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Methodological rigour in the study of addictions

Rigor metodológico en el estudio de las adicciones

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The methodological advances of recent years in the study of addictive behaviour have been astounding. A whole set of methods and techniques have been developed which would have been unimaginable a few decades ago and which allow a better understanding of the phenomena we study in our field, in turn leading to the development of new forms of evaluation, diagnosis and intervention. Latent class models, network analysis, or multilevel models are just a few examples. In addition, the growing specialisation of some related areas such as neuroscience or behavioural genetics (Costas, 2015), means that sophisticated methodological advances are incorporated which are very often difficult to understand by non-specialists in the field. Nevertheless, despite these advances, researchers should not lose sight of the three key aspects of the methodological approach to any research: design, measurement of variables and analysis of data. Progress has been made in each of these central aspects. We on the editorial committee of *Adicciones* wish to emphasise the need to take these three parameters into account to serve as a guide for updating the methodological review criteria of the papers sent in to the journal, leading to an improvement in the scientific quality of the research published. This process of methodological updating and standardization to which *Adicciones* is committed is similar to that already carried out by other scientific journals (Ato, López & Benavente, 2013). The technical requirements to be met by all research are already well documented in the specialised literature (Abad, Olea, Ponsoda & García, 2011; Ato & Vallejo-Seco, 2015; Muñiz, 2000; Ruiz-Ruano & Puga, 2017; Wells & Faulkner-Bond, 2016). We will limit ourselves here to highlighting those issues that seem to us most relevant.

The first step of the research process from a methodological point of view is the design, that is, the strategy we propose to follow in order to test our objectives and hypotheses. Crucial aspects covered by the research design include the selection and allocation of participants and the control of extraneous and confounding variables. A design should basically consider two types of validity: internal and external. These will determine the quality of the study. While internal validity refers to the degree to which the design guarantees the attribution of causality by controlling the influence of possible extraneous variables, external validity has to do with the degree to which the results can be generalised to other participants, contexts and/or times. A detailed description of the participants (number, age, gender, nationality, origin, diagnosis, etc.), of the type of sampling performed, the possible experimental conditions, the context and circumstances in which the study is performed, and the procedures used to control the extraneous variables is therefore an essential requirement in any research. All this needs to be clearly reflected so that readers and other researchers have the necessary information to assess the relevance of the study.

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The second pillar is the process of measuring the variables, involving their identification and definition as well as measurement. It is necessary to select the variable of interest, to provide it with an operative definition and to assign numbers to its attributes according to certain rules. The scale of measurement used, which, according to Stevens' classical approach, may be nominal, ordinal, interval or ratio must be explicitly stated. The issue is not a trivial one, as this in turn bears a direct relationship to the statistical analysis procedures to be performed subsequently. Measuring also requires the use of an instrument to collect data, samples of behaviour. It should not be forgotten that in the study of addictive behaviour we frequently work with latent variables or constructs, leading to an unobservable variable being postulated from a set of indicators. In almost all measurement contexts, the scores contain a certain degree of error. The size of such measurement error must be clearly stated when drafting all scientific papers. To put it bluntly, if the measurement process is flawed, both the inferences drawn and the decisions made on the basis of the data obtained could be incorrect and groundless.

As for the measuring instruments, detailed information on the metric quality of the instruments, and especially on the reliability of the scores, as well as evidence of validity, must be provided. Reliability refers to the accuracy of the scores, that is, to the quality of the data, while validity involves the quality of the inferences (Prieto & Delagado, 2010). A test itself is not reliable; what is reliable are its scores. A test is not valid; what is valid are the inferences made on the basis of its scores. Note that what may be valid for a given group of people or population may not be valid for another, and what may be valid in one assessment context need not be so in a different context. The new classification proposed by the *Standards for educational and psychological testing* (American Educational Research Association, American Psychological Association & National Council on Measurement in Education, 2014) refers to five types of validity evidence, namely test content, response processes, the internal structure of the test, relations with other variables and the consequences arising from the use for which they are proposed. According to this conceptualization of validity, terms such as construct validity begin to fall into disuse, and it is becoming preferable, for example, to speak of evidence of internal structure instead of factorial validity. For more detailed information the reader may consult previous studies (Sireci & Padilla, 2014; Leong, Bartram, Cheung, Geisinger & Iliescu, 2016).

When a measuring instrument is newly created, it is necessary to justify the need for its development and to provide detailed information about the construction and validation process (Lane, Raymond & Haladyna, 2016; Muñiz & Fonseca-Pedrero, 2017). When the instrument is adapted to Spanish, standards for the translation and adaptation of tests from one culture to another must be followed (Muñiz, Elosua, & Hambleton, 2013). If it is not a new construction or an adaptation, the researcher must select those measuring instruments that have been duly validated and for which information on their psychometric properties in the population under study is available (Zumbo, 2007). Similarly, measuring instruments should be used appropriately, and impartiality should be ensured throughout the measurement and evaluation process, for example by analyzing the measurement invariance or the differential item functioning (e.g., Mezquita, Stewart, Kuntsche & Grant, 2016). In order to analyze measurement tool quality, a model for test evaluation has been developed (Hernández, Ponsoda, Muñiz, Prieto, & Elosua, 2016) which in essence allows us to separate the wheat from the chaff. A rigorous assessment with a suitable measurement tool is a key requirement for accurate diagnoses from which effective interventions based on empirical evidence can be derived (Muñiz & Fonseca-Pedrero, 2017).

