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Cannabis use and cognitive impairment in schizophrenia and first-episode psychosis

Consumo de cannabis y alteraciones cognitivas en esquizofrenia y primeros episodios psicóticos

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Cannabis is used extensively worldwide, although its effects on the brain and cognition remain controversial (Block et al., 2000; Jager et al., 2007; Martin-Santos et al., 2010). The use of this substance has been linked to a greater risk of psychosis (Casajuana Kögel, López-Pelayo, Balcells-Olivero, Colom & Gual, 2018; Gage, Hickman, & Zammit, 2016; Koskinen, Lohonen, Koponen, Isohanni, & Miettunen, 2010; López Pelayo, de Miquel Montagut, Casajuana Kögel & Balcells Oliveró, 2018; van Os et al., 2002), and it has also been observed with greater frequency among patients with schizophrenia than in the general population (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006). The prevalence rate of cannabis use disorders is below 10% in the general population (Moore et al., 2007) but rises to 27.1% among patients with schizophrenia (Koskinen et al., 2010). Moreover, in the case of cannabis use in first-episode psychosis (FEP), these figures are even higher, with rates up to 65.7% reported (Schimmelmann et al., 2012).

Cognitive impairments and functional impairments secondary to them develop early in schizophrenia and remain stable and persistent throughout the development of the disorder (Heaton et al., 2001). In addition, premorbid cannabis use has been associated with more symptoms and worse functioning in patients with schizophrenia spectrum disorders (Ringen et al., 2016). However, earlier studies of how cannabis use affects patients with schizophrenia at the cognitive level are varied (Potvin, Stavro, & Pelletier, 2012).

The impact of cannabis use

Although different studies have observed a positive association between cannabis use (history of cannabis use or current consumption) and cognition, both in patients with schizophrenia (DeRosse, Kaplan, Burdick, Lencz, & Malhotra, 2010; Helle, Loberg, Gjestad, Schnakenberg Martin, & Lysaker, 2017; Meijer et al., 2012; Yucel et al., 2012) and in first-episode psychosis (Cunha et al., 2013; de la Serna et al., 2010; Leeson, Harrison, Ron, Barnes, & Joyce, 2012; Rodriguez-Sanchez et al., 2010; Yucel et al., 2012), such better performance has not always been found in all areas assessed (Bahorik et al., 2014; Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009). Furthermore, many of these positive results come from studies which included patients with a lifetime history of use rather than current or recent users (Yucel et al., 2012), while other studies have yielded a relationship between a history of cannabis use or current consumption and worse cognitive performance in patients with psychosis (Waterreus, Badcock, Di Prinzio, Martin-Iverson, & Morgan, 2017), schizophrenia (Meijer et al., 2012; Sanchez-Torres et al., 2013) and FEP (Gonzalez-Pinto et al., 2016), although in the latter case, this worse per-

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formance has been related to the intensity of use during the previous year (Nunez et al., 2016) or with an absence of a family history of psychosis (Gonzalez-Pinto et al., 2016). Similarly, it has been reported that cognitive functions improve in cannabis dependent patients with schizophrenia and FEPs on cessation (Rabin et al., 2017; Setien-Suero et al., 2018), while such improvements are less notable in healthy controls (Rabin et al., 2017). In other cases, the differences observed disappear once certain confounding variables such as age, age of onset of illness, premorbid IQ or socioeconomic factors are controlled for (Leeson et al., 2012; Power et al., 2015). Finally, in a smaller number of studies, cognitive differences in terms of cannabis use in this type of patient were not found (Bugra et al., 2013).

In addition to all the above, better or worse cognitive performance in cannabis users has been related to the diagnostic picture; thus cognitive performance in purer psychoses with less interference from affective psychopathology seem to be better (Hanna et al., 2016) or at least not worse (Waterreus et al., 2017) than in those with other types of psychosis, where the affective component is fundamental. Similarly, besides different patient profiles, different cannabis user profiles could also result in cognitive performance variation (Schnakenberg Martin et al., 2016).

Cognitive variables assessed

Neurocognitive deficits among patients with schizophrenia have been widely documented and are considered one of its central features (Elvevag & Goldberg, 2000; Green, Kern, & Heaton, 2004). They appear to be present from the first episode of psychosis and even in first-degree relatives of patients with schizophrenia without evidence of psychotic symptoms (Asarnow et al., 2002), suggesting that certain cognitive impairments could be components of a genetic vulnerability to schizophrenia.

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative of the National Institute of Mental Health (NIMH) includes seven cognitive domains as being characteristic of schizophrenia: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Kern et al., 2008; Nuechterlein et al., 2008). In research on cannabis and cognition in schizophrenia, different studies have assessed neurocognitive functions such as attention/vigilance, memory, verbal learning, processing speed, executive functions, verbal fluency, etc., as well as also others such as social cognition, emotional recognition or theory of mind. However, the tests used to measure the different cognitive variables have been diverse, and very few studies have used MATRICS (Bahorik et al., 2014), as recommended by the NIMH.

Neurocognitive variables

Regarding attention capacity in patients with schizophrenia who use cannabis, the results are controversial. Some studies observe greater attention capacity in more frequent users (Schnell et al., 2009), while others report that patients who use cannabis but had not done so in the previous 30 days performed better (Bahorik et al., 2014). Likewise, lower IQ in cannabis users predicts worse attentional performance in healthy controls but not in patients with schizophrenia or their siblings (Sanchez-Torres et al., 2013). In FEPs, patients with a history of cannabis use or those using cannabis before the onset of the disorder suffered fewer attention impairments compared to those without a history of cannabis use (Cunha et al., 2013; Rodriguez-Sanchez et al., 2010). Nevertheless, it has also been observed that heavy users in the year prior to the assessment had worse cognitive performance than non-users or those with a weaker pattern of use (Nunez et al., 2016).

The memory types assessed in the various studies have been diverse: visual (Sanchez-Torres et al., 2013; Yucel et al., 2012), verbal (Rabin et al., 2017; Sanchez-Torres et al., 2013; Schnell et al., 2009; Setien-Suero et al., 2018), episodic (Mallet, Ramoz, Le Strat, Gorwood, & Dubertret, 2017), immediate (Nunez et al., 2016), working (Gonzalez-Pinto et al., 2016; Meijer et al., 2012; Menendez-Miranda et al., 2019; Nunez et al., 2016; Schnell et al., 2009; Yucel et al., 2012) or long-term memory (Nunez et al., 2016), and their results are not conclusive. Patients with schizophrenia and a history of cannabis use have, in some cases, shown better knowledge acquisition (Meijer et al., 2012) and better performance in memory tasks (DeRosse et al., 2010; Menendez-Miranda et al., 2019); even patients who had been heavy users before the onset of the disease seemed to show better episodic memory (Mallet et al., 2017). However, a lifetime history of cannabis use among siblings of patients with schizophrenia has been linked to a negative effect on declarative memory, both visual and verbal (Sanchez-Torres et al., 2013). Furthermore, current use of cannabis in patients with schizophrenia has been associated in some studies with worse working memory performance (Meijer et al., 2012), while other studies link higher consumption to better performance (Schnell et al., 2009). Others find that verbal memory improves when patients with schizophrenia quit cannabis, but not when healthy controls do so (Rabin et al., 2017). In FEPs, both with and without a history of cannabis use, worse memory scores have been observed than in healthy controls (de la Serna et al., 2010). It has also been observed in cases of FEP that heavy cannabis users in the previous year showed impairments in immediate, short-term and long-term verbal memory compared to non-users (Nunez et al., 2016), although one study observes this relationship between cannabis use and worse verbal memory only in FEP cases without a family history of psychosis, but not in those who with one. Likewise, FEP

sufferers who stop cannabis use have displayed improved verbal memory (Setien-Suero et al., 2018). In terms of working memory, FEPs with cannabis use seem to perform worse (Gonzalez-Pinto et al., 2016).

Research on verbal learning in patients with schizophrenia again yields contradictory results. Patients with schizophrenia and a history of cannabis use perform better in verbal learning compared to patients without a history of use (DeRosse et al., 2010), while at the same time current cannabis use is associated with worse performance in immediate verbal learning (Meijer et al., 2012). In FEPs, both patients with a history of cannabis use and those without it have lower verbal learning scores than healthy controls (de la Serna et al., 2010).

Lifetime cannabis use in people with psychotic disorders (Power et al., 2015) or schizophrenia (Menendez-Miranda et al., 2019) has also been linked to processing speed, but results again diverge; while some studies observe better performance (DeRosse et al., 2010; Rabin, Zakzanis, Daskalakis, & George, 2013), others find the opposite (Meijer et al., 2012). However, once certain confounding variables are controlled for (age, age of onset of illness, premorbid IQ, and socioeconomic factors) the association between cannabis and processing speed disappears (Power et al., 2015). Likewise, in siblings of patients with schizophrenia, a history of lifetime cannabis use seems to have a negative effect on processing speed, but this is not the case in healthy controls, unless tobacco use is included. i.e., a negative relationship is observed between lifetime use of cannabis and smoking and processing speed in healthy controls (Sanchez-Torres et al., 2013). In FEP, heavy cannabis use during the previous year is associated with slower processing speed (Nunez et al., 2016).

Finally, executive functions have been positively associated with the use of cannabis in patients with schizophrenia (Helle et al., 2017; Schnell et al., 2009). In FEP cases, a history of cannabis use before the onset of the disorder has been linked to better executive function performance (Cunha et al., 2013; Rodriguez-Sanchez et al., 2010; Yucel et al., 2012). However, a variable that again appears to mediate is family history of psychosis, given that FEPs with cannabis use but no family history of psychosis perform worse in executive functions, while those with a family history of psychosis did better (Gonzalez-Pinto et al., 2016).

Social cognition

With regard to the relationship between cannabis use and social cognition in schizophrenia patients, the data are again contradictory. While some observe better recognition of facial emotions and identity in patients with schizophrenia and a history of cannabis use (Meijer et al., 2012), others find worse emotional recognition (Helle et al., 2017) and social cognition (Sanchez-Torres et al., 2013) as well as better performance when cannabis use ceases 30 days before assessment. In addition, others find no relationship between cannabis use and theory of the mind (Helle et al., 2017).

Possible explanations for the inconsistency in results

Various hypotheses have been posited to explain the observed results. It may be the case that patients who use cannabis constitute a subgroup of patients with better premorbid adjustment and better premorbid prefrontal cognitive functions (Rodriguez-Sanchez et al., 2010). Perhaps the etiological process of the psychotic picture of these patients is different, with FEPs who use cannabis and develop psychosis representing a group of patients with less damage at the neurodevelopmental level, and, therefore, a greater cognitive reserve than other psychotic patients (Cunha et al., 2013). The use of cannabis could trigger initial psychosis among people who may otherwise have had a good prognosis with later onset or even without developing the symptoms due to the toxic action of cannabis rather than the intrinsically greater severity of the disease (Leeson et al., 2012). It has also been suggested that better cognitive function in patients with schizophrenia who use cannabis could reflect less vulnerability to psychosis (higher level of functioning and cognitive ability) compared to other patients with schizophrenia (Schnell et al., 2009). An attempt has also been made to explain the fact that patients with schizophrenia and a history of cannabis use have better cognitive performance on the basis of greater social cognition, but results do not support this hypothesis (Helle et al., 2017). Likewise, it has been suggested that the different pattern of associations between the use of cannabis and cognitive performance in patients with schizophrenia in comparison to siblings of patients or healthy controls could already be explained by the negative impact produced by the disorder itself (Sanchez-Torres et al., 2013). Finally, it seems that the cannabis dose used may be a variable influencing the differences found at the cognitive level (Nunez et al., 2016).

Conclusions

The different studies of psychosis, cannabis and cognition differ in aspects that may be relevant and connected to the differences observed in the results. Thus, there are studies which have focused on psychosis in general, including affective psychoses, while others have focused specifically on schizophrenia or on first psychotic episodes. Nevertheless, it is well known that the differential characteristics of the clinical pictures involved should be studied in isolation so that results can be verified and replicated. Similarly, some studies observe differences depending on

whether or not patients have a family history of psychosis, which therefore becomes another variable to be taken into account when replicating the different results. Likewise, on the subject of cannabis use, some studies focusing on a history of lifetime use may include subjects who have used it only at relatively specific moments or who have not used it for years, while others focus on current consumption, which may involve different patterns of use (mild, moderate, severe) with different consequences. Other aspects of this use which are also important to consider with respect to the time of onset of schizophrenia are whether it preceded the disease, whether it continued during the first years or whether it occurred uninterruptedly. Finally, on the subject of cognitive impairments, assessments have also diverged, not only regarding the cognitive variables measured or in terms of the number of areas included, but also in the tests used. Although there is a consensus in the assessment of cognition among patients with schizophrenia through MATRICS, there are few studies that use this test. Therefore, before firm conclusions about the obtained results can be reached, uniformity is required in the type of patients included, as well as in the variables to be assessed and the way to measure them. At the same time it would be very important to carry out longitudinal studies to see the changes in the cognitive variables depending on the pattern of concurrent or prior use and include all the confounding variables which may be intervening.

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Conflict of interests

The authors declare no conflict of interest.

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Willingness of patients with SUD to participate in research: prevalence and associated factors

Disposición para participar en investigación en población adicta: prevalencia y factores asociados

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Abstract

Greater attention is focusing on the motivations of subjects recruited for research protocols, especially in vulnerable populations. Although addiction is a highly stigmatized condition, very little research has focused on the factors influencing the decision to participate of patients with an addiction. Our aim is to gather further evidence in relation to the motivations of people with Substance Use Disorders (SUD), comparing their reasoning and willingness to participate in a hypothetical research study of 53 subjects with DSM-5 diagnoses of SUD and 50 controls. Responses on the MacArthur Competence Assessment Tool for Clinical Research were documented and correlated with several variables. There were no significant differences in willingness to participate in research and reasons for doing so between SUD and controls. Among SUD subjects, 59% mentioned altruism, 53.8% expected therapeutic benefits, and 43.6% desired to help others; none mentioned money. Of those patients with SUD who refused to participate in research, 69.2% cited aversion and 46.2% mentioned risk. Willingness to participate was correlated with higher computer literacy and better cognitive performance. In the multivariate analysis, aversion was a significant predictor of willingness to participate in research. When research is not related to their diagnosis, the motivations of SUD and controls are similar and flowed logically from the study. However, elements associated with therapeutic misconceptions were also evident. Therefore, negative views about the motivations of SUD subjects' participation in research are unfounded. Consequently, to improve study recruitment, assessments may be targeted to specific vulnerabilities rather than to diagnoses.

Keywords: Addictions; Research ethics; Motivation; Decision-making.

Resumen

Cada vez se presta más atención a las motivaciones de las personas reclutadas para ensayos clínicos, especialmente si pertenecen a colectivos vulnerables. Aunque la participación en investigación de las personas con trastorno por uso de sustancias (TUS) suscita estereotipos negativos, muy pocos estudios se han centrado en los factores que influyen en la misma. Nuestro objetivo es analizar sus motivaciones comparando las razones y la disposición a participar en un ensayo hipotético de 53 pacientes con diagnósticos DSM-5 de TUS y 50 controles. Las respuestas que dieron a la entrevista MacArthur Competence Assessment Tool for Clinical Research se correlacionaron con diversas variables. No encontramos diferencias significativas entre ambas poblaciones en términos de motivaciones y disposición a participar. El 59% de la población TUS mencionó altruismo, un 53,8% esperaba beneficio terapéutico, y el 43,6% deseaba ayudar a otros. De los pacientes con TUS que rechazaron participar, el 69,2% alegó miedo y el 46,2% incomodidad por los riesgos. La disposición a participar se relacionó con un mayor nivel cognitivo y de alfabetización informática. En el análisis multivariante, la aversión a la investigación permaneció como factor predictivo significativo de la disposición a participar. Cuando la investigación no está relacionada con su diagnóstico, las motivaciones de la población TUS son similares a las de los controles y se deducen lógicamente del estudio, aunque también se evidenciaron elementos de "error terapéutico". Por consiguiente, las visiones negativas sobre las motivaciones de los TUS como participantes en investigación son infundadas. Para mejorar el reclutamiento, las valoraciones deben dirigirse a vulnerabilidades especificas en lugar de al diagnóstico.

Palabras clave: Adicciones; Ética en investigación; Motivación; Toma de decisiones.

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Biomedical research is critical for advancing scientific knowledge and for improving patient treatment. The success of research is dependent on recruitment rates and sufficient participant retention. Recent studies are focusing on the motivations and willingness to participate in research (Geppert, Candilis, Baker, Lidz & Appelbaum, 2014; Lawton et al., 2016; Tromp, Zwaan & van de Vathorst, 2016), especially in vulnerable or marginal populations (Barrat, Norman & Fry, 2007; Candilis, Geppert, Fletcher, Lidz & Appelbaum, 2006). Although addiction is a stigmatised condition that raises doubts about the real motivation for contributing toward scientific progress, a review of the scope of research on addictions (Nogué & Miró, 2015) detects very few studies that focus on factors influencing participation (Barrat et al., 2007; Fry & Dwyer, 2001).

Previous studies with the general population have explored the reasons given by research participants: access to information, monetary gain, curiosity, desire to help others and contribute toward science (Candilis et al., 2006; Seelig & Dobelle, 2001). In addition, negative factors, like fear and uneasiness with regards to the procedures, may act as barriers to participation or decrease adherence in studies (Ammassari et al., 2002; Brintnall-Karabelas et al., 2011). The extent to which these findings may be extrapolated to the SUD population is unknown. The few studies with people with SUD in this regard have explored the role of economic incentives in research (Barrat et al., 2007; Fry et al., 2001). Some researchers argue that, from an ethical perspective, receiving monetary payment for participation in research could invalidate informed consent (Fry, Hall, Ritter & Jenkinson, 2006a; Misra, Socherman, Park, Hauser y Ganzini, 2008). Participants might take risks which they would not assume in the absence of the incentive, and this would nullify the principle of justice by conditioning, more so, socioeconomically disadvantaged groups, like those with SUD (Carter & Hall, 2012; Dunn, Kim, Fellows & Palmer, 2009).

Another reason for trying to better understand the reasons for participating in research of the SUD population is related to the prevalence of negative stereotypes about addiction (Morera, 2000) and the assumptions about this group, even by professionals offering treatment (Barrat et al., 2007).

To the extent of our knowledge, no studies using the Spanish population review those factors which encourage or deter SUD patient participation in research. Detecting this population's motivations will enable professionals to define the aspects and information these patients consider important and relevant for decision-making. This will allow for designing the recruitment and informed consent process from the perspective and needs of patients with SUD. The purpose of this study is to provide greater evidence as to why SUD subjects participate in research in our setting.

Method

Study type

This is a transversal study, approved by our hospital's Research Ethics Committee (University Hospital of Cartagena).

Participants

This study derives of another that compares the capacity for participating in research of the SUD population. The complete details may be consulted separately (Morán-Sánchez, Luna, Sánchez, Aguilar & Pérez-Cárceles, 2016). This study focuses on the motivations and willingness to participate of 53 patients treated for the use of alcohol and/or illegal substances at a Drug Addiction Treatment Centre and 50 controls without a psychiatric disorder at a Health Centre. All of those patients with an ongoing participation at the study centres during a 4-month period were invited to participate. The participants included outpatients with DSM-5 and SUD diagnoses, and controls with diagnoses of hypertension, diabetes mellitus or other chronic illnesses. Inclusion criteria were: (a) minimum age of 18 years, (b) diagnoses of the study's target disorders, (c) fluent Spanish speaker, (d) score of 20 or higher in the Spanish version of the Mini-Mental State Examination: MEC (Lobo et al., 1999), and (e) signing the voluntary consent.

Controls were excluded if they (a) met current criteria for SUD or other DSM-5 diagnoses (American Psychiatric Association, 2014), (b) were currently patients of the Mental Health Centre or Drug Addiction Treatment Centre, or (c) were receiving psychiatric treatment through their primary care physician.

Users were excluded if they showed signs of intoxication or drug withdrawal symptoms when requesting their consent.

Measures

Participant information was collected using a questionnaire designed to gather demographic and clinical variables. The level of functioning of the SUD population was evaluated using the Global Assessment Scale (Endicott, Spitzer, Fleiss & Cohen, 1976), and the severity of their symptoms was evaluated using the Clinical Global Impression Scale (Guy, 1976).

Motivations and willingness to participate in research were collected from the responses obtained in the Spanish version of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) scale (Baón, 2013). This instrument is a semi-structured interview adapted to the elements of a specific research protocol, and evaluates the 4 most well-known dimensions of decision-making capacity: (a) *understanding* of information; (b) *appreciation* of consequences, given each patient's circumstances; (c) *reasoning* for deciding on whether or not to participate, and (d) *ability to express a choice* with regards to project participation

(Appelbaum & Grisso, 2001). Applying the MacCAT-CR interview entails providing information about the study and requesting the subjects to consider participating, followed by questions that evaluate their capacity, scored between 0-2, with a higher score reflecting better performance. The Understanding scale contains thirteen questions, the Appreciation scale contains three questions, the Reasoning scale contains four questions and the Ability to express a choice scale contains just one question. This instrument has been widely used in research, and is described in detail separately (Appelbaum et al., 2001). The subjects' willingness to participate in the hypothetical study was obtained from their responses to the Ability to express a choice subscale (*"Now that you have had more time to think about this, I'd like to ask you again if you think it is more likely that you will participate, or not, in this study"*). Motivations to participate in research were obtained from the responses to the Reasoning subscale (*"So, you think that you will decide to participate/not participate in the study. What makes this the best option for you?"*) that were collected and coded, according to their content.

The hypothetical consent designed for this study described a randomised clinical trial using a placebo of an experimental compound for headache treatment. The form described blood extraction and the risk of non-vital side effects. Also, information was given on the voluntary nature of participation, the inability to guarantee any personal benefit and the possibility of withdrawing.

Procedures

Once the participants signed their informed consent, the MEC-30 was implemented to evaluate their cognitive level, excluding those with advanced deterioration. Afterward, the hypothetical project was read to them aloud, and the MacCAT-CR interview was administered and scored in accordance with the criteria set forth in its manual.

Statistical analysis

Statistical analysis was performed using the SPSS (version 19) package. Before the analysis, we verified the distribution of continuous variables to check their normality. The differences in ordinal and continuous data were analysed using the Mann-Whitney *U* test. For differences between categorical variables, we used the Pearson χ^2 or the Fisher exact test for nonparametric data.

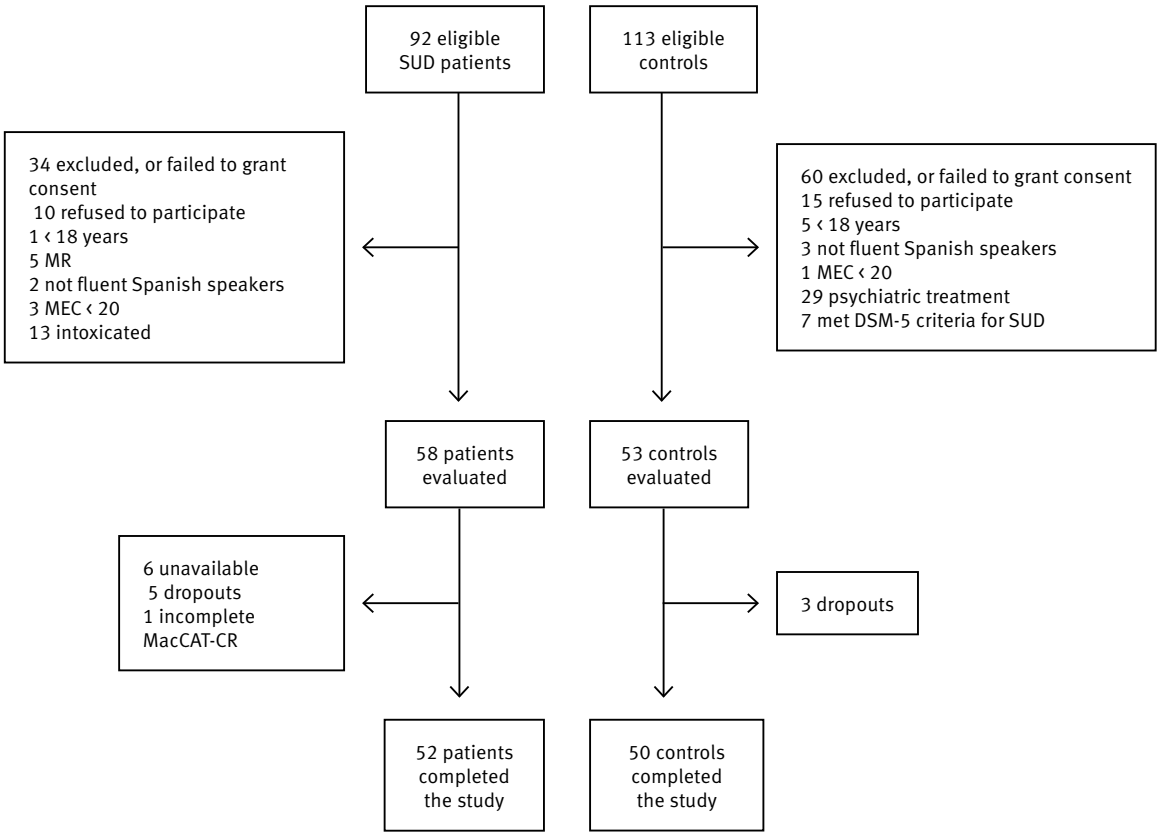

Figure 1. Participant inclusion flow chart

Note. SUD: Substance Use Disorder; MEC: Mini-Mental State Examination; MR: mental retardation; MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research

Table 1. *Study participant baseline characteristics*

	SUD (*n* = 53)	**Control** (*n* = 50)	**p**
Age (Average in years -*SD*-)	42.9 (*11.9*)	48.6 (*11.9*)	.037[b]
Females (%)	28.3	62	‹.001[a]
Marital status (%)			‹.001[a]
Married/cohabitation	32.1	82	
Never married	41.5	6	
Previously married	26.4	12	
Type of cohabitation (%)			‹.001[c]
Alone	15.1	12	
With own family	45.3	88	
With family of origin/foster family	39.6		
Level of education (%)			‹.001[a]
Primary	58.2	20	
Secondary	32.1	20	
University	9.4 5	40	
Employment status (%)			‹.001[c]
Employed	20.8	84	
Unemployed	45.3	2	
Retired	13.2	14	
Disabled	20.8		
Previous research study (%)			‹.001[a]
Yes	1.9	46	
No	98.1	54	
Computer literacy (%)			‹.001[a]
Yes	81.1	96	
No	18.9	4	
MEC (range, 0-30) (Average score -*SD*-)	28.2 (*4.2*)	29.6 (*0.9*)	‹.001[b]

Note. SD: standard deviation; SUD: Substance Use Disorder; MEC: Mini-Mental State Examination. [a] Pearson χ 2. [b] Mann-Whitney U. [c] Fisher's statistic.

To identify those factors that predictor willingness to participate in research, we performed a logistic regression analysis, calculating the Odds Ratios (OR) and the 95% confidence interval (CI). The multivariate analysis included statistically significant independent variables from the univariate analysis, and others that, despite being nonsignificant statistically, were clinically relevant. This study's sample size was the maximum possible obtained during the recruitment period. A minimum of 10 cases for each possible value of the response variable was considered sufficient for the logistics regression analysis, according to the calculation formula proposed by Peduzzi (Ortega & Cayuela, 2002). In line with recommendations given in literature, we used the method of directly introducing the variables to obtain a model with variables directly related with the dependent variable (Aguayo, 2010; Nuñez, Steyerberg & Nuñez, 2011).

The model's validity was tested using omnibus tests of coefficients, the Cox-Snell and Nagelkerke R square tests and the Hosmer-Lemeshow test. A significance level of .05 was used for all analyses.

Results

Of the study's 205 eligible subjects, 103 were excluded or unavailable to participate for various reasons. Figure 1 shows the patients' flow chart during the study.

Table 1 displays the study participants' baseline characteristics.

The 53 patients with SUD had the following diagnoses (not shown): 45.3% (n = 24) had alcohol or cannabis use disorder, 18.9% (n = 10) used cocaine and 35.8% (n = 19) used alcohol and another substance. THC users were younger, 32.92 years (*SD* = 12.72), and alcohol users were older, 51.67 years (*SD* = 7.63); χ *2* (2, N = 53) = 11.81, p =.003. Illness duration was also longer in the alcohol user group, 19.67 (*SD* = 13.26) than in the remaining groups (7.42 years (*SD* = 7.13) in THC users; 9.80 years (*SD* = 6.56) in cocaine users and 18.11 years (*SD* = 9.13) in users of alcohol and another substance; χ *2* (2, N = 53) = 6.45, p = .04. The remaining variables studied did not have statistically significant differences.

Willingness to participate in research and related factors

Of the SUD group and the control group, 75% (n = 39) and 78% (n = 39), respectively, were willing to participate in the hypothetical research project, without statistically significant differences between both groups, χ *2* (1, N = 102) = 7.21, p =.721.

Table 2 describes the characteristics of SUD patients according to their willingness to participate in the hypothetical research project. We found significant differences in MEC scores (Z = -1.99, p = .047) and in computer literacy level (87% high computer literacy level among those willing to participate *vs* 61.5% among those unwilling to participate; χ *2* (1, N = 52) = 4.13, p =.042). There were no statistically significant differences between patients willing and unwilling to participate for the remaining variables studied (sociodemographic, clinical and decision-making capacity).

Motivations for participating in research.

The responses to the MacCAT-CR Reasoning subscale on the patients' motivations for deciding to participate, or not, in a study, were classified into six categories, shown in Table 3:

a. Altruism/desire to contribute toward scientific progress.
b. Expectation of personal gain.
c. Desire to help others.
d. Uneasiness concerning side effects.
e. Aversion to the study.
f. Other reasons, different from the above.

Of the patients with SUD, 59% (n = 23) were willing to participate in the hypothetical study, mentioning altruism as their motivation, 53.8% (n = 21) expected a personal gain and 43.6% (n = 17) mentioned the desire to help others. The reason most frequently mentioned for refraining from

Table 2. *Characteristics of SUD population according to willingness to participate in the study*

	Willingness to participate		**p**
	Yes (*n* = 39)	No (*n* = 13)	
Age (Average in years -*SD*-)	44.1 (*11.1*)	40.5 (*13.9*)	.533[c]
Females (%)	35.9	7.7	.078[b]
Marital status (%)			.614[b]
Married/cohabitation	33.3	23.1	
Never married	38.5	53.8	
Previously married	28.2	23.1	
Type of cohabitation (%)			.641[b]
Alone	12.8	16.7	
With own family	48.7	62.5	
With family of origin/foster family	38.5	20.8	
Level of education (%)			.263[b]
Primary	59	53.8	
Secondary	28.2	46.2	
University	12.8		
Employment status (%)			.947[b]
Employed	23.1	15.4	
Unemployed	43.6	46.2	
Retired	12.8	15.4	
Disabled	20.5	23.1	
Previous research study (%)			1.00[b]
Yes	2.6		
No	97.4	100	
Computer literacy (%)			.042[b]
Yes	87.2	61.5	
No	12.8	38.5	
Psychiatric diagnosis (%)			.166[c]
Psychotic disorder	12.8	30.8	
Mood disorder	23.1	38.5	
Anxiety disorder	33.3	23.1	
No psychiatric diagnosis	30.8	7.7	
CGI (%)			1.00[a]
≤ Moderately ill	23.1	23.1	
≥ Moderately ill	76.9	76.9	
EEAG (range, 0-100) (Average score -*SD*-)	67.1 (*15.1*)	63.1 (*17.0*)	.444[b]
Duration of illness (Average in years -*SD*-)	14.9 (*10.3*)	14.2 (*11.5*)	.734[b]
Psychiatric hospitalisations (Average in units -*SD*-)	1.1(*2.4*)	1.1 (*1.9*)	.981[b]
Inpatient in therapeutic communities (Average in units -*SD*-)	0.47 (*0.9*)	0.23 (*0.4*)	.571[b]
MEC (range, 0-30) (Average score -*SD*-)	28.5 (*1.6*)	29.5 (*0.8*)	.047[b]
Group (%)			.593[c]
Alcohol	23.1	23.1	
THC	15.4	38.5	
Cocaine	25.6		
Alcohol + another	35.9	38.5	
MacCAT-CR (Average score -*SD*-)			
Understanding score (range, 0-26)	20.9 *(4.2)*	19 *(5.0)*	.840[b]
Appreciation score (range, 0-6)	5.1 *(1.3)*	5.1 *(0.7)*	.549[b]
Reasoning score (range, 0-8)	6.3 *(1.5)*	5.9 *(1.9)*	.178[b]
Ability to express a choice (%)			.672[c]
2	92.3	84.6	
1	5.1	15.4	
0	2. 6		
Capacity (%)			.735[c]
Yes	69.2	61.5	
No	30.8	38.5	

Note. SD: standard deviation; CGI: Clinical Global Impression Scale; EEAG: Global Assessment Scale; THC: Tetrahydrocannabinol; MEC: Mini-Mental State Examination; MacCAT-CR, MacArthur Competence Assessment Tool for Clinical Research. [a] Pearson χ 2. [b] Mann-Whitney U. [c] Fisher's statistic

Table 3. *Motivations for participating or not in research*

	Control	SUD	p
Reasons to accept participation (%)			
Altruism/desire to contribute toward scientific progress	59 (*n* = 23)	59 (*n* = 23)	1.00 [a]
Expectation of personal gain	46.2 (*n* = 18)	53.8 (*n* = 21)	.497 [a]
Desire to help others	48.7 (*n* = 19)	43.6 (*n* = 17)	.650 [a]
Other reasons, different from the above	20.5 (*n* = 8)	17.9 (*n* = 7)	.774 [a]
Reasons to reject participation (%)			
Aversion to the study	90.9 (*n* = 10)	69.2 (*n* = 9)	.327 [b]
Uneasiness concerning side effects	36.4 (*n* = 4)	46.2 (*n* = 6)	.697 [b]
Other reasons, different from the above	9.1 (*n* = 1)	15.4 (*n* = 2)	1.00 [b]

Note. SUD: Substance Use Disorder. [a] Pearson χ 2. [b] Fisher's statistic.

Table 4. *Motivations for participating in the study according to willingness to participate and group*

	Willingness to participate	Control			SUD		
		%	OR CI 95%	p	%	OR CI 95%	p
Altruism	Participates	59	1.69 (1.23-2.31)	‹.001[a]	59	4.79 (1.14-20.21)	0.25 [a]
	Does not participate	0			23.1		
Personal gain	Participates	46.2	1.52 (1.19-1.96)	.004[b]	53.8	6.42 (1.26-32.84)	‹.001 [a]
	Does not participate	0			15.4		
Help others	Participates	48.7	9.5 (1.11-81.51)	.033 [b]	43.6	4.25 (0.83-21.78)	.099 [a]
	Does not participate	9.1			15.4		
Aversion to the study	Participates	2.6	35.46 (5.08-247.63)	‹.001[b]	5.1	10.75 (4.23-27.35)	‹.001[b]
	Does not participate	90.9			69.2		
Side effects	Participates	5.1	4.19 (1.73-10.14)	.017 [b]	5.1	6.57 (3.32-13.00)	.002[b]
	Does not participate	36.4			46.2		
Other motivation	Participates	20.5	2.58 (0.29- 23.24)	.662 [b]	17.9	1.20 (0.22- 6.69)	.832[b]
	Does not participate	9.1			15.4		

Note. CI: Confidence interval; OR: Odds Ratio; SUD: Substance Use Disorder. [a] Pearson χ 2. [b] Fisher's statistic.

participation by the SUD population was aversion to the study by 69.2% (*n* = 9) followed by uneasiness concerning side effects by 46.2% (*n* = 6). As Table 3 shows, we did not find statistically significant differences between the control and SUD groups with regard to their motivations for participating in clinical research.

Table 4 shows that it was approximately 2 times more likely for controls to participate in the study if they mentioned altruism, compared with those who did not (OR 1.69, CI 95% 1.23 - 2.31; p < .001); for the SUD population, this probability was 5 times greater (OR 4.79, CI 95% 1.14 - 20.21; p = .025). Those subjects with SUD who cited receiving better treatment were approximately 7 times more likely to participate in the study (OR 6.42, CI 95% 1.26 - 32.84; p = < .001). None mentioned the possibility of receiving monetary payment as motivation for deciding to participate.

To the contrary, those who expressed aversion to the study were more likely to refrain from participating than those who did not (OR 10.75, CI 95% 4.23-27.34; p < .001). In the control group, this probability increased 35 times (OR 35.46, CI 95% 5.08-247.63; p < .001). In the SUD group, uneasiness concerning side effects was associated with the probability 7 times greater of not participating (OR 6.57, CI 95% 3.32-13.00; p = .002).

In the univariate analysis, all of the motivations cited were significantly associated in both groups with willingness/unwillingness to participate, with the exception of the domain *"Other reasons"* and, furthermore, in the SUD group, with the domain *"Desire to help others"* (Table 4). The logistic regression model included the significantly relevant variables associated with willingness to participate in the univariate analysis and variables that were relevant for limiting participation (Table 5). Just one of the variables included in the univariate analysis remained in the multivariate model: aversion to the study (OR 14.24, IC 95 % 1.31-154.8; p = .028), which made it 14 times more likely for someone to refrain from participating in the research if citing fear.

