in developing problematic use of video games (Echeburúa-Odriozola, 2012; Fernández-Villa et al., 2015) and in the deterioration of academic performance. This is one of the main alarm signals warning families of the existence of problems with video games (Echeburúa & Corral Gargallo, 2010), with both areas becoming a focus for treatment.

In terms of the preferred time for games playing, patients with an internalizing profile tended to play at night. As described in the literature, sleep-wake inversion has been described as one of the warning signs of a problematic pattern of use (Echeburúa & Corral Gargallo, 2010; Fernández-Villa et al. 2015), and seriously interferes with the daily activities of the young person (Griffiths & Meredith, 2009; Marco & Chóliz, 2014).

With regard to the proposed treatment approaches, the results of this study support the theory that treatment needs to be adapted to suit the profile in question. Patients with an externalizing profile responded better to fewer visits and started showing changes after three months (Matalí-Costa et al., 2014). The majority of cases received outpatient care and treatment was chiefly psychotherapeutic, aimed at changing the patterns of maladaptive games playing (Echeburúa & Corral Gargallo, 2010; King & Delfabbro, 2014). This can be explained by the fact that patients in this profile follow the model proposed for explaining IGDs, where the problematic behaviour is seen as an impulse control disorder (Young, 2007). Therefore, we found that they responded well to limits being set with the help of the family aimed at achieving partial abstinence in order to aid relearning of video games use (Echeburúa & Corral Gargallo, 2010; Grant, Potenza, Weinstein & Gorelick, 2010; King & Delfabbro, 2014). Conversely, patients with an internalizing profile made slower, more sluggish progress, more frequently requiring a combined and comprehensive approach (King & Delfabbro, 2014) which prioritizes a focus on the comorbidity, such as problems with social relationships (King & Delfabbro, 2014; Matalí-Costa et al., 2014).

This study is not free from limitations. The first of these concerns the small sample size which may limit the statistical power and the results obtained. Furthermore, the sample being a clinical one the results cannot be generalized to the general population. On the other hand, IGD criteria have only recently been established and the number of studies working with and validating the model empirically is still small. Nevertheless, given the results obtained more empirical research is needed to prove its relevance and explore different IGD profiles with the aim of developing a more efficient and personalised psychotherapy approach.

The present study has proposed that different profiles of adolescents diagnosed with IGD be established according to the comorbid mental disorder (internalizing/externalizing). The results of the study allow the following conclusions to be drawn. Assessing the comorbid mental disorder accompanying the diagnosis of IGD helps to understand the main reasons why the young person plays video games and at times develops maladaptive patterns of use. It can be seen that interpersonal relationship issues or social skills deficits, as well as loneliness, are important in driving adolescents to seclude themselves behind video games. The games of preference in these cases are specifically MMORPG, used as a coping strategy for discomfort as well as a tool for socialization for young people with internalizing comorbid diagnoses.

Thus, it is important to define the profile of the adolescent with IGD because it helps us establish the intervention plan and identify those people which are at risk in order to contribute to prevention. It must be understood that response to treatment can vary according to the profile of the patient and that the approach therefore needs to be planned accordingly, bearing in mind that cases of IGD with an internalizing profile are more complex and generally require the cooperation of different professionals and care resources for psychotherapeutic treatment. Problems with the use of video games generally mask other issues at the interpersonal, emotional and/or cognitive level which require more extensive approaches, focused on individual, family and social aspects.

Conflict of interests

The authors declare no conflict of interests.

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Perspectives in the treatment of cannabinoid hyperemesis syndrome

Perspectivas en el tratamiento del síndrome de hiperémesis por cannabis

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Cannabinoid hyperemesis syndrome (CHS) is a clinical condition described in 2004 (Allen, de Moore, Heddle & Twartz, 2004) with which healthcare professionals that treat cannabis users (Contreras Narváez et al., 2016; Pélissier, Claudet, Gandia-Mailly, Benyamina & Franchitto, 2016) as well as Hospital Emergency Room (ER) staff who treat its acute effects (Aguilar-Salmerón et al., 2016) are becoming more familiarised. However, its etiological mechanism is still unclear, and is most likely multifactorial (Allen et al., 2014; Contreras Narváez et al., 2016; Pélissier, Claudet, Gandia-Mailly, Benyamina & Franchitto, 2016). In Spain, its prevalence could reach 18% among chronic users (Bruguera, López-Pelayo, Miquel & Balcells-Oliveró, 2016). Nevertheless, it is quite probably even higher, given that many healthcare professionals are still unaware of its existence. In North American states in which marihuana use is legal, furthermore, visits of patients with CHS to ER have doubled in merely one year after the legalisation of this drug (Kim & Monte, 2016).