The third methodological pillar is data analysis. Here we have to use the most appropriate statistical procedures based on both the objectives and hypotheses postulated initially and the nature of the data. This is not a simple task. Assuming that the statistical analyses applied are appropriate, it is necessary to report on the statistical instrument used, the level of significance, the degrees of freedom, the confidence intervals and, of course, the effect size. Articles subject to *Adicciones* should incorporate information about the magnitude of effect, i.e. the practical significance of the results, and go beyond the mere statistical significance, or *p*-value. All this will have a bearing on the validity of the statistical conclusions. Likewise, if the statistical technique used is novel or difficult to understand due to its complexity or for any other reason, information that allows it to be fully understood by non-specialists in the subject has to be provided. Data analysis is an essential aspect of scientific advancement because sooner or later anyone wishing to investigate the empirical study of a variable has to resort to the statistical analysis of the data.

In sum, this editorial emphasises the need to incorporate quality standards of scientific research, in this case, of a methodological nature, in the manuscripts submitted to the journal *Adicciones*. We call for a statistical re-education as well as the use of checklists and guidelines that allow the methodological quality of the scientific studies to be assessed. Students and professionals should be trained continuously in the different methodological changes and innovations, particularly considering the increase in levels of specialisation of professionals and the rapid assimilation of statistical advances. We must never lose sight of the fact that proper application of research design, measurement procedures and statistical analysis influences the accumulation of scientific knowledge and has an impact, whether we like it or not, on our professional work and, therefore, on people.

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References

Abad, F. J., Olea, J., Ponsoda, V. & García, C. (2011). *Medición en ciencias sociales y de la salud*. Madrid: Síntesis.

American Educational Research Association, American Psychological Association & National Council on Measurement in Education. (2014). *Standards for Educational and Psychological Testing*. Washington, DC: Author.

Ato, M., López, J. J. & Benavente, A. (2013). Un sistema de clasificación de los diseños de investigación en psicología. *Anales de Psicología, 29*, 1038–1059.

Ato, M. & Vallejo-Seco. G. (2015). *Diseños de investigación en psicología*. Madrid: Pirámide.

Costas, J. (2015). Un abordaje genómico del alcoholismo. *Adicciones, 27*, 87–89. doi:10.20882/adicciones.693.

Hernández, A., Ponsoda, V., Muñiz, J., Prieto, G. & Elosua, P. (2016). Revisión del modelo para evaluar la calidad de los tests utilizados en España. *Papeles del Psicólog*o, *37*, 161–168.

Lane, S., Raymond, M. R., & Haladyna, T. M. (2016). *Handbook of test development (2nd edition)*. New York, NY: Routledge.

Leong, F.T.L., Bartram, D., Cheung, F.M., Geisinger, K.F. y Iliescu, C. (Eds.) (2016). *The ITC International Handbook of Testing and Assessment*. New York: Oxford University Press.

Mezquita, L., Stewart, S. H., Kuntsche, E. & Grant, V. V. (2016). Estudio transcultural del modelo de cinco factores de motivos de consumo de alcohol en universitarios Españoles y Canadienses. *Adicciones, 28*, 215–220. doi:10.20882/adicciones.822.

Muñiz, J. (2000). *Teoría Clásica de los Tests*. Madrid: Pirámide.

Muñiz, J. & Fonseca-Pedrero, E. (2017). *Construcción de instrumentos de medida en psicología (2ª edición)*. FOCAD. Madrid: Consejo General de Colegios Oficiales de Psicólogos.

Muñiz, J., Elosua, P. & Hambleton, R. K. (2013). Directrices para la traducción y adaptación de los tests: segunda edición. *Psicothema, 25*, 151–157.

Prieto, G., & Delgado, A. R. (2010). Fiabilidad y validez. *Papeles del Psicólogo, 31*, 67–74.

Ruiz-Ruano, A. M. & Puga, J. L. (2017). *Fundamentos de estadística*. Murcia: Iuris Universal.

Sireci, S. & Padilla, J.-L. (2014). Validating assessments: Introduction to the Special Section. *Psicothema, 26*, 97–99. doi:10.7334/psicothema2013.24.

Wells, C. S. & Faulkner-Bond, M. (2016). *Educational Measurement. From Foundations to Future*. New York, NY: The Guilford Press.

Zumbo, B. D. (2007). Validity: Foundational issues and statistical methodology. En C. R. Rao & S. Sinharay (Eds.), *Handbook of statistics: Vol. 26. Psychometrics* (pp. 45–79). Amsterdam, Netherlands: Elsevier Science.

Intervention on early-onset conduct problems as indicated prevention for substance use: A seven-year follow up

Intervención sobre problemas de conducta tempranos como prevención indicada del consumo de drogas: Siete años de seguimiento

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Abstract

The aim of this study is to evaluate the long-term effects of a manualised program which intervenes on children with early-onset conduct problems, their families and teachers. The program evaluation involved 14 primary schools which were randomly assigned to the intervention (45 participating families) and control (30 families) conditions during 2007-2008. After a screening process which identified children with significant conduct problems both at home with their family and at school, the program was implemented in eight schools. Seven years later, 58 families (37 from the intervention group and 21 from the control group), with characteristics equivalent to those of the study's entire initial group, were contacted again. With measures administered to the children and their parents, comparisons through multivariate analyses of variance between intervention and control groups supported the program's efficacy in reducing both conduct problems and relations with antisocial peers. Furthermore, the program fostered social and communication skills. As regards drug use, the intervention group showed less favourable attitudes towards drugs, lower intention of drug use, lower frequency of tobacco use and lower intensity of alcohol use. These results support the usefulness of multicomponent programs for conduct problems as a way to prevent, in the long term, unfavourable developmental trajectories, where drug use is a key element.