Table 5. *Factors associated with willingness to participate in research*

Associated factors	Univariate analysis		Multivariate analysis*	
	OR IC 95%	p	OR IC 95%	p
MEC	1.94 (0.99-3.79)	.054	-	-
Computer literacy	4.25 (0.988-18.29)	.052	-	-
Altruism	4.79 (1.14-20.21)	0.25	-	-
Personal gain	6.42 (1.26-32.84)	‹ .001	-	-
Aversion to the study	10.75 8 4.23-27.34) ·	‹ .001	14.24 (1.31-154.8) ·	.029
Side effects	6.57 (3.32-13.00) ·	.002	-	-

Note. MEC: Mini-Mental State Examination; OR: Odds Ratio; CI: Confidence Interval; SUD: Substance Use Disorder. *Only those factors with values of $p < .05$ are shown. The reciprocal OR is shown when the OR ‹ 1.

The model was significant χ 2 (6, N = 52) = 29.61, p = .001), explains between 43.4-64.3% of the dependent variable, and correctly classified 90.4% of the cases and is, therefore, acceptable. The Hosmer-Lemeshow test obtained a high p value, indicating that the difference between observed and predicted variables was small, χ 2 (8, N = 52) = 8.79, p = .361.

Qualitative responses

The majority of the subjects willing to participate cited altruistic reasons: they desired to *"help" "science"* or *"doctors" or "contribute toward the development of improved medications"*. Others wanted to *"improve the well-being of people"* or *"of society"*.

The second most-frequently cited reason given by those willing to participate from both groups was the expectation of receiving better treatment. These subjects mentioned that they would participate *"for their personal gain"*, "*to feel better, because I have pain"* or *"to fix my head, because it's not working properly"*. Others wanted to know more about their headache, *"let's see if you study me and tell me why this happens to me"* or *"if more doctors examine me, then I'll learn more about what's happening to me"*. Of the 53 subjects with SUD, 13 expressed altruistic and personal reasons simultaneously.

The subjects who expressed aversion to the study cited not participating *"out of fear"*, not wanting to be *"guinea pigs, there are animals for that"* or because *"experiments are dangerous"*. Some preferred to refrain from risk, given the availability of other already-contrasted medication. Neither were they willing to take new medication: *"because I don't take pills I am not familiar with"*. Others mentioned the inconvenience of *"needing to have my blood drawn"*, or claimed their dislike of taking pills *"because of their side effects"*.

Some of those who mentioned other reasons claimed that they would participate because they trusted the interviewer: "*because you request this of me, have explained it quite clearly and are very pleasant"*. Others perceived the project as an opportunity to *"interact with others"* or *"compensate for all of my previous wrongdoing"*.

Discussion

The importance of this study arises from the fact that it's the first to specifically evaluate the motivations and willingness to participate in research by people diagnosed with SUD in our setting. The majority of the participants were willing to participate in this study, in a proportion similar to that resulting in other studies (Candilis et al., 2006). This also corresponds with the 30-40% dropout rate that is commonly estimated when calculating sample sizes in epidemiological research (Marrugat, Vila, Pavesi & Sanz, 1999). No significant differences were found between the SUD and control populations concerning their willingness to participate, nor between the different substance use subgroups.

Approximately 80% of the sample (of the 205 individuals invited to participate, rejected 25) granted their consent to participate in the study applying the MacCAT-CR interview. This proportion was lower, approximately 75%, when the hypothetical trial is proposed, with a risk exceeding the minimum, given its inclusion of blood tests and side effects. This decrease in the subjects' willingness to participate allows for verifying how the perception of risk impacts participation in research. The difference between both studies could be higher, given the subjects' awareness of lower potential risk of the hypothetical trial. Likewise, having previously granted consent to participate in our study could have increased participation in the hypothetical project.

One of the elements that has the greatest influence on participation in research is the trust subjects deposit on the persons inviting them to participate (Roberts, Warner, Anderson, Smithpeter & Rogers, 2004; Stroup et al., 2005). In the CATIE study using the MacCAT-CR interview, the most

important predictive element of willingness to participate was the participant referral centre. This result could be due to the training of the professionals involved and their previous relationship with the interviewees (Stroup et al., 2005). In our case, the doctors in charge of SUD patients informed them of the possibility of this study, something which could have contributed to increasing their participation. In the controls, neither the interviewer nor another health centre staff member was directly in charge of the patients, despite having worked rotations at their centre. Though trust in researchers was a hardly cited reason for participating in the hypothetical study, it could be a factor influencing the subjects' acceptance of the MacCAT-CR interview (Figure 1).

The decision to participate or not in the hypothetical study was related only with cognitive level and computer literacy level in SUD patients. We know of no other previous research studies on the impact of computer literacy levels for the purpose of comparing our results. These findings require further exploration in future studies. In the bibliography, the relationship between willingness to participate and cognitive level, clinical severity and decision-making capacity is unclear, with results pointing in both directions. Stanley and Stanley (1982) found no differences concerning the decision to participate or not according to clinical severity or cognitive functioning. However, Candilis (2006) found an association between the decision to participate and greater decision-making capacity in accordance with the MacCAT-CR scale, lower clinical severity and lower cognitive deterioration. Our study, which concludes that there is no relationship between clinical severity, decision-making capacity and willingness to participate, is another addition to the existing bibliography on this issue that fails to endorse that association.

Previous participation in research was neither associated with higher willingness to participate nor identified as a barrier. Consequently, subjects that have never been recruited for clinical trials could be recruited if offered suitable information. Studies with user groups (Fry, Madden, Brogan & Loff, 2006b) suggest the usefulness of explaining the potential benefits of participation to research participants, and of more actively informing them of the possible impact of the results on approaches to their pathology. Even though the ethical imperatives of informed consent and the beneficence principle consider this (Beauchamp & Childress, 2009), greater emphasis is required concerning its implementation (MacNeil & Fernández, 2006).

The subjects' motivations to justify their decision to participate or not in the proposed project were coherent with the bibliography (Barrat et al., 2007; Candilis et al., 2006; Roberts et al., 2002). The arguments reasoned in favour and against were suitable, and a logical deduction of the study, for the clinical and control populations alike. Altruism as the main motivation for participating, expressed as a contribution toward science, appears in prior studies using the general population and different groups (Barrat et al., 2007; Candilis et al., 2006; Tromp et al., 2016).

The second reason for participating was the possibility of obtaining personal gain. The responses given here are related to expectations of obtaining better treatment and of gaining more knowledge about one's illness, as expressed in other studies (Candilis et al., 2006; Roberts et al., 2004). Elements associated with therapeutic error also became evident, when the expectation of obtaining a benefit shifts from being perceived as a possibility to being expressed as a conviction. This element is especially important when evaluating decision-making capacity, and is included in the MacCAT-CR interview questions. The split between reasonable therapeutic optimism and the erroneous conviction that participation entails personal well-being is governed by the level of certainty (Jansen, 2006) which is evaluated in a way similar to the assessment of thought content disorders. Therapeutic error appears as an important element in our sample, as occurred in other studies (Barrat et al., 2007; Tromp et al., 2016).

Both altruism and the possibility of personal gain were univariately associated with willingness to participate. These positive factors may be understood as potential incentives for participation in research by the SUD population, and underscore the fact that a study's real and potential benefits alike are both important for potential participants.

As also occurs in other studies, some subjects mention both motivations, altruistic and those relating to personal gain, when deciding whether or not to participate (Candilis et al., 2006). This fact reflects the complexity of properly evaluating the subjects' assessment of the research study, given its numerous determinations.

Our study did not mention economic incentives as motivation for participating in the study. This may be due to the fact that no compensation was offered for participating in the initial study, or because in our setting the idea of participating in research in exchange for money is not widespread, as is the case in other contexts (Dunn et al., 2009). Controversy exists about incentives not merely compensating for the participants' time and the inconveniences associated with participation, but that they also drive participation (Candilis et al., 2006; Misra et al., 2008). Data demonstrates the relationship between the size of the incentive and the modification of perceptions about risk and obtained benefits (Dunn et al., 2009). Research on incentives with SUD patients has attempted to establish practical guidelines for their application from an ethical perspective, respecting the principle of justice that enables distributing the research's benefits equally (Carter et al., 2012; Fry et al., 2006a).

Most participants who refused to participate expressed aversion to the study. Their responses include pejorative

language, such as being used like "guinea pigs", also frequently mentioned in the bibliography (Lebensburger et al., 2013). This factor remains in the multivariate analysis. Thus, efforts should focus on trying to overcome this limiter of participation in research.

The assessment of the risk of side effects is highly variable, and does not hinder participation if considered of minor importance, yet hinders participation when given greater importance. According to legislation currently in effect (Royal Decree 1090/2015, 2015), a research project is considered ethically acceptable if the risk/benefit ratio for the participant is adequate. Nevertheless, even in this situation, the assessment of risk differs according to a subject's personal and cultural experiences and even depends on economic incentives. However, better information could increase the similarity between perceived and real risk (Mullin, 2002) and evaluating the understanding and perception of risks could contribute toward truly validating consent. Considering these factors would allow for effectively implementing strategies to improve recruitment and adherence to clinical studies with the SUD population.

Limitations

We must consider some limitations when interpreting our results. First, our study was implemented in an urban setting with a limited number of outpatients. Further studies are necessary to evaluate our results in other settings and with different participants. A larger sample size would also allow for performing a multiple regression analysis with more variables.

Another limitation is the fact that our non-random sample and absence of other substances (like heroine and anxiolytics/hypnotics) pose concerns regarding the generalization of our results. Future studies should consider these aspects.

Given the fact that the subjects were considering a hypothetical drug for a pathology different from their own, it would be important to replicate these findings with drugs related to their illness.

Conclusions

In this study, willingness to participate of the SUD and control populations was similar. Higher cognitive level and computer literacy were more frequent among those willing to participate. Regardless of their decision to participate or not, the reasons given were adequate and coherent with literature, though elements associated with therapeutic error were also observed in both groups. Therefore, negative views about the motivations of SUD patients as research participants are unfounded. Efforts should focus on the predictive factors of willingness to participate that we have identified for the purpose of improving recruitment.

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

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Development and Validation of the Marijuana Motives Measure Short Form

Desarrollo y validación de la versión breve del cuestionario de motivos de consumo de marihuana (MMM SF)

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Abstract

Marijuana motives are a proximal variable to marijuana use. This research aimed to adapt and validate the short form of the Marijuana Motives Measure (MMM; Simons, Correia, Carey, y Borsari, 1998), the MMM SF, in Spanish.

The sample comprised 232 participants (mean age = 25.11 (7.58), 50.43% males) who had tried marijuana at least once in their lifetime. Item and Rasch analyses were performed to choose the final pool of 15 items. Confirmatory Factor Analysis (CFA) showed an adequate 5-factor structure ($_{S\text{-}B}X^2(80) = 121.30$, $p = .002$; NNFI = .944; CFI = .958; IFI = .959; MFI = .915; RMSEA = .047(0.029, 0.063); AIC = -38.70), and the multi-group CFA between males and females showed acceptable fit indices ($_{S\text{-}B}X^2(160) = 230.01$, $p = .000$; NNFI = .900; CFI = .924; IFI = .927; MFI = .860; RMSEA = .062(.043, .078); AIC = -89.99). The questionnaire indicated metric ($_{S\text{-}B}X^2_{diff}(15) = 13.61$, $p = .556$)), scalar ($_{S\text{-}B}X^2_{diff}(15) = 23.15$, $p = .081$)) and error measurement invariance ($_{S\text{-}B}X^2_{diff}(15) = 8.65$, $p = .895$)) between gender groups. The internal consistencies and ordinal omega of the scales were between .79 and .90. In the regression analysis, enhancement, coping and low conformity motives predicted frequency and quantity of marijuana smoked. The best predictor of frequency and quantity consumed during the heaviest smoking period was enhancement, while coping and, to a lesser extent, low conformity, were the only predictors of cannabis-related problems when marijuana frequency and quantity were controlled for.

The MMM SF shows adequate psychometric properties and is a suitable instrument to assess marijuana motives, especially during time-limited sessions.

Keywords: Marijuana motives; Cannabis; MMM SF; Psychometric properties; Marijuana outcomes.

Resumen

Los motivos de consumo son una variable proximal al uso de marihuana. Este estudio pretende adaptar y validar la versión española breve del Marijuana Motives Measure (MMM; Simons, Correia, Carey, y Borsari, 1998), el MMM SF.

La muestra estaba compuesta por 232 participantes (edad media = 25,11 (7,58), 50,43% hombres) que habían probado la marihuana al menos una vez. Se realizaron análisis de los ítems y de Rasch para seleccionar los 15 ítems. El Análisis Factorial Confirmatorio (AFC) mostró una estructura de cinco factores adecuada ($_{S\text{-}B}X^2(80) = 121{,}30$, $p = ,002$; NNFI = 0,944; CFI = 0,958; IFI = 0,959; MFI = 0,915; RMSEA = 0,047(0,029, 0,063); AIC = -38,70), y el AFC multigrupo entre hombres y mujeres mostró índices de ajuste aceptables ($_{S\text{-}B}X^2(160) = 230{,}01$, $p = ,000$; NNFI = 0,900; CFI = 0,924; IFI = 0,927; MFI = 0,860; RMSEA = 0,062(0,043, 0,078); AIC = -89,99). El cuestionario mostró invarianza métrica ($_{S\text{-}B}X^2_{dif}(15) = 13{,}61$, $p = ,556$)), escalar ($_{S\text{-}B}X^2_{dif}(15) = 23{,}15$, $p = ,081$)) y de los errores de medida ($_{S\text{-}B}X^2_{dif}(15) = 8{,}65$, $p = ,895$)) entre grupos de género. Los alfas de Cronbach y omega ordinal de las escalas fueron de 0,79 a 0,90. Los motivos de animación, afrontamiento y bajos motivos de conformidad predijeron el consumo de marihuana. El mejor predictor durante la época de mayor consumo fueron los motivos de animación, mientras que los motivos de afrontamiento, y en menor medida los bajos motivos de conformidad, fueron los mejores predictores de los problemas derivados una vez se controló el efecto de frecuencia y cantidad fumada.

El MMM SF presenta unas propiedades psicométricas adecuadas y es una medida útil para evaluar los motivos de consumo de marihuana, especialmente durante sesiones de evaluación con tiempo limitado.

Palabras clave: Motivos de consumo de marihuana; Cannabis; MMM SF; Propiedades psicométricas; Variables de consumo de marihuana.

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Cannabis (marijuana) is the most widely used illicit drug worldwide (UNODC, 2015). In 2013, an estimated 181.8 million people aged 15-64 years used cannabis for nonmedical purposes (uncertainty estimates 128.5–232.1 million) (UNODC, 2015). Cannabis acutely impairs several cognitive function components, and its use is a risk factor for traffic fatalities, cardiovascular and psychotic symptoms, among others (WHO, in press). For these reasons, it is important to prevent and reduce cannabis use and, to do so, it is important to know the reasons why people smoke this drug.

One of the most widely used questionnaires to assess cannabis smoking motives is the Marijuana Motives Measure (MMM; Simons et al., 1998). The MMM was developed by Simons et al. (1998), and is based on the Drinking Motives Questionnaire-Revised (DMQ-R) developed by Cooper (1994) to assess reasons for alcohol consumption. Consequently, the MMM (Simons et al., 1998) is composed of four marijuana smoking motives based on the (a) type of reinforcement desired (positive or negative reinforcement) and (b) the source of reinforcement (internal or external). Crossing these two dimensions results in four distinct marijuana motives: social motives (external, positive) refer to smoking to facilitate social relationships; enhancement motives (internal, positive) refer to using cannabis to increase positive affect; conformity motives (external, negative) relate to smoking to form part of a group of people; coping motives (internal, negative) relate to smoking cannabis to manage negative affects. Simons et al. (1998) also added a fifth type of marijuana motive, expansion motives, which refer to smoking cannabis to be more creative and original, to understand things differently, or to be more open to experiences. This five-factor questionnaire structure has received support from exploratory (Chabrol, Ducongé, Casas, Roura, & Carey, 2005; Simons et al., 1998) and confirmatory factor analyses (Zvolensky et al., 2007). The resulting five scales showed good internal consistencies with Cronbach's alphas of .70 or higher (Chabrol et al., 2005; Simons et al., 1998; Zvolensky et al., 2007). However, recent studies conducted with the MMM have found that some factor loadings of the original items were inadequate (Benschop et al., 2015). These items (2, 8, 9 and 16) were the same as those removed from the short versions of the DMQ-R (Kuntsche & Kuntsche, 2009; Mezquita et al., 2018).

Regarding sources of evidence for concurrent and predictive validity, and similarly to those found with alcohol, it seems that each marijuana motive type relates differently to cannabis outcomes (Simons et al., 1998). Cross-sectional studies with the MMM (Simons et al., 1998) have found that enhancement motives are related to cannabis use (Buckner, 2013; Foster, Allan, Zvolensky, & Schmidt, 2014; Simons, Simons, & Spelman, 2016), and also with cannabis-related problems through cannabis use (Simons, Gaher, Correia, Hansen, & Christopher, 2005). Coping motives have been related to cannabis use, cannabis-related problems (Buckner, 2013; Buckner & Zvolensky, 2014; Buckner, Zvolensky, & Schmidt, 2012; Foster et al., 2014; Simons et al., 2016) and cannabis dependence (Moitra, Christopher, Anderson, & Stein, 2015). Expansion motives have been associated with cannabis frequency and cannabis dependence in females with borderline symptomatology (Chabrol et al., 2005), and also with cannabis-related problems in a sample of current cannabis users (Buckner & Zvolensky, 2014). Finally, social motives and conformity motives have been negatively related to cannabis frequency (Buckner, 2013; Buckner & Zvolensky, 2014), while only conformity motives have been positively related to cannabis-related problems (Buckner et al., 2012; Foster et al., 2014).

Very few prospective studies about marijuana motives and related outcomes have been conducted. Anderson, Sitney and White (2015) assessed 434 community recruited youths and found that positive reinforcement use motives were associated with increased cannabis use and cannabis-related problems, while negative reinforcement motives predicted cannabis-related problems when controlling for past marijuana use motives and behaviors. Expansion motives in adolescence have been related to lower cannabis use in emerging adulthood. Liebregts et al. (2013) found that coping motives predicted marijuana dependence in a cohort of frequent cannabis users.

The general aim of the present research was to develop a short version of the MMM that may facilitate the inclusion of cannabis-smoking motives in surveys, or in prevention or treatment programs, for which administration time and space are limited (Kuntsche & Kuntsche, 2009). We intended to develop a short version that includes the items that really works properly to assess marijuana motives and to delate others that have been shown to not help assess the construct (Benschop et al., 2015). Specifically, the aims of the present research were to: 1) translate and adapt the MMM into Spanish; 2) create a short version of the measure using Item and Rasch analyses; 3) explore the structure of the short questionnaire version; and 4) study criterion validity sources of evidence of the questionnaire. We hypothesized that in spite of item reduction, MMM SF will show a structure, reliability indices and evidence to predict cannabis outcomes that are at least as good as the original MMM.

Method

Participants

The original sample was composed of 390 participants. However, as in previous studies about motives, we analyzed only the data of those who had tried marijuana at least once in their life. Of the remaining 236 respondents, two did not complete the MMM, and two answered the questionnaires

apparently by chance. The final sample was composed of 232 participants (50.53% males, *M*age= 25.11, *SD* = 7.58), whose age range went from 16 to 58 years. The rest of the descriptive sample data is presented in Table 1.

Table 1. *Descriptive Data of the Final Sample of 232 Participants.*

Descriptive data		% of the total sample
Level of education completed	Elementary school	9.05
	High school	53.02
	University degree	37.98
Level of income	Less than €450	55.17
	€450 to €900	15.52
	€900 to €1500	16.38
	€1500 to €2100	8.19
	€2100 to €2700	4.31
	€2700 to €3600	0.43
Family level of income	Less than €450	14.36
	€450 to €900	21.03
	€900 to €1500	24.10
	€1500 to €2100	21.54
	€2100 to €2700	11.28
	€2700 to €3600	5.13
	€900 to €1500	2.56
Live (with)	Alone	9.48
	Parents or family	58.62
	Partner	20.26
	Others (e.g., roommates)	11.64
Primary occupation	Student	67.10
	Worker	28.57
	Unemployed	4.33

Procedure

We followed the Muñiz, Elosua and Hambleton (2013) recommendations for translating and adapting questionnaires. First after reviewing the literature, we chose the most suitable questionnaire to assess cannabis motives. Second, we requested the permissions to use, translate and adapt the questionnaire. To translate and adapt the questionnaire, two researchers experienced in psychometric test construction, and familiar with cannabis research, translated the MMM items into Spanish. Afterward, an English language teacher, unfamiliar with the inventory, did out a back translation. The analysis of the back translation indicated the Spanish version could be considered comparable to the original scale. We also took into account the differences between the Spanish and American cultures in which the original questionnaire was developed when we adapted the MMM.

Sample recruitment was done following two methods. First, the participants who attended vocational training at different high schools in the province of Castellón (east Spain) were assessed: Politécnico, Matilde Salvador and Salvador Seguí (N= 149). During assessment sessions, trained psychologists followed standard instructions: handed out scales, guaranteed confidentiality, and encouraged participants to provide sincere answers. In this case, the Ministry of Education of the Valencian Government approved the use of the battery of questionnaires in the assessment session. Second, an online survey was devised and participants answered the questionnaires on the Internet (N = 83). They filled in the scales as a response to an announcement displayed in Facebook. In this case, information about the study, including deontological issues, was facilitated on the first questionnaire page after being approved by the Ethical Committee of the Universitat Jaume I.

In both cases, all the respondents provided informed consent to participate in the study, completed the questionnaires voluntarily and anonymously, and did not receive any compensation for doing so.

Measures

Marijuana use was assessed with the *Cannabis and Other Drugs Intake Scale* (CODIS), which was developed by our research group according to a variety of previous measures. CODIS includes a measure of frequency of cannabis use in one's lifetime (Fq life: *Indicate if you have consumed cannabis from never 0 to daily 5*), frequency of cannabis use during the week (Fq weekdays: *number of days you smoke cannabis from Monday to Thursday: 0 - 4*), and at weekends (Fq weekend: *number of days you smoke cannabis from Friday to Sunday: 0 - 3*), number of joints smoked on weekdays (Qn weekdays) and at weekends (Qn weekend), frequency of use during the heaviest cannabis smoking period (Fq heaviest*: during your heaviest smoking period, what was the frequency you smoked from never 0 to twice a day 6*) and number of joints smoked during the week (Qn heaviest weekdays) and at weekends (Qn heaviest weekend) during a typical week of the heaviest cannabis smoking period. While the questions about the number of joints smoked were open-ended, those about frequency took a Likert scale answer format.

The MMM (Simons et al., 1998) consists of 25 items, and each contributes to one of five subscales: social, coping, enhancement, conformity and expansion. After taking into account all the occasions on which they smoked marijuana, the participants indicated how often they smoked for the reason specified in each item on a 5-point Likert scale that ranged from 1 (almost never/never) to 5 (almost always/always).

The *Cannabis Problems Questionnaire* (CPQ; Copeland, Gilmour, Gates, & Swift, 2005) assesses cannabis-related problems using 27 items. The participants informed if they

had experienced a series of consequences due to their marijuana use in the last 3 months. Items were dichotomous (yes/no). The Cronbach's alpha of the scale in the present sample was .90.

Missing data imputation

The missing values in the MMM in the final sample (N = 232) were .21% of all the data. For this reason, a person mean imputation approach was followed on each scale (Bentler, 2006) in both the CFA and the Item and Rasch analyses. In the regression analysis, pair-wise deletion of missing values was used, although there were only 19 missing values in all in the eight cannabis use measures and descriptive data.

Data analysis

Item selection strategies. The aim was to cut the global scale length by keeping a suitable conceptual breadth. To select items, the classical item analysis and the Rasch measurement procedures were combined (Meyer, 2014). Joint Maximum Likelihood Estimation (JMLE) was used. First, item-total correlations were performed (i.e., classical item discrimination). By taking into account number of points on the Likert scale, the discrimination index should be .60 or higher. Second, the person-item outfit and infit were evaluated with the Unweighted Mean Square (UMS) and the Weighted Mean Square (WMS) fit statistics. In both cases, values between .80 and 1.20 were recommended, and more attention should be paid to high, rather than to low, values (Meyer, 2014). Before running the item analysis, the dimensionality and local independence assumptions were confirmed.

In addition to these statistical considerations, when items showed good indices, the items that measured different aspects of one motive dimension were selected. The items that were a crucial component of a motives scale were not removed (see Mezquita, Camacho, Suso, Ortet, & Ibáñez, 2018, for a similar procedure). All the item analyses were performed with the jMetrik software (Meyer, 2014).

Testing the questionnaire structure. After selecting the final pool of 15 items, and similarly to previous studies done with the MMM (Zvolensky et al., 2007) and the DMQ-R SF (Kuntsche & Kuntsche, 2009; Mezquita et al., 2018), a correlated CFA of five factors was performed. Other competing models derived from the literature with the DMQ-R (Cooper, 1994; Hauck-Filho, Pereira & Cooper, 2012) were also performed: a unidimensional model in which all the items loaded in one single factor; a bifactor model that compared positive (social, enhancement and expansion) and negative (coping and conformity) reinforcement; a bifactor model that compared internal (enhancement, coping and expansion) and external (social and conformity) sources.

For all the structural equation modeling analyses, Satorra-Bentler's robust method was employed since our data were non normally distributed. To consider that a model has an *excellent* fit, the ${}_{S\text{-}B}\chi^2$ must be non significant, but this is uncommon in CFA. So using other fit indices to compare competing models is interesting: Non Normed Fit Index (NNFI), Comparative Fit Index (CFI), Incremental Fit Index (IFI), McDonald's Fit Index (MFI), Root Mean Square Error of Approximation (RMSEA), and Akaike's Information Criterion (AIC). Lower AIC values indicate a better fit. A model with NNFI, CFI, IFI, and MFI ≥ .90, RMSEA ≤ .10 is considered an *acceptable* fit, and NNFI, CFI, IFI and MFI ≥ .95, and RMSEA ≤ .06 an *adequate* fit (Byrne, 2006).

Reliability of scores. To test the reliability of the subscales, the Cronbach's alphas and ordinal omegas (Dunn, Baguley, & Brunsden, 2014) were calculated with 95% CI using the jMetriK software (Meyer, 2014) and the R 3.4.0 (R Core Team, 2013) software, respectively.

Measurement invariance across gender groups. Structural Equation Models (SEM) were performed to determine the measurement invariance of the questionnaire across males and females. In the first step, the model was tested separately for each gender group. Second, configural invariance was explored across groups by performing a multi-group analysis between males and females. Then metric, scalar and error invariances were tested (Milfont & Fischer, 2010). The relative goodness-of-fit between increasingly constrained models was calculated by the scaled ${}_{S\text{–}B}X^2$ difference test (Satorra & Bentler, 2001). All the CFAs were performed with version 6.1 of the EQS software (Bentler & Wu, 2002).

Relation between marijuana motives and marijuana outcomes. Descriptive analyses, Pearson's correlations and regression analyses were performed by SPSS 22 (IBM Corp, 2013). Eight different regression analyses were performed in which the gender and age effect were controlled for. In these analyses, marijuana motives were the independent variables, while marijuana outcomes were the dependent variables. For cannabis-related problems, an additional regression analysis was performed that also controlled for cannabis use frequency and quantity.

Results

Item selection

The Item and Rasch analyses are presented in Table 2. First by taking into account discrimination indices, items 5 and 16 from the social motives scale, item 9 from the enhancement scale, and item 2 from the conformity scale were deleted. Second by considering the UMS and the WMS indices, item 15 from the coping scale and item 21 from the expansion scale were also removed. Of the remaining items, those crucial for the motive scale and those that presented less overlap in content were chosen (e.g.,

"Because I like the feeling" was kept rather than "Because it gives me a pleasant feeling"). The final pool of 15 items, three per scale, is presented in bold in Table 2.

Sources of validity evidence for the MMM structure

The fit indices of the correlated five-factor model of the MMM and MMM SF scales are presented in Table 3. While the fit indices of the MMM were not acceptable, those presented by the MMM SF were generally adequate. The correlated five-factor model of the MMM SF showed also better fit indices than the unidimensional and bifactor models (see Table 3). The factor loading, standard errors and covariances of the five-factor model of the MMM SF are found in Figure 1.

Measurement invariance of the scale across gender groups

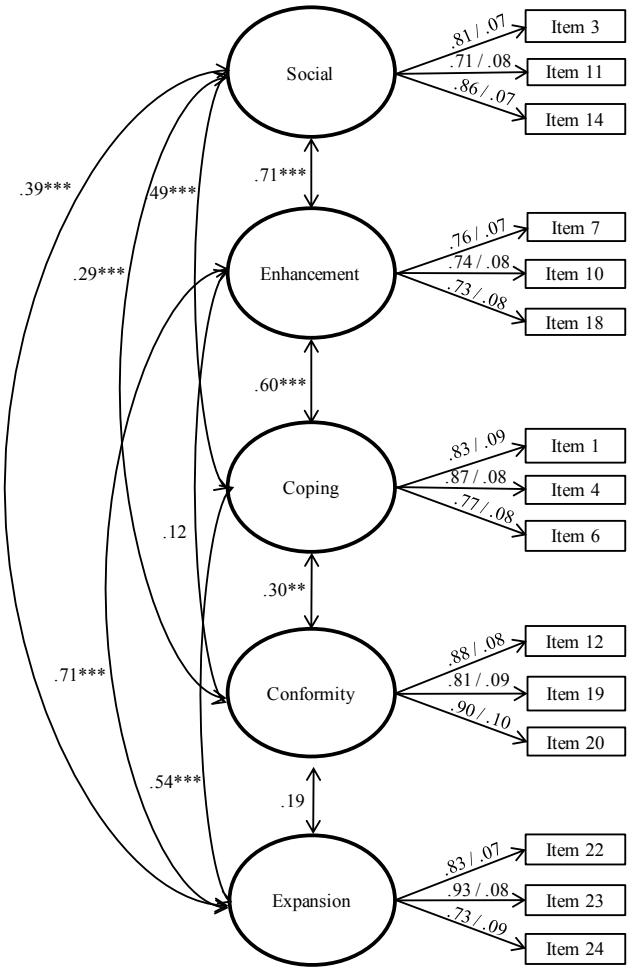
The sample wase split into males and females, and the fit indices of the MMM SF were slightly worse than in the whole sample, but were acceptable (see Table 3). Thus a multi-group analysis was performed to test configural invariance, and the fit indices were also acceptable (see Table 3). The addition of constraints among the factor loading ($_{S\text{-}B}X^2_{diff}$ (15) = 13.61, p = .56), means ($_{S\text{-}B}X^2_{diff}$ (15) = 23.15, p = .08) and measurement errors ($_{S\text{-}B}X^2_{diff}$ (15) = 8.65, p = .90) of males and females did not show significant reductions in fit. This indicated that the MMM SF showed metric, scalar and error measurement invariance between gender groups.

Reliability of scores

Table 2. *Item and Rasch Analysis of the Marijuana Motives Questionnaire.*

Subscale	Items	Discrimination	Difficulty	UMS	WMS
	Item 3	.66	-.19	.81	.85
	Item 5	.42	.87	1.38	1.70
	Item 11	.65	-.20	.92	.90
	Item 14	.74	-.02	.65	.70
Social	Item 16	.57	-.46	1.12	1.21
	Item 7	.74	-.87	.73	.73
	Item 9	.34	1.49	2.23	2.23
	Item 10	.68	-.06	.98	.98
	Item 13	.74	-.68	.71	.71
Enhancement	Item 18	.64	.13	.95	.95
	Item 1	.80	-.14	.76	.86
	Item 4	.78	-.12	.94	.93
	Item 6	.72	-.32	1.07	1.11
	Item 15	.69	.87	1.41	1.37
Coping	Item 17	.80	-.28	.87	.92
	Item 2	.55	-.89	1.43	1.53
	Item 8	.66	1.06	.94	1.18
	Item 12	.79	-.45	.64	.75
	Item 19	.74	-.01	.98	1.05
Conformity	Item 20	.84	.28	.53	.58
	Item 21	.62	.60	1.13	1.37
	Item 22	.76	-.40	.98	.90
	Item 23	.83	-.18	.63	.69
	Item 24	.68	.46	.91	1.11
Expansion	Item 25	.69	-.48	1.09	1.05

Note. The items retained in the MMM SF are shown in bold. The content of the items can be consulted in Simons et al. (1998).



Note. Above unidirectional arrows are factor loadings and standard errors. Above bidirectional arrows are correlations. All factor loadings were significant at p < .001.
*p < .05. **p < .01. ***p < .001. The content of the items can be consulted in Simons et al. (1998).

Figure 1. Correlated CFA of the final 15-items solution of the MMM SF.

Table 3. *Fit Indices of the Different Structural Models and the Multi-group Analysis between Males and Females of the MMM SF.*

			S-BX^2	g.l.	*p*	NNFI	CFI	IFI	MFI	RMSEA (90%CI)	AIC
MMM	Correlated five-factor model	Whole sample	497.51	265	.000	.837	.856	.859	.606	.062 (.053, .070)	-32.49
MMM SF	Correlated five-factor model	Whole sample	121.30	80	.002	.944	.958	.959	.915	.047 (.029, .063)	-38.70
	Unidimensional model	Whole sample	549.56	90	.000	..450	.528	.535	.371	.149 (.136, .160)	369.56
	Bifactorial model internal *vs.* external source	Whole sample	509.42	89	.000	.491	.568	.575	.404	.143 (.131, .155)	331.42
	Bifactorial model positive *vs.* negative reinforcement	Whole sample	569.69	89	.000	.418	.507	.515	.355	.153 (.141, 165)	391.69
	Correlated five-factor model	Males	119.13	80	.003	.896	.921	.925	.846	.065 (.038, .088)	-40.87
		Females	112.13	80	.010	.900	.924	.923	.870	.059 (.030, .083)	-47.87
	Multi-group analysis of the correlated five-factor model	Configural invariance	230.01	160	.000	.900	.924	.927	.860	.062 (.043, .078)	-89.99
		Metric invariance	239.03	175	.001	.916	.930	.933	.871	.056 (.037, .073)	-110.97
		Scalar invariance	261.06	190	.000	.903	.925	.929	.855	.057 (.038, .073)	-118.94
		Error variance invariance	259.24	205	.006	.929	.944	.946	.994	.051 (.031, .068)	-150.76

Table 4. *Descriptive Analysis for the Whole Sample and Differentiating between Males and Females.*

	Whole sample				Males		Females			
	X	SD	α	Ω	X	SD	X	SD	*t*	*d*
Social	5.75	2.95	.83 (.79, .88)	.82 (.79, .86)	6.03	3.19	5.47	2.68	1.44	.19
Enhancement	7.09	3.41	.79 (.74, .84)	.79 (.73, .83)	7.60	3.80	6.57	2.88	2.33*	.31
Coping	5.05	2.84	.86 (.82, .91)	.86 (.83, .89)	5.23	3.17	4.87	2.45	.97	.13
Conformity	3.68	1.88	.90 (.84, .96)	.89 (.86, .91)	3.52	1.64	3.83	2.10	-1.27	-.16
Expansion	4.65	2.53	.83 (.76, .91)	.86 (.83, .89)	4.86	2.66	4.43	2.38	1.32	.17
Fq weekdays	.67	1.30		-	.90	1.44	.45	1.10	2.66**	.35
Fq weekend	.79	1.12		-	.90	1.18	.68	1.03	1.46	.20
Qn weekdays	1.29	3.27		-	1.67	3.70	.89	2.72	1.80	.24
Qn weekend	1.65	3.16		-	2.09	3.72	1.21	2.37	2.12*	.28
Fq heaviest	3.33	1.99		-	3.54	2.12	3.11	1.83	1.63	.22
Qn heaviest weekdays	4.14	6.74			5.50	7.90	2.76	4.98	3.13**	.41
Qn heaviest weekend	4.77	6.19			5.82	7.05	3.70	4.99	2.63**	.35
Cannabis-related problems	2.51	3.99			3.26	4.66	1.75	3.01	2.92**	.38

Note. Fq weekdays = frequency of cannabis use during the week; Fq weekend = frequency of cannabis use at the weekend; Qn weekdays = number of joints smoked on weekdays; Qn weekend = number of joints smoked at the weekend; Fq heaviest = frequency of use during the heaviest cannabis smoking period; Qn heaviest weekdays = number of joints smoked during the week in a typical week of the heaviest cannabis smoking period; Qn heaviest weekend = number of joints smoked at the weekend in a typical week of the heaviest cannabis smoking period. Cronbach's alphas and ordinal omega coefficients with 95% CI. Cohen's *d* values of 0.20, 0.50, and 0.80 correspond to the small, medium, and large effect sizes, respectively (Cohen, 1992).
*$p<$ .05. **$p<$ .01. ***$p<$ .001.

Table 5. *Pearson's Correlation Analyses Between Cannabis Motives and Cannabis-related Outcomes.*

	Social	Enhancement	Coping	Conformity	Expansion	Fq weekdays	Fq Weekends	Qn weekdays	Qn weekends	Fq heaviest	Qn heaviest weekdays	Qn heaviest weekend	Cannabis-related problems
Social	-	.59***	.44***	.30***	.38***	.12	.20**	.14*	.17**	.24***	.12	.16*	.21**
Enhancement		-	.52***	.10	.62***	.35***	.39***	.31***	.40***	.51***	.33***	.36***	.41***
Coping			-	.27***	.50***	.31***	.38***	.31***	.35***	.36***	.25***	.20**	.43***
Conformity				-	.17*	-.12	-.17*	-.08	-.13	-.13	-.10	-.10	-.12
Expansion					-	.26***	.30***	.24***	.28***	.30***	.17**	.14*	.36***

Note. Fq weekdays = frequency of cannabis use during the week; Fq weekend = frequency of cannabis use at the weekend; Qn weekdays = number of joints smoked on weekdays; Qn weekend = number of joints smoked at the weekend; Fq heaviest = frequency of use during the heaviest cannabis smoking period; Qn heaviest weekdays = number of joints smoked during the week in a typical week of the heaviest cannabis smoking period; Qn heaviest weekend = number of joints smoked at the weekend in a typical week of the heaviest cannabis smoking period.
*p< .05. **p< .01. ***p< .001.