As is known, the only way for patients to alleviate their symptoms (in addition to ending cannabis use) entails bathing or showering compulsively with hot water, as their symptoms are unyielding to treatment with antiemetics (Contreras Narváez et al., 2016; Pélissier, Claudet, Gandia-Mailly, Benyamina & Franchitto, 2016). Therefore, our contribution presents data on possible effective treatments to mitigate acute effects: the use of haloperidol and capsaicin.

There are 2 published cases that resolved vomiting, nausea and abdominal pain through the administration of haloperidol, both intravenously and orally, in doses of between 2.5 and 5 mg (Hickey, Witsil & Mycyk, 2013; Jones & Abernathy, 2016). The mechanism by which haloperidol reduces the symptoms could be related to blockade of postsynaptic dopamine receptors in the brain, ultimately reducing stimulation of vomiting at the medullary level (Jones & Abernathy, 2016).

On another hand, 9 cases presented the use of capsaicin-based creams, frequently applied as a topical analgesic for articular pain, that reduced or eliminated the symptoms between 30-45 minutes after its application on the torso, with neither local nor systemic side effects (Lapoint, 2014a; Lapoint, 2014b; Biary, Lapoint, Nelson, Hoffman & Howland, 2014; Román, Llorens & Burillo-Putze, in press). Its mechanism of action could be related with the capsaicin receptor, the *Transient Receptor Potential Vanilloid 1* (TRPV1), for its role in the transmission of pain (Carnevale & Rohacs, 2016). Recently, healthy volunteers have described improvement of esophageal peristalsis after the administration of capsaicin (Yi, et al., 2016). On an experimental level, TRPV1 may also be activated at temperatures above 42ºC, wherefore the patients' use of very hot water could act this way.

Though clinical experience is still limited, these two drugs seem to be efficient and, a priori, have a plausible physiopathological base, to be explored through clinical trials (Biary, Lapoint, Nelson, Hoffman & Howland, 2014).

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Evaluating nicotine dependence levels in e-cigarette users

Evaluación de los niveles de dependencia de la nicotina en usuarios de cigarrillos electrónicos

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Electronic cigarettes (e-cigarettes) are non-combustible electronic nicotine delivery systems (ENDS) that mimic the experience of smoking tobacco (Harrell, Simmons, Correa, Padhya, & Brandon, 2014). They consist of three main elements: a rechargeable battery, an atomizer, and a tank.

Since the e-cigarette entered the market in 2003, its prominence and use has greatly increased worldwide (Martínez-Sánchez et al., 2014). Recent data on e-cigarette prevalence in both European and American samples indicates that nearly 6.8% of adults are e-cigarette users to date (McMillen, Gottlieb, Shaefer, Winickoff, & Klein, 2015). Nevertheless, this growing popularity has raised several public health issues regarding its safety and effectiveness as an alternative for smoking cessation (Yu et al., 2016). Research focused on e-cigarettes and smoking cessation has provided mixed results. While several internet surveys and uncontrolled designs suggest e-cigarettes may be effective in promoting tobacco abstinence, others have not found such results. To date, recommendations of the World Health Organization points out that the effectiveness of e-cigarettes as a method for quitting is limited and requires more research (World Health Organization, 2014).