Keywords: Indicated prevention; Conduct problems; Childhood; Substance use.

Resumen

Este trabajo tiene como objetivo evaluar los efectos a largo plazo de un programa manualizado que interviene sobre niños con problemas de conducta, sus familias y sus profesores. El programa involucró, durante el curso 2007-08, a 14 escuelas que fueron asignadas aleatoriamente a las condiciones de intervención (45 familias participantes) y control (30 familias). A partir de un screening que identificó niños con problemas significativos de conducta en la familia y en la escuela, el programa fue aplicado en ocho de esos centros. Siete años más tarde, se pudo contactar de nuevo con 58 familias (37 de intervención y 21 control), con características equivalentes al total de participantes en el estudio inicial. Por medio de informes obtenidos de los participantes y de sus padres, y a través de comparaciones con análisis multivariables de la varianza, se apoya la eficacia del programa en la reducción de los problemas de conducta y de la implicación con amigos antisociales. Asimismo, se encuentra que el programa promueve la competencia social y comunicativa de los participantes. En cuanto al consumo de drogas, el grupo de intervención muestra actitudes menos favorables hacia las drogas, menor intención de consumo, menor frecuencia de consumo de tabaco y menor intensidad de consumo de alcohol. Estos resultados apoyan la utilidad de los programas multicomponente de intervención sobre los problemas de conducta como una vía para prevenir, a largo plazo, trayectorias de desarrollo desfavorables, en las que el consumo de drogas es una pieza fundamental.

Palabras clave: Prevención indicada; Problemas de conducta; Niñez; Consumo de drogas.

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Drug use prevention has been a widely developed field in recent decades (Scheier, 2015). However, despite the enormous volume of efforts invested in what Gordon (1983) called "universal prevention", "indicated" prevention (specifically targeted at individuals who display indicators that permit predicting a problem; see Foxcroft, 2014) is a less developed field. In recent years, both American (NIDA, 2003) and European (EMCDDA, 2009) agencies have expressed the need for increasing resources for prevention, with special attention to those individuals with an early risk of more severe use patterns. In this regard, research has shifted its focus toward early-onset conduct problems as a key indicator for predicting drug abuse and comorbidity with other problems, such as antisocial behaviour, maladjustment at school and emotional difficulties.

The study of disruptive behaviour disorders (or "externalising" problems) as part of the determinants for drug use has experimented a major boost in recent years (e.g., Martel et al., 2009; Sitnick, Shaw & Hyde, 2014). Developmental psychopathology (Cicchetti & Cohen, 2006) highlights the need for moving beyond immediate indicators to know how the trajectories leading to a high risk of drug abuse develop from childhood. In this regard, theoretical cascade models have been proposed (Dodge et al., 2010; Haller, Handley, Chassin & Bountress, 2010), positioning conduct disorders in the centre of an accumulative process where further difficulties are generated progressively. Therefore, behavioural problems, through reciprocal, influential links with family problems, rejection by peers, maladjustment at school, and limited self-control and emotional processing skills, generate a snowball effect, by which the opportunities for healthy development are increasingly reduced. In this context, conduct disorders become more chronic, and a maladjusted lifestyle becomes increasingly consolidated, resulting in problematic drug use, together with antisocial, impulsive and emotional disorders (Webster-Stratton & Hammond, 1997).

In support of these models, research has proven that behavioural problems are consistently associated with indicators of severity of use, including high rates of polydrug addiction, high involvement in criminal activities, high risk of abandoning treatment, and poor response unto interventions (Hawkins, 2009; Hser, Grella, Collins & Teruya, 2003). Therefore, programs that address early-onset conduct problems are considered necessary tools for preventing problematic drug use since childhood (EMCDDA, 2009; Glantz, 2002).

Given the breadth and complexity of the factors intervening in the aetiology and development of conduct disorders, prior studies have reiterated the need for multicomponent programs that simultaneously act upon different sources of risk (Conduct Problem Prevention Research Group, 2004; Foster, Olchowski & Webster-Stratton, 2007). Though earlier publications include many examples of intervention programs for conduct problems, databases on evidence-based prevention programs (e.g., Blueprints for Youth Health Prevention, Centre for Substance Abuse Prevention) identify a very low number of multicomponent programs that both target children with behaviour disorders and have undergone a long-term evaluation to verify their impact on drug use. The programs *Coping Power* (Zonnevylle-Bender, Matthys, Van De Wiel & Lochman, 2007) or *Linking the Interests of Families and Teachers* (Eddy, Reid, Stoolmiller & Petrow, 2003) are mentioned as exemplary interventions which, acting upon several psychosocial areas and focused on behaviour problems, have proven to be effective in relation to the subsequent behaviour of youth, including drug use prevention.