Table 6. *Regression Analyses: Cannabis Motives as Predictors of Cannabis-related Outcomes.*

IV	Fq weekdays		Fq Weekends		Qn weekdays		Qn weekends		Fq heaviest		Qn heaviest weekdays		Qn heaviest weekend		Cannabis-related problems		IV	Cannabis-related problems	
	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2		β	ΔR^2
Step 1																			
Sex	-.18**	.03*	-.10	.01	-.12	.02	-.14*	.02	-.11	.01	-.21**	.04**	-.17*	.03*	-.19**	.04*	Sex	-.09	.48***
Age	.06		-.01		.03		-.06		-.02		.02		-.01		-.01		Age	-.01	
																	Frequency	.39***	
																	Quantity	.32***	
Step 2																			
Social	-.14	.19***	-.01	.27***	-.08	.15***	-.08	.22***	-.07	.31***	-.11	.14***	-.06	.15***	-.05	.28***	Social	-.00	.05***
Enhancement	.29**		.23**		.22*		.31***		.49***		.34***		.43***		.21*		Enhancement	.05	
Coping	.26***		.32***		.26**		.28***		.23**		.19*		.10		.35***		Coping	.18**	
Conformity	-.20**		-.30***		-.16*		-.21**		-.22***		-.15*		-.13*		-.24***		Conformity	-.11*	
Expansion	.03		.06		.03		.01		-.06		-.07		-.13		.11		Expansion	.09	

Note. Fq weekdays = frequency of cannabis use during the week; Fq weekend = frequency of cannabis use at the weekend; Qn weekdays = number of joints smoked on weekdays; Qn weekend = number of joints smoked at the weekend; Fq heaviest = frequency of use during the heaviest cannabis smoking period; Qn heaviest weekdays = number of joints smoked during the week in a typical week of the heaviest cannabis smoking period; Qn heaviest weekend = number of joints smoked at the weekend in a typical week of the heaviest cannabis smoking period.
*p< .05. **p< .01. ***p< .001.

The Cronbach's alphas and ordinal omega coefficients of the scales with 95%CI are presented in Table 4. The reliability of all the scales went from good to excellent (all the alpha and ordinal omega coefficients were between .79 and .90).

Sources of validity evidence: motives as predictors of different marihuana outcomes

The descriptive analysis of the MMM SF and the marijuana outcomes are presented in Table 4. Males scored significantly higher than females in enhancement motives, smoking frequency during the week, smoking quantity at weekends, the quantity of marijuana smoked during the heaviest smoking period on weekdays and at weekends, and cannabis-related problems. However, the effect of differences was minor. The correlation analyses showed that the strongest correlations were found between the internal marijuana motives (enhancement, coping and expansion) and the marijuana outcomes (see Table 5).

The regression analyses showed that the enhancement, coping and low conformity motives predicted the frequency and quantity of marijuana smoked during the week and at weekends (see Table 6). The best predictor of the frequency and quantity of its use during the heaviest smoking period were enhancement motives, which was a stronger association at weekends than on weekdays. Although the coping, enhancement and low conformity motives predicted cannabis-related problems, the effect of enhancement motives was not significant when the effect of frequency and quantity was controlled for (see Table 6).

Discussion

The aims of the present study were to translate and adapt the MMM SF into Spanish, to explore its factor structure and reliability, and to also evaluate different sources of its criterion validity (predicting marijuana outcomes). The Item and Rasch analyses provided a final pool of 15 items, three per scale, with salient factor loadings (all of which were .71, or higher). Twelve items of the social, enhancement, coping and conformity scales were the same as those previously kept in the short DMQ-R version (Kuntsche & Kuntsche, 2009; Mezquita et al., 2018). This is important for future comparison studies about drug motives. If differences about drug motives are found, these might not be attributed to differences in the measure as the MMM SF and the DMQ-R SF are equivalents. The final 3-item solution of the expansion scale was composed of the three items that showed the highest factor loadings in the original questionnaire validation (Simons et al., 1998). The questionnaire showed also measurement invariance between males and females. Consequently, the MMM SF is an adequate instrument to compare marijuana motives between genders.

Regarding the reliability of scores, Cronbach's alphas were all above the standard cutoff of .70, even though shorter scales usually show lower internal consistencies than larger ones. When the endorsement of marijuana motives was explored in previous studies, enhancement motives were followed by the social, expansion, coping and conformity ones (Buckner et al., 2012; Foster et al., 2014; Simons et al., 2016, 1998; Zvolensky et al., 2007). However in the present research, the participants endorsed coping more than expansion motives. This was not due to a short questionnaire length, but indicated the existence of some cultural differences that could be explored in future cross-cultural studies.

When exploring the intercorrelations between motives scales, the highest correlations were found between enhancement and expansion motives. This result was expected because, as in enhancement motives, the positive reinforcement of marijuana effects was desired in the expansion motives, and the source of reinforcement was also internal. The lowest correlations were observed between conformity motives and the other scales, as in previous studies (Simons et al., 1998; Zvolensky et al., 2007).

Regarding the criterion validity sources, both coping and enhancement motives were similarly associated with smoking frequency and quantity during the week and at weekends. This result differed from those found with alcohol as previous studies have shown that enhancement motives are related mainly to weekend use, while coping motives are associated with alcohol use on weekdays (Mezquita, Ibáñez, Moya, Villa, & Ortet, 2014; Studer et al., 2014). Nevertheless, some similarities between drugs were found. enhancement motives were the best predictor of not only smoking frequency during the heaviest smoking period, but also of the quantity smoked on weekdays and at weekends during the heaviest smoking period. Previous findings on alcohol have also reported that enhancement motives are the best predictor of heavy alcohol use and binge drinking (Cooper, 1994; McCabe, 2002). Finally, the fact that the association between enhancement motives and cannabis-related problems disappeared when controlling for the effect of smoking frequency and quantity suggested that the association was mediated by marijuana use (Simons et al., 2005). In line with this, previous results about motives and alcohol-related problems have offered similar findings (Mezquita et al., 2014). Finally according to previous studies on marijuana (Simons et al., 2005) and alcohol (Mezquita et al., 2018, 2014), coping motives were the best predictor of drug-related problems, even when drug use was controlled for, which suggests that these motives are a vulnerability factor to marijuana use disorders.

A negative association between conformity motives and all the marijuana outcomes appeared in the regression analyses (Buckner & Zvolensky, 2014; Simons et al., 1998; Zvolensky et al., 2007). Previous studies that included drinking motives found similar results and offered different interpretations of these findings (e.g., Grant, Stewart, O'Connor, Blackwell, & Conrod, 2007; Mezquita, Stewart, Grant, & Kuntsche, 2016; Kuntsche, Wiers, Janssen, & Gmel, 2010). On the one hand, this result could be due to a suppression effect (Grant et al., 2007). The classical definition of the suppression effect in a regression analysis is that a potential covariate that is unrelated to the outcome variable (i.e. has a bivariate correlation of zero) increases the overall model fit within regression when this covariate (i.e., conformity motives) is added to the model (Tu, Gunnell, & Gilthorpe, 2008). However, this explanation is unlikely because even when some correlations between conformity and marijuana outcomes were not significant, they showed a negative association with a tendency to significance in most cases. On the other hand, it makes sense that people who report conformity motives indicate low smoking frequency and smoke small quantities of marijuana. As for fitting in with a group, a couple of puffs could be enough to achieve this aim; i.e., getting stoned might be even counterproductive for their aim of not feeling left out (Kuntsche et al., 2010).

Finally, expansion motives were not significantly associated with marijuana outcomes in the regression analysis. These results could be due to the high correlations found between expansion and enhancement motives, but could also be due to their association with coping motives (see Figure 1 and Table 5). The high intercorrelations between the motives scales could overshadow the influence of expansion motives on marijuana outcomes (Studer et al., 2014).

The present research has its limitations. First its sample size is modest, which also occurred in previous studies (Simons et al., 1998; Zvolensky et al., 2007). This is partly due to the fact that the questionnaire was designed to be

used with participants who had tried cannabis at least once in their life, and that cannabis use is not as frequent as alcohol or tobacco use. However, if we consider that the questionnaire is composed of only 15 items, our sample size may be considered adequate. Second, the study design is cross-sectional, and this was why it was not possible to explore the test-retest reliability of the scores and the sources of validity of the motives scales to predict marijuana outcomes. Third, drinking motives are not the only proximal variable to the cannabis used to be taken into account (Lloret Irles, Morell-Gomis, Laguía, and Moriano, 2018). Other variables should be studied to depict a complete view of cannabis use among smokers. Finally, the use of cannabis could be assessed more objectively rather than with only self-reports (Casajuana et al., 2017).

In short, the results support the notion that the MMM SF is better (in structure validity terms), or at least as good (in terms of its reliability of the scores and capability to predicting marijuana outcomes), as the MMM. The questionnaire appears a useful tool to assess reasons for smoking marijuana when administrations' time is limited, especially when various assessment instruments are being used.

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Conflicts of interest

The authors declare no conflict of interest.

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Creation of the TXP parenting questionnaire and study of its psychometric properties

Creación y estudio de las propiedades psicométricas del cuestionario de socialización parental TXP

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Abstract

Parenting is linked to conduct disorders (CD) and substance related disorders (SRD) in adolescents, but with differences according to cultural context. A questionnaire with two versions (parenting questionnaire *TXP-A* for adolescents and *TXP-C* for primary caregivers) was designed using the Delphi method to evaluate parenting practices related to CD and SRD in a Spanish population. It was validated in a community sample of 631 adolescents aged between 14 and 16 and their caregivers. Results suggest a 29-item *TXP-A* questionnaire with bifactorial structure: affection-communication and control-structure, with high internal (Cronbach's alpha=0.89) and test-retest (intraclass correlation coefficient=0.94) reliabilities. Both factors are related to SRD (r=0.273, p<0.001) and with most of the psychopathological dimensions studied. The total score and affection-communication are related to dissocial disorder (t=3.259, p=0.001) and its severity (r=-0,119; p=0.003). Inter-observer reliability between adolescents and caregivers is low, in part because the 16-item *TXP-C* has a different bifactorial structure: affection-communication and prosocial values. *TXP-C*'s internal (Cronbach's alpha=0.87) and test-retest (intraclass correlation coefficient=0.94) reliabilities are high. The total score and affection-communication were related to dissocial disorder (t=2.586; p=0.010) but *TXP-C* did not discriminate according to SRD.

In conclusion, the *TXP-A* questionnaire for adolescents seems to be a reliable, valid and unbiased instrument that evaluates the perception of parenting practices, relating higher affection-communication and control-structure to less psychopathology and alcohol and drug use. *TXP-C* also seems to be reliable and unbiased, but shows less evidence of validity regarding substance use and psychopathology.

Keywords: Parenting; Conduct disorders; Substance related disorders; Affection-communication; Control-structure; Prosocial values.

Resumen

El estilo parental de socialización se relaciona con trastornos de conducta (TC) y trastornos relacionados con sustancias (TRS) en adolescentes, con diferencias según el contexto cultural. Se diseñó mediante método Delphi un cuestionario con dos versiones (Cuestionario de socialización parental *TXP-A* para adolescentes y *TXP-C* para cuidador principal) para evaluar en población española las prácticas de socialización parental relacionadas con TC y TRS. Se validó en una muestra comunitaria de 631 adolescentes entre 14 y 16 años y sus cuidadores. Los resultados recomiendan un cuestionario *TXP-A* de 29 ítems y estructura bifactorial: afecto-comunicación y control-estructura, mostrando alta fiabilidad interna (alfa de Cronbach=0,89) y test-retest (coeficiente de correlación intraclase=0,94). Ambos factores correlacionan con TRS (r=0,273; p<0,001) y con la mayoría de las dimensiones psicopatológicas estudiadas. La puntuación total y afecto-comunicación se relacionan con el trastorno disocial (t=3,259; p=0,001) y su gravedad (r=-0,119; p=0,003). La fiabilidad interjueces entre adolescentes y cuidadores es baja, en parte porque el *TXP-C*, de 16 ítems, presenta una estructura bifactorial diferente: afecto-comunicación y valores prosociales. La fiabilidad interna (alfa de Cronbach= 0,87) y test-retest (coeficiente de correlación intraclase=0,94) del *TXP-C* son altas. La puntuación total y afecto-comunicación se relacionan con el trastorno disocial (t=2,586; p=0,010) pero no discrimina según el TRS.

En conclusión, el cuestionario *TXP-A* para adolescentes parece un instrumento fiable, válido y sin sesgos que evalúa la percepción de las prácticas de socialización parental, relacionando mayores puntuaciones en afecto-comunicación y control-estructura con menor psicopatología y consumo de alcohol y drogas. El *TXP-C* también parece fiable y sin sesgos, pero muestra menos evidencias de validez respecto al consumo de sustancias y la psicopatología.

Palabras clave: Socialización parental; Trastornos de conducta; Trastornos relacionados con sustancias; Afecto-comunicación; Control-estructura; Valores prosociales.

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The family is a key context for learning values, norms and customs during childhood and adolescence (Visser, de Winter, Vollebergh, Verhulst & Reijneveld, 2013) and one of the agents that can influence the worsening, maintenance or amelioration of psychopathological symptoms (Rosa-Alcázar, Parada-Navas & Rosa-Alcázar, 2014). Most of the studies on the family have focused on the parents and, more specifically, on the educational styles or parental socialization that they use (Rosa-Alcázar et al., 2014).

The traditional model of family socialization of Baumrind (1991) has two dimensions: responsiveness-warmth (the behavior of parents towards children through which children feel that they are loved and accepted as individuals within the family) and demandingness-control (degree of intensity or type of influence of parents on the behavior of children), along which parents are classified into three styles: authoritative (high control with high acceptance and sensitivity, emphasizing both the respect for the individuality of the child and the learning of social values), authoritarian (high demand and control with low sensitivity, emphasizing control and obedience) and permissive (low demand and control with high acceptance and sensitivity, emphasizing self-expression and self-regulation) (Bersabé, Fuentes & Motrico, 2001; Martínez, Díaz, Salazar & Duron, 2014). Maccoby and Martin (1983) add a negligent parenting style (low demand-control with low affect-communication). Other models and dimensions of parental socialization have been proposed, such as Olson's three-dimensional circumplex model (1988), with three dimensions: cohesion, flexibility and communication, which classifies families into 25 types (Rees & Valenzuela, 2003).

Despite the diversity of models, it is believed that there are two basic dimensions of educational styles (Sansinenea & Sansinenea, 2004): one related to the emotional tone of the relationship and communication (affect and communication, acceptance/rejection, warmth/coldness, affection/hostility, proximity/distance) and another with the behaviors that come into play when controlling and guiding the behavior of children (control and discipline). These practices are normally present in all families, with the use of one or the other depending on the specific situation in which it is applied, although there is usually a dominant style that is set in motion more frequently (Rodríguez & Torrente, 2003). Although autonomy increases during the transition to adolescence, parents continue to be important for adolescent development (Visser et al., 2013), with adolescents perceiving that the patterns of education their parents use are relatively stable (Rodríguez & Torrente, 2003).

Research over many decades has highlighted the importance of parenting style in the development of antisocial behaviors (Waller, Gardner & Hyde, 2013). Negative affect correlates with aggressive behavior alongside attention and behavioral problems, while an authoritarian style correlates with depression and anxiety, criminal behavior and other internalizing problems (Rosa-Alcázar et al., 2014). Violence and neglect are two of the factors that best predict conduct disorders and antisocial behavior (Holmes, Slaughter & Kashani, 2001). Monitoring, warmth and behavioral control are associated with lower levels of behavior problems in adolescence (Trudeau, Mason, Randall, Spoth & Ralston, 2012). Affection and support alongside moderate and consistent discipline can inhibit behavior problems (Loke & Mak, 2013). In addition, affection and the feeling of family togetherness act as protective factors against many of the high-risk behaviors of adolescents (Loke & Mak, 2013). Parental monitoring is thus associated with positive effects in the use of substances by adolescents, leading to a reduction in consumption and a lower probability of having substance-using peers, while also protecting adolescents from potentially negative peer influence (Tornay et al., 2013).

The authoritative style is the one that has yielded the greatest benefits in child development (Fernández, 2009), and is recognized as the most beneficial in American society (Lidner, 2013); authoritative and authoritarian styles have acted as a protective factor there against substance use, while indulgent and negligent styles were a risk factor (Martínez, Fuentes, García & Madrid, 2013). However, in ethnic minority groups, in contexts other than the Anglo-Saxon and in families with low socio-economic status, an authoritarian parenting style based on imposition rather than parental affection seems to be a more appropriate style (Fuentes, García, García & Alarcón, 2015). In Spain, various studies associate an indulgent style, based on affect, with the best results regarding the psychosocial adjustment of children (Fuentes et al., 2015). A remarkable number of publications agree that adolescent children of indulgent parents obtain equal or better scores in different adjustment criteria than children with authoritative parents (Pérez, 2012) and that the indulgent style acts as a protection against substance use in adolescence (Martínez et al., 2013). This contrasts with studies of Spanish adolescents which find that high permissiveness is linked to alcohol consumption (Mezquita et al., 2006).

Numerous instruments have been developed to evaluate parenting styles, significant examples being: *Children's Reports of Parental Behavior Inventory* (CRPBI, Schaefer, 1965); *Family Social Climate Scale* (Moos, Moos & Trickett, 1984), *FACES III (Family Adaptability and Cohesion Evaluation Scale, third version*; Olson, Portner & Lavee, 1985); *Parental Authority Questionnaire* (*PAQ*; Buri, 1991), *Alabama Child Parenting Questionnaire* (*ACPQ*; Shelton, Frick & Wootton, 1996), *Parental socialization scale in adolescence* (*ESPA29*; Musitu & García, 2001), *Parenting style scale* (Oliva, Parra, Sánchez-Quija & López, 2007) & *Perceived parental rearing style questionnaire* (*EMBU*; Arrindell et al., 2005). These instruments are limited in the sense that only the *ESPA29* and the *Evaluation of Parenting Style Scale* have been devel-

oped in the Spanish cultural context. Additionally, these two instruments only assess the perception of the adolescent and not of the parent. This would justify the creation of an instrument assessing both perspectives in a Spanish environment.

According to Bersabé et al. (2001), the questionnaires on parental educational styles are problematic with regard to content (they assess parents' intentions or opinions rather than specific practices, or the items are formulated in a generic or third-person manner, which encourages a social desirability bias and makes them ambiguous) and methodology (many do not specify the ages of the children to which they are directed, some give no information as to their psychometric properties or the response scale used; the number of items varies greatly and is in some cases excessive; many only collect the opinion of parents and not how their educational styles are perceived by children). Moreover, given the paucity of questionnaires on educational styles in Spain, in many cases researchers have had to adapt or translate the questionnaires validated in other populations (Bersabé et al., 2001).

In clinical practice with adolescents, it is fundamental to work with parents. While the efficacy of multicomponent programs has been proven (Romero, Rodríguez, Villar & Gómez-Fraguela, 2017), in order to determine the components to be included in these programs it is necessary to know on which factors of parental socialization the intervention must focus to prevent or alleviate certain pathologies. It is thus much more functional to include interventions on concrete parenting practices than on global parenting style. However, the components of educational styles are related in different ways to different psychopathological symptoms. For example, monitoring, warmth and control have been linked to behavioral problems (Trudeau et al., 2012), while degrees of cohesion, adaptability, and family strengths and bonds, and the marital happiness of the parents, are associated with drug use (Rees & Valenzuela, 2003). For these reasons, in order to design clinical interventions, it seems more operational to use a questionnaire based on those concrete parenting practices considered by the experts to be relevant to the appearance and maintenance of these pathologies rather than one that assesses global parenting style.

In addition, the relationship of parental socialization and pathologies differs depending on the cultural context in which socialization occurs, with certain practices being more effective than others in certain contexts. For example, in ethnic minority groups, in contexts other than the Anglo-Saxon, and even in families with low socio-economic status, imposition could work better than affection, while in Spain the reverse would be true (Fuentes et al., 2015). This highlights the importance of using instruments designed for the cultural context in which they are to be used.

These reasons, together with the limitations found in the existing questionnaires, warrant the creation of our questionnaire. To this end we set ourselves the objective of designing and analyzing the psychometric properties in a community sample of a questionnaire that assesses the practices of parental socialization in a Spanish population that influence the appearance and maintenance of conduct disorders (CDs) and substance-related disorders (SRDs), taking into account both the perception of the adolescent and that of their primary caregiver. Hypothesis 1 is that the questionnaire will have a two-factor structure (affect-communication and control-discipline), with a secondary objective to verify how the factors and total scores are related to personality, psychopathology and the use of alcohol and drugs, as well as how to assess the extent to which they can differentiate adolescents with dissocial disorder or with an oppositional defiant disorder from the general population. Hypothesis 2 is that low scores in both factors and in total will be related to greater psychopathology, with the questionnaire showing evidence of convergent, discriminant and criterion validity.

Methods

Questionnaire design

The questionnaire was designed in three stages using the Delphi method (Bravo & Arrieta, 2005):

1. Preliminary phase: delimitation of context (limitations in the parenting styles scales) and objective (to design a parental socialization questionnaire relevant to the appearance and maintenance of CDs and SRDs) and selection of a group of experts both national (from Valencia and Galicia) and international (from Uruguay, Venezuela, Argentina and USA), with psychiatrists and psychologists specializing in childhood and juvenile disorders, with accredited experience in care, teaching and research from the perspective of different theoretical models (cognitive, behavioral, systemic and dynamic).
2. Exploratory phase: preparation and implementation of the surveys. Based on the main scales available on parental socialization and their own professional experience, the experts suggested those parenting practices that they considered relevant to the appearance and maintenance of CD and SRT. Initial material for analysis was prepared, consisting of a list of key concepts and definitions with which a survey was created that the experts had to complete, indicating the relevance of the concept and justifying their opinion. After several cycles of survey analysis, with feedback from the results of the previous round, the concepts to be used in the final questionnaire were obtained. It was decided that in order to evaluate these concepts, a questionnaire of ordered categories would be used, with items answered on a 5-point Likert scale from disagree completely to agree completely. Next, each of the experts proposed several items to assess each

of the concepts. The following guidelines were to be observed when preparation items: present tense, relevant, clear, one single point, direct and inverse, and avoiding the use of negation (Abad, Olea, Ponsoda & Garcia, 2011). Once this item bank for each concept was completed, the experts were again asked to select the item they considered most appropriate to assess each concept and to justify their selection. After three cycles of survey analysis, with feedback from the results of the previous round, the items to be included in the final questionnaire were obtained.

3. Final phase: based on the results obtained from the statistical analysis, the 38 main relevant concepts and the 38 most suitable items to assess them were selected, and the questionnaire was thus drawn up.

Version 1 of the questionnaire was obtained following the above procedure.

Sample

The sample consisted of 631 adolescents of both sexes attending public secondary schools in the Autonomous Community of Valencia (Spain) and their main caregivers. The adolescents were in the 3rd or 4th grade of ESO (compulsory secondary education). Inclusion criteria were: a) aged between 14 and 16, b) living in the family home, c) informed consent given by both the adolescent and the family to participate in the study. The exclusion criterion was having been adopted. Purposive convenience sampling was carried out, offering participation in the study to all 3rd and 4th grade ESO pupils attending the eleven secondary schools that took part in the study. Of the 706 adolescents thus approached, 10.62% declined to participate, and of the resulting 631 caregivers, 485 returned the completed questionnaires (23.13% dropout rate)

Instruments

- *Parental socialization questionnaire TXP version 1*: comprising 38 items evaluating 38 practices of parental socialization involved in the appearance and maintenance of CD and SRD. Designed with the Delphi method. Responses are given on 5-point Likert scales, from *disagree completely* to *agree completely*. It is believed that the higher the score on the item and the questionnaire, the less likely that CDs and SRDs will appear. Two versions were used: one for the adolescent (*TXP-A*) and another one for his/her main caregiver (*TXP-C*). The main caregiver was designated by the adolescents themselves as the person who most influenced their education and spent more time with them. Six inverse items were included in *TXP-A* (2, 15, 35, 36, 37, 38) which were recoded for correction. In *TXP-C*, five inverse items were included (2, 12, 35, 36, 37).
- Structured interview for collecting socio-familial data and family history of alcoholism, drug dependence and mental illness.
- Structured interview for the assessment of the DSM-IV-TR diagnostic criteria regarding dissocial and oppositional defiant disorders (American Psychiatric Association, 2002).
- *Clinical Analysis Questionnaire* (CAQ, Krug, 1994), which evaluates 12 clinical scales: hypochondriasis, suicidal depression, agitated depression, anxious depression, low energy depression, guilt and resentment, boredom and withdrawal, paranoia, psychopathic deviation, schizophrenia, psychastenia and psychological inadequacy. It consists of 144 items of three options. The Spanish version has a satisfactory mean alpha coefficient value and moderate discriminant validity (Forns, Amador, Abad &Martorell, 1998).
- *High school personality questionnaire* (HSPQ, Cattell & Cattell, 1981). Consisting of 140 items with three response options, it allows the measurement of 18 personality dimensions: anxiety, extraversion, excitability, independence, reserved-open, intelligence, stability, calmness-excitability, submission-dominance, enthusiasm, cheerfulness, entrepreneurial, sensitivity, self-sufficiency, serenity, sociability, integration, relaxation. The indices of internal consistency of the scales range from 0.66 and 0.86 and those of test-retest reliability from 0.69 to 0.87 (Cattell & Cattell, 1995).
- *Problem Oriented Screening Instrument for Teenagers* (POSIT, National Institute on Drug Abuse, 1991). The abbreviated version composed of 19 dichotomous response (yes/no) items, was used for the assessment of drug use/abuse. The higher the score, the fewer the problems with drugs and alcohol, using 33 as a cut-off point, with subjects considered to have significant problems with a score equal to or below 33. The Spanish version has high internal consistency (alpha = 0.82), sensitivity (94.3%) and specificity 83.9%) (Araujo, Golpe, Braña, Varela & Rial, 2018).

Procedure

Authorization was obtained from the Ministry of Education of the Generalitat Valenciana and the research ethics committee of the Castellón Provincial Hospital Consortium (April 11, 2008). Declaration of Helsinki principles were observed. The schools were contacted to offer them the possibility of participating in the study. A psychologist went to those schools that agreed to collaborate and requested the voluntary and disinterested participation of adolescents and their families, who agreed to participate by signing the informed consent form.

Once participation was accepted, a psychologist carried out the assessment in two sessions. Both sessions were held during school hours, at the school, and within the pupil's

class schedule whenever possible. In the first session, the adolescent took part in an interview to obtain sociodemographic data, identify the main caregiver (the person who, according to the adolescent, had the most influence on their education and spent the most time with them) and evaluate the family background and diagnostic criteria for dissocial conduct disorder and oppositional defiant disorder. The *CAQ* and the *TXP-A* were also administered and the adolescent was given the *TXP-C* to take to the main caregiver who was to return it completed for the next session. During the second session two weeks later, the *TXP-C* was collected and the *HSPQ*, the *POSIT* and the *TXP-A* (again) were administered to the adolescent. The *TXP-C* was also provided a second time for the teenager to take home and return once completed by the primary caregiver.

Data analysis

SPSS v.20 (IBM Corp. Released, 2011) and Factor 10.5.03 (Lorenzo-Seva & Ferrando, 2006) were the programs used for factor analyses, and Jmetrik 4.0.5 (Meyer, 2014) for item analysis with classical test theory and item response theory. The descriptive analysis of the variables revealed kurtosis in the questionnaire data. The percentage of missing data was less than 5%, and these values were eliminated pairwise or listwise, depending on the procedure. Psychometric validation of the *TXP-A* was performed. The sample was randomly divided into two halves. The inverse items were recoded. To find out whether factor analysis of the questionnaire was appropriate, the Kaiser-Meyer-Olkin index (KMO) and the Bartlett sphere test were used. Exploratory factor analysis was performed on one half of the sample of version 1 of the questionnaire based on the polychoric correlations with extraction of unweighted least squares, with parallel analysis and Cattell's scree-test used as methods of factor extraction. The Promin rotation method was used. Items that saturated less than 0.35 were eliminated from the factors obtained, thus creating version 2 of the questionnaire. With the other half of the sample, a confirmatory factor analysis of version 2 was performed with the polychoric correlation matrix. Calculations were made of the RMSR index (acceptable values between 0.05 and 0.08), the goodness of fit index (GFI) (with values greater than 0.9 indicating good fit), the RMSEA index (acceptable values between 0.05 and 0.08) and the minimum fit ($p > 0.05$ indicates goodness of fit) to measure the fit of the factorial model obtained (Hair, Anderson, Tatham & Black, 1998). Items saturating less than 0.35 were eliminated from the factors obtained, leading to the creation of version 3 of the questionnaire. EFA and CFA of the *TXP-C* were performed in the same way, and version 3 of the questionnaire was obtained. In the total sample, the factorial saturations of the items in the final versions were obtained, as were the RMSR index, the GFI, the RMSEA index and the minimum fit. Item analysis was also carried out using classical test theory and item response theory, including Rasch analysis and differential functioning using the Mantel-Haenszel procedure. The percentiles of both versions of the questionnaire were calculated. Cronbach's alpha and the greater lower bound (GLB) were used to measure score reliability. Pearson correlation coefficient was used to measure convergent and discriminant validity and interrater reliability, with the intraclass correlation coefficient used for test-retest reliability, and the Pearson correlation coefficient, t-test and ANOVA to analyze possible differential functioning. The effect size (ES) of the t-test was calculated with Cohen's d (0.2 small, 0.5 medium and 0.8 large effect) and that of ANOVA by partial squared eta (0.01 small, 0.06 medium and 0.14 large effect).

Results

Sociodemographic and psychopathological sample data

Males made up 42.8% (n = 269) of the sample and females 57.2% (n = 359). Mean age was 15.27 years (SD = 0.70), with an age range between 14 and 16, with 58% in the 3rd grade of compulsory secondary education (ESO) and 42% in the 4th grade. The great majority were Spanish nationals (85.1%), with 9.4% coming from other European countries, 3.6% from Central and South America, 1.3% from Africa and 0.6% had other nationalities.

Of the adolescents, 15.6% were only children, 1.9% had one sibling and 82.5% had two or more siblings. The majority (78.9%) of parents were married (including domestic partnerships), 7.1% were in second marriages, 4.7% were separated, 6.6% were divorced, 2.1% were widowed and 0.5% single. In 90.7% of cases the main caregiver was the mother, in 7.3% the father and in 2% the grandparents, uncles, the sister or partner of the father or mother took on this role.

A family history of alcoholism was found in 13.3% of cases, 8.4% adolescents had a family member with drug addiction problems and 13.9% had a family history of mental illness. Dissocial disorder criteria were met by 0.6% (n = 4) and oppositional defiant disorder by 0.6% (n = 4) of the adolescents. Table 1 shows the *CAQ* and *HSPQ* scores. The mean *POSIT* score was 36.56 (SD = 2.07), indicating that 7.4% (n = 46) of the sample had problems with drugs or alcohol.

Item analysis of version 1 (n adolescents = 316 and n caregivers = 235)

In version 1 of *TXP-A*, mean item scores ranged from 2.72 to 4.66. The descriptive item analysis can be seen in Table 2. The highest-scoring item was 37 and the lowest 35. Internal consistency of 0.89 was obtained for the total scale. The range of correlations of each of the items with the total score of the corrected scale ranged between -0.009 (item 1) and 0.71 (items 17 and 18).

Mean item scores in version 1 of *TXP-C* ranged from 2.17 to 4.97. The descriptive item analysis is also shown in Table 2. The item that scored highest was 24 and the one with the lowest score was 35. Internal consistency of 0.80 was obtained for the total scale. The range of correlations of each of the items with the total score of the corrected scale ranged from -0.17 (item 12) to 0.63 (item 17).

Exploratory factor analysis of TXP-A version 1 (n = 316)

The KMO index was 0.90 and Bartlett's sphericity test (703) = 4367.009; $p < 0.001$. The parallel analysis and Cattell's scree-test indicated a two-factor structure. Both factors presented a correlation of 0.74. Items 3, 11, 15, 16, 32 and 36 were eliminated due to saturations below 0.35, resulting in version 2 with 32 items. Table 2 shows the factor saturations of each item.

Confirmatory factor analysis of TXP-A version 2 (n = 315)

The KMO index was 0.90 and Bartlett's sphericity test (496) = 3842.3; $p < 0.001$. Items 7, 10 and 31 were eliminated due to saturations of below 0.35, resulting in version 3 with 29 items. The eigenvalue for factor 1 was 11.42 and the percentage of variance explained 35.6%; for factor 2, the eigenvalue was 2.65 and the percentage of variance explained 8.3%. The total variance explained was 43.9%. The correlation between both factors was 0.72. The RMSR was 0.05, the GFI 0.97, the RMSEA 0.03 and the minimum adjustment (433) = 546331 ($p < 0.001$). Table 2 shows the factor saturations of each item.

Exploratory factor analysis of TXP-C version 1 (n = 235)

The KMO index was 0.79 and Bartlett's sphericity test (703) = 2475.547; $p < 0.001$. The parallel analysis and Cattell's scree-test indicated a two-factor structure. With saturations below 0.35, items 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 15, 18, 19, 20, 30, 31, 33, 35, 36, 37, and 38 were eliminated, resulting in version 2 with 17 items. Table 2 shows the factor saturations of each item.

Confirmatory factor analysis of TXP-C version 2 (n = 250)

The KMO index was 0.89 and Bartlett's sphericity test (136) = 1611.0; $p < 0.001$. Item 16 was eliminated due to saturation below 0.35, resulting in version 3 with 16 items. The eigenvalue for factor 1 was 6.65 and the percentage of variance explained 39.1%; for factor 2, the eigenvalue was 1.66 and the percentage of variance explained 9.7%. The total variance explained was 48.9%. The correlation between both factors was 0.67. The RMSR was 0.06, the GFI 0.98, the RMSEA 0.05 and the minimum adjustment (103) = 112812 ($p < 0.23$). Table 2 shows the factor saturations of each item.