A further concern involves abuse liability in current e-cigarette users (Cobb, Hendricks, & Eissenberg, 2015). Recent evidence has shown that nicotine levels as measured through plasma and saliva are similar to those seen in smokers, and even higher than observed levels in nicotine replacement therapy users (Marsot & Simon, 2015). On the other hand, low levels of self-reported nicotine dependence when vaping and a greater number of minutes between waking up and first use have been found among vapers, thereby accounting for lower nicotine dependence levels among this former group when compared to tobacco cigarette smokers (Foulds et al., 2015). This study aimed to explore nicotine dependence levels in a sample of experienced e-cigarette users (n=39; males=77%) and to compare them with current tobacco cigarette smokers (n=42; males=57%). Among e-cigarette users 20.5% were using second generation devices, while 79.5% were using third generation ones. We conducted several face-to-face interviews in order to assess sociodemographic and dependence related characteristics in both e-cigarette users and in smokers. Adapted versions of both the Fagerström test for nicotine dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and the nicotine dependence syndrome scale (NDSS; Shiffman, Waters, & Hickcox, 2004) were used to analyze nicotine dependence in each of the groups. Biochemical markers of carbon monoxide and urinary cotinine analysis were also collected. Our findings extend previous research on e-cigarette use and nicotine addiction. Two main findings can be drawn from this work: (1) e-cigarette users were dependent on e-liquids containing nicotine, (2) e-cigarette users were found to be less ni-

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cotine dependent than current tobacco cigarette smokers (see table 1).

Several mechanisms may explain these results. First, because nicotine dependence and abuse liability are influenced by nicotine bioavailability, the oral route of e-liquid administration might have strongly influenced rates of both nicotine absorption and exposure, therefore accounting for self-reported nicotine dependence levels among e-cigarette users. Second, in addition to the nicotine itself, using e-cigarettes has been shown to involve other psychosocial components which could explain addictiveness among e-cigarette users. For instance, the use of e-cigarettes enables the user to replace most of the sensorial-motor and social components associated with smoking such as the hand to mouth ritual or the visualization of exhaled vapor. Third, due to the fact that the sample of e-cigarette users were former smokers or current tobacco cigarette smokers, it might be that when they first used e-cigarettes, they were already nicotine dependent on tobacco cigarettes. Thus, nicotine delivered by means of e-cigarette use might lead to the maintenance of nicotine dependence.

This study is not exempt of limitations. First, we did not employ validated versions of the dependence scales we used. However, the validation test could not be performed because during the recruitment process we were not able to obtain enough sample size of e-cigarette users. Nonewithstanding, data suggest that e-cigarette use in Spain probably is not as prevalent as other European and U.S. countries. Second, the fact that a 35.9% of e-cigarette users were also smoking at the time of the interview preclude us to yield firm conclusions on nicotine dependence levels.

Despite these limitations, these findings add substantially to our understanding of e-cigarette abuse liability. Although e-cigarette users were found to be nicotine dependent, biochemical measures of carbon monoxide and self-reported questionnaires found nicotine dependence on e-cigarettes to be lower than was observed in tobacco cigarette smokers. Considerably more longitudinal research is needed in order to better ascertain addictiveness levels among e-cigarette users. Further research should therefore focus on properly exploring the levels of nicotine dependence in e-cigarette users as measured by adapted and validated questionnaires.

Conflict of interest

No conflict declared.

Role of funding sources

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Table 1. *Dependence levels among e-cigarette users and smokers*

	E-cigarette users (n = 39)	Smokers (n = 42)	t	p	r
CO (ppm)	8±6.77	15.24±7.18	-4.657	‹.001	0.49
Cotinine (ng/ml)	1891.26±1452.11	2383.51±1129.07	-1.710	.091	0.16
FTND (tobacco/e-cigarette)[a]	4.38±1.93	5.57±1.48	-3.118	.003	.74
NDSS-T (tobacco/e-cigarette)[a]	26.26±5.29	40.50±8.14	-9.405	‹.001	.75
NDSS-Impulsivity (tobacco/e-cigarette)[a]	10.46±4.72	19.98±5.14	-8.659	‹.001	.70
NDSS-Priority (tobacco/e-cigarette)[a]	4.82±1.57	7.81±3.07	-5.452	‹.001	.52
NDSS-Tolerance (tobacco/e-cigarette)[a]	14±3.41	22.19±3.93	-9.987	‹.001	.75
NDSS-Continuity (tobacco/e-cigarette)[a]	23.13±3.91	25.90±4.86	-2.819	.006	.30
NDSS-Stereotypy (tobacco/e-cigarette)[a]	11.64±2.95	13.21±3.47	-2.191	.031	.24

Note. Nicotine dependence among e-cigarette dual users was assessed using scores on questionnaires evaluating dependence on e-cigarette use; CO = carbon monoxide; ppm = parts per million; ng/ml = nanogram/milliliter. [a] = Means ± SD; t= Student´s t test; r= Cohen's d effect size; FTND; Fagerström Test for Nicotine Dependence; NDSS; The Nicotine dependence syndrome scale.