Likewise, reviews of this issue have highlighted the need for pursuing further research on the preventive effect of the intervention on children with emotional and behavioural problems (Salvo et al., 2012). For all of these reasons, this study evaluates, seven years after its implementation, a multicomponent program that targeted children with early-onset conduct problems. The EmPeCemos program (see Romero, Villar, Luengo & Gómez-Fraguela, 2009; http://www.emcdda.europa.eu/html.cfm/index52035EN.html?project_id=ES_03&tab=overview) is based upon cascade models proposed by developmental psychopathology (Dodge et al., 2010; Granic & Patterson, 2006) and offers a manualised and coordinated intervention that involves the family, the teachers and the children themselves. Previous studies on the efficacy of each of its components as well as of the program as a whole showed that the intervention decreases conduct problems (including hyperactivity and rebellious behaviours), with *d* effect sizes between .72 and .78 for global measures of conduct problems, and that these effects were maintained for one year (Robles, 2009; Romero, Villar, Luengo, Gómez-Fraguela & Robles, 2014). Furthermore, the program has significant short-term effects on theoretically mediating variables: parenting practices, children's socioemotional skills and teachers' self-efficiency in managing disruptive behaviours (Romero, Villar & Gómez-Fraguela, 2010), in accordance with the program's immediate goals.

The purpose of this study is to complete a long-term follow-up of this program by examining its effects when the participants are adolescents. Bearing in mind the approach of developmental psychopathology in addition to the role of early-onset conduct problems in drug use, our analysis includes both these youths' disruptive behaviour patterns and substance use.

Methods

Participants

The participants were selected during the 2007-2008 academic year through a screening at 14 randomly selected grade schools in the geographical area near Santiago de Compostela in Galicia. This screening used a 10-item instru-

ment based on the Teacher Report Form (TRF, Achenbach, 1991a), in accordance with the indications given by previous programs aimed at children with conduct problems (Larson & Lochman, 2002). The teachers of grades two to four, who were mentors of the children, completed this instrument. A detailed evaluation was completed of those cases which the screening identified as more suitable for the intervention, taking into account information provided by parents (using the CBCL by Achenbach, 1991b) and teachers (using the full version of the TRF). This evaluation was used to select the families whose children had significant conduct problems (t-scores higher than 70 in the "Externalising" dimension) at home with the family and at school. Criteria for exclusion included a diagnosis of mental retardation or a pervasive developmental disorder. Of the 88 families selected, 75 agreed to participate in the study. Of the 14 participating schools, 8 were randomly assigned to the "intervention" condition (with 45 children with conduct problems; average age: 8.34 years) and 6 to the "control" condition (with 30 children with conduct problems: average age: 8.27 years). No significant differences were found between the groups as to basic sociodemographic variables (age, sex, household composition) or degree of conduct problems.

The multicomponent program was implemented at the 8 schools of the intervention group during the academic years 2007-2008 (basic program) and 2008-2009 (booster modules). The participants were contacted again in 2014 for purposes of this long-term follow-up. Of the 75 families participating in the initial study, 64 were contacted. Changes in telephone number and/or address impeded contacting the other families. Of the 64 families contacted, 58 agreed to participate. Of these families that refrained from participating, four claimed limited availability and/or temporary health problems; another two families declined to participate without offering specific reasons. The attrition rate, therefore, was 22% over seven years; lost cases from the intervention group amounted to 17% (37 of the 45 families participated) while, as is expected, participation from the control group was lower (21 of the 45 families participated; 30% attrition rate). Finally, the sample of participants included in our evaluation was comprised of 58 children (56 boys and 2 girls) with an average age of 15.25 years at the time of the evaluation.

Description of the intervention

The EmPeCemos program is comprised of three components. The 12-session family program trains parents in skills for establishing positive relationships with their children, promoting positive behaviours in them and facing problematic conduct themselves. Furthermore, the program includes training modules on self-control, problem-solving and communication skills as support for the parenting strategies these parents need to learn and, as support, in addition, for the children's cognitive and emotional development. The 12-session children program trains children with conduct problems in skills for recognising their emotions, self-control, problem-solving, acknowledgment of other viewpoints, and socialization skills (a detailed program description is given in Romero et al., 2009). Last of all, the 8-session teacher program provides training on strategies for managing disruptive behaviours and for promoting collaboration with the family and stimulating suitable conduct at school. The booster modules (two sessions for parents and children and one session for teachers) were implemented six months and one year after this basic program.

The program's three components are implemented in groups (of between 5 and 10 participants) using techniques based on social learning: instructions, discussion, modelling (in vivo and audiovisual), role-playing and, especially, guided practice in a natural setting. With the goal of achieving coherent changes in the children and their environment, previously trained therapists implement the components simultaneously and in coordination.

The multicomponent program was implemented at the schools themselves. The program's participation rates are quite high, especially given the fact that the program participants had a high risk of social maladjustment. The abandonment rate between the start and end of the basic program was 8% for the parents and children component (4 of 45) and somewhat higher for the teacher component (15%; 19 of 125). Participation in the sessions was also high: on the average, parents attended 9.24 sessions, children attended 10.43 (in both cases, with a possible maximum of 12), and teachers attended 5.05 (maximum of 8). On another hand, follow-up of the implementation process showed that an average of 88% (70 of 79) of the proposed activities for families, 76% (59 of 77) of the proposals for children and 73% (30 of 41) of the proposals for teachers were applied. This provides support for the integrity of the program's application which, in addition, was applied with a high degree of fidelity as to the program's rationale and principles, verified through the implementation diaries, the virtual monitoring platform used and the self- and hetero-evaluation questionnaires completed by therapists during each session.