Item analysis of version 3 (n adolescents = 631 and n caregivers = 485)

Table 3 shows the results of the item analysis and the factor saturations of *TXP-A* version 3. For factor 1, the eigen-

Table 1. *Mean scores of adolescents on the Krug Clinical Analysis Questionnaire (CAQ) and the Cattell and Cattell High School Personality Questionnaire (HSPQ).*

Clinical Analysis Questionnaire CAQ		**Adolescent Personality Questionnaire HSPQ**	
Dimension	**Mean (SD)**	**Dimension**	**Mean (SD)**
Hypochondriasis	5.78 (1.81)	Anxiety	1.55 (2.90)
Suicidal depression	5.89 (1.73)	Extraversion	7.04 (2.93)
Agitated depression	5.92 (1.84)	Excitability	11.43 (2.18)
Anxious depression	5.69 (1.76)	Independence	7.03 (2.93)
Low energy depression	5.78 (1.92)	Reserved-open	5.86 (1.84)
Guilt-resentment	5.15 (1.95)	Intelligence	4.36 (1.92)
Boredom-withdrawal	5.23 (1.84)	Stability	6.23 (2.00)
Paranoia	5.86 (1.81)	Calmness-excitability	4.61 (1.77)
Psychopathic deviation	5.75 (1.78)	Submission-dominance	6.48 (1.74)
Schizophrenia	5.35 (1.77)	Enthusiasm	5.37 (1.89)
Psychasthenia	4.97 (1.91)	Cheerfulness	5.56 (1.77)
Psychological inadequacy	5.17 (1.82)	Entrepreneurial	6.51 (1.77)
		Sensitivity	5.83 (1.75)
		Self-sufficiency	6.26 (1.71)
		Serenity	4.68 (1.90)
		Sociability	5.83 (1.84)
		Integration	5.94 (1.94)
		Relaxation	4.31 (1.77)

Table 2. *Item analysis and factor saturation in exploratory factor analysis of version 1 and factor saturation in confirmatory factor analysis of version 2 of the questionnaire for adolescents and caregivers.*

ÍTEM	ADOLESCENTS					CAREGIVERS				
	M	SD	RC	FSE (n=316)	FSC (n=315)	M	SD	RC	FSE (n=235)	FSC (n=250)
1. In my family my parents clearly impose everybody`s functions and roles without allowing changes/In our family, we parents clearly impose everybody`s functions and roles without allowing changes.	3.13	1.14	-0.009	F1=0.72	F2=0.86	3.01	1.27	-0.04	F2=0.03	E
2. Without resorting to physical punishment, my parents often punish me/Without resorting to physical punishment, I often apply punishments to modify my child's behavior.	3.45 (I)	1.30	0.14	F2=0.85	F1=0.61	2.84 (I)	1.47	0.07	F1=0.07	E
3. My parents know and control all my activities and friendships/I usually know and control all my son's activities and friendships.	3.25	1.29	0.23	F1=0.33	E	4.06	1.00	0.13	F2=0.03	E
4. My parents let me participate in the making of rules/ My children participate in drawing up family rules.	3.44	1.19	0.34	F2=0.62	F1=0.44	3.83	1.18	0.24	F1=0.13	E
5. In my family we all feel very close and we stay together and faithful to each other.	4.07	1.05	0.63	F2=0.56	F1=0.63	4.48	0.83	0.55	F1=0.66	F2=0,77
6. I believe that my parents are approachable and willing to help/I believe that in our family we are approachable and available for one another.	4.42	0.87	0.57	F2=0.54	F1=0.53	4.59	0.78	0.52	F1=0.59	F2=0,51
7. In my family we often carry out tasks and activities together.	3.36	1.13	0.53	F1=0.35	F1=0.34	4.03	1.07	0.42	F1=0.34	E
8. In our family the roles, tasks and responsibilities of parents and children, are clearly differentiated and boundaries between them are maintained.	3.46	1.13	0.08	F1=0.65	F2=0.71	3.79	1.15	0.22	F2=0.11	E
9. In my house the rules are usually observed, and if not, my parents apply corrective measures/In our house the rules are usually observed, and if not, we parents apply corrective measures	3.62	1.09	0.23	F1=1.009	F2=0.97	3.78	1.20	0.22	F2=0.12	E
10. Although in our family we talk about things that happen to us, I can decide what to do for myself/I think that my family members are self-confident, self-sufficient and make their own decisions.	3.78	1.12	0.31	F2=0.37	F2=0.18	3.96	1.06	0.26	F2=0.20	E
11. My family has taught me that I can trust others: the world is a safe place/We transmit to our children that they can trust others: the world is a safe place.	2.81	1.11	0.16	F2=0.23	E	2.83	1.29	0.23	F1=0.07	E
12. My parents favor relationships with other people outside the family, encourage me to do activities outside the home and accept that I bring friends home./We like to be together more than with people from outside the family.	4.26	0.94	0.47	F2=0.62	F1=0.51	2.58 (I)	1.26	-0.17	F2=0.01	E
13. In my family we attach importance to social values such as respect, solidarity, tolerance, etc./We educate our children with values such as respect, solidarity, tolerance, etc.	4.40	0.86	0.51	F1=0.51	F2=0.37	4.81	0.57	0.26	F2=0.58	F1=0,67
14. My parents fulfill their role as parents and feel comfortable doing it/We are happy to be parents and to take on this role.	4.55	0.75	0.57	F2=0.48	F2=0.50	4.68	0.60	0.45	F1=0.40	F1=0,44
15. My parents continue to treat me as they did when I was a child./As the family and circumstances change, I change my relationship with the children and adapt to the changes.	3.58 (I)	1.30	0.17	F2=0.16	E	4.40	0.81	0.40	F2=0.28	E
16. In my family, we express our emotions often and with intensity.	3.32	1.04	0.43	F1=0.32	E	4.16	0.99	0.38	F2=0.45	F1=0,31
17. In our home we have a friendly atmosphere, full of warmth and positivity.	4.03	1.03	0.71	F2=0.66	F1=0.62	4.42	0.82	0.63	F1=0.77	F2=0,81
18. In my family we understand each other/As parents we try to understand our children.	3.77	1.09	0.71	F2=0.63	F1=0.72	4.82	0.52	0.40	F1=0.33	E
19. I have been taught to take responsibility for my actions and their consequences/In our family we each take responsibility for our actions and their consequences.	4.55	0.60	0.31	F1= 0.55	F2=0.51	4.30	0.87	0.23	F2=0.21	E

20. My parents support me emotionally/When I have a problem, I can get emotional support from my children.	4.26	0.92	0.68	F2=0.60	F1=0.70	3.30	1.36	0.14	F2=0.09	E
21. In my family we know how to resolve problems without too much tension.	3.37	1.13	0.61	F2=0.63	F1=0.47	3.57	1.13	0.47	F1=0.56	F2=0,73
22. In my family we can talk about all our feelings without any problems: happiness, sadness, affection, fear, anger, etc.	4.00	1.05	0.62	F2=: 0.49	F1=0.50	4.55	0.73	0.32	F2=0.64	F1=0,38
23. In my family, we express ourselves and understand each other very well.	3.77	1.04	0.64	F2=0.54	F1=0.55	4.24	0.91	0.62	F1=0.65	F2=0,80
24. I feel important to and valued by my parents/I value my children as an important part of the family.	4.31	0.96	0.65	F2=0.78	F1=0.69	4.97	0.25	0.23	F2=0.68	F1=1,01
25. In my family I am treated with affection/In our family, we usually treat each other with affection.	4.56	0.75	0.68	F2=0.88	F1=0.77	4.67	0.69	0.60	F1=0.56	F2=0,63
26. My parents (or those responsible for my upbringing at home) agree on the way to bring me up/My partner and I agree and act together, without contradicting each other, in the tasks of parenting and raising the children (in case you share this with someone who is not your partner, refer to him/her).	4.42	0.75	0.46	F1=0.37	F2=0.53	3.90	1.12	0.39	F1=0.56	F2=0,65
27. My parents allow me, teach and encourage me to relate to my friends and other people/I teach and encourage my children to relate to people in an appropriate way.	4.48	0.76	0.52	F2=0.64	F1=0.44	4.85	0.43	0.31	F2=0.88	F1=0,76
28. My parents respect my rights and my privacy/In my family we respect each other and we take into account the privacy and individuality of each one of us.	4.14	0.97	0.51	F2=0.64	F1=0.73	4.57	0.73	0.47	F1=0.51	F2=0,48
29. In my family, I am treated justly and fairly/ In my family, we treat each other justly and fairly.	4.09	0.95	0.64	F2=0.59	F1=0.65	4.40	0.80	0.50	F1=0.56	F2=0,48
30. In my family the rules are clear: my actions always have the same consequences/In our family, discipline is clear: an action always has the same consequences.	3.49	1.08	0.10	F1=0.69	F2=0.78	3.39	1.23	0.17	F2=0.11	E
31. My parents congratulate me or reward me if I behave well/I reinforce the good behavior of my child with praise, expressions of support or material rewards.	3.48	1.30	0.37	F1=0.36	F1=0.24	4.16	1.00	0.22	F2=0.22	E
32. My parents, as educators, maintain a satisfactory relationship between them based on affection, respect and support/As educators, our partner relationship is satisfactory and based on affection, respect and support (mark "Not applicable" in the absence of a partner).	4.25	1.02	0.35	F2=0.30	E	4.60	0.74	0.40	F1=0.62	F2=0,44
33. In my family we have clear rules regarding how the family functions that we all know and understand.	3.90	0.94	0.49	F1=0.81	F2=0.74	4.29	0.86	0.50	F1=0.32	E
34. I have fun and enjoy being with my family/In my family we have fun and enjoy being together.	4.12	0.96	0.67	F2=0.55	F1=0.72	4.47	0.71	0.51	F1=0.74	F2=0,70
35. My parents usually tell me what they don't like about me and criticize what I do/I usually tell my children what I don't like about them and criticize what they do.	2.72 (I)	1.25	0.08	F2=0.46	F1=0.39	2.17 (I)	1.28	0.13	F1=0.04	E
36. My parents protect me too much/I predict and solve my children's problems to avoid their suffering and protect them from going through difficulties.	2.74 (I)	1.24	0.04	F2=0.21	E	2.44 (I)	1.38	0.08	F1=0.05	E
37. My parents usually hit me when I behave badly/ When my children do something bad, I usually give them a slap or similar.	4.66 (I)	0.77	0.18	F2=0.49	F1=0.61	4.24 (I)	1.16	0.21	F1=0.13	E
38. I feel isolated and outside my family/No family member is isolated from the rest because we are all involved with and relate to each other.	4.58 (I)	0.93	0.37	F2=0.48	F1=0.71	4.62	0.78	0.36	F1=0.27	E

Note. M: mean; SD: standard deviation; RC: reliability coefficient (correlation of each scale item with the corrected scale score); I: inverse item with recoded score; FSE: factor saturation in the exploratory factor analysis of version 1; FSC: factor saturation in the confirmatory factor analysis of version 2; F1: item saturates in factor 1; F2: item saturates in factor 2; E: item eliminated in exploratory factor analysis

Table 3. *Item analysis, factor saturations and correlation with the corrected scale of version 3 of the questionnaire for adolescents (n = 631) and the questionnaire for caregivers (n = 485).*

QUESTIONNAIRE	ITEM	M	SD	DI	RC	FS	CI(95%)FS	WMS	UMS
QUESTIONNAIRE FOR ADOLESCENTS VERSION 3	1	3.09	1.15	0.04	0.04	F2=0.81	0.68-0.96	1.54	1.73
	2	3.50	1.28	0.12	0.12	F1=0.73	0.64-0.87	1.77	1.96
	4	3.41	1.19	0.29	0.29	F1=0.53	0.38-0.67	1.27	1.43
	5	4.06	1.07	0.63	0.63	F1=0.58	0.45-0.68	0.89	0.83
	6	4.41	0.87	0.54	0.54	F1=0.51	0.38-0.63	1.01	0.95
	8	3.39	1.14	0.11	0.11	F2=0.70	0.59-0.84	1.42	1.54
	9	3.53	1.15	0.24	0.24	F2=0.99	0.90-1.11	1.29	1.35
	12	4.25	0.99	0.46	0.46	F1=0.52	0.36-0.67	1.14	1.11
	13	4.41	0.82	0.49	0.49	F2=0.46	0.31-0.59	0.97	0.88
	14	4.52	0.75	0.58	0.58	F2=0.40	0.27-0.52	0.85	0.76
	17	4.01	1.01	0.69	0.69	F1=0.63	0.50-0.73	0.67	0.67
	18	3.80	1.05	0.67	0.67	F1=0.66	0.56-0.78	0.65	0.66
	19	4.51	0.68	0.36	0.36	F2=0.59	0.45-0.74	0.94	0.91
	20	4.20	0.92	0.65	0.65	F1=0.62	0.52-0.71	0.74	0.68
	21	3.32	1.14	0.62	0.62	F1=0.51	0.40-0.63	0.69	0.69
	22	3.96	1.09	0.61	0.61	F1=0.46	0.35-0.55	0.88	0.84
	23	3.79	1.03	0.63	0.63	F1=0.52	0.37-0.62	0.68	0.68
	24	4.35	0.93	0.62	0.62	F1=0.72	0.61-0.82	0.94	0.80
	25	4.54	0.75	0.66	0.66	F1=0.80	0.69-0.90	0.81	0.66
	26	4.41	0.77	0.52	0.53	F2=0.52	0.37-0.63	0.81	0.81
	27	4.47	1.77	0.57	0.57	F1=0.48	0.35-0.65	0.84	0.73
	28	4.09	1.02	0.51	0.51	F1=0.64	0.52-0.77	1.00	0.92
	29	4.10	0.92	0.66	0.66	F1=0.59	0.48-0.67	0.62	0.61
	30	3.50	1.04	0.15	0.16	F2=0.72	0.57-0.86	1.24	1.37
	33	3.87	0.95	0.50	0.50	F2=0.79	0.69-0.90	0.77	0.76
	34	4.12	0.94	0.65	0.65	F1=0.62	0.51-0.72	0.68	0.75
	35	2.76	1.25	0.11	0.11	F1=0.40	0.27-0.55	1.63	1.78
	37	4.65	0.77	0.27	0.27	F1=0.53	0.37-0.68	1.68	1.58
	38	4.58	0.93	0.47	0.47	F1=0.58	0.41-0.72	1.73	1.59
QUESTIONNAIRE FOR CAREGIVERS VERSION 3	5	4.44	0.85	0.59	0.63	F2=0.67	0.42-0.87	0.89	0.80
	6	4.61	0.78	0.54	0.56	F2=0.57	0.37-0.78	1.29	0.99
	13	4.82	0.57	0.29	0.27	F1=0.81	0.63-1.17	1.82	1.61
	14	4.72	0.63	0.48	0.49	F2=0.41	0.15-0.68	1.20	1.06
	17	4.44	0.85	0.70	0.71	F2=0.77	0.61-0.95	0.72	0.67
	21	3.59	1.14	0.51	0.52	F2=0.76	0.59-0.97	1.07	1.14
	22	4.53	0.76	0.39	0.34	F1=0.73	0.45-1.007	1.30	1.56
	23	4.23	0.91	0.59	0.63	F2=0.72	0.57-0.87	0.83	0.85
	24	4.96	0.25	0.40	0.41	F1=0.87	0.66-1.05	1.01	0.43
	25	4.62	0.69	0.60	0.65	F2=0.59	0.43-0.74	0.91	0.80
	26	3.97	1.30	0.47	0.49	F2=0.85	0.60-1.18	1.34	1.33
	27	4.86	0.43	0.45	0.44	F1=0.88	0.68-1.15	1.07	0.80
	28	4.57	0.73	0.52	0.55	F2=0.64	0.38-0.83	1.06	0.99
	29	4.45	0.80	0.58	0.59	F2=0.63	0.48-0.84	0.89	0.85
	32	4.61	1.48	0.28	0.46	F2=0.75	0.52-1.002	1.45	1.38
	34	4.48	0.71	0.61	0.64	F2=0.77	0.65-0.94	0.70	0.79

Note. M: Mean; DT: Standard deviation; DI: Discrimination index; RC: reliability coefficient (correlation of each scale item with the corrected scale score); FS: factor saturation in the confirmatory factor analysis of version 3; F1: item saturates in factor 1; F2: item saturates in factor 2; CSI(95%)SF: 95% confidence interval in factor saturation; WMS: Weighted mean squared residual (*Infit*); UMS: Unweighted mean squared residual (*Outfit*).

value was 10.83 and the percentage of variance explained 37.3%; for factor 2, the eigenvalue was 2.63 and the percentage of variance explained 9.09%. The total explained variance was 46.4%. The correlation between both factors was 0.73. The RMSR was 0.04, the GFI 0.98, the RMSEA 0.03 and the minimum adjustment (349) = 608468 ($p < 0.001$).

Table 3 shows the results of the item analysis and the factor saturations of *TXP-C* version 3. For factor 1, the eigenvalue was 8.07 and the percentage of variance explained 50.4%; for factor 2, the eigenvalue was 1.60 and the percentage of variance explained 10.04%. The total variance explained was 60.4%. The correlation between both factors was 0.71. The RMSR was 0.05, the GFI 0.98, the RMSEA > 0.1 and the minimum adjustment (89) = 170783 ($p < 0.001$).

This third version was accepted as the final version of the questionnaire. The final version of *TXP-A* comprises 29 items. In factor 1, 20 items saturate: 2, 4, 5, 6, 12, 17, 18, 20, 21, 22, 23, 24, 25, 27, 28, 29, 34, 35, 37 and 38. Nine items saturate in factor 2: 1, 8, 9, 13, 14, 19, 26, 30 and 33. The final version of *TXP-C* comprises 16 items. In factor 1, 4 items saturate: 13, 22, 24 and 27, while twelve items saturate in factor 2: 5, 6, 14, 17, 21, 23, 25, 26, 28, 29, 32 and 34.

Questionnaire scores

The mean score for *TXP-A* was 80.45 (SD = 11.84) in factor 1, with 35.28 (SD = 4.79) in factor 2 and 115.74 (SD = 14.42) in the total. The mean score for *TXP-C* was 19.14 (SD = 1.40) in factor 1, with 52.79 (SD = 6.66) in factor 2 and 71.97 (SD = 7.38) in the total. The percentiles of adolescents and caregivers can be seen in Table 4.

Score reliability

The *TXP-A* questionnaire has a GLB of 0.97 and Cronbach's alpha of 0.89, factor 1 of 0.89 and factor 2 of 0.71. *TXP-C* has a GLB of 0.97, Cronbach's alpha of 0.87, factor 1 of 0.58 and factor 2 of 0.87.

Interrater reliability (correlations between scores of adolescents and their caregivers) can be seen in Table 5.

The test-retest reliability (intraclass correlation coefficient) of the *TXP-A* was 0.94 ($p < 0.001$) and that of the *TXP-C* 0.94 ($p < 0.001$).

Proof of convergent and discriminant validity

Regarding the psychopathological variables, Tables 6 and 7 show the multiple significant correlations found between the total scores and the two factors, both *TXP-A* and *TXP-C*, along with the *CAQ* and *HSPQ* scores.

Table 4. *Percentiles of factor 1 and 2 scores and total score of parental socialization questionnaire for adolescents and caregivers.*

	ADOLESCENTS			CAREGIVERS		
PERCENTILE	FACTOR 1	FACTOR 2	TOTAL	FACTOR 1	FACTOR 2	TOTAL
1	42.96	23.32	68.32	14	32	49.43
5	59	27	90	16	40	57
10	64.2	29	96	18	43.3	62
15	69	30	100.8	18	47	65
20	72	31	106	18	48	67
25	74	32	109	19	50	68
30	76	33	111	19	51	70
35	78	34	113	19	52	71
40	80	34	114	19	53	72
45	81	35	116	20	54	73
50	82	36	118	20	55	74
55	84	36	119.6	20	55	75
60	85	37	121	20	56	76
65	87	37	123	20	57	76
70	88	38	125	20	57	77
75	89	39	126	20	58	77
80	90	40	128	20	58	78
85	92	40	130	20	59	78
90	94	42	133	20	59	79
95	95	43	135	20	60	80
99	98	45	138	20	60	80

Table 5. *Correlations between the scores of adolescents and their caregivers on the parental socialization questionnaire.*

		ADOLESCENT		
		Total score	**Factor 1**	**Factor 2**
CAREGIVER	**Total score**	**0.398****	0.384**	0.242**
	Factor 1	0.226**	0.185**	0.221**
	Factor 2	0.399**	**0.391****	0.228**

Note. **p < 0.01. In bold: interrater reliability. Underlined: multitrait-multimethod matrix values.

In terms of substance use, the correlation of *POSIT* with *TXP-A* was r = 0.275 (p < 0.001) with factor 1, r = 0.140 (p < 0.001) with factor 2 and r = 0.273 (p < 0.001) with the total score. There are differences in factor 1 (t = 5.104, p < 0.001, ES = 0.70), 2 (t = 2.541, p = 0.011, ES = 0.37) and total score (t = 5.046, p < 0.001, ES = 0.70) between subjects presenting problems with drugs or alcohol (Factor 1 = 72.21, SD = 14.03, Factor 2 = 33.54, SD = 5.29, Total = 105.76, SD = 16.99) and those without (Factor 1 = 81.19,

Table 6. *Correlations between factors 1 and 2 and the total scores on the parental socialization questionnaire TXP and the Krug Clinical Analysis Questionnaire (CAQ).*

CAQ Dimensions	**ADOLESCENTS**			**CAREGIVERS**		
	F1	**F2**	**TOTAL**	**F1**	**F2**	**TOTAL**
Hypochondriasis	-.396**	-.209**	-.395**	-.078	-.133**	-.127**
Suicidal depression	-.407**	-.248**	-.417**	-.107*	-.155**	-.156**
Agitated depression	-.131**	-.061	-.128**	-.050	-.127**	-.128**
Anxious depression	-.168**	-.145**	-.186**	-.059	.036	.027
Low energy depression	-.371**	-.175**	-.363**	-.091*	-.124**	-.123*
Guilt-resentment	-.272**	-.184**	-.285**	-.011	-.046	-.036
Boredom-withdrawal	-.307**	-.261**	-.339**	-.117*	-.150**	-.154**
Paranoia	-.409**	-.201**	-.403**	-.043	-.125**	-.116*
Psychopathic deviation	-.004	-.019	-.009	-.040	-.052	-.058
Schizophrenia	-.390**	-.200**	-.387**	-.073	-.091	-.089
Psychasthenia	-.133**	-.076	-.135**	-.056	.077	.055
Psychological inadequacy	-.382**	-.237**	-.393**	-.070	-.071	-.070

Note. *p < 0.05 **p < 0.01

Table 7. Correlations between factors 1 and 2 and the total scores on the parental socialization questionnaire TXP and the Cattell and Cattell adolescent personality questionnaire (HSPQ).

HSPQ Dimensions	**ADOLESCENTS**			**CAREGIVERS**		
	F1	**F2**	**TOTAL**	**F1**	**F2**	**TOTAL**
Anxiety	-.430**	-.216**	-.427**	-.009	-.147**	-.134**
Extraversion	.087*	.084*	.100*	.029	-.039	-.037
Excitability	-.103*	-.019	-.092*	.092*	.008	.022
Independence	-.166**	-.058	-.156**	-.080	-.135**	-.133**
Reserved-open	.099*	.102*	.115**	.038	.046	.045
Intelligence	.023	.041	.032	-.097*	.041	.015
Stability	.345**	.180**	.344**	.021	.096*	.092
Calmness-excitability	-.240**	-.074	-.222**	-.016	-.088	-.082
Submission-dominance	-.087*	-.055	-.090*	-.129*	-.112*	-.122*
Enthusiasm	-.229**	-.098*	-.221**	.053	-.163**	-.140**
Cheerfulness	.359**	.179**	.356**	.012	.187**	.178**
Entrepreneurial	.123**	.078	.128**	-.031	-.014	-.022
Sensitivity	.186**	.122**	.194**	.080	.161**	.161**
Self-sufficiency	-.126**	-.078	-.130**	.018	.022	.026
Serenity	-.222**	-.121**	-.223**	.004	.006	.011
Sociability	-.030	-.053	-.043	-.028	.021	.019
Integration	.282**	.145**	.281**	.069	.131**	.127**
Relaxation	-.229**	-.137**	-.234**	.030	-.030	-.024

Note. *p < 0.05 **p < 0.01

SD = 11.25, Factor 2 = 35.40, SD = 4.73, Total = 116.59, SD = 13.75).

The correlation of the *POSIT* with *TXP-C* was r = -0.010 (p = 0.830) with factor 1, r = -0.127 (p = 0.008) with factor 2 and r = 0.116 (p = 0.015) with the total score. However, there are no significant differences between those with alcohol and drug problems and those without.

As far as behavioral problems are concerned, *TXP-A* yields differences in the factor 1 scores (t = 4.084, p < 0.001, ES = 2.27) and total (t = 3.259, p = 0.001, ES = 1.55) among the subjects who have a dissocial disorder (Factor 1 = 57, SD = 9.05, Total = 92.75, SD = 15.52) and those who do not (Factor 1 = 80.66, SD = 11.56, Total = 115.93, SD = 14.17) Furthermore, there are correlations of factor 1 (r = -0.180, p < 0.001) and the total score (r = -0.141, p < 0.001) with the number of criteria for dissocial disorder, and of factor 1 (r = -0.149; p < 0.001) and the total score (r = -0.119; p = 0.003) with the severity of dissocial disorder. There are no differences in the scores according to the presence of oppositional defiant disorder, although there was a correlation between the number of criteria of oppositional defiant disorder and factor 1 (r = -0.237, p < 0.001), 2 (r = -0.151, p < 0.001) and total score (r = -0.245, p < 0.001).

In *TXP-C*, there are differences in factor 2 (t = 2.820, p = 0,005, ES = 1.49) and the total score (t = 2.586, p = 0.010, ES = 1.44) among the caregivers of adolescents with dissocial disorder (Factor 2 = 42, SD = 7.81, Total = 61, SD = 7.93) and those without (Factor 2 = 52.84, SD = 6.62, Total = 72.02, SD = 7.36). In addition, there are correlations of factor 2 (r = -0.127, p = 0.008) and total score (r = -0.121, p = 0.011) with the number of criteria for dissocial disorder, and of factor 2 (r = -0.114, p = 0.017) and the total score (r = -0.108, p = 0.024) with the severity of dissocial disorder. There are no differences according to the presence of oppositional defiant disorder.

Differential functioning of the questionnaire

In *TXP-A* there is significant correlation of family history of alcoholism with factor 2 (r = -0.088, p = 0.028) and the total score (r = -0.085, p = 0.034), and family history of drug addiction with factor 1 (r = -0.133; p = 0.001) and the total score (r = -0.127, p = 0.002).

There are differences in the scores of factor 1 (F = 3.121, p = 0.009, ES = 0.025) and the total (F = 2.706, p = 0.020, ES = 0.022) according to the number of siblings. Only children score higher in factor 1 than those with three siblings and only children and those with two siblings have a higher total score than those with three siblings.

There are no differences in the *TXP-A* scores according to sex, the school year of the adolescents, their nationality and kinship with the main caregiver. Regarding sex, all the items are class AA (little or no differential functioning) except 5 and 9, which are BB (moderate differential functioning slightly favoring males).

In *TXP-C* there is significant correlation of family history of alcoholism with factor 2 (r = -0.131, p = 0.006) and the total score (r = -0.125, p = 0.009)

There are differences in factor 2 (F = 3.721, p = 0.003, ES = 0.041) and total score (F = 3.809, p = 0.002, ES = 0.042) according to the number of siblings. Only children score higher than those with three siblings in factor 2 and total score.

There are no differences in *TXP-C* according to the sex of the caregiver or adolescent, the school year of the adolescents, their nationality nor the kinship between them. In terms of sex, all items are AA class (little or no differential functioning).

Discussion

The final version of *the parental socialization questionnaire TXP-A* comprises 29 items while *TXP-C* comprises 16 items. Two versions were created because parental practices are defined from a bidirectional perspective as a set of attitudes and global trends in parental behavior that determine interaction with children and have a clear effect on child development (Escribano, Aniorte & Orgilés, 2013). From this perspective, we need to know not only how parents perceive their own parental practices, but also how the children view their parents. This information allows us to understand current parental practices from different perspectives and is a prerequisite for developing any intervention program (Escribano et al., 2013).

It seems that the child's perception of his/her parents' behavior may be more related to his/her adjustment than the parents' behavior itself, whether actual (Schaefer, 1965) or reported (González & Landero, 2012), and that the correlation with an external observer is greater in the case of the self-reports of adolescents than with the self-reports of parents (Iglesias & Romero, 2009). There is also evidence that children display lower social desirability bias than parents (García & Gracia, 2010). However, by relying on information from adolescents on parenting styles, it is difficult to assess whether parents truly use each style as the adolescents report they do (Trinkner, Cohn, Rebellon & Van Gundy, 2012). Therefore, it is useful to include both adolescents' perceptions of parenting style and reports from parents about their own behavior (Trinkner et al., 2012).

As supposed in hypothesis 1, a two-factor structure is confirmed in both versions of the questionnaire. In *TXP-A*, factor 1 would be labeled as affect and communication (with affective and communicative variables, and low use of punishment and criticism) and factor 2 as control and structure (with roles, discipline, rules and limits). This two-factor structure coincides with the two basic dimensions found in most studies: emotional tone-communication and control-discipline (Sansinenea & Sansinenea, 2004). In our study, however, factor 2 would be broader

than the control-discipline dimension, since it would also encompass aspects referring to another factor frequently found in the literature: the family structure, the degree to which parents provide their children with a predictable, organized and consistent environment (Power, 2013). In this sense, relationships of affection and open communication are usually believed to facilitate the establishment of a regime with clear and well-structured rules (García & Gracia, 2010).

Moreover, because the use of punishment and criticism does not saturate with the other variables related to control, it is included in the affect-communication factor, perhaps reflecting the distinction found in other studies between authoritarian control (highly directive and often critical parental behavior) and democratic control (forms of control that promote autonomy), with warmth being low in the first and high in the second (Power, 2013). It has been found that families with lower levels of communication tend to use more coercion and physical punishment (Ramírez, 2005), and the affect factor usually includes parental acceptance (García & Gracia, 2010), which in our case would be reflected in low use of criticism.

Although both versions have a two-factor structure, only one of the factors is the same in both, while the composition of the other factor differs in *TXP-C*, thereby contrasting with our hypothesis 1 assumptions. Thus factor 2 would correspond, albeit with fewer items, to factor 1 of *TXP-A*, also labeled as affection and communication but excluding punishment and criticism. Furthermore, factor 1 of *TXP-C*, composed of only four items, does not correspond to the factor of control and structure, but would have the label prosocial values (education in values, expression of feelings, promotion of family and social relationships). The correlations show that the affect and communication factors of both questionnaires are the most closely related to each other, while the prosocial value factor of *TXP-C* is more closely related to the control and structure factor of *TXP-A*. It is rather striking that items reflecting discipline practices and the establishment of norms and limits are not included in *TXP-C*, with the closest to these dimensions being education in prosocial values. This could reflect the tendency that appears to exist Spain towards the use of a more permissive or forgiving parenting style (Fuentes et al., 2015), or that caregivers are affected more by social desirability when they talk about control and structure than when talking about affection and communication; thus making these items less reliable and coherent and more subject to social desirability when caregivers respond to them than when adolescents do (Oudhof, Rodríguez & Robles, 2012).

In addition to one of the factors differing in both questionnaires, *TXP-A* also includes many more items than *TXP-C*. Instead of eliminating those items not found in both versions or the two factors that do not match so that the two versions are identical, which would artificially inflate interrater reliability, we have chosen to keep them, since we believe that they can reflect real differences in the perception of parental socialization by parents and children, given the finding that the level of agreement between informants with the same role is greater than between those with different roles (Molinuevo, Pardo & Torrubia, 2011), and that parents and children have different perspectives on their relationships and behaviors (Rebholz et al., 2014). Indeed, there are authors who consider that these discrepancies provide important information about parent-child relationships and can directly affect the adjustment of the adolescent (Reidler & Swenson, 2012). Conversely, other authors choose to force the parallelism between both versions to allow comparisons between informants, while warning that this may suppose a loss of exploratory power (Molinuevo et al., 2011). Subsequent studies may evaluate whether maintaining these items and different factors provides relevant information for the development of CD and SRD.

Item analysis shows that all means except one are greater than 3, which indicates that they are 'easy' items, with the majority of the sample scoring high on them. This is logical given that ours is a general population with a low frequency of psychopathology. We consider that this will allow better discrimination between subjects without pathology and those who present SRD and CD when the questionnaire is applied to clinical samples. Most of the discrimination indices are greater than 0.25. It was decided to keep the six *TXP-A* items with the lowest discrimination index because they also have lower means than most items (indicating "worse" socialization), leading us to believe that while they may not discriminate well in the general population, they may do so in a clinical population. The means of the weighted and unweighted squared residuals are all less than 2 and greater than 0.5. In both versions, most items yield the recommended values of greater than 0.5 and below 1.2 (Wright, Linacre, Gustafson & Martin-Löf, 1994).

Regarding the psychometric characteristics of the questionnaire, the fit indices in *TXP-A* were satisfactory except for the minimum fit. However, we consider that the fit can be considered good since this index is very sensitive to the presence of kurtosis and also matches with the null hypothesis that the data fit the model 'perfectly', which is quite unlikely and makes this test very restrictive (Diamantopoulos and Siguaw, 2000). Although the RMSR and the GFI in *TXP-C* show good fit and the minimum adjustment can be justified by the above, the RMSEA is not satisfactory, and so adjustment to the data appears moderate. The percentages of total variance explained in both versions were similar to those found for the *ACPQ* in the Spanish population (Escribano et al., 2013). In both versions the questionnaire features high internal reliability and excellent test-retest reliability. The lowest internal reliability is yielded by the prosocial values factor of *TXP-C*, although it is similar to

that found in some *ACPQ* factors (Escribano et al., 2013). This lower internal reliability may be due to the low number of factor saturating items or, as mentioned previously, that the information from children regarding their perception of parenting habits is more reliable, coherent and less subject to social desirability than that provided by their parents (Oudhof et al., 2012).

While interrater reliability is low, it is similar to that found in other studies (Escribano et al., 2013). However, we believe that this low concordance between the perception of adolescents and that of their caregivers is not due to the quality of the questionnaire but to the real differences between parents and children when reporting parental socialization, as also revealed in other studies (Bersabé et al., 2001, González & Landero, 2012).

In terms of validity evidence, the multitrait-multimethod matrix shows adequate convergent and discriminant validity, since the highest correlation is found between factor 1 of *TXP-A* and factor 2 of *TXP-C* (both measuring affection and communication). The score on the affect-communication factor and the *TXP-A* total correlate significantly with all the variables of the *CAQ* except psychopathic deviation. The control-structure factor correlates significantly with all the variables except agitated depression, psychopathic deviation and psychasthenia. The lack of correlation with psychopathic deviation could be due to the fact that this dimension is especially influenced by genetic or endophenotypical aspects (Pardini, Raine, Erickson & Loeber, 2014) and less by parental socialization style, and because learning by punishment is modified in adolescents with psychopathic deviation (Salamone & Correa, 2012) or because this scale of the *CAQ* may not be well defined (Gómez, De Paz, Tejerina, Pérez & Luna, 2007). As assumed in hypothesis 2, all correlations go in the expected direction: the higher the questionnaire scores, the lower the levels of psychopathology.

In *TXP-C*, all significant correlations also go in the expected direction with regard to hypothesis 2, and both factors and the total score correlate significantly with the psychopathology variables, although less than in *TXP-A*. Additionally, the prosocial values factor of *TXP-C* only correlates significantly with three of the variables (suicidal depression, low energy depression and boredom-withdrawal), which seems to indicate that this variable may not be so strongly linked with psychopathology in general but with internalizing disorders and depressive symptoms in particular, in line with studies that find prosocial behavior to be a protective factor against depression (Llorca, Mesurado & Samper, 2014).

As in other studies, parental socialization variables are significantly related to personality variables (Castañeda, Garrido-Fernández & Lanzarote, 2012) measured by the *HSPQ*, probably reflecting the complex reciprocal relationships between the personality of the adolescent, their behavior, received parental socialization and their perception of parental socialization (Iglesias & Romero, 2009). However, *TXP-C* again presents fewer significant relationships, especially in the case of the prosocial values factor.

As regards evidence of criterion validity, in *TXP-A* factors 1 and 2 and the total score are related to the use of drugs and alcohol, and the questionnaire differentiates between those who have problems with drugs and alcohol and those who do not. In addition, the affect-communication factor and the total score are linked to dissocial disorder and differentiate between those with and without it. Both factors and the total score are related to the presence of oppositional defiant disorder, although the questionnaire does not differentiate between those with the disorder and those without it. This concurs with studies that find warmth and behavioral control associated with lower levels of behavior problems in adolescence (Trudeau et al., 2012), that less emotional warmth and greater parental rejection are associated with substance abuse, and that cohesion and adaptability are negatively linked to alcoholism (Abasi & Mohammadkhani, 2016). Other authors also find that parental control is a protective factor against alcohol abuse and other problems of adolescence (Cabanillas-Rojas, 2012).

In *TXP-C*, the affect and communication factor and the total score are related to the use of drugs and alcohol, although the questionnaire does not differentiate between those who have problems with drugs and alcohol and those who do not. The affect and communication factor and the total score are linked to dissocial disorder and the questionnaire differentiates between adolescents with this disorder and those without. However, the questionnaire and oppositional defiant disorder are not linked.

These data all support the claim that *TXP-A* measures what it was designed to do: parental socialization practices related to the presence of SRD and CD. In the case of the *TXP-C*, however, while the affect-communication factor does seem to show evidence of validity, the prosocial values factor is not related to SRD or CD. This may be due to the fact that the adolescent's perception of parental educational practices (linked to control-structure in *TXP-A* and prosocial values in *TXP-C*) is related more than that of the caregiver with psychopathology in general, CD and SRD (González & Landero, 2012); but it could also be that, since the adolescent also completes the *CAQ* and the *POSIT* and answers questions in the interview on CD, the correlation of these external criteria with the *TXP-A* is greater given that they are completed by the same informant (Molinuevo et al., 2011). Future studies could consider assessing CD and SRD from the caregiver's perspective to check whether the correlation increases or whether the result is repeated that the caregivers' perception of their socialization in prosocial values is not related to the presence of SRD and CD.

It should be noted that no differences were found in either of the two versions between those who presented oppositional defiant disorder and those who did not. This may be due to the scarcity in the sample of subjects with this diagnosis or to the fact that the questionnaire is designed with serious behavioral disorders in mind while oppositional defiant disorder is considered less serious than dissocial disorder (American Psychiatric Association, 2014); although the number of subjects in the sample with the latter is also low, differences are nevertheless found in the data. Since validation was performed with the general population, there are very few subjects in the sample with CD and relatively few with problematic use of drugs and alcohol. In addition, it could be that adolescents who did not participate in the study are precisely those who present more psychopathology and/or experience more dysfunctional parental practices. It would be interesting to conduct a validation study in the clinical population in order to better study which parental practices are more closely related to behavior problems and drug use. This would make longitudinal studies possible and thus allow cut-off points to be established for detecting subjects with a high risk of presenting CD and SRD, which in turn would permit the implementation of preventive interventions.

Finally, it should be pointed out that neither version of the questionnaire presents differential functioning to limit application since no biases are found by sex, school year, nationality and kinship with the caregiver. We believe the other differences in functioning that were found are not a limitation but rather reflect the logical relationship already described in the literature between family socialization variables and the other variables. Thus, with increasing age, the adolescent need structure, rules and limits less and less, while autonomy is encouraged (Oliva, 2006); the presence of a family history of alcoholism and drug dependence is associated with worse parental socialization (Slesnick, Feng, Brakenhoff & Brigham, 2014), and having more children in the family is related to a worse perception of emotional climate, perhaps due to less time available for the caregiver to spend on each child (Beltrán, 2013).

Limitations

The main limitation of the study is that no other parental socialization questionnaires were used to assess convergent validity. Apart from the limitations of those scales (Bersabé et al., 2001), most of them are designed to evaluate styles of parental socialization in general, while we were interested in an instrument that measured specific parental practices related to the presence of SRD and CD. Following Mâsse and Watts (2013), the general parenting style reflects the parental attitudes and beliefs that create the global emotional climate in which parent-child interactions take place; parenting style is described by typologies that classify parents on the basis of their levels of responsiveness and demandingness (authoritarian, democratic, permissive and negligent); while parenting practices are the specific strategies that parents use to achieve desired results. Although there are scholars who consider parenting styles to be more clearly linked to the psychosocial adjustment of children than parenting practices (García & Gracia, 2010), we consider it to be much more useful with a view to designing prevention and intervention strategies to measure the specific parenting practices related to the presence of disorders. Given that definitions of parenting factors in the literature lack consistency, frequently overlapping conceptually, they limit the understanding of which specific parenting strategies are effective in reducing substance use in adolescents (Ryan, Jorm & Lubman, 2010). Therefore, to improve research on the topic, it is necessary to establish well-defined and different parental variables with consistent assessment methods (Ryan et al., 2010).