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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.

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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.

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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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

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

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

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

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TREVICTA®
palmitato de paliperidona
suspensión inyectable de liberación prolongada

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. COMPOSICIÓN 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 CLÍNICOS. 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 (preferblemente 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 mas alta como se indica en a 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 iniciara 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 preferblemente durante cuatro meses o más. *Cambio desde TREVICTA a otros medicamentos antipsicóticos.* Si se suspende la administración de TREVICTA, se debe 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, cimbiendo 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 dirarios 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 estabilizados 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 13, 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 dirarios se debe adaptar siempre al paciente individual, teniendo en cuenta los posibles cambios en los motivos de 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. Pero 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 menos de 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 preferblemente 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 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

*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 establizará el 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 sólo 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 facilitan en el envase de TREVICTA. Para la administración de TREVICTA no se utilizarán las agujas que se facilitan en el envase de la inyección mensual de palmitato de paliperidona ni otras agujas comercialmente disponibles (ver *Información reservada para médicos y 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 transurren 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 1 ½ (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 debido 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 a 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 use 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 SNM, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía. 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, incluida la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. 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 10⁹/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 particular 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 previsiblente 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 o 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 el 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 metanálisis 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 transurso 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 prescribe TREVICTA a pacientes que vayan a experimentar circunstancias que pueden 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 adquirido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto anticolinérgico. En los estudios preclínicos con paliperidona se observó un efecto anticolinérgico. Si se produce este efecto en los seres humanos, puede aumentar 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. **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, fenotiazinas 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 a 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 de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento 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. **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 teratogenos 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 ellas síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultar 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 mediante 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 administre 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 del medicamento observadas con mayor frecuencia notificados en 2≥1% 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 estimado en los ensayos clínicos realizados con TREVICTA y con palmitato de paliperidona inyectable mensual. 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 conocidas
Infecciones e infestaciones		infección de vías respiratorias altas, infección urinaria, gripe	neumonía, bronquitis, infección de vías respiratorias, sinusitis, cistitis, otitis, amigdalitis, oncomicosis, celulitis	infección ótitmica, dermatomatitis, 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 profiláctica
Trastornos endocrinos			hiperprolactinemia*	secreción inadecuada de hormona antidiurética, glucosuria	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, pérdida de peso	diabetes mellitus, hiperinsulinemia, aumento del apetito, anorexia, disminución del apetito, triglicéridos en sangre elevados, colesterol en sangre elevado	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio*	agitación, depresión, ansiedad	trastornos del sueño, disminución de la libido, nerviosismo, pesadillas	manía, estado de confusión, embotamiento afectivo, anorgasmia	
Trastornos del sistema nervioso		parkinsonismo*, sedación, somnolencia, distonía, mareo, disestesias, 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 consciencia, convulsiones*, trastornos del equilibrio	coma diabético, coordinación anormal, 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
Trastornos del oído y del laberinto			vértigo, acufenos, dolor de oídos		
Trastornos cardíacos		taquicardia, taquicardia	bloqueo auriculoventricular, trastornos de la conducción, prolongación del intervalo QT en el electrocardiograma, síndrome de taquicardia postural ortostática, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	

Trastornos vasculares		hipertensión	Hipotensión, hipotensión ortostática	trombosis venosa, rubor	embolia pulmonar, siqueria
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, dolor faringolaringeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, congestión respiratoria, sibilancias	hiperventilación, neumonía por aspiración, estertores, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, odontalgia	molestias abdominales, gastroenteritis, sequedad de boca, flatulencia	pancreatitis, edema lingual, incontinencia fecal, fecaloma, disfagia, 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		erupción de la piel	urticaria, prurito, 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 lumbar/cervical, artralgia	valores elevados de creatinfosfoquinasa en sangre, espasmos musculares, rigidez articular, debilidad muscular, dolor cervical		rabdomiólisis, 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	disfunción eréctil, trastornos de la eyaculación, retrasos de la menstruación, trastornos menstruales*, ginecomastia, galactorrea, disfunción sexual, dolor mamario	hinchazón a 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†, alteraciones de la marcha, dolor torácico, malestar en el pecho, malestar general, induración	hipotermia, escalofríos, aumento de la temperatura corporal, polidipsia, 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		