Finally, the abandonment rate between the start of the intervention and end of the support modules was 11% for the parents and children component (5 of 45) and 25% for the teacher component (31 of 125). As regards the booster sessions six months later, on average, 90% of the planned activities for parents (9 of 10), 100% of those for children (9 of 9) and 75% of those for teachers (3 of 4) had been applied. As regards the support modules one year later, on average, 100% of the planned activities for parents (10 of 10), 100% of those for children (10 of 10) and 66% of those for teachers (2 of 3) had been applied.

Instruments

This evaluation included data collected through self-reports and rating scales completed by parents.

Self-reports as instruments

Drug use. The Drug Use Questionnaire (Luengo, Romero, Gómez-Fraguela, Garra & Lence, 1999) includes a broad range of indicators related with substance use, including attitudes, intention of use, age at onset of use, frequency and quantity consumed. The instrument has been used in many previous studies and has proved its efficiency for evaluating drug use patterns amongst youth (e.g., Luengo, Villar, Sobral, Romero & Gómez-Fraguela, 2009; Sobral, Gómez-Fraguela, Romero, Luengo & Villar, 2012).

Disruptive behaviour problems. The Antisocial Behaviour Questionnaire (CCA; Luengo, Otero, Romero, Gómez-Fraguela & Tavares, 1999), allowed for evaluating, through 37 items, the implication of youth in antisocial conduct over the last 12 months. A specific evaluation of aggressive conduct patterns was completed using the self-reported Reactive/Proactive Aggression Scale (Dodge & Coie, 1987), a brief 6-item scale that allows for evaluating involvement in premeditated and instrumental conduct (proactive aggression) and aggressive emotional conduct as a reaction to real or perceived provocations (reactive aggression).

Adaptation at school. The School Adaptation Scale by Berry, Phinney, Sam & Vedder (2006) includes 8 items for measuring absenteeism, performance and socialization at school.

Adaptation to the group setting. To examine the degree of integration and adaptation to the peer group setting, in addition to a direct item that asks about the number of friends, we also used the Trust in Friends Scale (taken from the Inventory of Parent and Peer Attachment (IPPA), Armsden & Greenberg, 1987), that evaluates closeness and caring attitude in one's relationship with peers, and the Involvement with Antisocial Friends Scale (adapted from Thornberry, Lizotte, Krohn, Farnworth & Jang, 1994), with five items evaluating relations with friends having antisocial conduct.

Empathy. Given the relevance of empathy and acknowledgment of other viewpoints as ingredients of social competencies required for healthy development, a self-reported empathy indicator was included: the abbreviated version of the Empathy Scale for Children (Del Barrio, Aluja & García, 2004), comprised of 10 items that evaluate children's capacity for feeling affected by others' emotions.

All of the self-reported instruments had been widely used in previous studies in our sociocultural context, with suitable psychometric properties (e.g., López-Romero, Romero & Andershed, 2015).

Rating scales completed by fathers/mothers

Conduct problems. The children's fathers/mothers completed the Child Behaviour Checklist (CBCL; Achenbach, 1991b) that allows for evaluating externalising and internalising problems, the Disruptive Conduct Rating Scale (Barkley, 1997) that allows for obtaining, through 26 items, measures of attentional difficulties, hyperactivity/impulsivity and oppositional/defiant conduct. Furthermore, to evaluate aggressive conduct patterns, the parent version of the Reactive/Proactive Aggression Scale (Dodge & Coie, 1987) was used.

Emotional and social competencies. The Fast Track Social Competency Scale (Conduct Problems Prevention Research Group, 1995) provides, through 12 items, measures on Prosocial/Communication Skills and Emotional Control Skills.

Families were asked to have the parental figure that spends the most time with the child complete the hetero-informed instruments; in 77% of cases, the mother was the source of information.

Again, these instruments had been adapted and widely used in previous studies (López-Romero et al., 2015; Romero, Robles & Lorenzo, 2006), with suitable psychometric properties.

Procedure

In February 2014, seven years after the program had been applied, the families that had participated previously in the study as part of the intervention or control group were contacted by phone or letter to request their collaboration in this follow-up. The evaluation instruments were applied between April and July, at the places of residence of these families, by specialised personnel without prior involvement in the program's implementation. While no incentives were given for participation in the study during the program's application, each family that participated in this follow-up was awarded 20 euros. All of the procedures were approved by the Bioethics Committee of the University of Santiago de Compostela, and both informed consent of the parents and willingness to participate of children were obtained for participation in the initial study as well as the follow-up.

Results

Analysis of attrition

First, we examined the extent to which differential attrition had occurred, depending on variables that, a priori, could be considered relevant for evaluating the program's effects. As to the intervention group, no significant differences were found between the participants and the lost cases in terms of age (participants' initial age of 8.42, compared with 8.38 for the lost cases; $F = 0.007$, 1/43 df, ns). As concerns previous conduct problems, the lost cases tended toward higher scores (average global score in disruptive conduct of the Barkley scale of 46.89, compared with 38.49 of the participants), but, even so, these differences were not statistically significant ($F = 2.05$, 1/42 df, ns). Differential attrition did occur depending on sex in the intervention group. Though the sample size of girls was already small (5 girls, 11% of the total sample, reflecting the different prevalence of early-onset conduct problems between boys and girls), more girls

than boys were lost during follow-up (chi-squared: 10.18, 1 df, $p < .01$).