One possible limitation is the dropout rate, since there is a possibility that adolescents who reject participation in the study are precisely those with greater psychopathology and that the caregivers who drop out of the study are those with less effective parental socialization practices. However, a 23% caregiver dropout rate is well below the 36% found in the study by Bersabé et al. (2001) and the 49.7% in the study by Molinuevo et al. (2011), and thus appears to be an acceptable percentage.

A further possible limitation is having focused the assessment of parental socialization only on the primary caregiver. This option was chosen for several reasons. Currently the number of single-parent households is increasing (Instituto Nacional de Estadística, 2016), making it inappropriate in some cases to ask for both parents. In addition, although most of the literature tends to focus on the socialization of the mother, fathers also play a significant role in the development of their children and, in many homes and cultures, other relatives, friends and caregivers also contribute to raising the children (Lomanowska, Boivin, Hertzman & Fleming, 2017). We believe that focusing on the person whom the adolescent considers their main caregiver optimizes the information, especially as the correspondence found between the educational styles of both parents has been low (Winsler, Madigan & Aquilino, 2005).

Another limitation is that, although both the perspectives of the adolescent and the caregiver were considered, the complex interactive relationships between the behaviors of both and the appearance and maintenance of CD and SRD were not taken into account. Parental socialization is a bidirectional transactional process, where adolescent behavior and psychopathology also change parental behavior (Kerr, Stattin & Özdemir, 2012). Structural equations could be used in future longitudinal studies to model these relationships.

The limitations of the study also include those linked to the use of self-report questionnaires: social desirability

bias, recall biases, limited awareness of one's own behavior and careless or random responses (Power et al., 2013).

Conclusions

TXP-C seems a reliable instrument without biases, but has yet to provide sufficient evidence of validity. The affect-communication factor seems to be related to psychopathology in general, CD and SRD; while the prosocial values factor is related only to depression and not to SRD and CD. Subsequent studies using CD and SRD assessment instruments and informed by the caregiver or third parties would make it possible to confirm these relationships of the affect-communication factor and whether the caregiver's perception of the prosocial values factor is related to adolescent SRD and CD or not.

TXP-A appears to be a reliable, valid and unbiased tool to measure the perception of parental socialization practices related to the appearance of CD and SRD in adolescents aged between 14 and 16. It is validated in the general population and it would seem relevant to validate it in other age groups and in the clinical population. The implementation of longitudinal studies with this instrument could make it possible to establish cut-off points for detecting populations at risk of developing CD and SRD, identifying parental practices more closely linked to CD and SRD, and focusing on preventive interventions.

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Conflict of interests

There are no conflicts of interest. The questionnaire is not subject to copyright restrictions and its use is free of charge.

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Setting the stage to quit smoking in Bipolar Disorder patients: brief advice in clinical practice

Preparando el escenario para dejar de fumar en el paciente con Trastorno Bipolar: intervención breve en la práctica clínica

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Abstract

Tobacco consumption is the main preventable factor of mortality in smokers with bipolar disorder (BD), and any possible solutions are often blocked by prejudices over desire, and the possibilities and risks for these patients in giving up tobacco consumption. Adults with BD were recruited at 8 Mental Health Centres. Smokers were evaluated before and after a brief intervention based on the 3 A's and classified into a 'Stage of Change' (SOC) and their 'Readiness to Change' (RTC). A multiple linear regression was used to analyze the progression in their RTC and the independent effect of different variables (pharmacological treatment, history of psychotic symptoms, current anxiety symptoms, willingness, self-perceived capacity to quit smoking and subjective perception of cognitive functioning). Of 212 stable patients diagnosed with BD, current smokers (n=101; 47.6%) were included in the intervention phase, and 80.2% completed it. At baseline, 75.2% were considering the idea of giving up smoking and, after the brief intervention, 30.9% of the patients progressed in their SOC. A significant increase in the level of RTC was observed (53.3 vs 59.3, P=0.019). Perception of cognitive performance (β=-0.35;P=0.002), the degree of willing to quit (β=0.32;P=0.008), self-perceived capacity to quit tobacco smoking (β=-0.30;P=0.012), the patient's age (β=-0.72;P=0.004), the age of onset of smoking (β=0.48;P=0.022) and years as a smoker (β=0.48;P=0.025) were all factors that significantly influenced the chances of improving after the short intervention. Smokers with BD consider the idea of quitting and a brief intervention developed in the every day mental health care setting improves the level of readiness. The neurocognitive dysfunction associated with BD may limit patients' readiness to quit smoking.

Keywords: Bipolar disorder; Tobacco; Smoking cessation; Brief advice; readiness to change.

Resumen

El consumo de tabaco es el principal factor prevenible de mortalidad en pacientes con trastorno bipolar (TB), y las posibles soluciones se encuentran bloqueadas por prejuicios acerca del deseo, posibilidades y riesgos al dejar el consumo de tabaco en estos pacientes. En 8 Centros de Salud Mental se reclutaron consecutivamente pacientes con TB. Los fumadores fueron evaluados antes y después de una intervención breve basada en las 3 As y clasificados según los "estadios de cambio" (EC) y su "disposición para el cambio" (DC). Mediante una regresión lineal múltiple se analizó la evolución del DC y su efecto sobre otras variables independientes (tratamiento farmacológico, historias de síntomas psicóticos, presencia de síntomas de ansiedad, deseo de abandono, capacidad auto-percibida y la percepción subjetiva de funcionamiento cognitivo). Se incluyeron 212 pacientes con TB estabilizados, los fumadores activos (n=101; 47.6%) pasaron a la fase de intervención, y un 80.2% la completaron. Basalmente, 75.2% consideraban la idea de dejar de fumar, después de la intervención breve, el 30.9% de los pacientes progresó en su EC. Se observó un incremento significativo del nivel de DC (53.3 vs 59.3, P=0.019). La autopercepción del rendimiento cognitivo (β=-0.35;P=0.002), el deseo de abandono (β=0.32;P=0.008), la autopercepción de la capacidad para dejar de fumar (β=-0.30;P=0.012), la edad del paciente (β=-0.72;P=0.004), la edad de inicio del tabaquismo (β=0.48;P=0.022) y los años fumando (β=0.48;P=0.025) fueron los factores que influyeron significativamente en la posibilidad de cambio tras la intervención breve. Los fumadores con TB consideran la idea de dejar de fumar y una intervención breve desarrollada en el marco de la atención a la salud mental diaria, mejoraría el nivel de preparación. La disfunción neurocognitiva asociada con el TB podría limitar la disposición de los pacientes a dejar de fumar.

Palabras clave: Trastorno bipolar; Tabaco; Abandono tabaquismo; Intervención breve; Disposición para el cambio.

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Mental disorders and poverty are currently the niche areas of tobacco consumption in Western populations (Schroeder, 2014). In patients with Serious Mental Illness (SMI), prevalence rates of tobacco use are two to four times higher than in the general population (Diaz et al., 2009). More than half of the patients with bipolar disorder (BD) smoke (Tidey & Miller, 2015; Jackson, Diaz, Lopez & de Leon, 2015) and tobacco is the substance of abuse they consume the most (George, Wu & Weinberger, 2012). They start smoking younger, smoke more intensely – consuming more per day and inhaling more deeply – and have a greater degree of nicotine dependence (Heffner, Strawn, DelBello, Strakowski &Anthenelli, 2011).

The mechanisms which may explain this increased prevalence are complex and may involve gene-environmental interaction (Gonzalez-Pinto et al., 1998). The choice of smoking as self-medication, a commonly-debated theory concerning patients with schizophrenia and depressive disorders (Al-Halabí et al., 2017), can apparently be ruled out in BD (de Leon, Diaz, Aguilar, Jurado & Gurpegui, 2006). Compared to BD non-smokers, BD patients who smoke present: more severe symptoms, a higher frequency of rapid cycling, greater risk of suicide, a greater number of hospital admissions (Heffner et al., 2011), a worse quality of life at a mental level (Gutiérrez-Rojas et al., 2008) and a cardiovascular and respiratory mortality rate which is double and triple, respectively, that of the general population (García-Portilla et al., 2010).

Tobacco use is the main preventable risk factor of mortality in this population (Callaghan et al., 2014), and with the increasing evidence of effective and safe of pharmacological and psychological treatments (Anthenelli et al., 2016; García-Portilla et al., 2016; Almadana et al., 2017), the literature stresses the need to address this problem in everyday psychiatric care (Prochaska et al., 2011).

Evaluating the subjects' willingness to change and taking steps to raise motivation and control the factors which limit it, are the first steps in any treatment plan for quitting. In BD, the first trials in smokers have begun recently (Weinberger, Krishnan-Sarin, Mazure & McKee, 2008; Wu et al., 2012; Chengappa et al., 2014; Evins, Cather & Laffer, 2015; Anthenelli et al., 2016; García-Portilla et al., 2016). These trials include patients who have expressed the desire to quit smoking but do not evaluate the initial motivation level specifically. So far, the main references have been from studies in patients with schizophrenia (Etter & Etter, 2004). Weinberguer et al. (2008) and Wu et al. (2012) were the first to report serious problems of recruitment since they could not find bipolar patients prepared to attempt to give up. Recently, however, members of our group have published results of a multi-component treatment in a clinical setting (Garcia Portilla et al., 2016), which puts the main emphasis on the preparation and motivation stage, before active treatment is started for schizophrenia and BD. (Prochaska et al. (2011)) An online survey in the USA revealed that of smokers with BD who had made an average of 4 previous attempts, up to 74% express willingness to quit smoking and only one third had been given a recommendation by their psychiatrist (Prochaska et al., 2011).

Although there are multiple theories to explain the concept of motivation and changes in behaviour (Miller, 2011), the Transtheoretical Model (TTM) developed by Prochascka and DiClemente (1983) has been the reference model for addictions. The TTM algorithm in the Stages of Change (SOC) and the Contemplation Ladder, (Biener & Abrams, 1991) have been the most commonly used scales, in the few studies that have analyzed motivation levels for quitting smoking in people with mental disorders (Siru, Hulse & Tait, 20094). The TTM has been the most widely used tool in research into smoking cessation and recognizes the SOC as starting, transit or arrival points in the process, to which a predictive value of the possibilities of change can be added (Chou et al., 2015). Despite the popularity of the TTM, the debate remains open about whether to use the SOC classification, based on arbitrary cut-off points, or to calculate a 'Readiness to Change' index (RTC) (Ceccarini, Borrello, Pietrobissa, Manzoni & Castelnuovo, 2015).

Success in giving up smoking is proportional to the intensity of the intervention (Fiore & Panel, 2008), but in the first objective of generating motivation, the brief interventions using the 5 A's (Ask, Advice, Assess, Assist and Arrange) and the 3 A's (Ask, Advice and Assess) have been shown to be cost-effective in the general population (Rice & Stead, 2008) and have been endorsed by clinical practice guidelines (West, McNeill & Raw, 2000). The EPA (European Psychiatry Association) guidance on smoking cessation strategies (Rüther et al., 2014) recommends trying out these interventions in smokers with mental illness. In SMI patients, so far only DiClemente et al. (2011) have evaluated the intervention with 5 A's, and point out the importance of the number of repetitions of the first three A's in the long-term possibilities of success in SOC (DiClemente et al., 2011). In BD patients, although the possibilities of the brief intervention are not known, perhaps the first objective of the 3 A's intervention would be to try to increase the smoker's level of readiness through the different stages of motivation for change (precontemplation, contemplation, and preparation).

On the other hand, BD is associated with persistent neurocognitive deficits across the broad domains of sustained attention, verbal memory and prefrontal/executive cognition, which in turn are major predictors of patients' functional outcomes (Vieta et al., 2013). Moreover, neuropsychological status is related to decision making and attitudes such as motivation for lifestyle changes: neurocognitive dysfunction may therefore decrease the chances of progress on a motivation level (Baune & Malhi, 2015). In the same way, the anxiety symptoms present in over 50% of patients with BD (Goes, 2015), among other factors which

increase comorbid addictions (Cazard & Ferreri, 2013), worsen the prognosis, require specific treatment and could influence the possibilities of this type of intervention.

The community care environment available to this population offers advantages through the frequency of contacts, the credibility of the health professionals and the regular advice given. Despite these advantages, we are faced with a serious health problem and cost-effective interventions such as the brief 3 A's intervention could serve to identify the level of motivation and raise initial willingness to quit among smokers with BD.

Aims of the study

(1) to describe and quantify the prevalence of smoking and how it is currently dealt within a representative sample of Bipolar Disorder patients studied in a community environment; (2) to learn the level of motivation of smoking bipolar patients, based on Transtheoretical Model; (3) to evaluate the effectiveness of the brief intervention that Asks, Advises and Assesses (3 A's) to raise the patient's motivation level; and (4) to identify the socio-demographic, clinical or smoking variables that may influence the chances the intervention has of success.

Methods

Design and settings

The multi-centre study was conducted according to a mixed design including: (1) a cross-sectional, observational and descriptive study performed at the baseline visit and (2) a post-intervention design, in which patients who were identified as smokers at the baseline visit were given a brief anti-smoking intervention over three sessions.

The study lasted 6 months and was carried out in 8 Mental Health Centres of 4 provinces of Andalusia, in southern Spain (Cordoba, Granada, Jaen and Malaga). The study was given the approval of the Research Ethics Committee of the Reina Sofia University Hospital in Cordoba.

Subjects

Recruitment according to ICD-10 criteria (1992) was carried out consecutively-when attending their scheduled review appointments-among adult patients with BD (18-65 years old) who were clinically stable and attended their scheduled review appointments. Clinical stability and the absence of suicidal behaviour in the 6 months before commencing the study were assessed by the patient's usual psychiatrist. All of them signed to give their informed consent for their data to be used in the study database.

In addition, the patients who were current smokers (1 cigarette or more a day) at the recruitment appointment were invited to participate in the pre- and post-intervention evaluation (Figure 1).

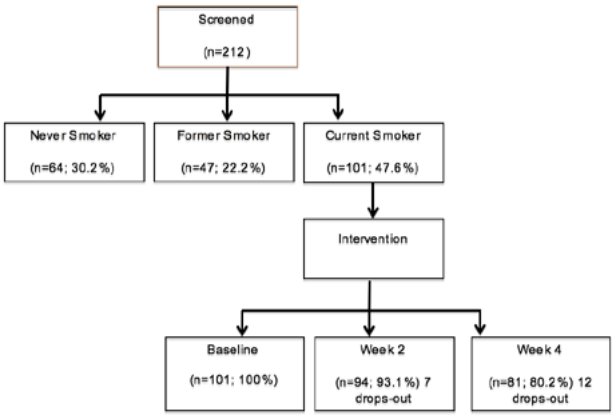

Fig. 1. Recruitment of the subjects and disposition after intervention.

Measurements and outcomes

The total sample was subdivided into 3 groups according to their smoking habits (current smoker, former smoker and never-smoker). Socio-demographic and clinical data were collected from all of them.

Current smokers were assessed using the following instruments at the baseline visit:

The Hamilton Anxiety Scale (HARS) (Hamilton, 1959) was used to assess whether the patient suffered from anxiety symptoms. This scale is hetero-administered by a clinician after an interview in which 0 to 4 points are scored for each item, which assess both intensity and frequency of anxiety symptoms. There are no cut-off points, and a higher score indicates a greater intensity of anxiety.

Fagerström's Nicotine Dependence Test (FTND) (Fageström, 1978) the modified version of this scale (Heatherton, Kozlowski, Frecjer & Fageström, 1991), is hetero-administered and consists of 6 items which evaluate nicotine dependence. The scores are divided into: below 4 (low dependence), 4 - 7 (moderate dependence) and over 7 (high dependence) on nicotine.

The Visual Analogic Scale (VAS) from 0 to 10 was used to measure patients' perceived desire and self-perceived capacity to quit smoking, because its predictive value equivalent to scales with multiple items (Gwaltney, Metrik, Kahler & Shiffman, 2009).

The URICA (University of Rhode Island Change Assessment) (Di Clemente et al., 1991) is a 32-item self-report scale that includes 4 subcategories measuring the stage of change (SOC) based on Prochascka's TTM. Items are rated on a 5-point Likert scale ranging from 1 (strong disagreement) to 5 (strong agreement). The Spanish version of the scale (Gómez-Peña et al., 2011) has shown adequate internal consistency both globally and in each of the 4 sub-scales (between 0.69 and 0.89). Two possible means of evaluation have been described: a) discrete measurements where the highest score ranks the patient on a particular SOC and b) a continuum in which the subscales are combined arithme-

tically (Contemplation + Action + Maintenance - Precontemplation) to produce a second order continuous score which can be used to assess Readiness to Change (RTC). Subjects completed the URICA as a way of carrying out the third A (Assess) at baseline (URICA 1) and week 4 (URICA 2), thus giving us two continuous measurements for RTC. The difference between the two was the main variable for the analysis (RTC_{2-1}).

The COBRA, disfunción cognitiva en el trastorno bipolar (Rosa et al., 2013), is a 16-item questionnaire that measures BD patients' perception of cognitive deficits in several areas, such as: executive functions, processing speed, working memory, learning and verbal memory and attention/concentration. Responses are given on a 3-point Likert scale ranging from 0 (never limited) to 3 (always limited). The total score is a result of the sum of the items. We have used the Spanish version, with a Cronbach's alpha of 0.913.

Intervention

A brief motivational intervention to quit smoking was carried out based on the idea of the 3A's (Ask -Do you smoke?, Advice –Advise the patient to quit in a clear, firm and personalized way, Assess -Would you be willing to quit smoking next month?) discussed above (Rice & Stead, 2008), distributed over 3 sessions (baseline, week 2 and week 4) lasting no more than 10 minutes each and with a total duration of 30 minutes. The first and last contacts were conducted face-to-face and the contact at week 2 by phone. At baseline and at week 4, the 3A's were completed, using URICA to measure the readiness to quit, while the phone interview was used to reinforce the advice given in the baseline intervention. To minimize any inter-observer differences, the three interventions were carried out by the same professional (psychiatrist or nurse) in each centre.

Statistical Analyses

Statistical analysis was performed using the SPSS program (version 15.0). Dimensional variables and frequencies were compared by parametric or non-parametric tests, as appropriate. Continuous variables were analyzed by analysis of variance (ANOVA) or Student *t* tests, and categorical variables by chi-square or Fisher´s exact tests. Relationships between variables were expressed as Pearson's product-moment *(r)* or Spaerman rank-order (r_s) correlations. Multiple linear regression, using the conditional back procedure, was used to analyse the independent effect of each variable (pharmacological treatment, history of psychotic symptoms, current anxiety symptoms, willingness, self-perceived capacity to quit smoking and subjective perception of cognitive functioning), and the change of RTC after the intervention. For this reason we calculate a new variable (RTC after the intervention minus RTC before: RTC_{2-1}), the fundamental dependent variable. The multivariate models include the statistically significant variables in the bivariate analysis or those of special clinical relevance. The statistical significance level was set at $P<0.05$.

Results

Of 212 patients diagnosed with BD, 101 (47.6%) were current smokers and were included in the intervention phase. Of the remaining patients, 47 were former-smokers and 64 had never smoked. Table 1 shows the socio-demographic, and clinical data of the three groups (smokers, former smokers and never-smokers). On comparing these three groups, we found some differences: the intervention group (current smokers) contained a higher proportion of male patients, patients whose marital status either separated or divorced, unemployed and disabled patients and patients with a comorbid psychiatric disorder. We found no differences as regards level of education, length of illness, presence of psychotic symptoms or pharmacological treatment received (Table 1).

Eighty one patients (80.2%) from the intervention group completed the follow-up. All non-completer cases were due to subjects expressing their wish to abandon the study. We found no statistically significant differences between those who had completed the intervention and those who did not, in the variables analyzed (socio-demographic, clinical and smoking history, SOC, RTC, dependence and anxiety level, self-perception capacity to quit and cognitive function).

In those patients who were current smokers, 80.2% of them had never been offered a specific anti-smoking treatment during the years of follow-up at their mental health centre and 62.1% had never been asked about their smoking habits. In the 'former smokers' group, 75% reported that they had given up smoking without specific treatment and 81.8% reported no clinical worsening of their illness in any way after giving up smoking (this measures were patients self-reported).

In the intervention group, the mean age at onset of smoking behaviour was 18.9 years (SD 7.1), with a mean consumption of around 18.1 cigarettes per day (SD 11.2) for 28.5 years (SD 10.5). 16.8% of these smokers had high nicotine dependence (FTND> 7). 80.2% of the current smokers had tried to quit smoking with an average of 2.7 attempts (SD 2.5), and had achieved an average of 11.8 months without smoking (SD 21.4). The clinical and tobacco use variables are summarized in Table 2.

In the VAS, smokers obtained a score of 6.2 in their willingness to quit smoking (SD 3.4), and 4.7 on their self-perceived capacity of quitting (SD 3.1). In the URICA scale evaluation of level of motivation performed in the first contact (URICA 1), 17 (16.8%) of our patients were in the pre-contemplative phase, 76 (75.2%) in the contemplative phase and 8 (7.9%) in the action stage. 30 days after completing the brief intervention (URICA 2), 30.9% of

Table 1. *Description of the sample*

	Current Smoker (101; 47.6%)	Former Smoker (47; 22.2%)	Never smoker (64; 30.2%)	Statistical test, *p*
Mean Age (sd)	47.5 (9.8)	49.7(8.2)	50.7(11.1)	2.159[1]. 0.118
Gender [n (%)]				
Male	45(56.2)	21(26.2)	14(17.5)	10.056[2]. **0.007**
Female	56(42.7)	25(19.1)	50(38.2)	
Marital status [n (%)]				
Never married	28(54.9)	8(15.7)	15(29.4)	11.295[2]. **0.023**
Married or cohabiting	35(36.5)	25(26.0)	36(37.5)	
Widowed or separated/divorced	36(61.0)	12(20.3)	11(18.6)	
Educational level [n (%)]				
Without formal studies	8(42.1)	2(10.5)	9(47.4)	6.753[2]. 0.344
Primary school	41(47.1)	17(19.5)	29(33.3)	
Secondary school	33(51.6)	15(23.4)	16(25.0)	
University	18(43.9)	13(31.7)	10(24.4)	
Work status [n (%)]				
Unemployed	22(51.2)	10(23.3)	11(25.6)	16.074[2]. **0.013**
Working (full/part-time)	24(55.8)	9(20.9)	10(23.3)	
Disabled (temporary/permanent)	46(51.7)	21(23.6)	22(24.7)	
Others*	9(24.3)	7(18.9)	21(56.8)	
Diagnosis [n (%)]				
Bipolar disorder I	62(45.3)	26(19.0)	49(35.8)	6.087[2]. **0.048**
Bipolar disorder II	38(51.4)	21(28.4)	15(20.3)	
Comorbid disorder [n (%)]				
Anxiety disorder	16(55.2)	2(6.9)	11(37.9)	13.996[2]. **0.030**
Personality disorder	14(60.9)	2(8.7)	7(30.4)	
Substance use disorder	8(72.7)	3(27.3)	0(0)	
Length of illness, months [Median (range)]	162(536)	168(416)	170(468)	0.731[1]. 0.483
Psychotic symptoms, yes [n (%)]	68 (50.4)	31(23.0)	36(26.7)	2.000[2]. 0.368
Treatment, yes [n (%)]				
Mood stabilizers	88(48.9)	37(20.6)	55(30.6)	2.224[2]. 0.329
Antipsychotics	75(47.8)	35(22.3)	47(29.9)	0.050[2]. 0.975
Antidepressants	37(46.2)	16(20.0)	27(33.8)	0.950[2]. 0.622
Benzodiazepines	53(47.3)	21(18.8)	38(33.9)	2.653[2]. 0.265
Hypnotics	19(51.4)	7(18.9)	11(29.7)	0.381[2]. 0.827

Note. *Other includes housewife, student and retired.
1. ANOVA test, 2. Chi-square test.

Table 2. *Current smokers, baseline clinical and smoking characteristics (n=81)*

	Media	(SD)
HAM-A	13.6	10.4
COBRA	13.0	9.5
Self-reported CPD	18.1	11.2
FTND	4.9	2.6
Willingness to quit tobacco smoking	6.2	3.4
Self-perceived capacity to quit tobacco smoking	4.7	3.1
RTC 1	53.3	25.9
RTC 2	59.3	25.9
RTC2-1	7.1	22.5
Number of attempts	2.7	2.5
Mean duration of attempts in months	11.9	21.4

Note. SD: Standard deviation; COBRA: Cognitive complaints in bipolar disorder rating assessment; FTND: Fagerström Test for Nicotine Dependence HAM-A: Hamilton anxiety rating scale. CPD: Cigarettes per day.

Table 3. *Multiple linear regressions of factors associated with change in Readiness to change after the intervention (RTC2-1) in current smokers (n=81)*

Variables	Coefficient of partial correlation (β) t_{exp}		valor *P*
Readiness to change*			
Age (years)	- 0.72	- 2.96	0.004
Length of smoking (years)	0.58	2.28	0.025
Age at onset of smoking behaviour (years)	0.48	2.34	0.022
Willingness to quit tobacco smoking	0.32	2.71	0.008
Self-perceived capacity to quit tobacco smoking	- 0.30	- 2.57	0.012
COBRA cognition scale score	-0.35	-3.28	0.002

Note. *Coefficient of determination (adjusted R2) = 0.16, F = 3.38, df = 1, 74, P =0.003.

patients had advanced in their SOC; 7 (8.6%) were in the pre-contemplative phase, 53 (65.4%) in the contemplative phase and 21 (25.9%) in the action stage (Figure 2). Baseline SOC assessed by the 'Readiness to Change' (RTC) continuous quantitative variable showed a significant increase from 53.3 at the beginning, to 59.3 after completing the intervention ($P = 0.019$).

A multiple linear regression model with the number of years that the patient had been smoking, the age at onset of smoking behaviour and the willingness to quit smoking all linked with a greater evolution of the RTC. Moreover, using the total score of the COBRA scale, the variables that were associated with a lower progress on the RTC were age, self-perceived capacity for quitting smoking and subjective cognitive status (Table 3).

Discussion

Concurring with previous results in BD (Diaz et al., 2009; Tidey & Miller, 2015), we found smoking rates that doubled those published in the general population and the recurrent alerts in the literature about the passivity of the patient's normal health care environment have been confirmed (Evins et al., 2015).

Within the conceptual framework of stages of motivation and change process, and for the first time in BD, this study of an anti-smoking intervention conducted in a community setting shows that a low-intensity intervention based on the 3A's has a significant impact on the level of motivation for change in patient who smoke - independently of the degree of tobacco consumption. The subjective perception of the neurocognitive functioning predicted the chances of progress after the intervention.

The 30.9% of the smokers increased their SOC and there was a significant increase in the RTC index - both measurements are based on the Transtheoretical Model of Behaviour Change (Prochaska & DiClemente, 1983). This type of intervention, strongly supported in the literature for generating motivation and attempts to quit smoking in general populations (Rice & Stead, 2008), has been scarcely studied in SMI patients who smoke and to date, there is no specific works referring to BD. Di Clemente et al. (2011) reported how up to 60% of patients with psychotic disorders make progress in their SOC when followed up over a year, with a scheduled intervention using the 5 A's. In addition, patients exposed to more frequent repetition of the first 3 A's were the ones that progressed most at this stage.

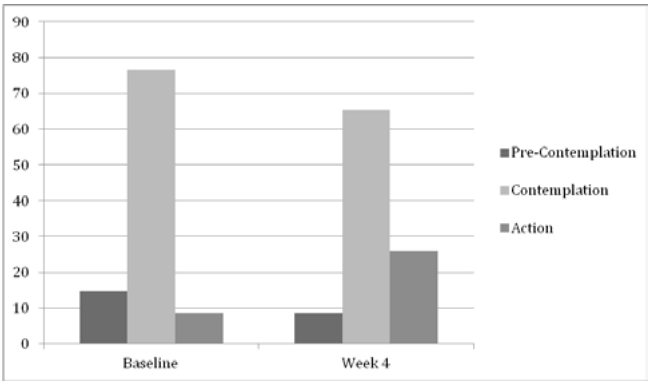

Fig. 2. Motivational stages (before and after the intervention) measured by URICA scale in the intervention group (%).

The level of willingness to quit smoking expressed at the beginning of the intervention, having started smoking later in life and having smoked for more years were the variables that independently predicted a greater advance in readiness to give up after the intervention. These variables also predict the possibilities of a first attempt to give up in the general population (West et al., 2015). It showed that the younger the patient at the time of the intervention, the greater the evolution in the level of readiness. This, in theory, goes against what is usually published in the health advice given to the general population, where older people tend to be more receptive to these kind of interventions (Zolnierek & Dimatteo, 2009; Marín, Gil & Romero, 2017), but does concur with the favourable characteristics of a recently-published study on first attempt in smokers (Sharma & Szatkowski, 2014). Despite the fact that the psychiatric population has been less receptive to the campaigns to reduce smoking than the general population, those who are younger – who may feel less stigmatized and have failed on fewer occasions - may in fact benefit from them more and be more receptive to the kind of intervention mentioned above. Those smokers who expressed a higher level of self-capacity for change at the start of the intervention improved their level of readiness less. While recognizing the value of self-perceived capacity as a predictor of attempting to give up (Borland et al., 2010), we may assume that in a sample of BD where many of the patients are asked for the first time about their tobacco use and wishes, the self-capacity expressed may have an unrealistic value and offer little insight into the true depth of their problem. This is similar to the conclusion reached in the meta-analysis of smokers from the general population (Gwaltney et al., 2009), where self-capacity was evaluated prior to the attempt to quit.

A greater perception of functional limitation at the neurocognitive level meant that less progress could be made on the level of readiness. Regarding cognition, the present findings are difficult to interpret, since no previous study has examined the potential role of neurocognitive status to predict either changes in motivation or quitting smoking. Some indirect evidence, however, may be extrapolated from studies of smokers with schizophrenia or without psychiatric disorders. In a set of placebo-controlled clinical trials, baseline dysfunction, as measured by sustained attention, spatial working memory and executive cognition, has been associated with the failure of smoking cessation treatment in smokers with schizophrenia seeking treatment

(Moss et al., 2009). It is worth noting that schizophrenia and BD share a core neurocognitive dysfunction, with high rates of comorbid nicotine dependence and low rates of smoking abstinence. In other clinical populations, cognitive impairments decreased response to treatment among subjects with marijuana or cocaine dependence (Aharonovich, Brooks, Nunes & Hasin, 2008). Moreover, the key cognitive predictors of attaining abstinence in smokers without psychiatric disorders are also sustained attention, working memory and executive functioning (Ashare, Falcone & Lerman, 2014). Since the prefrontal cortex is involved in all these cognitive deficits, it represents a potential target for the development of pharmacological and psychological therapies aimed at treating cognitive deficits. In turn, targeting prefrontal-related dysfunctions may enhance the success rates for giving up smoking in all these populations and possibly also in BD.

In our study, the impact generated was independent of gender, the number of cigarettes per day and the dependency level. In the results found by DiClemente et al (2011), women progressed less than men over one year, and this result was also independent of tobacco consumption and dependence. The literature leaves no room for doubt about the prognostic value of the dependence level on the rates of initial cessation and possible recurrences (Japuntich et al., 2011). Even so, the results we obtained from a BD sample seem coherent with an intervention designed to be carried out in large target populations, with the aim of generating a first approach to the motivation level without specifying the gender or the severity of the smoking addiction (Kruger, O´Halloran, Rosenthal, Babb & Fiore, 2016).

The results of the URICA scale, which positions the patient in a SOC or quantifies an RTC value and its evolution, have a predictive value regarding the possibilities of a treatment designed to break the habit (Chou et al., 2015). Moreover, this is the first study to specifically assess SOC in bipolar smokers. Our results confirm that up to two-thirds of the patients asked about their habit in a normal psychiatric care setting are placed in the contemplation stage, which means that they plan to quit in the next 6 months and therefore could be target patients for intensive treatments. These results are higher than those described in samples of patients with schizophrenia (DiClemente et al., 2011) and, as noted in the age factor, they certainly give us an insight into the greater permeability in BD for changes in tobacco consumption that have occurred in recent years in the general population.

The motivation to change when suffering an addiction plays a key role in recognizing the problem and finding solutions. Although it is urgent to know the level of motivation in this population of smokers and generate steps to increase it, how to quantify the level of motivation and its progress over time remains as a challenge. The concepts of SOC and RTC and their quantification through the URICA scale constitute a key option in addiction research, but it also has its drawbacks (DiClemente, Schlundt & Gemmell, 2004). Understanding motivation from the SOC allows us to position the patient and provides a model by which we can observe the process of change; however, quantifying it in discrete stages or as a continuum also generates debate (DiClemente & Prochaska, 1998). In tobacco addiction, a specific stage or a figure for readiness does not determine a specific treatment, but as has been stressed above, it has a predictive value about the possible success of the behaviour of change.

Considering the representativeness of the sample studied and its development in the real environment of community care, our study may illustrate the real chances of success of administering the brief anti-tobacco intervention in BD patients and shows that it can be a simple, cost-effective first step which paves the way for more specific interventions which would aim at producing change. In any case, we must be aware of the difficulty of the problem being addressed and controlled studies with larger samples are needed as a first step to confirm the effectiveness of this type of intervention in clinical practice, and as a way to assess objectively the influence of factors such as cognitive performance. We evaluated neurocognitive factors by means of a validated survey, the COBRA questionnaire. Nevertheless, subjective perception of neurocognitive functioning does not always correlate with objective performance on neuropsychological tests and this remains a matter of debate (Miskowiak et al., 2016). Future studies should use formal neuropsychological batteries to confirm or refute the results of this study.

Finally, identifying predictors of motivation/abstinence in further studies of smokers with BD may help devise novel treatments for nicotine addiction. Interventions such as cognitive and functional remediation have proved to be effective in BD (Torrent et al., 2013). Moreover, from a public health perspective, smoking cessation programs aimed at patients with BD could take into account the potential limiting effects of neurocognitive dysfunction to enhance their motivation to quit smoking.

Conflict of interest

V.B.-M. has received grants and served as consultant, advisor or continuing medical education (CME) speaker during the last 5 years for the following entities: Angelini Spain, Angelini Portugal, AstraZeneca, Bristol-Myers-Squibb, Ferrer, Janssen. Juste, Lundbeck, Nutrición Médica, and Otsuka. JA Alcalá-Partera has served as advisor to: Adamed, Lundbeck, Otsuka, Janssen-Cilag, Pfizer, Rovi y Servier; and as speaker to: Janssen-Cilag, Pfizer y Servier. L. Gutiérrez-Rojas has been speaker for and advisory board member of Bristol-Myers Squibb, Janssen-Cilag, Astra-Zeneca, Rovi, Lundbeck, Otsuka, GSK and Pfizer.

All other researchers report no biomedical financial interests or potential conflicts of interests.

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Impulsivity and problem awareness predict therapy compliance and dropout from treatment for gambling disorder

Impulsividad y conciencia del problema predicen la adherencia terapéutica y el abandono del tratamiento en el trastorno por juego de azar

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Abstract

This study investigates the predictive value of impulsivity traits (as measured by the UPPS-P impulsive behaviour scale) and relevant covariates (sociodemographics, gambling severity, dysphoric mood, other potentially addictive behaviours, and non-verbal intelligence) with regard to treatment dropout and level of adherence to therapy guidelines and instructions in patients with gambling disorder. Sixty-six patients seeking treatment for gambling disorder, and recruited to participate in a larger protocol (G-Brain), were initially assessed in impulsivity traits and relevant covariates in the first six months after admission. Of these, 24 patients dropped out (DO) and 42 patients remained in therapy (NDO) during the subsequent 6-month follow-up period. A multivariate analysis of impulsivity subscales suggested prospective differences between DO and NDO, with affect-driven dimensions (positive and negative urgency) seemingly driving these differences. Among these, only positive urgency independently predicted a slight increase in the drop-out probability. In the NDO group, a higher degree of adherence to therapy was independently predicted by lower sensation-seeking scores and stronger awareness of gambling-related problems. Results suggest the presence of affect-driven impulsivity traits as dropout predictors in patients with gambling disorder. Awareness of gambling-related problems and lower sensation-seeking enhanced compliance with therapeutic guidelines and instructions.

Key words: Gambling disorder; Treatment; Impulsivity; Positive urgency; Sensation seeking; Awareness.

Resumen

Este estudio investiga el valor predictivo de la impulsividad como rasgo (evaluada con la escala de conducta impulsiva UPPS-P) y de covariados relevantes (variables sociodemográficas, severidad del juego de azar, estado de ánimo disfórico, otras conductas adictivas e inteligencia no verbal), con respecto al abandono del tratamiento y los niveles de cumplimiento de las prescripciones terapéuticas en pacientes con trastorno por juego de azar. Sesenta y seis pacientes con este trastorno, participantes del proyecto G-Brain, fueron evaluados inicialmente en impulsividad rasgo y en los covariados mencionados. Dicha evaluación se realizó durante los seis primeros meses desde el inicio de su tratamiento. En el seguimiento realizado a los 6 meses, 24 pacientes habían abandonado (grupo ABD) y 42 continuaban el tratamiento (grupo NABD). Los análisis multivariados con las subescalas de impulsividad mostraron diferencias prospectivas entre ambos grupos. Aparentemente, estas diferencias son atribuibles a las dimensiones afectivas de impulsividad (urgencias positiva y negativa). Entre ambas dimensiones, solo la urgencia positiva fue un predictor independiente de un ligero incremento en la probabilidad de abandono. Dentro del grupo NABD, un mayor grado de adherencia terapéutica vino predicho, de manera independiente, tanto por una baja búsqueda de sensaciones como por una mayor conciencia de los problemas vinculados al juego. Estos resultados sugieren que los rasgos de impulsividad de origen afectivo son predictores de abandono del tratamiento en pacientes con trastorno por juego. La conciencia de problemas asociados al juego de azar y una baja búsqueda de sensaciones predisponen a una mayor adherencia a las prescripciones terapéuticas.