*No es posible determinar la frecuencia de las reacciones adversas notificadas después de la comercialización, ya que dependen de notificaciones espontáneas. Por tanto, la frecuencia de estas reacciones adversas se define como "no conocida". Ver el apartado "Hiperprolactinemia" a continuación. Ver el apartado "Síntomas extrapiramidales" a continuación. †Insomnio comprende: El insomnio inicial y el insomnio medio. Convulsiones incluye: Convulsiones, y convulsiones del gran mal; trastornos menstruales incluye: Trastornos menstruales, menstruación irregular, oligomenorrea. Edema incluye: Edema generalizado, edema, edema periférico, edema puerperal.

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 inducración, rubefacción e hinchazón no se presentaron a fuerzas leves en ≥95% de los 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%, 0,5%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (mostrano extrapiramidal), síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, fobias 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, espasmo facial, crisis oculógiras, distonía bucomandibular, risa sardónica, tetania, hipertonía, tortícolis, contracciones musculares involuntarias, contractura muscular, blefarospasmo, oculogiración, parálisis lingual, espasmo facial, faringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurostótonos, 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 11% 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 11% 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 TEV, entre ellos de embolia pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos. 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 trastorno 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 especie isomérica 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 1 adrenérgicos 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 aleatorizado, 526 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 pasó fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 233 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 3,31 (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%]).

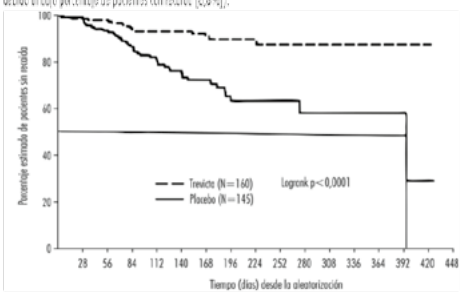


Figura 1. Gráfico de Kaplan-Meier del tiempo hasta la recaída – Análisis final

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 (entre 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 49 semanas. Los pacientes recibían 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 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 los 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 mayorías 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.