As regards the control group, no differential attrition occurred depending on initial age (8.54 in the case of participants, 8.21 in the lost case group, $F = 1.90$, 1/28 df, ns), in previous conduct problems (though, once again, the lost case group tends to show more previous problems, though these were not statistically significant: 37.50 vs. 45.23, $F = 1.90$, 1/28 df, ns). Neither is there a differential loss of participants depending on sex (chi-squared: 0.12, 1 df, ns).

Finally, when both groups of participants in the follow-up (intervention and control) are compared as regards these basic variables, no significant differences are found for sex (chi-squared: 0.20, 1 df, ns), initial conduct problems (38.19 in the intervention group vs. 37.50 in the control group; $F = 0.03$, 1/54 df, ns) nor for current age (15.06 in the intervention group vs. 15.43 in the control group, $F = 1.25$, 1/55, ns).

Therefore, the analysis of attrition suggests that the participants of both intervention and control groups who participated in the final follow-up comprise two groups that are equivalent to those that initially participated in the study. This supports the internal validity of the comparisons made in this evaluation.

Differential development of conduct problems during the seven-year period

For purposes of knowing how disruptive conduct problems develop in both groups (as measured using the Disruptive Conduct Rating Scale, Barkley, 1997) in this long-term evaluation, a 2x3 Analysis of Variance was performed with an intrasubject measure, represented by evaluation periods T1 (pretest, before applying the program), T2 (postest, upon completion of the basic program) and T3 (follow-up, seven years later). The purpose of this is to identify the development trajectories of conduct problems over the seven years of follow-up, taking a suitable measure (the Barkley scale) for use during the three evaluation periods. The results display a significant interaction between the treatment condition (intervention vs. control) and time ($F = 8.70$, 2/45 df, $p < .001$), therefore indicating that the conduct problems developed differently in both groups. Figure 1 represents this development.

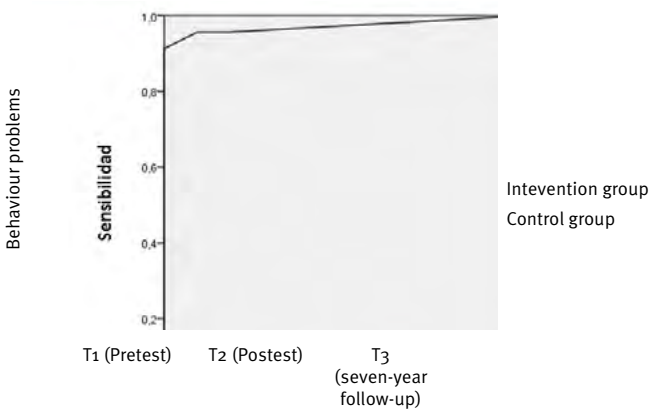

Figure 1. Development of conduct problems between pretest and seven-year follow-up

The figure displays the decrease in conduct problems for the intervention group between pretest and postest, $t(35) = 6.58$, $p < .001$, and that this decrease continues over time, without significant differences between postest and follow-up, $t(34) = 0.17$, ns. The control group, however, maintained high levels of conduct problems in the postest (without significant differences between both periods; $t(19) = -.29$, ns, and, though the seven-year period shows a decreasing trend, the difference between postest and evaluation is not statistically significant, $t(20) = 1.19$, ns, and conduct problems remain high in comparison with the intervention group. No differences were found in intergroup comparisons of the intervention and control groups in the pretest, as already mentioned, $F(1/54) = .03$, ns, but the opposite occurred in the postest, $F(1/54) = 12.46$, $p < .001$, and in follow-up, $F(1/53) = 4.67$, $p < .05$, with the control group obtaining higher scores in both cases.

Comparison of the intervention and control groups in follow-up: Behavioural difficulties, psychosocial functioning and drug use

Once having compared that 1) the intervention and control groups were comparable with each other, in that they adequately represented the groups comprising the initial study; and that 2) the groups developed differently over time in the basic marker of conduct problems, the next step was to compare both groups in a wide range of variables indicative of the adolescents' psychological adjustment. This allowed us to analyse the extent to which participation in the program relates with markers of wellbeing and social adaptation, including drug use.

In particular, this analysis included three clusters of variables: 1) behavioural problems (externalising and internalising), 2) psychosocial skills and functioning (in family, school and group settings), and 3) drug use. Bearing in mind the multicollinearity of the variables, multivariate analysis of variance (MANOVA) was performed, considering each group of variables jointly; when the multivariate analysis resulted in significant differences, univariate analysis of variance was subsequently performed. In accordance with the multi-informant perspective adopted by this study, each analysis included, as pertinent for those indicators, information given by the parents and by the youth themselves.

The results of the comparison of the intervention and control groups are explained below.

Comparison as regards behavioural problems.

For comparing behavioural problem measures, we used, on one hand, indicators of general behaviour problems and, on another hand, aggressive conduct (reactive and proactive) as a specific category of behaviour problems.

Table 1 displays the results corresponding to the comparison of the intervention and control groups in diverse global measures of behaviour problems.

The results of the multivariate analysis revealed the existence of significant differences in this group of variables. Specifically, the univariate analysis revealed that the boys that participated in the intervention presented, seven years later, lower levels of externalising and disruptive problems as reported by parents, less impulsivity and less oppositional-defiant conduct. However, no differences were found as regards attentional problems, nor in self-reported antisocial conduct. Neither were there differences as regards internalising problems.