Palabras clave: Trastorno de juego de azar; Tratamiento; Impulsividad; Urgencia positiva; Búsqueda de sensaciones; Conciencia.

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Gambling disorder (GD) is characterized by the inability to reduce or eliminate excessive participation in games of chance involving monetary stakes, in spite of severe negative consequences (American Psychiatric Association, 2013). Its prevalence in adolescent and adult populations ranges from 0.4% to 7.6%, (including both land-based and online gambling modalities, and depending on the sample age, variability of tools and methods, and the stringency of clinical significance thresholds), with an average worldwide prevalence of 2.2% (Jiménez-Murcia, Fernández-Aranda, Granero & Menchón, 2014). The currently recommended therapeutic approaches present a premature dropout rate around 30% (Aragay et al., 2015; Melville, Casey & Kavanagh, 2007).

At present, there is an almost unanimous agreement on considering GD a behavioral addiction (Leeman & Potenza, 2012; Petry, 2010); a consensus not yet reached for other putative behavioral addictions (Chacón-Cuberos et al., 2018; Martín-Fernández et al., 2017). Nonetheless, there is also evidence of a high level of individual variability among patients with GD (Albein-Urios, Martinez-González, Lozano, Clark & Verdejo-García, 2012; Blaszczynski & Nower, 2002; Steward et al., 2017), which is likely to determine differential responses to treatment (Aragay et al., 2015; Chu & Clark, 2015; Melville et al., 2007).

Impulsivity and course of gambling disorder treatment

A number of studies have tried to identify contextual or individual measures that can predict treatment outcomes. For example, Weinstock et al. (2011) concluded that sociodemographic factors, gambling severity, indebtedness, and the level of coercion exerted by legal and social networks predict treatment acceptance/reluctance. Gambling patterns (Pickering, Keen, Entwistle & Blaszczynski, 2018), comorbidities (Maniaci et al., 2017), and interpersonal support (Jiménez-Murcia et al., 2017) have also emerged as valuable indices of treatment course and outcomes.

Here we focus on impulsive personality –the proneness to carry out rash, non-premeditated acts– and its potential value for predicting dropout and compliance with the therapist's advice during treatment. Related evidence converges in showing that: (1) impulsive people are more likely to develop future gambling problems (Secades-Villa, Martínez-Loredo, Grande-Gosende, y Fernández-Hermida, 2016; van Holst, van den Brink, Veltman & Goudriaan, 2010; Vitaro, Brendgen, Ladouceur & Tremblay, 2001); (2) patients with GD with high levels of impulsivity are more likely to prematurely terminate treatment (Leblond, Ladouceur & Blaszczynski, 2003; Maccallum, Blaszczynski, Ladouceur & Nower, 2007); (3) impulsivity is linked to increased psychopathological comorbidity, including other addictions (Grall-Bronnec et al., 2012; Petry, 2010); and (4) impulsivity correlates with GD severity (Billieux et al., 2012).

Impulsivity is however better understood as a multidimensional construct (Cyders & Smith, 2007; Evenden, 1999). Recent factorial models distinguish between a *conscientiousness-planning* factor, reflecting the integrity of top-down executive mechanisms, a *reward seeking* factor, characterized by the subjective overvaluing of reinforcement (despite possible negative consequences), and a *negative emotionality dysregulation* factor (Knezevic-Budisin, Pedden, White, Miller & Hoaken, 2015; Sharma, Markon & Clark, 2014).

Customary psychometric tools rely on factorial analyses of responses to self-report items to idendify the components of impulsive behavior. In this regard, the UPPS-P model of impulsive behavior (Cyders et al., 2007; Whiteside, Lynam, Miller & Reynolds, 2001) has been shown to be advantageous over other impulsivity assessments, based on its discriminative capacity and correspondence with dissociable psychobiological systems (Rochat, Billieux, Gagnon & Van der Linden, 2017). In spite of their undeniable theoretical value, alternative assessment methods, based on neuropsychological or decision-making tasks (see, for example, Torres et al., 2013a, 2013b), have yielded very modest associations with self-report tools even in very large samples (Cyders et al., 2011; MacKillop et al., 2016), and, to date, there is not a battery of tasks of this sort that can be considered as an overarching and time-efficient alternative to assess impulsivity as a multidimensional construct (Stahl et al., 2014).

According to the UPPS-P model, impulsivity is composed of (1) *positive* and (2) *negative urgency*, representing the tendencies to lose control under positive and negative emotions, respectively; (3) *lack of premeditation*, the tendency to make decisions without taking consequences into consideration; (4) *lack of perseverance*, the inability to remain focused on a demanding task; and (5) *sensation seeking*, the predisposition to try new and exciting activities. Convergent validity analyses suggest that urgencies respond to a combination of emotional reactivity and executive dysregulation; lack of premeditation and perseverance mostly overlap with the conscientiousness/planning factor; and sensation seeking reveals a tendency for seeking reward in novel and exciting activities (Cyders & Smith, 2007; Sharma et al., 2014).

Among UPPS-P dimensions, negative urgency emerges as the clearest marker of severity in clinical levels (Billieux et al., 2012), although positive urgency and sensation seeking have also been observed to predict severity in treatment-seeking gamblers (Savvidou et al., 2017). Here, however, our interest is focused on the relationship between UPPS-P dimensions and treatment outcomes. To our knowledge, no previous studies have investigated the putative relationship between impulsivity, assessed in

a multidimensional manner, and adherence/dropout during treatment.

Still, some related evidence allows us to make substantive predictions. On the one hand, at least two studies have focused on the possible link between constructs largely overlapping with sensation seeking and treatment dropout (Aragay et al., 2015; Jiménez-Murcia et al., 2012). These studies did not directly investigate impulsivity, but personality as assessed by the TCI questionnaire (*Temperament and Character Inventory*, Cloninger, Svrakic & Przybeck, 1993). Both of them reported one of these dimensions (*novelty seeking*) to predict dropout. Relatedly, a recent study (Mestre-Bach et al., 2016) has showed high scores in a trait also related to impulsivity and sensation seeking (reward sensitivity) to be associated with an increased probability of treatment dropout, but not disorder severity, occurrence of relapses, or treatment compliance. In view of this evidence, UPPS-P sensation seeking arises as a candidate to predict dropout.

On the other hand, given the connection of negative urgency with addictive behaviors via altered emotion regulation and dysfunctional coping skills (Adams, Kaiser, Lynam, Charnigo & Milich, 2012), a significant contribution of negative urgency to poor adherence and treatment dropout seems highly plausible.

Aims and clinical implications

To date, most studies either have failed to consider other measures of adherence beyond permanence in treatment, or have not explicitly distinguished between dropout and compliance (Melville et al., 2007). In Aragay et al. (2015), therapeutic compliance was not explicitly assessed. In Mestre-Bach et al. (2016), dropout was not considered when computing the number of relapses (making relapse and dropout somewhat confounded), and compliance was analyzed dichotomously (good vs. poor). To our knowledge, only Jiménez-Murcia et al. (2012) have assessed compliance (in 3-point good/fair/poor scale) separately from dropout. As noted earlier, in this study, an association was found between novelty seeking and dropout, but no significant predictors were identified for therapy compliance.

The aims of the present study are as follows: (1) to estimate the degree to which UPPS-P dimensions predict dropout from psychological treatment (in the six months following the initial assessment), taking into account several potential confounders; and (2) to test if these variables further predict the degree of compliance with therapeutic tasks and recommendations, specifically in those patients who remain in treatment.

Results potentially have direct clinical relevance. Changes in the gambling market associated with the emergence of new gambling modalities are posing a serious challenge for clinicians and rehabilitation services. As we have shown elsewhere (Navas et al., 2017, 2018), new gamblers also present distinct psychological traits, and clarifying the prognostic value of such traits is a necessary step for tailoring treatment (Raylu & Oei, 2016).

Method

Participants

Sixty-six patients in treatment for GD [2 females, recruited from the Asociación Granadina de Jugadores de Azar en Rehabilitación (AGRAJER), a mutual help association based in Granada, Spain] participated in this study. As part of their admission protocol, all patients underwent a semi-structured interview based on DSM-IV for axis I and II disorders with their therapist, comprising all the necessary information to check for exclusion criteria. GD diagnosis was established by the therapist on the basis of such an interview, and was confirmed by a score equal to or above 5 on the South Oaks Gambling Screen (SOGS, Spanish version; Echeburúa, Báez, Fernández-Montalvo & Páez, 1994).

Inclusion criteria were: (1) a GD diagnosis; (2) having been in treatment for less than 6 complete months. Exclusion criteria were: (1) suffering any comorbid DSM-IV psychiatric disorder; and (2) any history of neurological disease or brain damage (as reported by the participant). Participants potentially suffering comorbid disorders or with a history of neurological damage were not invited to participate in the study. Signs of problematic alcohol or drug use were further assessed using the MultiCAGE CAD-4 clinical screening questionnaire (Pedrero Pérez et al., 2007).

Procedure

Initial assessment. The initial assessment session lasted approximately three hours. It comprised several self-report questionnaires and neuropsychological tests, some of which are not directly relevant to the aims of this study, as were part of a larger protocol (G-Brain research project, PSI2013-45055-P), and have been described elsewhere (see, for example, Navas et al., 2017; Navas, Verdejo-García, López-Gómez, Maldonado & Perales, 2016; Perales, Navas, Ruiz de Lara, Maldonado & Catena, 2017).

Importantly, given the characteristics of the treatment center, and the restricted availability of patients, it was not always possible to complete the initial assessment immediately after admission. In all cases, the initial assessment took place in the six first months of treatment. More specifically, this assessment took place in the first month of treatment for twenty-two patients, in the second month for twenty, in the third month for eight, in the fourth month for three, in the fifth month for seven, and in the sixth month for six (see average time in treatment in Table 1).

Follow-up. Six months after the initial assessment (and thus in all cases still within the first year of treatment), the

patients' therapist was contacted again in order to collect information on the occurrence or non-occurrence of dropout and/or treatment compliance (see treatment compliance in the instruments section). Based on that information, the original sample was divided into two groups: 24 patients who dropped out from treatment (DO), and 42 patients who did not drop out from treatment (NDO). Descriptive statistics for the two groups are displayed in Table 1 (upper panel).

Instruments

Severity of gambling and other problematic behaviors.

South Oaks Gambling Screen (SOGS, Lesieur & Blume, 1987; Spanish version, Echeburúa et al., 1994). This 20-item questionnaire is aimed to assess gambling severity, indebtedness, and dependence. It has adequate psychometric properties, and is the most widely used tool in GD research. Only the global severity score was used in the present study.

MultiCAGE CAD-4 (Pedrero Pérez et al., 2007). This screening tool consists of a series of dichotomous items checking for the current self-perceived presence of problems associated with poor impulse control in several domains (including gambling and alcohol and illegal drug use). In the present study we used only the gambling, alcohol, and drug subscales, all of which have been reported to have good psychometric properties. The remaining subscales (excessive internet and videogame use, disordered eating, hypersexuality, and compulsive buying) are not relevant for the aims of the present study.

Estimated non-verbal intelligence. A non-verbal Intelligence Quotient (IQ) was estimated using the matrix reasoning task from the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008).

Impulsivity. The *UPPS-P* brief impulsivity scale (Spanish version, Cándido, Orduña, Perales, Verdejo-García & Billieux, 2012) comprises 20 Likert-type items aimed at assessing negative and positive urgency, sensation seeking, lack of premeditation and lack of perseverance.

Dysphoric mood. Subclinical signs of poor mood were assessed by using the *Beck Depression Inventory–II* (BDI-II; Spanish version, Sanz, Perdigón & Vázquez, 2005). The BDI questionnaire was included in the protocol when some participants had been already assessed. That said, BDI data are missing for a total of 4 patients, all of whom were in the NDO group.

Treatment compliance. Treatment compliance in NDO patients was defined considering (1) attendance to therapeutic activities (e.g., group sessions); and (2) task completion and fulfillment of the therapist's guidelines for daily life functioning (e.g., keeping diaries up to date, not drinking alcohol). The therapist's records were used to assess all patients on a five-point scale, on which 5 meant full attendance and fulfillment, 4 meant attendance and fulfillment above 50%; 3 meant attendance above 50%, but a fulfillment of task and recommendations below 50%; 2 meant attendance and fulfillment of task and recommendations below 50%; and 1 attendance below 50% and nearly complete disregard of tasks and recommendations. Compliance level was assessed independently by two judges (second and fourth authors), with a concordance of r = 0.952. In the cases in which the judges' assessments did not match, the discordance was resolved by mutual agreement. Among the 42 patients who did not drop out from treatment, 6 scored five points, 13 four points, 14 three points, 7 two points, and 2 one point.

Treatment characteristics

All participants followed the same treatment protocol, with the same therapist, and in the same facilities. This treatment is similar to the treatment implemented in other facilities belonging to the same Regional Federation as AGRAJER [*Federación Andaluza de Asociaciones de Jugadores de Azar en Rehabilitación (FAJER)*]. Treatment is mostly based on groups of mutual help –complemented with professional supervision and individual cognitive-behavioral therapy– and lasts for approximately two years. Features and stages of treatment are described in supplementary materials S1.

Ethical standards

Procedure of this study complies with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and was approved by Ethics Committee for Human Research of the University of Granada (Spain), as part of the PSI2013-45055-R research project. All participants were informed about study's objectives and signed informed consent.

Statistical analyses

Dropout analyses. In order to describe differences between the NDO and DO groups, we first ran between group t-tests on sociodemographic and control variables. This analysis was carried out to identify possible confounders before analyzing between-group differences on impulsivity measures.

Secondly, we ran a multivariate analysis of variance/covariance (MANOVA-MANCOVA) on the five UPPS-P subscales. In case potential confounders were identified, these were intended to be included in the MANCOVA as covariates. A significant between-group multivariate effect was planned to be followed by variable-by-variable t-tests, in order to identify where the global multivariate effect originated. For all t-tests, p-values and Bayes factors are reported.

Third, variable-by-variable analyses were complemented with a stepwise logistic regression analysis, with group membership as the dependent variable (NDO vs DO) and

impulsivity dimensions as predictors. This analysis was carried to test whether any of the impulsivity variables differing between the two groups predicted group membership independently of the others.

Compliance analyses in the NDO group. Fourth, for the NDO group only, we ran bivariate correlation analyses to estimate relationships between sociodemographic/control variables and the compliance measure. Again, these analyses were carried out to identify potential confounders to be considered in subsequent steps.

And lastly, impulsivity measures, along with potential confounders, were entered into a stepwise regression analysis of compliance. This was complemented with a Bayesian Regression analysis, to identify the most predictive combination of factors (including impulsivity measures and potential confounders), and the individual contribution of each of those factors therein.

Bayesian analyses and simple t-tests were carried out with JASP statistical software (http://jasp-stats.org). Bayesian analyses were performed with default software settings. MANOVA/MANCOVA and logistic regression analyses were run on SPSS 20.0 (IBM Corp, 2011).

As there were only 2 female participants in our sample, all analyses were run with and without them. Results were virtually identical in all cases, so we found no reason to exclude them. Reported results correspond to the whole sample.

Results

Group comparability checks

No significant differences were observed between DO and NDO groups in sociodemographic and control variables (Table 1, upper panel). Of particular importance is the corroboration that the two groups were well matched in duration of treatment at the moment of the initial assessment. Given that assessment was more delayed for some participants than for others, differential attrition prior to the first assessment could have unbalanced this variable in favor of one of the two groups. Matching thus ensures between-group comparability despite inter-individual differences in the moment of the initial assessment. Additionally, Bayes factors are consistently below 1 for all potential confounders, and below 1/3 in some cases, which indicates a good general matching between the two groups.

Due to slight changes in the form used to collect sociodemographic information during the study, age of gambling onset was available for only 49 participants. Of these, 17 were in the DO group and 32 in the NDO group. These two subgroups were far from substantially differing in onset age [mean (SD) 21.61 (7.69) and 19.47 (5.72), for NDO and DO subgroups, respectively, $t(47)=1.01$, $p=0.32$, $BF_{10}=0.45$]. Complementarily, we had data on gambling modality preference (type I vs type II games, as defined in Navas et al., 2017) for 65 participants. A Chi-squared test on the relationship between preferences and dropout was also non-significant [$\chi^2(1)=1.475$, $p=0.225$].

Dropout

In view of the absence of potential confounders among the variables under consideration, no covariates were included in the subsequent multivariate analysis of impulsivity measures. The corresponding MANOVA yielded a main multivariate effect of group [Wilks' $\lambda=0.823$, $p=0.035$, $\eta^2_p=0.177$]. Variable-by-variable t-tests (Table 1, lower panel) yielded significant differences in positive and negative urgency between the two groups. The logistic regression model correctly classified 62.10% of participants (see Table 2), with positive urgency as the only predictor in the final model.

It is important to take into account, however, that according to Bayes factors, t-tests on specific impulsivity dimensions portray only anecdotal evidence in favor of the alternative hypothesis. Significant p-values should thus be interpreted cautiously, as they are merely suggestive of the specific location of effects on general impulsivity, in the case that there are any.

Compliance

In the correlation analysis in the NDO group, compliance positively correlated with WAIS matrix reasoning score, the gambling subscale on the MultiCAGE CAD-4 questionnaire (MC-gambling), and BDI (Table 3). Gambling preferences (type I vs type II) did not significantly influence compliance [$t(63)=-0.63$, $p= 0.532$]. In other words, compliant patients had better reasoning abilities, presented a worse mood state, and regarded their gambling as more troublesome.

The stepwise linear regression analysis with these three factors and UPPS-P scores yielded significant effects for UPPS-P sensation seeking and MC-gambling score, with the former inversely predicting compliance and the latter positively predicting it (Table 4). As noted above, due to BDI data loss, there were 4 participants missing from this analysis. So, we re-ran it without BDI scores. Results from this analysis were qualitatively identical but notably neater [Adjusted $R^2=0.308$, $p<0.001$; MC-gambling: $\beta=0.470$, $p<0.001$; Sensation seeking: $\beta = -0.330$, $p=0.015$].

These regression analyses were complemented with Bayesian regression modeling. As reported in Table 5, the model with the highest Bayes factor (31.73 relative to the null model), and thus best accounting for data, included UPPS-P negative urgency and sensation seeking, and MC-gambling. However, the three factors contributed differently to the model's predictive fit. The Bayes factor of the best model, relative to the equivalent ones without each of the three of factors, was 1.22, 4.65, and 49.57, when removing negative urgency, sensation seeking, and MC-gambling, respectively. In accordance with the standard regres-

Table 1. *Independent Sample t-tests and Bayesian t-tests on sociodemographic, control variables and impulsivity (UPPS-P) variables.*

	NDO	DO			
	Mean (SD)	***Mean (SD)***	**t**	***p***	***BF_{10}***
Sociodemographic and control variables					
Age	37.67 (11.33)	33.92 (10.46)	1.330	0.188	0.546
Years of education	12.86 (4.55)	12.42 (2.38)	0.440	0.661	0.283
Months in treatment	2.85 (1.72)	2.36 (1.34)	1.193	0.237	0.473
Matrix reasoning (WAIS-IV)	96.31 (14.86)	99.17 (14.42)	-0.759	0.450	0.332
BDI Dysphoric mood	9.92 (8.62)	12.13 (8.48)	-0.987	0.328	0.398
SOGS Severity	10.43 (3.26)	10.38 (3.54)	0.062	0.950	0.261
MC Gambling	3.07 (0.89)	2.75 (0.94)	1.377	0.173	0.576
MC Alcohol	1.14 (1.37)	0.79 (1.22)	1.042	0.301	0.411
MC Drugs	0.52 (1.04)	0.42 (0.93)	0.418	0.678	0.280
UPPS-P					
Negative Urgency	2.73 (0.72)	3.10 (0.69)	-2.047	**0.045**	1.481
Positive Urgency	2.48 (0.59)	2.78 (0.53)	-2.061	**0.043**	1.516
Sensation Seeking	2.14 (0.66)	2.46 (0.91)	-1.647	0.104	0.808
(Lack of) Premeditation	2.19 (0.73)	2.28 (0.64)	-0.508	0.614	0.290
(Lack of) Perseverance	1.97 (0.68)	1.81 (0.64)	0.929	0.356	0.374

Note. Abbreviations: NDO = No dropout group; DO = dropout group; MC = MultiCAGE CAD-4. Significant tests are marked in bold.

Table 2. *Results from the forward logistic regression analysis for group membership (no dropout [NDO] vs dropout [DO]).*

Dependent variable	Variables included	Variables excluded	$-2\Delta LL$	*Wald*	*p*	*N-R^2*
NDO vs DO	*Positive urgency*		4.285	3.882	**0.049**	0.086
		Negative urgency *Sensation seeking* *Lack of premeditation* *Lack of perseverance*				

Note. p values for significant tests are indicated in bold. $-2\Delta LL$: -: -2 log-likelihood change for positive urgency inclusion in the model; *N-R^2*: Nagelkerke's R^2.

Table 3. *Therapy compliance correlations with sociodemographic and control variables in the no-dropout group.*

	Therapy compliance	
	r	***p***
Age	0.053	0.737
Years of education	0.175	0.269
Gambling onset age	0.058	0.752
Months in treatment	0.190	0.228
Matrix reasoning (WAIS-IV)	0.392	**0.010**
Dysphoric mood (BDI)	0.366	**0.024**
Gambling severity (SOGS)	-0.042	0.792
MC Gambling	0.482	**0.001**
MC Alcohol	-0.132	0.403
MC Drugs	-0.007	0.964

Note. p values for significant tests are indicated in bold. Abbreviations: MC = MultiCAGE CAD-4. For instruments details, see text. The correlation between gambling onset age and therapy compliance was performed on the 32 participants of the NDO group for whom these data were available.

Table 4. *Results from the stepwise linear regression analysis for therapy compliance scores in the no dropout group.*

Variables included	Variables excluded	β	*t*	*p*	*Adj. R²*
MC Gambling		*0.465*	*3.311*	*0.002*	*0.272*
Sensation seeking		*-0.319*	*-2.274*	*0.029*	
	Matrix reasoning				
	Dysphoric mood				
	Negative Urgency				
	Positive Urgency				
	Lack of Premeditation				
	Lack of Perseverance				

Note. p values for significant tests are indicated in bold. MC: MultiCAGE CAD-4. See text for details of the measures.

Table 5. *Results from the Bayesian linear regression analysis regarding therapy compliance in the no dropout group.*

Models	P(M)	P(M|data)	BF_M	BF10
Null	0.004	$9.095 \cdot 10^{-4}$	0.232	1
MC Gambling +Negative Urgency + Sensation Seeking	0.004	0.029	7.576	31.725
MC Gambling +Sensation Seeking	0.004	0.024	6.172	25.982
MC Gambling	0.004	0.009	2.442	10.429
MC Gambling +Negative Urgency	0.004	0.006	1.591	6.817
Negative Urgency + Sensation Seeking	0.004	0.000582	0.148	0.64

Note. P(M): prior probability of the models. P(M|data): posterior probability of the models given data. BF_M: model Bayes factors. BF10: model Bayes factors, relative to the null. The model performing best is marked in bold.

sion analysis described above, whereas the models with and without negative urgency performed almost equally well (so negative urgency contributed very modestly to model predictive fit), the contributions of sensation seeking and MC-gambling were substantial and strong (as indicated by Bayes factors above 3 and 10, respectively).

Discussion

Existing research has identified a number of individual variables that influence the risk of discontinuing therapy before completion (e.g., Ramos-Grille, Gomà-i-Freixanet, Aragay, Valero & Vallès, 2013), as well as some therapy features that increase or decrease clinical efficacy (e.g., Cowlishaw et al., 2012; Jiménez-Murcia et al., 2015). However, to our knowledge, none of these studies performed a detailed assessment of the different dimensions of impulsivity as predictors of dropout and therapy compliance, while controlling for potential confounders. Our results add upon the evidence that individual features determine patients' reaction to therapy (Billieux et al., 2012; Blaszczynski & Nower, 2002; Ledgerwood & Petry, 2006).

First, our results suggest that affect-driven dimensions of impulsivity discriminate between patients continuing and discontinuing therapy (DO and NDO). However, on the basis of theoretical relationships between negative urgency and key emotion regulation processes (see Billieux et al., 2012; Clark et al., 2012; Michalczuk, Bowden-Jones, Verdejo-Garcia & Clark, 2011), we had predicted this dimension to strongly and independently predict dropout. Although we found some evidence suggesting that negative urgency was higher in the DO group, that effect was explained away by positive urgency.

Aragay et al. (2015) and Jiménez-Murcia et al. (2012) had reported novelty seeking to predict dropout. The partially corresponding measure in the present study, sensation seeking, failed to discriminate between DO and NDO patients. However, sensation seeking and novelty seeking are not fully overlapping constructs (Cloninger, 1991; Cyders & Coskunpinar, 2011), and, most importantly, novelty seeking and positive urgency encompass similar appetitive motivational processes. This is consistent with the link between dropout and reward dependence we have observed in treatment for other addictions (López-Torrecillas, Perales, Nieto-Ruiz & Verdejo-García, 2014)

If confirmed, a potential predictive superiority of positive urgency relative to other reward-related dimensions of impulsivity could arise from the fact that urgency is more heavily weighted by control-related and executive processes (Billieux, Gay, Rochat & Van der Linden, 2010; Cyders & Smith, 2008; Dir, Karyadi & Cyders, 2013; Grall-Bronnec et al., 2012). Indeed, recent studies have identified two different pathways in which impulsivity might have an impact on potentially addictive behaviors. The first would involve the weakness of self-regulatory systems, and the second, an overreaction of automatic-affective systems (Lannoy, Billieux & Maurage, 2014). Our results suggest that these same two paths might also be involved in the risk of early therapy dropout in GD. Both motivation to continue gambling (driven by the rewarding properties of gambling activities), and inability to regulate behavior under the influence of emotions generated by such appetitive

motivators, might interfere with motivation to stay in treatment. Nonetheless, it is important to keep in mind that the difference between groups in positive urgency, although significant, portrayed little evidence of an actual effect. As noted earlier, any interpretation of this effect must be made cautiously.

With regard to therapeutic compliance in patients who did not abandon therapy during the follow-up period, results are more straightforward. Considered together, higher intelligence, depressive mood, more severe self-perceived gambling status, and lower sensation seeking scores positively correlated with compliance with the therapist's advice and instructions. In other words, not only do appetitive motives seem to increase the probability of discontinuing therapy, but also some degree of dysphoria seems to facilitate adherence in patients who do not abandon treatment.

Sensation seeking was the only impulsivity dimension predicting non-compliance, and, somewhat unexpectedly, higher scores on the MultiCAGE CAD-4 independently enhanced compliance. Tentatively, this relationship can be accounted for by awareness of the negative consequences of excessive gambling. In fact, the four MultiCAGE CAD-4 gambling-related items assess the presence of craving, feelings of guilt, recognition of having deceived others, and acknowledgement of family, financial or work problems. At least three of these items can contribute to a heightened perception of gambling disutility (and therapy utility), especially if we take into account that the MultiCAGE CAD-4-compliance link was found only in the less complicated cases of patients who had remained in therapy. This interpretation is compatible with previous reports that drug and alcohol users with higher scores in the CAGE questionnaire for alcohol abuse (the antecessor of MultiCAGE CAD-4: Mayfield, McLeod & Hall, 1974), and more severe perceived drug-related problems, as assessed by CAGE-inspired measures, are more likely to seek treatment (Ferri, Gossop, Rabe-Hesketh & Laranjeira, 2002).

Clinical implications

The present study identifies two possible targets that therapists should take into consideration when treating patients with GD. First, the inability to manage emotions seems to block early therapeutic efforts, which implies that emotion regulation should be addressed in the initial phases of treatment (Jiménez-Murcia et al., 2015). And second, sensation seeking could interfere with therapists' efforts to make negative consequences of gambling evident to patients. In fact, motivational factors have been proposed to bias gambling-related cognitions, as predicted by motivated reasoning models (Navas et al., 2016). In consequence, problem awareness could be sensitive to metacognitive training strategies (Mansueto et al., 2016).

Relatedly, the emergence of new types of gamblers is posing a serious challenge for treatment providers. Aspects of impulsivity related to reward and positive affect (positive urgency and sensation seeking) seem prevalent in at-risk and pathological users of new gambling devices and venues (Barrault & Varescon, 2016; Goldstein et al., 2016). Our results suggest that current prevalent treatments are probably more likely to fail with these patients, and the cause of such an increased risk of failure is more readily attributable to patients' psychological characteristics than to their gambling preferences *per se*.

Finally, the present study is also a call for caution for therapists treating GD patients. Early dropout precludes availability of feedback on the efficacy of therapy in complicated cases, namely those with the poorest emotion regulation abilities. There is some risk that the feedback the therapist receives on the efficacy of treatment is inflated by early information loss (Einhorn & Hogarth, 1978), as pre-post changes attributed to therapy tend not to take early dropout into consideration.

Limitations and strengths

The present study presents some limitations that should be taken into account. First, the initial assessment was not always carried out as soon as the patient was admitted to therapy. As noted above, some patients had been in treatment for up to six months before assessment. This delay in the assessment of some of the patients opens the possibility that some early dropouts were never detected, and thus were not included in this study. Although this fact could somewhat limit generalizability, DO and NDO groups did not differ in their treatment duration when they were initially assessed. It also is important to address that the follow-up assessment only included dropouts occurring during the first year of a two-year treatment protocol. This could imply that the variables identified could be predictive of relatively early outcomes, but not later ones. Results regarding later treatment stages (currently in progress) will be released in future works.

The second limitation relates to the fact that participants received a specific therapy protocol, so results do not necessarily generalize to patients receiving other forms of therapy. In the present case, the fact that therapy was provided by a mutual help association introduces a number of characteristics (for example, the presence of non-professional co-therapists, or the possible occurrence of confrontations between members of the association) that are not present in more standard forms of cognitive-behavioral therapy.

And finally, the study sample size is limited by the inflow of new patients in the treatment center where the study was carried out during a reasonable window of time. Underpowered samples could be liable for some potential

predictors not reaching significance, particularly in the regression analysis in the NDO group.

Still, the main strengths of this study are, first, the effort to control for sociodemographic and intellectual prowess variables, quite often disregarded in prospective studies; and second, the assessment of compliance, in a careful, quasi-quantitative way, and independently of dropout; and third, its potential clinical relevance.

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Conflict of interest

All the authors declare that they have no conflict of interest.

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S1. Supplementary materials
Treatment Characteristics

All participants followed the same treatment protocol, with the same therapist, and in the same facilities (AGRAJER). This treatment is similar to the one offered by other associations that make up the Regional Federation *Federación Andaluza de Asociaciones de Jugadores de Azar en Rehabilitación* (*FAJER*). The mean duration of the complete treatment program is approximately two years. The specific techniques used in the program are based on the cognitive-behavioral model.

The treatment protocol comprises 4 phases. In the first (1 session, *Pre-welcome*) the prospective patient has his/her first contact with the institution and a welcome session is scheduled. In the second phase (1 session, *Welcome*), two co-therapists (a rehabilitated gambler and a relative) welcome and encourage the patient to accept treatment. Sessions in the third phase (*self-help* and *mutual help*) are group-based, and comprise preliminary, start, and actual rehabilitation stages. Sessions in this stage are programmed on a weekly basis, hosted by rehabilitated gamblers and supervised by a professional therapist. Partially in parallel, a fourth stage (*individual psychotherapy*), is held by the AGRAJER clinical psychologist. Individual intervention has a psychoeducational theme, and is designed to assess the evolution of the patient in therapy in order to allow him/her to become more aware of the addictive process and its symptoms, to teach strategies to prevent relapse, to examine cognitive distortions in gambling, to strengthen self-esteem, social abilities, and assertiveness, to train him/her in anger management, self-control and problem-solving, and to promote rewarding activities. It generally takes one year for the patients to advance through these three stages, in dependence of goals fulfillment.

After this stage, abstinent patients who had not abandoned the group are discharged and start a final, follow-up stage. Patients in this stage meet once a month for an hour and a half. Patients can attend these meetings as long as they like to, as their objective is reinforcing abstinence and providing tools to manage risky situations that could lead to relapse.

In the present study, recruitment and the first assessment were carried out while patients were in the welcome phase or during the initial part of the self-help and mutual-help phase.

Empirical validation of the CRAFFT Abuse Screening Test in a Spanish sample

Validación empírica del CRAFFT Abuse Screening Test en una muestra de adolescentes españoles

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Abstract

The CRAFFT Substance Abuse Screening Instrument, developed by the *Center for Adolescents Substance Abuse Research* (CeASAR) (Knight et al., 1999), is a screening tool for high-risk alcohol and drug risk consumption designed for use with adolescents. Since its publication it has been the subject of translations and validations in different countries, populations and contexts that have demonstrated its enormous potential. However, there is still no empirical validation study that would ensure its good psychometric performance in Spain. The aim of this paper is to develop an adapted version of the CRAFFT in Spanish and to analyze its psychometric properties in a sample of Spanish adolescents. For this purpose an individual interview was conducted on 312 adolescents aged between 12 and 18 years of age (M = 15.01; SD = 1.83) from the Galician community. The interview included a part of the Adolescent Diagnostic Interview (ADI) and the Problem Oriented Screening Instrument for Teenagers (POSIT). The results obtained, similar to those found in other countries, allow us to report that the Spanish version of the CRAFFT has a good psychometric behaviorproperties. It was found to have a satisfactory internal consistency with a Cronbach's alpha value of .74. In terms of sensitivity and specificity, values of 74.4% and 96.4% respectively, were obtained and the area under the ROC curve was .946. The Spanish version of the CRAFFT is made available to researchers and professionals in the field of addictive behaviors, so that it can be used with the necessary psychometric guarantees.

Key words: Adolescents; Alcohol; CRAFFT; Screening; Drugs.

Resumen

El *CRAFFT Abuse Screening Test*, desarrollado por el *Center for Adolescents Substance Abuse Research* (CeASAR) (Knight et al., 1999), es una herramienta de cribado del consumo de riesgo de alcohol y otras sustancias diseñada para su uso con adolescentes. Desde su publicación ha sido objeto de numerosas traducciones y validaciones en diferentes países, poblaciones y contextos que han dado cuenta de su enorme potencial. No obstante, seguimos sin disponer de estudios de validación empírica que garanticen su adecuado comportamiento psicométrico en España. El objetivo del presente trabajo consiste en desarrollar una versión adaptada del CRAFFT en castellano y analizar sus propiedades psicométricas en una muestra de adolescentes españoles. Para ello, se realizó una entrevista individual a 312 adolescentes de entre 12 y 18 años (*M* = 15,01; *DT* = 1,83) de la comunidad gallega, que incluyó una parte de la *Adolescent Diagnostic Interview* (ADI) y del *Problem Oriented Screening Instrument for Teenagers* (POSIT). Los resultados obtenidos, similares a los encontrados en otros países, permiten informar que la versión española del CRAFFT presenta un buen comportamiento psicométrico. A nivel de consistencia interna se obtuvo un a de Cronbach satisfactorio de ,74. En cuanto a la sensibilidad y especificidad se obtuvieron unos valores del 74,4% y el 96,4% respectivamente, con un área bajo la curva COR de ,946. Por lo tanto, queda a disposición de investigadores y profesionales del ámbito de las conductas adictivas la versión española del CRAFFT, para que pueda ser utilizada en adelante con las garantías psicométricas necesarias.

Palabras clave: Adolescentes; Alcohol; CRAFFT; Cribado; Drogas.

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The *CRAFFT Substance Abuse Screening Test* (Knight et al., 1999) is one of the most widely used tools to screen for high-risk use of alcohol and other drugs among adolescents (Mitchell et al., 2014). So much so that its use is recommended in Alcohol Screening and Brief Intervention for Youth: Practitioner's Guide (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2011) and by the American Academy of Pediatrics in its Policy Statement : "Substance use screening, brief intervention, and referral to treatment for pediatricians" (Committee on Substance Abuse, 2011).

This quick and easy-to-use instrument was developed in Boston by the Center for Adolescent Substance Abuse Research (CeASAR) (Knight et al., 1999) to aid early identification of children and young people under 21 at high risk of developing an alcohol or drug use disorder. It consists of 6 dichotomous response (yes/no) items, preceded by 3 additional items acting as filters, scored 1 or 0 depending on whether the adolescent responds affirmatively or not. The scoring range of the scale is from 0 to 12, with 2 being the cut-off point established by its original authors (Knight, et al., 1999) to identify high-risk consumption.

The data revealed in the latest National Survey of Drug Use in Secondary Education [ESTUDES 2014-2015] (Plan Nacional sobre Drogas, 2016) highlights the need for detection instruments for use with adolescents. Despite a decline in levels of drug use over recent years, prevalence figures remain high. Of students between 14 and 18, 76.8% drank alcohol in the last year (68.2% in the last month), while 31.4% reported smoking tobacco in the last year (25.9% in the last month) and 25.4% admitted using cannabis (18.6% in the last month). The other substances recorded in the study, such as cocaine, ecstasy, amphetamines or hallucinogens have much lower prevalence figures of below 3%.