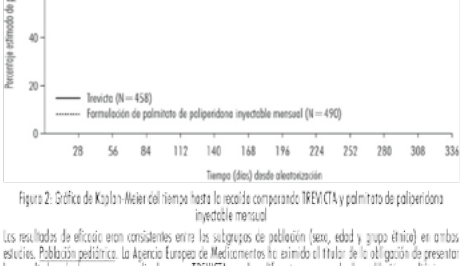


Figura 2: Gráfico de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

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 el 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 con 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_{max}. 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 reclínica 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 intensivamente en 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 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se sugirieron que los 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 observa ninguna diferencia conocable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentes 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, CYP2B6/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP2C8. 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 mas 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 (ClCr=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (ClCr=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (ClCr=10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{∞}) 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_{ss} 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 este 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. Otras antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la methidiol 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 (rata), 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 FARMACEÚTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajustar el 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, tapa-husera 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). Formato del envase: Envases con 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 515,00 €; PVP: 570,91 €; PVP (IVA): 593,75 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 673,00 €; PVP: 725,91 €; PVP (IVA): 754,95 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 924,00 €; PVP: 879,91 €; PVP (IVA): 915,11 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.236,00 €; PVP: 1.291,91 €; PVP (IVA): 1.343,59 €. **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 de 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.** 09/2016. 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. 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 a 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 o 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), dicho 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 recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con Xeplion. Algunos pacientes se pueden beneficiar de una retirada gradual. Xeplion debe iniciarse según se describe al principio de la sección 4.2 anterior. ***Cambio desde Risperidona inyectable de acción prolongada 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 necesario 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 inicición de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y las siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8 ± 4 días), el momento se reinicia recomendada dependerá 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 en 25 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. ***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. Se 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, ambas administradas 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 a 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 determinado por el peso del paciente. En los pacientes ≥90 kg, se recomienda la aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). En los pacientes <90 kg, se recomienda la aguja de calibre 23 de 1 pulgada (25,4 mm x 0,64 mm). Las inyecciones en el deltoides se deben alternar entre los dos músculos deltoides. ***Administración en el músculo glúteo.*** El tamaño de la aguja recomendado para la administración de mantenimiento de Xeplion en el músculo glúteo es el de una aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). La administración se debe realizar en el cuadrante superior externo de la zona glútea. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en pacientes que se encuentran en un estado sumamente agitado o psicótico grave. Xeplion no se debe utilizar para el tratamiento de estados agitados agudos o psicóticos graves cuando esté justificado el control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al recetar paliperidona a pacientes con enfermedad cardiovascular conocida o antecedentes familiares de prolongación del intervalo QT, y en caso de uso concomitante con otros medicamentos que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos del Síndrome Neuroléptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la consciencia y elevación de los niveles séricos de creatina fosfocinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiolisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de paliperidona. Discinesia tardía. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (< 1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB en ausencia de otras factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados para 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 basal 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 post-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 aparecen 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 induce coma diabético y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica coherente 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 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-1 bloqueante. Según los datos agrupados de las 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 oral 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, olanzapino 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. Los 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 la 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 reciben 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. Esta 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 de 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 alfa1-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 alfa1-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir Xeplion con medicamentos que prolonguen el intervalo QT, p. ej. antiarrítmicos de clase IA (p. ej., quinidina, disopiramida) y antiarrítmicos de clase III (p. ej. amiodarona, sotalol), algunos antihistamínicos, algunos otros antipsicóticos y algunos antipalúdicos (p. ej. mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que Xeplion afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos que sean metabolizados por las isoenzimas del citocromo P-450. Dado que los efectos principales de paliperidona se ejercen sobre el sistema nervioso central (SNC) (ver sección 4.8), Xeplion debe utilizarse con precaución en combinación con otros medicamentos de acción central, p. ej., ansiolíticos, la mayoría de los antipsicóticos, hipnóticos, opiáceos, etc. o con el alcohol. Paliperidona puede antagonizar el efecto de levodopa y otros agonistas de dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se debe recetar la dosis mínima eficaz de cada tratamiento. Debido a la posibilidad de que induzca hipotensión ortostática (ver sección 4.4), se puede observar un efecto aditivo si se combina con fármacos que también tengan esta posibilidad, p. ej., otros antipsicóticos, triciclicos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenotiazinas o butirofenonas, triciclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de comprimidos orales de paliperidona de liberación prolongada en estado estacionario (12 mg una vez al día) con comprimidos de divalproex sódico de liberación prolongada (de 500 mg a 2000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xeplion y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a Xeplion. Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vitro ni in vivo* de que esas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{ss} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad de principio activo inalterada excretada en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP o en la biodisponibilidad de paliperidona. Con dosis más altas de carbamazepina, podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al inicio del tratamiento con carbamazepina, se debe reevaluar y aumentar la dosis de Xeplion, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xeplion, si es necesario. La administración concomitante de una sola dosis de un comprimido de paliperidona oral de liberación prolongada de 12 mg con comprimidos de divalproex sódico de liberación prolongada (dos comprimidos de 500 mg una vez al día) tuvo como resultado un aumento de aproximadamente el 50% en la C_{max} y el AUC de paliperidona, probablemente como resultado de un aumento de la absorción oral. Dado que no se observó ningún efecto sobre el aclaramiento sistémico, no se espera que se produzca una interacción clínicamente significativa entre los comprimidos de divalproex sódico de liberación prolongada y la inyección intramuscular de Xeplion. Esta interacción no se ha estudiado con Xeplion. Uso concomitante de Xeplion y risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando Xeplion sea administrado de forma conjunta con risperidona o con paliperidona oral durante periodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrado por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a paliperidona durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xeplion no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas o medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estos, 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	Raros	No conocidas*
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, otitis, infección de oídos, amigdalitis, candidiasis, celulitis	infección de ojos, dermatomicosis, 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†		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‡, 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†	agitación, depresión, ansiedad	trastorno del sueño, manía, disminución de la libido, nerviosismo, pesadillas	estado confusional, embotamiento afectivo, orgasmo	
Trastornos del sistema nervioso		parkinsonismo†, acatisia†, sedación/somnolencia, distonía†, mareos, discinesia†, temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotora, marcha 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†, 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, acufenos, dolor de oído		
Trastornos cardíacos		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, hipertensión ortostática	hemtosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, 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, 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			[illegible]	[illegible]	[illegible]
Trastornos musculoesqueléticos y del tejido conjuntivo		[illegible]	[illegible]	[illegible]	[illegible]
Trastornos renales y urinarios			[illegible]	[illegible]	
Embarazo, puerperio y enfermedades perinatales					[illegible]
Trastornos del aparato reproductor y de la mama		[illegible]	[illegible]	[illegible]	[illegible]
Trastornos generales y alteraciones en el lugar de administración		[illegible]	[illegible]	[illegible]	[illegible]
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			[illegible]		