When aggressive conduct was analysed specifically, including measures of proactive (premeditated, instrumental) and reactive (hostile, emotional) aggression, as reported both by parents and the children themselves, the multivariate analysis showed the inexistence of significant differences between both groups (F = 0.59, 4/49, ns).

Comparisons of psychosocial skills and functioning.

The analysis of variables for this area considered, on one hand, psychosocial skills, on another hand functioning at school, and on another, social functioning amongst the group of friends.

Table 2 displays the results of the comparison of both groups as regards psychosocial skills: emotional control skills, prosocial/communication skills, and empathy (self-reported).

The results of the multivariate analysis revealed the existence of significant differences in this group of variables. The differences occur, specifically, in prosocial/communication skills, where the intervention group obtained higher scores than the control group.

When analysing functioning at school (socialization at school, absenteeism, academic performance), the multivariate comparison was not significant (F = 1.77, 3/52, ns), though the univariate comparison did indicate that unjustified absences of the control group were significantly more frequent than those of the intervention group (F = 5.01, 1/54, $p < .05$).

Table 3 displays the results corresponding to the variables of the group of friends.

Table 3 shows that both groups also differ in this group of variables, and that these differences are established, in particular, in the antisocial conduct of one's friends, higher in the control group than in the intervention group.

Table 1. *Multivariate analysis of variance for comparing the intervention and control groups in measures of behaviour problems (seven-year follow-up)*

	Intervention Group N = 37 Average (SD)	**Control Group** N = 21 Average (SD)	λ	**F(df)**	**η²**
			0.65	3.64 (6/42)**	0.34
CBCL-Externalising (Parent Inf.)	12.86 (8.36)	21.20 (10.36)		8.91 (1/47)**	0.16
CBCL-Internalising (Parent Inf.)	12.80 (8.36)	9.18 (5.96)		2.46 (1/47)	0.05
Attentional difficulties (Parent Inf.)	12.76 (7.96)	14.00 (7.17)		0.26 (1/47)	0.05
Hyperactivity/Impulsivity (Parent Inf.)	6.69 (4.86)	9.66 (4.46)		4.06 (1/47)*	0.08
Oppositional-defiant conducts (Parent Inf.)	6.11 (5.55)	11.20 (5.10)		9.14 (1/47)**	0.16
Self-reported antisocial conduct	9.09 (9.21)	12.66 (11.48)		1.33 (1/47)	0.02

Note. * p<.05; ** p<.01

Table 2. *Multivariate analysis of variance for comparing the intervention and control groups in measures of psychosocial skills (seven-year follow up).*

	Intervention Group N = 37 Average (SD)	**Control Group** N = 21 Average (SD)	λ	**F(df)**	**η²**
			0.81	3.83 (3/51)*	0.18
Emotional control skills (Parent Inf.)	10.99 (4.42)	8.85 (3.85)		3.26 (1/53)	0.05
Prosocial/communication skills (Parent Inf.)	15.91 (4.46)	11.45 (5.09)		11.46 (1/53)**	0.17
Empathy (self-reported)	7.26 (2.36)	6.20 (2.23)		2.69 (1/53)	0.04

Note. * p<.05; ** p<.01

Table 3. *Multivariate analysis of variance for comparing the intervention and control groups in measures concerning peers (seven-year follow-up)*

	Intervention Group N = 37 Average (SD)	**Control Group** N = 21 Average (SD)	λ	**F(df)**	**η²**
			0.22	3.47 (3/41)*	0.22
Number of friends	7.04 (5.79)	8.00 (6.56)		1.00 (1/40)	0.00
Trust in friends	3.82 (0.95)	4.13 (0.68)		0.77 (1/39)	0.02
Antisocial conduct of friends	1.53 (1.52)	3.50 (2.93)		7.79 (1/40)**	0.17

Nota. * p<.05; ** p<.01

Table 4. *Multivariate analysis of variance for comparing the intervention and control groups in attitudes and intention of drug use (seven-year follow-up)*

	Intervention Group N = 37 Average (SD)	**Control Group** N = 21 Average (SD)	λ	**F(df)**	**η²**
			0.77	3.61 (4/51)*	0.83
Attitude toward drugs	6.46 (3.69)	10.30 (4.08)		12.87 (1/54)**	0.19
Intention tobacco	0.40 (0.87)	1.29 (1.30)		9.47 (1/54)**	0.14
Intention alcohol	0.77 (1.06)	1.48 (1.16)		5.22 (1/54)*	0.08
Intention cannabis	0.26 (0.61)	0.67 (1.01)		3.56 (1/54)	0.06

Note. * p<.05; ** p<.01

Drug use comparison.

For the multivariate analyses, the variables related with drug use were grouped into the following groups for analysis: attitudes and intentions, age at onset of use, frequency and quantity of alcohol consumed.

First, attitudes and intentions as regards drug use were analysed. The Attitudes toward Drugs Scale is part of the Drug Use Questionnaire (CCD; Luengo et al., 1999), and evaluates the degree to which adolescents rate the use of drugs and its effects positively (e.g., "Smoking joints is a pleasant experience that must be experimented", "Drinking alcohol will be prejudicial for my studies", "You can't talk to others about the effects of drugs unless you use them first yourself", "Alcohol makes parties more fun"). The Intentions Scale, specifically, asks about the likelihood that the adolescent thinks he or she will use drugs (tobacco, alcohol, cannabis) next weekend, if given the opportunity ("Surely not", "Probably not", "Probably yes", "Surely yes"; these responses are scored from 0 to 3). The results are presented in Table 4.