These levels of consumption still remain high today, and two other issues that concern both professionals and researchers must be added. The first has to do with the early age at which adolescents start drug use. For example, according to ESTUDES data for 2012-2013, the onset age for alcohol was 13.9 years of age, for tobacco 13.6 and cannabis 14.9. At the European level, the latest report by the *European School Survey Project on Alcohol and Other Drugs* (ESPAD) (ESPAD Group, 2016) states that of students aged 16-18, 47% started drinking, 23% smoking tobacco and 3% using cannabis before the age of 14. The available empirical evidence shows that the age at which adolescents begin to use different substances is not a trivial issue (Cadaveira, 2009; Fontes et al., 2011). In addition, a change in the pattern of alcohol use among the youngest has been observed for some years now (Calafat & Juan, 2003; Sánchez, Moreno, Rivera & Ramos, 2015). The drinking of large quantities of alcohol in short periods of time, known as binge drinking, is a serious social health problem with clearly negative consequences (DeCamp, Gealt, Martin, O'Connell & Visher, 2015; López-Caneda et al., 2014; Moure et al., 2014; Parada et al., 2011).

The fact that prevalence figures for the use of different substances, as well as for binge drinking, are still high, coupled with earlier onset ages (Cortés, Espejo & Giménez, 2007; Golpe, Isorna, Barreiro, Braña & Rial, 2017) only reinforces the need for the early detection of the use of alcohol and other drug. This makes it essential to have screening tools which, in addition to being adapted to Spain and having proven psychometric properties, are quick, simple and easy to use with an increasingly younger population. The CRAFFT has certain advantages that make it a particularly useful tool in this context. Firstly, it is a very easy instrument to apply given the small number of items it comprises. Secondly, its widespread international implementation and the rich tradition of validation studies in different countries, contexts and populations account for its good psychometric properties. Finally, it is an instrument that has formed an integral part of existing prevention plans and strategies, having been implemented in programs for early detection and brief intervention (SBIRT, Screening, *Brief Intervention and Referral to Treatment*) (Committee on Substance Abuse, 2011; Harris, Louis-Jacques & Knight, 2014; Pilowsky & Wu, 2013).

Since its publication, the CRAFFT has been widely translated and validated in different countries, populations and contexts. With regard to internal consistency, a review of numerous papers reveals somewhat modest values, with Cronbach's α coefficients which in some cases do not reach .70 (Bertini et al., 2015; Knight, Sherritt, Shrier, Harris & Chang, 2002; Skogen, BØe, Knudsen & Hysing, 2013; Wartberg, Kriston, Diestelkamp, Arnaud & Thomasius, 2016). In terms of its screening capacity, the CRAFFT can be seen as having adequate psychometric properties (Dhalla, Zumbo & Poole, 2011), with generally high sensitivity and specificity indices (Gryczynski et al., 2015; Kandemir et al., 2015; Knight, Sherritt, Harris, Gates & Chang, 2003; Pereira, Schram & Azevedo, 2016). However, in studies that also include predictive values, one of the four indicators usually has a poorer result (Cook, Chung, Kelly & Clark, 2005; Kelly, Donovan, Chung, Cook & Delbridge, 2004; Knight et al., 1999), and it is important to note that methodological differences between the studies, such as the use of different standard criteria, produce some uncertainty in the interpretation of these properties. Regarding the factor structure of the CRAFFT, the unidimensionality of the scale has been shown in different studies (Subramaniam, Cheok, Verma, Wong & Chong, 2010; Wartberg et al., 2016).

Regarding the existence of versions of the scale in Spanish, up to three different versions can be found. The CRAFFT website offers a translation into Spanish by the authors of the scale themselves, and there are two different ver-

sions adapted for Columbia (Cote-Menendez, Uribe-Isaza & Prieto-Suárez, 2013; Perez & Scoppetta, 2011). In all three cases the wording of the items is adapted to the use of Spanish in Latin America, which makes them unsuitable for use in Spain. Thus, today we still do not have a version of the CRAFFT duly adapted and validated in Spain which would allow professionals and researchers to implement it with confidence.

Thus, the aim of the present study is precisely to create an adaptation of the *CRAFFT Abuse Screening Test* for Spain and to analyze its psychometric behavior in a sample of Spanish adolescents. More specifically, the hypothesis to be tested in the empirical study is that the Spanish version of the CRAFFT represents a psychometrically adequate instrument for detecting early problems of alcohol use and/or the use of other substances among Spanish adolescents.

Method

Participants

In order to achieve the research aim, a selective methodology was chosen, consisting of individual interviews with students in compulsory secondary education (ESO), baccalaureate and intermediate vocational training courses of the Autonomous Community of Galicia (Spain). Two-stage sampling was used to select the sample: by clusters for the selection of the first level units (schools) and by quotas for the second level units (individuals).

Although a total of 343 adolescents were initially interviewed, the final sample consisted of 312 individuals after 31 were rejected mainly because they were unable to complete the interview in its entirety or because of obvious inconsistencies in their responses. To ensure that there was no bias in the distribution of missing cases and that the distribution of these was random, the percentage of missing cases was checked for similarity in the different sample segments according to gender, age group, school attended and residential setting, with χ^2 contrast statistics calculated for the purpose.

With respect to the composition of the sample, males made up 56.4% and females 43.6% of the sample, with ages ranging from 12 to 18 (M = 15.01, SD = 1.83). Participants were randomly selected from a total of 33 educational centers (22 public and 11 private), where 64.9% were attending ESO (32.6% in the first cycle and 32.3% in the second), 21.3% in studying for the baccalaureate and 13.9% were on basic vocational training or an intermediate cycle of the same. Finally, 42.4% lived in an urban environment and 57.6% were from a rural or semi-rural background.

Instrument

Data were collected through a structured interview with the support of a questionnaire that included the *CRAFFT Abuse Screening Test* (Knight et al., 1999), the *Adolescent Diagnostic Interview* (ADI) (Winters & Henly, 1993) and the substance use and abuse subscale of the *Problem Oriented Screening Instrument for Teenagers* ($POSIT_{UAS}$) (Rahdert, 1991). To avoid possible bias in the order in which the three instruments were completed, this was duly counterbalanced.

The CRAFFT (Knight, et al., 1999) is a tool composed of only 6 dichotomous items (yes/no), designed specifically for the screening of high-risk use of alcohol and other substance among adolescents. The administration of CRAFFT begins with 3 initial questions. If the young person's answer to these questions is "no", the interviewer will only need to ask the first question of the CRAFFT itself. If the adolescent answers "yes" to one or more of the 3 initial questions, the interviewer will ask all 6 of the questions that make up the CRAFFT. For the purposes of the present study the CRAFFT was carefully translated and back-translated under the supervision of its original authors. Once adapted to Spanish, a pilot study was carried out with the aim of evaluating the ease of understanding and clarity of the questions. The sample consisted of 51 adolescents between 12 and 17 years old (M = 14.36, SD = 1.47). Accidental sampling was used for the selection of the sample, although an attempt was made to ensure that participants covered the age range of the target group. Data were collected in 5 different locations in an attempt to have participants from the three different environments (urban, rural and semi-rural). For data collection, a questionnaire was designed and administered through a personal interview with three different blocks. The first block featured the CRAFFT; in the second, four questions from a cognitive interview (*Probing Based Paradigm - Delayed Retrospective Probing Procedure*) were included in order to establish how easy they were to understand, and finally there was a brief socio-demographic section (gender, age and school year). The results of the pilot study indicated that the CRAFFT really is a brief, clear and easily understood tool.

The *Adolescent Diagnostic Interview* (ADI) (Winters & Henly, 1993) was used as a criterion to calculate the CRAFFT's sensitivity, specificity, and positive and negative predictive value (PPV and NPV respectively). This consists of a diagnostic interview of 213 items adapted to the DSM-5 criteria (American Psychiatric Association [APA], 2013) for the identification of substance use disorders in adolescents. Its items were translated and back-translated under the supervision of its original authors for application in this research. The reliability of the different diagnostic scales was high, yielding Cronbach's α values of .88 for the diagnosis of alcohol use disorder, .89 for the diagnosis of cannabis use disorder and .92 for the diagnosis of substance use disorder. These values are very similar to those obtained in the study by Araujo, Golpe, Braña and Varela (2018).

Finally, as a complementary indicator of criterion validity, the substance use and abuse subscale of the *Problem Oriented Screening Instrument for Teenagers* ($POSIT_{UAS}$) (Ra-

hdert, 1991) was included, consisting of 17 dichotomous items (yes/no) and validated in the research of Araujo et al. (2018), where good reliability (Cronbach's α of .82), as well as high values for sensitivity (94.3%) and specificity (83.9%) were recorded.

Procedure

Data were collected through a personal interview conducted in the schools, in rooms prepared for the purpose, by a team of psychologists with experience of this type of work. Each interview took between 45 and 60 minutes. Participants were informed of the purpose of the study, and were told that it was anonymous and their responses confidential. The study had the approval and collaboration of both the management of the schools and the respective parents' associations. Participation was completely voluntary and unpaid. The study was approved by the bioethics committee of the University of Santiago de Compostela.

Data analysis

First, a descriptive analysis was carried out by calculating percentages as well as the statistics of central tendency and dispersion. Comparisons of means by gender (through the application of Student's t test) and age group (using a single factor Anova and a Tukey post-hoc contrast) were also performed. Given the non-normality of the data, the Mann-Whitney U test for 2 groups and the Kruskal-Wallis test for more than 2 groups were applied. For an assessment of internal consistency, the KR-20 index, suitable for dichotomous variables (Kuder & Richardson, 1937) and the Omega Coefficient (Ω), were calculated. Sensitivity, specificity, PPV and NPV were determined in order to analyze the psychometric properties of the scale. In addition, the area under the ROC curve (Receiver's Operating Characteristics) was calculated with the aim of establishing the optimal cut-off point. Finally, to assess criterion validity, the degree of agreement of the CRAFFT with the $POSIT_{UAS}$ was analyzed. The analyses were performed with the IBM SPSS Statistics 20 statistical package.

Results

Descriptive statistics

Table 1 shows the direct responses of the 312 adolescents to each of the 9 items comprising the CRAFFT, along with the percentage of subjects who answered affirmatively to each. As can be seen, almost 50% of adolescents reported having drunk alcohol in the previous year, with 18.3% using marijuana or hashish and 4.2% some other substance. If we look at the items that make up the CRAFFT itself (items 4 to 9), the highest percentage corresponds to item 7 ("Have you ever forgotten things you did while drinking alcohol or taking any kind of drug?"), to which 45.2% answered affirmatively. Item 9 ("Have you ever got into trouble while drinking alcohol or taking any kind of drug?") is the one with the lowest percentage of affirmative answers (22.7%).

Descriptive statistics for the total score are shown in Table 2. The overall CRAFFT mean is 1.05 and the standard deviation is 1.60, with a score range of 0-6. Standardized skew and kurtosis statistics reveal the existence of positive skew and a leptokurtic distribution, which shows that the scores are not normally distributed. Non-normality was verified using the Kolmogorov-Smirnov test, with the corresponding Lilliefors correction (K-S = 0.302; $p < .001$).

The distribution of frequencies and the accumulated percentages for the different scores are presented next. Taking the scale's original cut-off point (≥ 2) indicates that 22.9% of the sample tests positive on the CRAFFT.

Comparing mean scores by sex reveals that although females score lower than males (0.94 vs. 1.13), this difference is not statistically significant ($t = 1.07$; $p = 29$, $Z = -0.9$, $p = .93$). The differences regarding age, however, between the three groups (12-14 years of age, 15-16 and 17-18) were statistically significant ($F = 50.567$, $p < .001$; $\chi^2 = 84.87$; p

Table 1. *Percentage of affirmative responses to each CRAFFT item*

Item	% yes
Have you consumed alcoholic drinks (more than a few sips) in the past 12 months?	47.8
Have you smoked marijuana or hashish in the last 12 months?	18,3
Have you taken any other substance to "get high" (illegal drugs, pills, medication or any snorted or inhaled substance)?	4,2
Have you ever been in/on a car/motorcycle driven by someone (including yourself) who previously drank alcohol or consumed any kind of drug?	25.7
Have you ever used alcohol or any kind of drug to relax, feel better about yourself, or fit into a group?	29.7
Have you ever used alcohol or any kind of drug when you were alone, without company?	32.9
Have you ever forgotten things you did while drinking alcohol or taking any kind of drug?	45.2
Have your family or friends ever told you that you should reduce your alcohol or drug use?	27.7
Have you ever got into trouble while drinking alcohol or using any kind of drug?	22.7

Table 2. *Descriptive statistics for CRAFFT total score*

			Value
Total CRAFFT score	Mean		1.05
	95% confidence interval for the mean	Upper limit	0.87
		Lower limit	1.23
	5% trimmed mean		0.86
	Variance		2.57
	Standard Deviation		1.60
	Minimum		0
	Maximum		6
	Range		6
	Skew		11.58
	Kurtosis		5.76
	Percentiles	25	0
		50	0
		75	1
		95	5

<.001), with the 17-18 group presenting the highest average (2.20), followed by 15-16 (1.04) and 12-14 (0.23).

Score reliability

As evidence of the CRAFFT's reliability, its internal consistency was analyzed. This was assessed by calculating the KR-20 index, with the resulting a value of .74 considered acceptable. In addition, the Omega coefficient was calculated, yielding an Ω value of .82.

Each item was also tested individually for consistency by calculating of the Corrected Homogeneity Index (CHI), and values between .38 and .61 were obtained. Items 2 and 4 were those found to be less consistent with regard to the scale as a whole. However, eliminating any of them did not lead to any improvement in the scale's overall consistency (Table 4).

Sensitivity, specificity, PPV, NPV and ROC

Table 5 shows the values for sensitivity, specificity, PPV and NPV for different cut-off points. The results obtained indicate that the CRAFFT offers good psychometric properties at cut-off points 1 and 2, but with a better balance between the four indicators when 2 is adopted.

When this original cut-off point (≥ 2) is used, the CRAFFT's sensitivity reaches 74.4% and specificity 96.4%. This means that it is able to detect true positives in 74.4% of cases and to reject true negatives in 96.4% of the time, both of which are very acceptable results. Looking at the predictive values obtained for this cut-off point we can see that the positive predictive value is 88.4%, while the negative predictive value is 91.1%., which means that the probability of an adolescent with a positive CRAFFT score actually having a substance use disorder is 88.4% and, conversely, that the likelihood of an adolescent scoring negatively does not present a disorder is 91.1%. In contrast, when the cut-off point is lowered to 1, the sensitivity index (97.6%) and the negative predictive value (98.8%) are enhanced, to the detriment of specificity and positive predictive value, which sink to 76.6 % and 60.6%, respectively. To complement this, a ROC (*Receiver Operating Characteristic*) curve analysis was performed, yielding an area under the curve of .946 (Figure 1).

Using the original cut-off point and analyzing the psychometric properties of CRAFFT according to gender, the CRAFFT behaves better when applied to males. As for age, the results are acceptable in all three groups, especially in the 12-14 year group (sensitivity = 75%, specificity = 100%, PPV = 100% and NPV = 99.1%), with all indices diminishing slightly with increasing age.

Table 4. *Consistency of CRAFFT items*

Item	KR-20 if item eliminated	CHI
1	.714	.431
2	.726	.385
3	.697	.487
4	.729	.384
5	.671	.583
6	.668	.605
GLOBAL	.738	

Table 3. *Frequency distribution for CRAFFT total score*

Total score	Frequency	Valid percentage	Cumulative percentage
0	173	55.8%	55.8%
1	65	21.3%	77.1%
2	17	5.5%	82.6%
3	19	6.1%	88.7%
4	14	4.5%	93.2%
5	14	4.5%	97.7%
6	7	2.3%	100%

Tabla 5. *Propiedades psicométricas del CRAFFT*

		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve
Cut-off point ≥1		97.6	76.6	60.6	98.8	
Cut-off point ≥2		74.4	96.4	88.4	91.1	.946
Cut-off point ≥3		61	98.2	92.6	87.2	
		Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**ROC curve**
		Cut-off ≥ 2				
Sex	Males	76.9	97.5	93	90.8	.958
	Females	70	95	80.8	91.4	.926
Years of age	12-14	75	100	100	99.1	.984
	15-16	74.1	97.2	90.9	90.9	.913
	17-18	74.5	82.9	86.4	69	.892

Validity evidence in relation to external variables

In order to assess criterion validity, the percentage of adolescents who tested positive with CRAFFT and ADI (22.9% and 26.8%, respectively) was compared, yielding a Kappa concordance index of .75 ($p < .001$). Additionally, the same comparison was made between CRAFFT and POSIT$_{UAS}$ (with a percentage of positives in the latter instrument of 39.4%), producing a Kappa concordance index of .67 ($p < 0.001$). Finally, the Pearson correlation coefficient between the CRAFFT and POSIT$_{UAS}$ scores was also calculated and returned a very high and statistically significant value of $r_{xy} = .86$ ($p < .001$).

Internal structure validity evidence

The sample was randomly divided into two halves. Exploratory factor analysis (AFE) was performed on the first, and confirmatory factor analysis (CFA) on the second. To carry out the AFE, the factor extraction method used was the method of main components. The KMO index was .77, and the Bartlett sphericity test value was 184.61 ($p < 0.001$). The analysis provided 1 factor, which explained 44.30% of data variance. The second half of the sample was submitted to CFA in order to confirm this one-dimensional structure. The standardized factor loading were higher than .45 and the goodness of fit index (GFI), adjusted goodness of fit index (AGFI), normed fit index (NFI) and the root mean square residual (RMSR) yielded highly acceptable values (GFI = .995, AGFI = .989 and NFI = .990) in accordance with the criteria established by Byrne (2009) and Kline (2005).

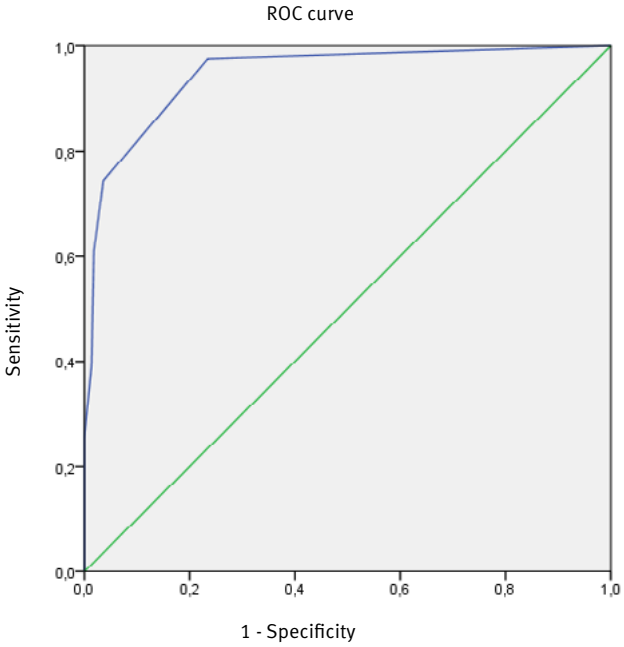

Figure 1. ROC curve for CRAFFT

Discussion

One of the most frequently used screening instruments worldwide for high-risk drug use is without doubt the CRAFFT. Its use in different countries and in different contexts bears witness to its enormous potential (Agley, Gassman, Jun, Nowicke & Samuel, 2015; Bernard et al., 2005; Cote-Menendez et al., 2013; Cummins et al. 2003; Dieppe, Stanhope & Rakhra, 2009; Harris et al., 2016; 2014, Karila et al., 2007; Van Weelden et al., 2016). In Spain, however, there are still no psychometric studies that guarantee the proper functioning of this instrument in our country, although some professionals and researchers have occasionally used the CRAFFT.

The results obtained from a sample of 312 students from the Autonomous Community of Galicia show that the CRAFFT possesses good psychometric properties. Firstly, as regards internal consistency, a satisfactory α value of .74 was obtained, which is higher than that obtained in the original validation study by Knight et al. (2002) (α = .68)

and other studies (Bertini et al., 2015; Kelly et al., 2004; Subramaniam et al., 2010; Wartberg et al., 2016). Secondly, in terms of screening, it is the original cut-off point (≥ 2) that results in the best balance between the four indicators used, with a sensitivity of 74.4%, a specificity of 96.4%, a PPV of 88.4% and an NPV of 91.1%. However, if we follow Latimer, Winters and Stinchfield (1997), who argue that since the most important function of a screening tool is to prevent an adolescent with drug abuse being omitted in screening, and consequently urge that sensitivity should be to maximized, we should rethink the possibility of lowering the cut-off point to 1, as Subramaniam et al. (2010) or Skogen et al. (2013) have already done. The section-by-section results using the original cut-off point show that CRAFFT presents good psychometric properties with both males and females, as well as with the different age groups. However, it should be noted that with females the values in the four indicators are slightly lower than with males, and this difference remains with increasing age.

Regarding the CRAFFT's construct validity, the analyses carried out have confirmed the one-dimensional structure of the scale, as already noted by Subramaniam et al. (2010) and Wartberg et al. (2016).

Finally, the CRAFFT's criterion validity is borne out by its high concordance indices with ADI and $POSIT_{UAS}$, as well as the high and significant correlation found between the CRAFFT and $POSIT_{UAS}$.

In short, the present study makes an adapted and empirically validated version of the CRAFFT *Abuse Screening Test* available to researchers and professionals in the field of addictive behavior. The results obtained show that the CRAFFT enjoys good psychometric properties and represents an appropriate tool to be used within a school context. Furthermore, it has been found that when administered by non-health personnel there is no loss in any of its properties, which increases its potential and the possibilities of being used. Our research also opens up the possibility of using the CRAFFT as the screening tool within the framework of possible early detection and brief intervention programs (SBIRT) to be developed in our country.

Notwithstanding the above, it is important to note that this study has some limitations. From a sampling perspective, although the sample size of 312 adolescents is similar or even higher than that of other validation studies (Bernard et al., 2005; Bertini et al., 2006; Cummins et al. 2003; Kelly et al., 2004) it is not sufficient for assessing the instrument in relation to different sociodemographic sectors. In addition, the fact that only adolescents from the Autonomous Community of Galicia were involved can in itself be seen as conditioning external validity. In an attempt to mitigate this limitation, the sample included students from public, private and 'concertado' (state funded private) schools, living in urban, rural or semi-rural environments. However, it is clear that future research needs to aim at analyzing the psychometric properties of the scale in other autonomous communities.

It would also have been interesting to have had some clinical information about participants, such as the presence of a comorbid diagnosis, the existence of a family history of the disorder, etc. However, it is worth noting that this is a first validation study in a school setting, where it is intended that the instrument be put to use immediately.

Finally, the fact that the data were gathered in schools themselves, and not in primary care services through a clinical interview as such, means that the variables analyzed were self-reported, which makes it impossible to know objectively to what extent adolescents may actually have underestimated or overestimated their levels of substance use. However, as has previously been pointed out by different experts in the field of addictive behavior, such as Babor, De La Fuente, Saunders and Grant (1989) or Winters, Stinchfield, Henly and Schwartz (1990) themselves, self-report measures have been shown to be reliable and even more accurate than other methods when assessing levels of alcohol and other drug use. Furthermore, the validation of the CRAFFT in a school setting makes it a tool of enormous potential, given that it is precisely in this area where a good part of the preventive work in our country is being carried out.

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Conflict of interests

The authors of this article declare that they have no conflict of interest

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Waterpipe and cigarette smoking among adolescents in Seville (Spain): prevalence and potential determinants

Consumo de pipas de agua y cigarrillos entre adolescentes de Sevilla (España): prevalencia y potenciales determinantes

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Waterpipe smoking has been linked to serious health problems (Waziry, Jawad, Ballout, Al Akel, & Akl, 2017) and, given its growth in recent years, is becoming a worldwide public health issue, especially among young people. It represents a new threat in the global fight against tobacco and its consequences in terms of morbidity and mortality (Maziak et al., 2017; WHO Study Group on Tobacco Product Regulation (TobReg), 2015).

Only very limited data are available on waterpipe smoking in Spain (Agaku et al., 2014; Jorge-Araujo, Torres-García, Saavedra-Santana, & Navarro-Rodríguez, 2017). As part of a project on the prevention of tobacco use among adolescents, this cross-sectional study was conducted between April and May 2014 in three state secondary schools (IES) in Seville (3057 students). The aims of the study were to assess the prevalence of waterpipe and cigarette smoking among adolescents and analyze the possible determinants of and beliefs about waterpipe smoking. To this end, we used an anonymous self-administered ad-hoc questionnaire comprising 12 questions on smoking and beliefs (available upon request) which was created in accordance with the recommendations of experts (Maziak, Ward, Afifi Soweid, & Eissenberg, 2005).

In each IES, one class was selected for each school year using a table of random numbers. Of the 501 participants in the selected classes, 139 (28%, 95% confidence interval [CI] 24 - 32) were habitual tobacco users, smoking either cigarettes or waterpipes (see table's footnote for definitions regarding stage of use). Irrespective of concomitant use of the other modality, 66 (13%, 95% CI 10-16) students were habitual waterpipe smokers, and 93 (19%, 95% CI 15-22) were habitual cigarette smokers; likewise, 343 (69%, 95% CI 64-73) students had used waterpipes at some point and 253 (51%, 95% CI, 46-55) had at some point smoked cigarettes.

The bivariate analysis of potential sociodemographic determinants of waterpipe smoking are presented in the table. We can highlight that 56% of those who had never smoked water pipes lived in a family with a habitual smoker, while 80% of students who were habitual smokers lived with one or more habitually smoking relatives; the higher the number of cohabiting smokers, the higher the prevalence of habitual waterpipe and cigarette use among students (figure). Students who were habitual waterpipe smokers also were habitual cigarette smokers more often (30%), while those who had never smoked water pipes were also far less likely to be habitual cigarette smokers (4%).

Regarding beliefs, habitual waterpipe users were more likely to consider this type of consumption to be less harmful to health than cigarettes, and to be something which does not affect passive smokers. They believe that waterpipe tobacco packages provide full information and warnings regarding the product's compounds and additives, that waterpipe smoking does not create addiction, and does not induce cigarette smoking ($p < 0.001$). Almost two thirds of

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the students (a third of habitual waterpipe smokers) did not know whether waterpipe tobacco packages specified all the information and warnings about the product's compounds and additives.

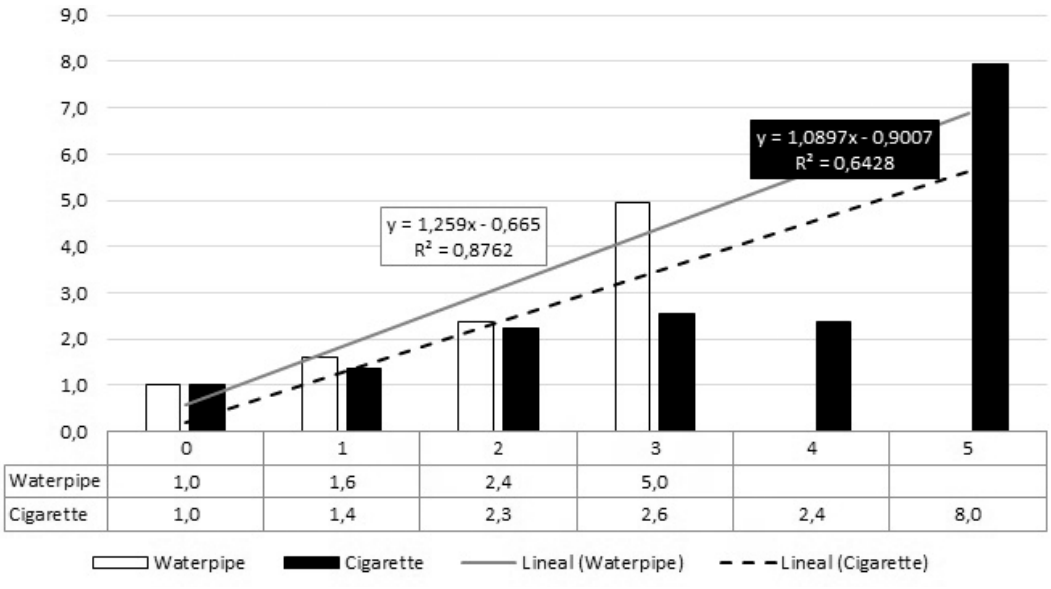
In conclusion, our study shows a high prevalence of habitual waterpipe smoking among adolescents (13%), which, if confirmed at the national level, would be among the highest reported in a range of countries or geographic regions (Agaku et al., 2014; Akl et al., 2011), and similar to the level among the Arab population in the USA (12-15%) or in the Persian Gulf region (9-16%) (Akl et al., 2011). This waterpipe smoking contributes significantly to total tobacco use among adolescents (28% in our survey), with higher figures in our study than those reported on tobacco consumption among adolescents for Spain in the 2014 *Health Behavior in School-aged Children* survey (Moreno et al., 2016); future versions of this latter survey will include waterpipe smoking and other modes of tobacco use, providing more accurate data regarding current smoking habits (Moreno, Ramos, & Rivera, 2017). Although limited by the cross-sectional design, in line with other studies (Jiang, Ho, Wang, Leung, & Lam, 2017), our data suggest that waterpipe use is associated with cigarette smoking. In addition to the need for studies at the national level, these results suggest that it is necessary to adopt preventive measures that should start early - before the third year of compulsory secondary education (ESO) (Diaz Geada, Busto Miramontes, & Caamano Isorna, 2018) – and be aimed at demystifying the supposedly less harmful nature of both waterpipe and electronic cigarette smoking (González Roz, Secades Villa, & Weidberg, 2017) among children and adolescents. Such measures must be applied in the family environment and should also include the development of specific regulations for this kind of smoking.

Table 1. *Bivariate analysis of the relationship between demographic characteristics and waterpipe smoking.*

	Waterpipe smoking			
	Never	**Occasional***	**Habitual***	**p value**
Characteristics	**N= 158**	**N= 277**	**N=66**	
Age (years), P50 (P25-P75)	15.5 (14.0-17.4)	17.4 (15.5-18.4)	16.5 (15.3-17.5)	<0.001‡
Sex, N (%)				0,18#
male	78 (49.4)	133 (48.0)	40 (60.6)	
female	80 (50.6)	144 (52.0)	26 (39.4)	
School type, N (%)				<0.001#
rural (IH)	39 (24.7)	59 (21.3)	31 (47.0)	
suburban (CL)	62 (39.2)	128 (46.2)	25 (37.9)	
central (JM)	57 (36.1)	90 (32.5)	10 (15.2)	
School year, N (%)				<0.001#
1st year ESO	37 (25.0)	25 (10.2)	8 (12.7)	
2nd year ESO	29 (19.6)	19 (7.8)	7 (11.1)	
3rd year ESO	24 (16.2)	42 (17.1)	15 (23.8)	
4th year ESO	16 (10.8)	39 (15.9)	14 (22.2)	
1st year Bachiller	30 (20.3)	69 (28.2)	13(20.6)	
2nd year Bachiller	12 (8.1)	51 (20.8)	6 (9.5)	
Vocational training	10 (6.3)	32 (11.6)	3 (4.5)	
Habitual smoker in the family, N (%)				0,001#
no	70 (44.3)	86 (31.0)	13 (19.7)	
yes	88 (55.7)	191 (69.0)	53 (80.3)	
Cigarette smoker†, N (%)				<0.001#
no	142 (89.9)	88 (31.8)	18 (27.3)	
occasional	10 (6.3)	122 (44.0)	28 (42.4)	
habitual	6 (3.8)	67 (24.2)	20 (30.3)	

Note. *Habitual waterpipe smoker: daily or weekly use; occasional smoker: monthly or sporadic use.
† Habitual cigarette smoker: daily or weekly use; occasional smoker: sporadic use ("sometimes").

P, percentile; CL, Carmen Laffón secondary school in San José de la Rinconada; IH, Heliche secondary school in Olivares; JM, Juan de Mairena secondary school in Mairena del Aljarafe; ESO, compulsory secondary education; Bachiller, higher secondary school certificate.
Bilateral hypothesis testing, 95% confidence interval; ‡Mann-Whitney U test; #Pearson chi-square (IBM-SPSS v.18).



	0	1	2	3	4	5
Waterpipe	1,0	1,6	2,4	5,0		
Cigarette	1,0	1,4	2,3	2,6	2,4	8,0

Figure 1. Prevalence ratios of habitual cigarette or waterpipe smoking depending on the number of habitual smokers in the family.

Note. The prevalence ratio (y-axis) is calculated for each category in relation to the number of relatives living in the family home who are smokers (x-axis) as the ratio of habitual smokers in the respective category to '0' smokers living at home (EPIDAT 3.1).

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Conflict of interests

On behalf of all authors, the first signatory of the manuscript declares that there is no conflict of interest in relation to this article.

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Detection of synthetic cannabinoid intoxication in the Emergency Department: when routine toxicological tests are not enough

Detección de la intoxicación por cannabinoides sintéticos en Urgencias: cuando las pruebas toxicológicas rutinarias no bastan

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Synthetic cannabinoids (SC) are a heterogeneous group of substances with high affinity for cannabinoid receptors. They represent an emerging class of new drugs, the use of which has been expanding rapidly in recent years (Ford, Tai, Fantegrossi & Prather, 2017). Initially sold through specialized websites as legal alternatives to marijuana in the form of a mixture of herbs under the names "Spice" (Europe) or "K2" (USA), they have been subject to surveillance by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) since 2008, when CS JWH-018 was shown to be present in these products (European Monitoring Centre for Drugs and Drug Addiction, 2017). The continuous modification and manipulation of these compounds by illegal laboratories has significantly accelerated the introduction of new molecules in the market (Ford et al., 2017): by December 2016, 169 SCs had been notified to the EMCDDA (European Monitoring Centre for Drugs and Drug Addiction, 2017), with progressively more potent substances being detected (Adams et al., 2017).

The increase in the use of illegal psychotropic substances, especially cannabis, among the youngest (Blasco-Fontecilla, 2018) and frequent maladaptive internet use in this population (Golpe, Gómez, Braña, Varela & Rial, 2017), could facilitate the acquisition and consumption of SC as early as adolescence: in the 2016 ESTUDES survey, 0.9% of students aged 14-18 years stated that they had tried "Spice" at least once in their lives (Plan Nacional sobre Drogas, 2016).

Synthetic cannabinoid products have higher affinity for the CB1 receptor than delta-9-THC: unlike cannabis herbal derivatives, which contain different molecules with variable psychoactive power (Casajuana Köguel, López-Pelayo, Balcells-Olivero, Colom & Gual, 2018), SCs act as pure receptor agonists (Ford et al., 2017). There is experimental evidence that SCs also act on non-cannabinoid receptors, such as the 5-HT2B receptor or dopaminergic receptors. (Adams et al., 2017). In addition, SCs lack cannabidiol in their composition, which is found in herbal cannabis and is capable of exerting antipsychotic effects, thereby moderating the action of delta-9-THC (Rowley et al., 2017). These characteristics mean SCs have a greater psychoactive effect, as well as increasing the frequency and severity of side effects.

Psychiatric symptoms of intoxication can include anxiety, agitation, hallucinations, confusion, amnesia, paranoid delusions, bizarre behaviors, heteroagressivity, and suicidal ideation. At the somatic level, they can cause tachycardia, hypertension, drowsiness, deterioration of the level of consciousness, vertigo, paresthesia, epileptic seizures, acute myocardial infarction and cerebrovascular accidents, even death in some cases (Tournebize, Gibaja & Kahn, 2017). The concomitant use of other substances is usually associated with greater clinical severity (Rowley et al., 2017).

Given the variety and nature of the substances available, procedures such as gas chromatography or mass spectrometry are required for their analytical determination, which makes SCs difficult to detect in routine clinical practice.

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Some cannabis users may opt for SCs to avoid testing positive (Rowley et al., 2017).

For this reason and given the nonspecific clinical manifestations in routine toxicological tests, symptoms of SC poisoning can be confused with other psychiatric or somatic pathologies.

Currently, there is an increase in people accessing emergency services due to SC poisoning (Tournebize et al., 2017). Cases of mass poisoning have been described: in New York, in July 2016, 33 people were treated during the notorious "zombie epidemic", caused by exposure to CS AMB-FUBINACA (Adams et al., 2017). This set alarm bells ringing in the general population, the media and health professionals.

Previous studies have highlighted the fact that SC users have a risk up to 30 times greater of needing emergency room treatment for the effects of acute poisoning compared to users of natural cannabis (Winstock, Lynskey, Borschmann & Waldron, 2015). Most patients are usually treated with intravenous fluid therapy, sedatives and antiemetics, although measures such as sedation or intubation may be necessary as well as, in a quarter of all cases, hospitalization (Rowley et al., 2017).

In light of the above, we would like to stress the particular relevance at this time of training professionals involved in emergency care services with regard to these new psychoactive substances. The growing spread of these drugs, especially among the young population, implies the need for updated knowledge to help detect possible SC intoxication, establish a correct differential diagnosis and permit the prompt application of the most appropriate treatment. And we should not forget that, given the usually negative toxicological test results, careful observation of clinical manifestations remains the most effective tool at our disposal.