[illegible]

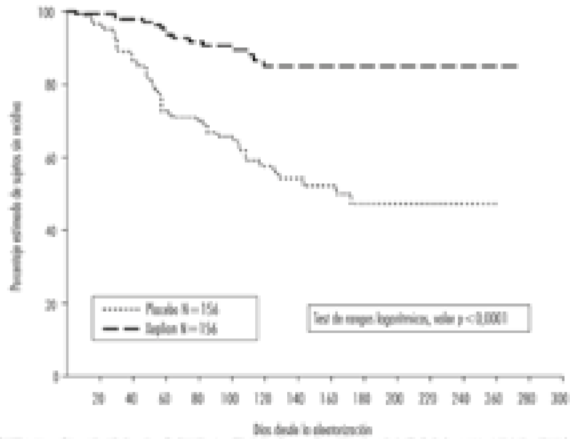
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

[illegible]

Figura 1 [illegible]



[illegible] **5.2 Propiedades farmacocinéticas** [illegible]

[illegible]

TREVICTA®

palmitato de paliperidona

suspensión inyectable de liberación prolongada

Único
Farmacocinética única trimestral[1-3]

Duradero
Protección frente a recaídas[¥4]

Predecible
Eficacia y tolerabilidad* similar a Xeplion®[§5]

Cómodo
Administración 4 veces/año[1]

AMPLIO RANGO DE DOSIS[1]

175 mg · 263 mg · 350 mg · 525 mg

Janssen-Cilag, S.A.
Paseo de las Doce Estrellas, 5-7
28042 Madrid
www.janssen.es

janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

[¥] N= 506. Estudio aleatorizado, doble ciego, controlado con placebo que evaluó la eficacia y seguridad del retraso del tiempo hasta la recaída de Trevicta® *vs.* placebo. 93% de los pacientes sin recaídas.
[§] N= 1.429. Estudio aleatorizado, doble ciego, de grupos paralelos, multicéntrico, de no inferioridad de Trevicta® *vs.* Xeplion®, de 48 semanas de duración. La tasa de recaídas fue similar en ambos grupos. Los perfiles de seguridad y tolerabilidad de Trevicta® y Xeplion® fueron comparables a lo largo de la fase doble-ciego de 48 semanas y consistentes con lo observado en otros ensayos con palmitato de paliperidona.

* Para más información consultar la sección 4.4 y 4.8 de las Fichas Técnicas.

1. Ficha Técnica Trevicta®. 2. Gopal S *et al.* Practical guidance for dosing and switching from paliperidone palmitate 1 monthly to 3 monthly formulation in schizophrenia. Current Medical Research and Opinion. 2015;31(11):2043-2054. DOI: 10.1185/03007995.2015.1085849. 3. Ravenstijn P *et al.* Pharmacokinetics, safety, and tolerability of paliperidone palmitate 3-month formulation in patients with schizophrenia: A phase-1, single-dose, randomized, open-label study. J Clin Pharmacol. 2016 Mar;56(3):330-9. DOI: 10.1002/jcph.597. Epub 2015 Oct 5. 4. Berwaerts J *et al.* Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: A randomized clinical trial. JAMA Psychiatry. 2015. DOI: 10.1001/jamapsychiatry.2015.0241. 5. Savitz AJ *et al.* Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. International Journal of Neuropsychopharmacology. 2016;1–14. DOI: 10.1093/ijnp/pyw018.