Conflicts of interests:

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

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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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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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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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1. NOMBRE DEL MEDICAMENTO. Xeplion 25 mg suspensión inyectable de liberación prolongada. Xeplion 50 mg suspensión inyectable de liberación prolongada. Xeplion 75 mg suspensión inyectable de liberación prolongada. Xeplion 100 mg suspensión inyectable de liberación prolongada. Xeplion 150 mg suspensión inyectable de liberación prolongada. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** 25 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 39 mg de palmitato de paliperidona equivalentes a 25 mg de paliperidona. 50 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 78 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. 75 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 117 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. 100 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 156 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. 150 mg suspensión inyectable de liberación prolongada. Cada jeringa precargada contiene 234 mg de palmitato de paliperidona equivalentes a 150 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). **4. DATOS CLÍNICOS. 4.1. Indicaciones terapéuticas.** Xeplion está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos estabilizados con paliperidona o risperidona. En determinados pacientes adultos con esquizofrenia y respuesta previa a paliperidona o risperidona oral, Xeplion puede ser utilizado sin necesidad de estabilización previa con tratamiento oral si los síntomas psicóticos son leves o moderados y es necesario un tratamiento con un inyectable de acción prolongada. **4.2. Posología y forma de administración.** Posología. Se recomienda iniciar Xeplion con una dosis de 150 mg en el día 1 de tratamiento y 100 mg una semana después (día 8), ambos administrados en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). La tercera dosis se debe administrar un mes después de la segunda dosis de inicio. La dosis de mantenimiento mensual recomendada es de 75 mg; algunos pacientes pueden beneficiarse de dosis inferiores o superiores dentro del rango recomendado de 25 a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. Los pacientes con sobrepeso u obesos pueden requerir dosis situadas en la parte superior del intervalo (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. El ajuste de la dosis de mantenimiento se puede hacer mensualmente. Al realizar ajustes de la dosis, se deben tener en cuenta las características de liberación prolongada de Xeplion (ver sección 5.2), dado que el pleno efecto de las dosis de mantenimiento puede no resultar evidente durante varios meses. *Cambio desde paliperidona oral de liberación prolongada o risperidona oral a Xeplion.* El tratamiento con Xeplion se debe iniciar según se describe al comienzo de esta sección 4.2 . Durante el tratamiento de mantenimiento mensual con Xeplion, los pacientes previamente estabilizados con diferentes dosis de paliperidona comprimidos de liberación prolongada, pueden alcanzar una exposición similar a paliperidona en estado estacionario por vía inyectable. La dosis de mantenimiento de Xeplion necesaria para alcanzar una exposición similar en el estado estacionario se muestra a continuación:

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

El tratamiento recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con Xeplion. Algunos pacientes se pueden beneficiar de una retirada gradual. Algunos pacientes que cambian de dosis orales más altas de paliperidona (p. ej., 9-12 mg diarios) a inyecciones en el glúteo con Xeplion pueden tener una exposición plasmática menor durante los primeros 6 meses después del cambio. Por lo tanto, alternativamente, se puede considerar administrar inyecciones en el deltoides durante los primeros 6 meses. *Cambio desde Risperidona inyectable de acción prolongada a Xeplion.* Al realizar el cambio de tratamiento de los pacientes desde risperidona inyectable de acción prolongada, inicie el tratamiento con Xeplion en lugar de la siguiente inyección programada. A partir de entonces, Xeplion se debe continuar en intervalos mensuales. No es necesario seguir el régimen de dosificación inicial de una semana incluyendo las inyecciones intramusculares (día 1 y 8, respectivamente) según se describe en la sección 4.2 anterior. Los pacientes previamente estabilizados con diferentes dosis de risperidona inyectable de acción prolongada pueden alcanzar una exposición similar a paliperidona en estado estacionario durante el tratamiento de mantenimiento con dosis mensuales de Xeplion según se describe a continuación:

Dosis de risperidona inyectable de acción prolongada y Xeplion necesaria para alcanzar una exposición a paliperidona similar en estado estacionario	
Dosis previa de risperidona inyectable de acción prolongada	Inyección de Xeplion
25 mg cada 2 semanas	50 mg mensualmente
37,5 mg cada 2 semanas	75 mg mensualmente
50 mg cada 2 semanas	100 mg mensualmente

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). Dosis omitidas. *Medidas para evitar la omisión de dosis.* Se recomienda que la segunda dosis de iniciación de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y los siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8±4 días), el momento de reinicio recomendado depende del tiempo que haya transcurrido desde la primera inyección del paciente. *Omisión de la segunda dosis de iniciación (<4 semanas desde la primera inyección).* Si han transcurrido menos de 4 semanas desde la primera inyección, se le debe administrar al paciente la segunda inyección de 100 mg en el músculo deltoides tan pronto como sea posible. Se debe administrar una tercera inyección de Xeplion de 75 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (entre 4 y 7 semanas desde la primera inyección).* Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xeplion, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (>7 semanas desde la primera inyección).* Si han transcurrido más de 7 semanas desde la primera inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. *Omisión de la dosis de mantenimiento mensual (1 mes a 6 semanas).* Tras la iniciación, el ciclo de inyección recomendado de Xeplion es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. *Omisión de la dosis de mantenimiento mensual (>6 semanas a 6 meses).* Si han transcurrido más de 6 semanas desde la última inyección de Xeplion, la recomendación es la siguiente: *Para los pacientes estabilizados con dosis de 25 a 100 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para los pacientes estabilizados con 150 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (>6 meses).* Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia y la seguridad en la población de edad avanzada >65 años. En general, la dosis recomendada de Xeplion en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (ver *Insuficiencia renal* más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). *Insuficiencia renal.* No se ha estudiado Xeplion sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se recomienda iniciar Xeplion con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver sección 4.4). *Insuficiencia hepática.* Basándose en la experiencia con paliperidona oral, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y la eficacia de Xeplion en niños y adolescentes <18 años de edad. No hay datos disponibles. Forma de administración. Xeplion se utiliza únicamente para uso intramuscular. No se debe administrar por ninguna otra vía. Se debe inyectar lentamente, profundamente en el músculo deltoides o en el glúteo. Cada inyección debe ser administrada por un profesional sanitario. La administración debe realizarse en una sola inyección. La dosis no se debe administrar en inyecciones divididas. Las dosis de iniciación del día 1 y del día 8 se deben administrar ambas en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. Se debe cambiar del glúteo al deltoides (y viceversa) en caso de dolor en el lugar de inyección si no se tolera bien el malestar en el lugar de inyección (ver sección 4.8). También se recomienda alternar entre los lados izquierdo y derecho (ver más adelante). Para consultar las instrucciones de uso y manipulación de Xeplion, ver prospecto (información destinada únicamente a médicos o profesionales del sector sanitario). *Administración en el músculo deltoides.* El tamaño de la aguja recomendado para la administración inicial y de mantenimiento de Xeplion en el músculo deltoides viene determinada por el peso del paciente. En los pacientes ≥90 kg, se recomienda la aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). En los pacientes <90 kg, se recomienda la aguja de calibre 23 de 1 pulgada (25,4 mm x 0,64 mm). Las inyecciones en el deltoides se deben alternar entre los dos músculos deltoides. *Administración en el músculo glúteo.* El tamaño de la aguja recomendado para la administración de mantenimiento de Xeplion en el músculo glúteo es el de una aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). La administración se debe realizar en el cuadrante superior externo de la zona glútea. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en pacientes que se encuentran en un estado sumamente agitado o psicótico grave. Xeplion no se debe utilizar para el tratamiento de estados agitados agudos o psicóticos graves cuando esté justificado el control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al recetar paliperidona a pacientes con enfermedad cardiovascular conocida o antecedentes familiares de prolongación del intervalo QT, y en caso de uso concomitante con otros medicamentos que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos del Síndrome Neuroléptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la consciencia y elevación de los niveles séricos de creatina fosfocinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiólisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de paliperidona. Discinesia tardía/síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar uno o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos <1x10^9/l) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia pos-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente que incluye coma diabético y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con Xeplion se les deben monitorizar los síntomas de la hiperglucemia (tales como polidipsia, poliuria, polifagia y debilidad) y a los pacientes con diabetes mellitus se les debe monitorizar regularmente el empeoramiento del control de glucosa. Aumento de peso. Se ha notificado un aumento de peso significativo con el uso de Xeplion. El peso debe controlarse regularmente. Uso en pacientes con tumores dependientes de prolactina. Los estudios de cultivo de tejidos sugieren que la prolactina puede estimular el crecimiento de células en los tumores de mama humanos. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona se debe utilizar con precaución en pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes sobre la base de su actividad alfa-bloqueante. Según los datos agrupados de los tres ensayos controlados con placebo, de dosis fijas y 6 semanas de duración con comprimidos orales de paliperidona de liberación prolongada (3, 6, 9 y 12 mg), el 2,5% de los pacientes tratados con paliperidona oral comunicaron hipotensión ortostática, en comparación con el 0,8% de los sujetos tratados con placebo. Xeplion debe utilizarse con precaución en pacientes con enfermedad cardiovascular conocida (p. ej., insuficiencia cardíaca, infarto de miocardio o isquemia, trastornos de la conducción), enfermedad cerebrovascular o afecciones que predispongan al paciente a la hipotensión (p. ej. deshidratación e hipovolemia). Convulsiones. Xeplion debe utilizarse con precaución en pacientes con antecedentes de convulsiones u otros trastornos que potencialmente puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona aumentan en pacientes con insuficiencia renal y por tanto, se recomienda un ajuste de la dosis en pacientes con insuficiencia renal leve. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos en pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en dichos pacientes. Pacientes de edad avanzada con demencia. No se ha estudiado Xeplion en pacientes de edad avanzada con demencia. Xeplion se debe utilizar con precaución en pacientes de edad avanzada con demencia y con factores de riesgo de padecer ictus. La experiencia con risperidona citada más adelante se considera válida también para paliperidona. *Mortalidad global.* En un metanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, tales como risperidona, aripiprazol, olanzapina y quetiapina, tenían un mayor riesgo de mortalidad en comparación con placebo. Entre los pacientes tratados con risperidona, la mortalidad fue del 4% frente al 3,1% con placebo. *Reacciones adversas cerebrovasculares.* Se ha observado un aumento de aproximadamente 3 veces del riesgo de reacciones adversas cerebrovasculares en los ensayos clínicos aleatorizados controlados con placebo en la población con demencia al utilizar algunos antipsicóticos atípicos, tales como risperidona, aripiprazol y olanzapina. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y los beneficios de prescribir Xeplion a los pacientes con enfermedad de Parkinson o Demencia con Cuerpos de Lewy (DCL), ya que ambos grupos pueden tener mayor riesgo de padecer Síndrome Neuroléptico Maligno, así como tener una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, obnubilación, inestabilidad postural con caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (incluida risperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Durante la vigilancia post-comercialización, también se han notificado casos de priapismo con paliperidona oral, que es el metabolito activo de risperidona. Se ha de informar a los pacientes de la necesidad de acudir al médico urgentemente en caso de que el priapismo no haya sido resuelto en el transcurso de 4 horas. Regulación de la temperatura del organismo. Se ha atribuido a los medicamentos antipsicóticos la interrupción de la capacidad del organismo para reducir la temperatura corporal central. Se aconseja proceder con especial cautela cuando se prescriba Xeplion a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p.ej., ejercicio físico intenso, exposición a calor extremo, que reciban medicamentos concomitantes con actividad anticolinérgica o que estén sujetos a deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con medicamentos antipsicóticos. Dado que los pacientes tratados con antipsicóticos suelen presentar factores de riesgo adquiridos de TEV, se han de identificar todos los posibles factores de riesgo de TEV antes y durante el tratamiento con Xeplion y adoptar medidas preventivas. Efecto antiemético. Se observó un efecto antiemético en los estudios preclínicos con paliperidona. Este efecto, si se produce en humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de enfermedades como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de Xeplion en un vaso sanguíneo. Síndrome del Iris Flácido Intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como Xeplion (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. Excipientes. Este medicamento contiene menos de 1 mmol (23 mg) de sodio por dosis; esto es, esencialmente "exento de sodio". **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir Xeplion con medicamentos que prolonguen el intervalo QT, p. ej. antiarrítmicos de clase IA (p. ej., quinidina, disopiramida) y antiarrítmicos de clase III (p. ej. amiodarona, sotalol), algunos antihistamínicos, algunos otros antipsicóticos y algunos antipalúdicos (p. ej. mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que Xeplion afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos que sean metabolizados por las isoenzimas del citocromo P-450. Dado que los efectos principales de paliperidona se ejercen sobre el sistema nervioso central (SNC) (ver sección 4.8), Xeplion debe utilizarse con precaución en combinación con otros medicamentos de acción central, p. ej., ansiolíticos, la mayoría de los antipsicóticos, hipnóticos, opiáceos, etc. o con el alcohol. Paliperidona puede antagonizar el efecto de levodopa y otros agonistas de dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se debe recetar la dosis mínima eficaz de cada tratamiento. Debido a la posibilidad de que induzca hipotensión ortostática (ver sección 4.4), se puede observar un efecto aditivo si se administra Xeplion con otros tratamientos que también tengan esta posibilidad, p.ej., otros antipsicóticos, tricíclicos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenotiazinas o butirofenonas, tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de comprimidos orales de paliperidona de liberación prolongada en estado estacionario (12 mg una vez al día) con comprimidos de divalproex sódico de liberación prolongada (de 500 mg a 2.000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xeplion y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a Xeplion. Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vitro* ni *in vivo* de que esas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{ss} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad del principio activo inalterado excretado en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP o en la biodisponibilidad de paliperidona. Con dosis más altas de carbamazepina, podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al inicio del tratamiento con carbamazepina, se debe reevaluar y aumentar la dosis de Xeplion, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xeplion, si es necesario. La administración concomitante de una sola dosis de un comprimido de paliperidona oral de liberación prolongada de 12 mg con comprimidos de divalproex sódico de liberación prolongada (dos comprimidos de 500 mg una vez al día) tuvo como resultado un aumento de aproximadamente el 50% en la C_{max} y el AUC de paliperidona, probablemente como resultado de un aumento de la absorción oral. Dado que no se observó ningún efecto sobre el aclaramiento sistémico, no se espera que se produzca una interacción clínicamente significativa entre los comprimidos de divalproex sódico de liberación prolongada y la inyección intramuscular de Xeplion. Esta interacción no se ha estudiado con Xeplion. Uso concomitante de Xeplion y risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando Xeplion sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. Uso concomitante de Xeplion y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a paliperidona durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xeplion no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreto por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonia. De estas, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10); *frecuentes* (≥1/100 a <1/10); *poco frecuentes* (≥1/1.000 a <1/100); *raras* (≥1/10.000 a <1/1.000); *muy raras* (<1/10.000); y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	No conocidas[a]
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonia, bronquitis, infección del tracto respiratorio, sinusitis, cistitis, infección de oídos, amigdalitis, onicomicosis, celulitis	infección de ojos, acarodermatitis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, recuento de eosinófilos aumentado	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia[b]		secreción inapropiada de la hormona antidiurética, presencia de glucosa en orina	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, disminución de peso, apetito disminuido	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, aumento de los triglicéridos en sangre, aumento del colesterol en sangre	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio[a]	agitación, depresión, ansiedad	trastorno del sueño, manía, disminución de la libido, nerviosismo, pesadillas	catatonía, estado confusional, somnambulismo, embotamiento afectivo, anorgasmia	trastorno alimentario relacionado con el sueño
Trastornos del sistema nervioso		parkinsonismo[a], acatisia[a], sedación/somnolencia, distonía[a], mareos, disquinesia[a], temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotora, mareo postural, alteración de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, sin respuesta a estímulos, pérdida de la consciencia, disminución del nivel de consciencia, convulsión[a], trastorno del equilibrio, coordinación anormal	coma diabético, temblor cefálico en reposo
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma, trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		

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

[a]La frecuencia de estas reacciones adversas se clasifica como "no conocidas" porque no fueron observadas en los ensayos clínicos con palmitato de paliperidona. Proceden de notificaciones espontáneas poscomercialización y la frecuencia no se puede determinar, o proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral y/o de informes poscomercialización. [b]Referido a "Hiperprolactinemia" a continuación. [c]Referido a "Síntomas extrapiramidales" a continuación. [d]En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con Xeplion comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,65% en todos los pacientes tratados con palmitato de paliperidona. **Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** retraso en la menstruación, menstruación irregular, oligomenorrea.

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

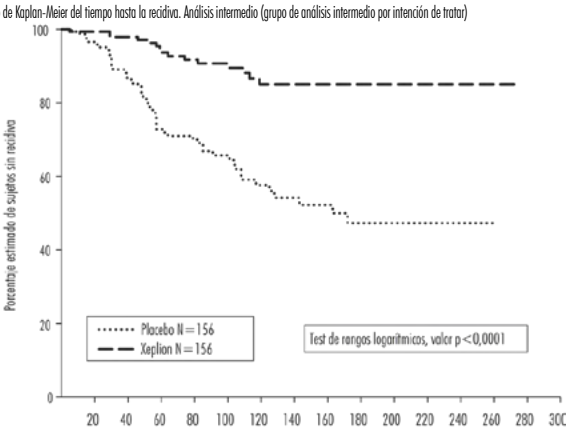
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminada intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radioactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (día 8 y día 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a las de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (ClCr=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (ClCr=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (ClCr =10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{inf}) de 1,5; 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de los simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. El análisis de la farmacocinética poblacional demostró que no había evidencia de diferencias en la farmacocinética relacionada con la edad. Índice de masa corporal (IMC)/Peso corporal. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de Xeplion. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. No se ha estudiado con Xeplion el efecto del consumo de tabaco en la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte mayoritariamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (en ambos especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30ºC. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Xeplion 50 mg suspensión inyectable de liberación prolongada PVL: 168,18 €; PVP: 214,09 €; PVP (IVA): 222,65 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 218,62 €; PVP: 269,53 €; PVP (IVA): 280,31 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 269,10 €; PVP: 320,01 €; PVP (IVA): 332,81 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 403,64 €; PVP: 454,55 €; PVP (IVA): 472,73 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** 25 mg: EU/1/11/672/001. 50 mg: EU/1/11/672/002. 75 mg: EU/1/11/672/003. 100 mg: EU/1/11/672/004. 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 16 de diciembre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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

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

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

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

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

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

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

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

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

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

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

Dosis omitidas

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

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

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

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

Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia ni la seguridad en la población mayor de 65 años. En general, la dosis de TREVICTA recomendada en pacientes de edad avanzada con función renal normal es la misma que para los adultos más jóvenes con función renal normal. Dado que los pacientes de edad avanzada pueden presentar una reducción de la función renal, ver debajo en Insuficiencia renal las recomendaciones de dosificación para pacientes con insuficiencia renal. *Insuficiencia renal.* TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal (ver sección 5.2). En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se debe ajustar la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min). *Insuficiencia hepática.* No se ha estudiado el uso de TREVICTA en pacientes con insuficiencia hepática. Según la experiencia con paliperidona oral no es necesario ajustar la dosis en pacientes con insuficiencia hepática leve o moderada. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, por lo que se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y eficacia de TREVICTA en niños y adolescentes menores de 18 años. No se dispone de datos. Forma de administración. TREVICTA está indicado para administración intramuscular únicamente. No se debe administrar por ninguna otra vía. Cada inyección se administrará solo por un profesional sanitario, que administrará la dosis completa en una sola inyección. Se debe inyectar lenta y profundamente en el músculo deltoides o en el glúteo. Si aparecen molestias en el lugar de inyección, se considerará el cambio del glúteo al deltoides (y viceversa) en sucesivas inyecciones (ver sección 4.8). TREVICTA se debe administrar usando únicamente las agujas de pared fina que se faciliten en el envase de TREVICTA. Para la administración de TREVICTA no se utilizarán las agujas que se faciliten en el envase de la inyección mensual de palmitato de paliperidona ni otras agujas comercialmente disponibles (ver *Información reservada para médicos o profesionales sanitarios*). Se inspeccionará visualmente el contenido de la jeringa precargada para descartar la presencia de cuerpos extraños o decoloración antes de la administración. Es importante agitar enérgicamente la jeringa con la punta hacia arriba y la muñeca relajada durante al menos 15 segundos para garantizar una suspensión homogénea. TREVICTA debe ser administrado dentro de los 5 minutos siguientes a la agitación. Si transcurren más de 5 minutos antes de la inyección, agitar otra vez enérgicamente durante al menos 15 segundos para resuspender el medicamento (ver *Información reservada para médicos o profesionales*). *Administración en el deltoides.* El tamaño especificado de la aguja para administración de TREVICTA en el músculo deltoides está determinado por el peso del paciente. • En pacientes de peso ≥90 kg, se debe utilizar la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm). • En pacientes de peso <90 kg, se debe utilizar la aguja de pared fina de 22 G 1 (0,72 mm x 25,4 mm). Se debe administrar en el centro del músculo deltoides. Las inyecciones deltoideas se deben alternar entre los dos músculos deltoides. *Administración en el glúteo.* Para la administración de TREVICTA en el músculo glúteo, se utilizará la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm), sin tener en cuenta el peso corporal. La administración se debe hacer en el cuadrante superior externo del músculo glúteo. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. *Administración incompleta.* Para evitar la administración incompleta de TREVICTA, se debe agitar enérgicamente la jeringa precargada durante al menos 15 segundos en los 5 minutos que preceden a la administración para asegurar una suspensión homogénea (ver *Información reservada para médicos o profesionales sanitarios*). Sin embargo, si la dosis inyectada ha sido incompleta, la dosis restante de la jeringa no se debe reinyectar y no se debe administrar otra dosis dado la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará clínicamente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en estados psicóticos graves o de agitación aguda. No se debe utilizar TREVICTA para controlar estados psicóticos graves o de agitación aguda en los que es necesario un control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se usa a la vez que otros medicamentos que se espera que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autónoma, alteración de la consciencia y elevación de la creatinfosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SMN, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía/Síntomas extrapiramidales. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, que se caracteriza por movimientos rítmicos involuntarios, predominantemente de la lengua y/o de la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la posibilidad de suspender la administración de todos los antipsicóticos, incluido la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Se requiere precaución en pacientes que reciben tanto psicoestimulantes (p. ej., metilfenidato) como paliperidona de forma concomitante, ya que pueden aparecer síntomas extrapiramidales al ajustar una o ambos medicamentos. Se recomienda la retirada gradual del tratamiento estimulante (ver sección 4.5). Leucopenia, neutropenia y agranulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y agranulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo clínicamente relevante o de leucopenia/neutropenia inducida por medicamentos se deben someter a vigilancia estrecha durante los primeros meses de tratamiento y se considerará la suspensión de TREVICTA ante el primer signo de leucopenia clínicamente relevante sin que intervengan otros factores causantes. A los pacientes con neutropenia clínicamente relevante se les monitorizará estrechamente a fin de detectar la aparición de fiebre u otros síntomas o signos de infección y, si se presentan estos síntomas, se administrará un tratamiento rápido. A los pacientes con neutropenia grave (recuento total de neutrófilos <1 x 10^9/l) se les retirará la administración de TREVICTA y se les hará un seguimiento de los niveles de glóbulos blancos hasta su recuperación. Se tendrá en cuenta la acción prolongada de TREVICTA. Reacciones de hipersensibilidad. Se pueden producir reacciones de hipersensibilidad incluso en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.8). Hiperglucemia y diabetes mellitus. Se han notificado hiperglucemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso coma diabético y cetoacidosis con el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica antipsicótica habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polidipsia, poliuria, polifagia y astenia) y los pacientes con diabetes mellitus deben ser monitorizados regularmente de un empeoramiento del control de la glucosa. Aumento de peso. Se han notificado casos de aumento significativos de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipotensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o isquemia de miocardio, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipotensión (p. ej., deshidratación e hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se ajustará la dosis y se estabilizará al paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos de pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en estos pacientes. Pacientes de edad avanzada con demencia. TREVICTA no se ha estudiado en pacientes de edad avanzada con demencia. No se recomienda la administración de TREVICTA a pacientes de edad avanzada con demencia, debido al riesgo aumentado de mortalidad global y de reacciones adversas cerebrovasculares. La experiencia obtenida con risperidona que se describe a continuación se considera aplicable también a paliperidona. *Mortalidad global.* En un metaanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como risperidona, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con risperidona, la mortalidad fue del 4% en comparación con el 3,1% de los pacientes que recibieron placebo. *Reacciones adversas cerebrovasculares.* En ensayos clínicos aleatorizados y controlados con placebo en los que pacientes con demencia recibieron tratamiento con algunos antipsicóticos atípicos como risperidona, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplica por 3 aproximadamente. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y beneficios de prescribir TREVICTA a pacientes con enfermedad de Parkinson o con demencia con cuerpos de Lewy (DCL), porque ambos grupos tienen un mayor riesgo de Síndrome Neuroléptico Maligno y una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, embotamiento, inestabilidad postural y caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Se indicará al paciente que solicite asistencia médica urgente si el priapismo no se ha resuelto en el trascurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de reducir la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescriba TREVICTA a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej., ejercicio intenso, exposición a calor extremo, tratamiento concomitante con medicamentos de actividad anticolinérgica o deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con el uso de antipsicóticos. Dado que los pacientes tratados con antipsicóticos presentan a menudo factores de riesgo añadido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transcurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto antiemético. En los estudios preclínicos con paliperidona se observó un efecto antiemético. Si se produce este efecto en los seres humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA en un vaso sanguíneo. Síndrome del iris flácido intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como TREVICTA (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. Excipientes. Este medicamento contiene menos de 1 mmol de sodio (23 mg) por dosis; esto es, esencialmente "exento de sodio". **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir TREVICTA con medicamentos que prolongan el intervalo QT, como antiarrítmicos de la clase IA (por ejemplo, quinidina o disopiramida) y antiarrítmicos de la clase III (por ejemplo, amiodarona o sotalol), algunos antihistamínicos, antibióticos (por ejemplo, fluoroquinolonas), algunos antipsicóticos y algunos antipalúdicos (por ejemplo, mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que TREVICTA afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos metabolizados por las isoenzimas del citocromo P-450. Dado que paliperidona actúa principalmente sobre el sistema nervioso central (SNC) (ver sección 4.8), se debe usar con precaución la combinación de TREVICTA con otros medicamentos que actúan sobre el sistema nervioso central, como los ansiolíticos, la mayoría de los antipsicóticos, los hipnóticos, los opiáceos etc. o el alcohol. La paliperidona puede antagonizar el efecto de la levodopa y de otros agonistas de la dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se prescribirá la dosis mínima eficaz de cada tratamiento. Debido a su capacidad de inducir hipotensión ortostática (ver sección 4.4), es posible observar un efecto aditivo cuando se administra TREVICTA con otros medicamentos que tienen esta capacidad, como otros antipsicóticos o los antidepresivos tricíclicos. Se recomienda precaución al combinar la paliperidona con otros medicamentos que disminuyen el umbral convulsivo (por ejemplo, fenotiacinas o butirofenonas, antidepresivos tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de los comprimidos de liberación prolongada de paliperidona en el estado estacionario (12 mg una vez al día) con comprimidos de liberación prolongada de valproato sódico (de 500 mg a 2.000 mg una vez al día) no afectó a la farmacocinética en el estado estacionario del valproato. No se han llevado a cabo estudios de interacción entre TREVICTA y el litio, sin embargo, no es probable que se produzcan una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a TREVICTA. Los estudios in vitro indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios in vitro ni in vivo de que esas isoenzimas desempeñen un papel importante en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración conjunta de paliperidona oral de liberación prolongada una vez al día con carbamazepina 200 mg dos veces al día produjo una reducción de aproximadamente un 37% de los valores medios de C_{max} y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP o la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la absorción oral. Dado que no se han observado efectos sobre el adaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante periodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. Uso concomitante de TREVICTA y psicoestimulantes. El uso concomitante de psicoestimulantes (p. ej., metilfenidato) y paliperidona puede provocar síntomas extrapiramidales conduciendo a cambios en uno o en ambos tratamientos (ver sección 4.4). **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratógenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellos síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición materna a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo incluso si la administración de TREVICTA es muy anterior a la lactancia. TREVICTA no se debe utilizar durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la visión, como sedación, somnolencia, síncope o visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a TREVICTA. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas al medicamento observadas con mayor frecuencia notificadas en ≥5% de los pacientes en dos ensayos clínicos controlados a doble ciego de TREVICTA, fueron aumento de peso, infección de las vías respiratorias altas, ansiedad, cefalea, insomnio y reacción en el lugar de inyección. Tabla de reacciones adversas. A continuación se recogen todas las RAM notificadas con paliperidona en función de la frecuencia estimada en los ensayos clínicos realizados con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1.000 a <1/100), *raras* (≥1/10.000 a <1/1.000), *muy raras* (<1/10.000) y *frecuencia no conocida* (no se puede estimar a partir de los datos disponibles).

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

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

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

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

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. Descripción de algunas reacciones adversas. *Reacción anafiláctica*. Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección*. En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la clasificación realizada por los investigadores, síntomas como induración, rubefacción e hinchazón no se presentaron o fueron leves en ≥95% de las evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP)*. En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,9%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (trastorno extrapiramidal, síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, facies en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y mioclonía), distonía (incluye distonía, espasmo cervical, empurstótonos, crisis oculógiras, distonía bucomandibular, risa sardónica, tetania, hipertonía, torticolis, contracciones musculares involuntarias, contractura muscular, blefaroespasmo, oculogiración, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurotótonos, espasmo lingual y trismus) y temblor. *Aumento de peso*. En el estudio a largo plazo de retirada aleatorizada, se notificaron aumentos anormales de ≥7% de peso corporal desde el momento inicial hasta el momento final del estudio, analizados a doble ciego, en el 10% de los pacientes del grupo de TREVICTA y el 1% de los pacientes del grupo de placebo. A la inversa, se notificaron reducciones anormales del peso corporal (≥7%) desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, en el 1% de los pacientes del grupo de TREVICTA y el 8% de los pacientes del grupo de placebo. Las variaciones medias del peso corporal desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, fueron de +0,94 kg y -1,28 kg en los grupos de TREVICTA y placebo, respectivamente. *Hiperprolactinemia*. Durante la fase de doble ciego del estudio a largo plazo de retirada aleatorizada, se observaron niveles de prolactina por encima del intervalo de referencia (>13,13 ng/ml en los varones y >26,72 ng/ml en las mujeres) en un porcentaje más elevado de varones y mujeres del grupo de TREVICTA que del grupo placebo (9% frente a 3% y 5% frente a 1%, respectivamente). En el grupo de TREVICTA, la variación media entre el momento inicial y el final en un estudio doble ciego controlado con placebo fue de +2,90 ng/ml para los varones (frente a -10,26 ng/ml en el grupo placebo) y de +7,48 ng/ml para las mujeres (frente a -32,93 ng/ml en el grupo placebo). Una mujer (2,4%) del grupo de TREVICTA tuvo una reacción adversa de amenorrea, mientras que no se observaron reacciones adversas potencialmente relacionadas con la prolactina en ninguna mujer del grupo placebo. No hubo reacciones adversas potencialmente relacionadas con la prolactina en ninguno de los grupos de varones. Efecto de clase. Con el uso de antipsicóticos pueden aparecer prolongación del intervalo QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicada, paro cardíaco y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, entre ellos de embolia pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del QT y síntomas extrapiramidales. Se han descrito Torsades de pointes y fibrilación ventricular en un paciente expuesto a sobredosis de paliperidona oral. En caso de sobredosis aguda se debe tener en cuenta la posibilidad de que estén implicados varios fármacos. Tratamiento. Al evaluar las medidas terapéuticas y de recuperación, se tendrán en cuenta la naturaleza de liberación prolongada del medicamento, así como la prolongada vida media de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio se deben tratar con las medidas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales graves, se debe administrar medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos y continuos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros fármacos antipsicóticos, código ATC: N05AX13. TREVICTA contiene una mezcla racémica de paliperidona (+) y (–). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de los monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une estrechamente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D-2. Asimismo, paliperidona bloquea los receptores alfa 1adrenérgicos y, en menor medida, los receptores histaminérgicos H-1 y los receptores alfa 2 adrenérgicos. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque se trata de un potente antagonista de D2, motivo por el que se cree que alivia los síntomas de la esquizofrenia, produce menos catalepsia y menos reducción de las funciones motoras que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. La eficacia de TREVICTA para el tratamiento de mantenimiento de la esquizofrenia en pacientes que han sido tratados adecuadamente durante al menos 4 meses con la formulación inyectable mensual de palmitato de paliperidona y las últimas dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retirada aleatorizado, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizada, 506 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual administradas en el músculo deltoides o glúteo (50-150 mg) durante 17 semanas (los ajustes de dosis fueron en las semanas 5 y 9). Un total de 379 pacientes recibieron una dosis única de TREVICTA en el músculo deltoides o glúteo durante la fase de estabilización abierta (la dosis era 3,5 veces la última dosis de palmitato de paliperidona mensual). Los pacientes que se consideraban clínicamente estabilizados al final de la fase de estabilización de 12 semanas se aleatorizaron en proporción 1:1 para recibir TREVICTA o un placebo en una fase doble ciego de duración variable (la dosis de TREVICTA fue la misma que la última dosis recibida durante la fase de estabilización; esta dosis se mantuvo fija durante toda la fase de doble ciego). En este periodo, 305 pacientes sintomáticamente estables fueron aleatorizados para continuar el tratamiento con TREVICTA (n=160) o placebo (n=145) hasta que se produjese la recaída, la retirada prematura o al final del estudio. La variable principal de eficacia fue el tiempo hasta la primera recaída. Se puso fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 283 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICTA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,81 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICTA en comparación con placebo. En la figura 1 se representa la gráfica de Kaplan Meier del tiempo hasta la recaída para cada grupo de tratamiento. Se observó una diferencia significativa (p<0,0001) entre los dos grupos de tratamiento en el tiempo hasta la recaída a favor de TREVICTA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICTA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

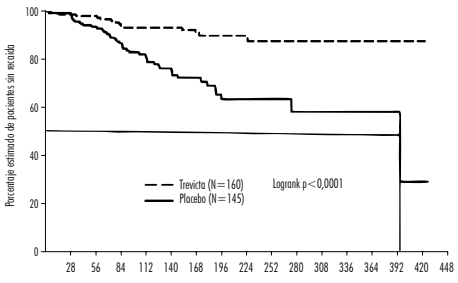


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída – Análisis final

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

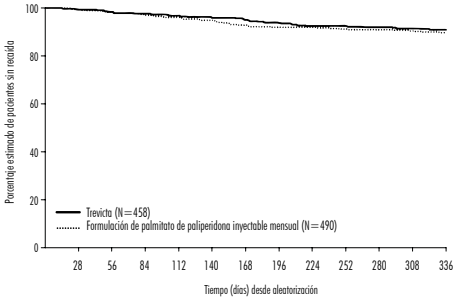


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{ss}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas in vivo, ninguna de las cuales representó más del 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios in vitro se señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. Estudios in vitro han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos in vivo y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona. TREVICTA está diseñado para liberar paliperidona durante un periodo de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{inf}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con personas sanas. Población de edad avanzada. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con la edad. Índice de masa corporal (IMC)/peso corporal. En los pacientes obesos y con sobrepeso se observaron valores de C_{max} más bajos. En el estado estacionario aparente de TREVICTA, las concentraciones valle eran similares en los pacientes normales, con sobrepeso y obesos. Raza. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el origen racial. Sexo. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el sexo. Tabaquismo. Según estudios in vitro realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no tiene un efecto en la farmacocinética de paliperidona. El efecto del consumo de tabaco sobre la farmacocinética de paliperidona no se ha estudiado en el caso de TREVICTA. Un análisis de farmacocinética poblacional basado en los datos obtenidos con comprimidos de liberación prolongada de paliperidona demostró una exposición a paliperidona ligeramente más baja en los fumadores que en los no fumadores. No es probable que esta diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) en inyección intramuscular y de paliperidona en administración oral a ratas y perros mostraron efectos fundamentalmente farmacológicos, como sedación y efectos mediados por la prolactina en glándulas mamarias y genitales. En animales tratados con palmitato de paliperidona se observó una reacción inflamatoria en el lugar de inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas con risperidona oral, que se convierte en gran medida en paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y en la supervivencia de las crías. No se han observado embriotoxicidad ni malformaciones después de la administración intramuscular de palmitato de paliperidona a ratas gestantes a dosis máximas (160 mg/kg/día), equivalentes a 2,2 veces el nivel de exposición de los humanos a la dosis máxima recomendada de 525 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la motricidad y del aprendizaje en las crías cuando se administraron a animales gestantes. Ni el palmitato de paliperidona ni la paliperidona han demostrado ser genotóxicos. En estudios sobre el potencial carcinogénico de la risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y de los adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico del palmitato de paliperidona administrado en inyección intramuscular a ratas. Se observó un incremento estadísticamente significativo de adenocarcinomas de las glándulas mamarias en ratas hembra a las que se administraron dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho experimentaron un incremento estadísticamente significativo de adenomas y carcinomas de las glándulas mamarias cuando se expusieron a dosis de 30 y 60 mg/kg/mes, que representan 0,6 y 1,2 veces el nivel de exposición humana a la dosis máxima recomendada de 525 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la relevancia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina cíclica) con émbolo, tope trasero y capuchón protector (goma bromobutílica), equipada con una aguja de seguridad de pared fina de 22 G 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 pulgadas (0,72 mm x 25,4 mm). Tamaño del envase: Envases con 1 jeringa precargada y 2 agujas. Presentaciones y precios. Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 489,25 €; PVP: 540,16 €; PVP (IVA): 561,77 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 636,50 €; PVP: 692,41 €; PVP (IVA): 720,11 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 782,80 €; PVP: 838,71 €; PVP (IVA): 872,26 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.174,20 €; PVP: 1.230,11 €; PVP (IVA): 1.279,31 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver Información reservada para médicos o profesionales sanitarios). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007. EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 5 de diciembre de 2014. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2018. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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