The multivariate analysis showed a significant F and, in particular, differences in attitudes (higher in the control group) and in the intention of using tobacco or alcohol (also higher in the control group). When the proportion of adolescents that will "probably yes" use tobacco is analysed, we find that 11% of the intervention group is willing to use, compared with 42% of the control group (chi-squared: 7.59, 1 df, $p < .001$). As to adolescents that will "probably yes" use alcohol, 11% of the intervention group chose this response, compared with 35% of the control group (chi-squared: 6.23, 1 df, $p < .01$).

No differences are found, however, in age at onset (multivariate F = 0.47, 2/29 df, ns), which was 13.00 years (intervention) and 13.77 years (control) for tobacco; 14.18 years (intervention) and 13.27 years (control) for alcohol; and 14.63 years (intervention) and 14.40 years (control) for cannabis.

Frequencies of use over the last month and over one's lifetime were also analysed: e.g., "How many times have you smoked cigarettes over the last month? "; "How many times have you drunk more than one sip of alcohol over your lifetime?". The response options range between "Never" (with a value of 0) and "Over 20" (with a value of 5). The comparison of averages did not yield significant differences between the intervention and control groups as to alcohol use (multivariate F = 1.09, 2/49, ns) or cannabis (multivariate F = 1.84, 2/38, ns), though in both cases, however, the averages tended to be higher in the control group than in the intervention group. However, there are significant differences in the frequency of tobacco use. The results are presented in Table 5.

Table 5. *Multivariate analysis of variance for comparing the intervention and control groups in frequency of tobacco use (seven-year follow-up).*

	Intervention Group N = 37 Average (SD)	**Control Group** N = 21 Average (SD)	λ	**F(df)**	**η²**
			.71	7.94 (2/39)**	0.28
Frequency of tobacco month	0.59 (1.50)	2.67 (2.19)		13.18 (1/40)**	0.24
Frequency of tobacco lifetime	1.44 (1.96)	3.87 (2.03)		14.26 (1/40)**	0.26

Note. ** p<.01

Table 6. *Multivariate analysis of variance for comparing the intervention and control groups in intensity of alcohol use (seven-year follow-up)*

	Intervention Group N = 37 Average (SD)	**Control Group** N = 21 Average (SD)	λ	**F(df)**	**η²**
			.77	5.53 (2/38)**	0.22
Number of drinks	0.86 (1.08)	1.87 (0.83)		9.87 (1/39)**	0.30
Number of episodes of drunkenness	0.19 (0.40)	0.60 (0.63)		6.39 (1/39)**	0.14

Note. ** p<.001

Significant differences were obtained as regards the frequencies of both measures. The control group shows higher frequencies of tobacco use than the intervention group. When this data is analysed from a categorical perspective, 33% of the adolescents from the intervention group affirmed having used tobacco more than once over their lifetime, compared with 75% of the adolescents of the control group (chi-squared = 6.98, 1 df, $p < .001$). Likewise, 11% of the adolescents from the intervention group claimed to have used tobacco over the last month, compared with 56% of the control group (chi-squared = 13.42, 1 df, $p < .001$).

Finally, differences are found in the measures of quantity of alcohol use ("How many drinks do you usually have when you drink alcohol?", "How many times have you gotten drunk over the past year?"). The results are presented in Table 6.

When this data is analysed from a categorical perspective, 26% of the adolescents from the intervention group affirmed that they usually have more than one drink when drinking, compared with 62% of the adolescents of the control group (chi-squared = 5.20, 1 df, $p < .05$). As to the number of times the adolescent got drunk over the last year, 19% of the adolescents from the intervention group claimed to have gotten drunk, compared with 56% of the control group (chi-squared = 6.10, 1 df, $p < .05$).

Discussion

The need for designing multicomponent indicated prevention programs has been repeatedly highlighted in recent years (Boxmeyer, Lochman, Powell, & Powe, 2015). The identification of unfavourable developmental trajectories, associated with early-onset conduct problems, has driven the proposal of programs that target children for the purpose of preventing numerous psychological and social dysfunctions, including severe drug use patterns. This study has allowed for verifying the long-term efficacy of a multicomponent program aimed at children with conduct problems, their parents and their teachers.

As shown, the developmental trajectories of conduct problems differ in the intervention and control groups.

The control group continued to have problems over the long term, without significant differences between measures, with a decreasing trend between postest and follow-up, congruent with the results of other studies that have examined the development of conduct problems since childhood as reported by parents (Anselmi et al., 2008; Hofstra, Van der Ende & Verhulst, 2000). The intervention group, however, shows decreases with the program that are maintained over time. Therefore, seven years after the start of the intervention, it is verified that the multicomponent program reduces disruptive behaviour problems in adolescence, particularly impulsive and oppositional types of conduct. Nevertheless, we must point out that the effects appear more clearly in the parents' reports, and less so when these are reported by the adolescents themselves. It is possible, given the program's prioritisation of intervention within the family context, that the program's positive effects are perceived more clearly within the context of parent-child interactions. On another hand, it is noteworthy that significant effects are

not appreciated in relation to aggressive conduct, despite the fact that coping with anger is one of the most emphasised contents of the component for children. Apparently, the program has a more generalised effect on impulsive conduct and the defiance of rules, but, however, the components aimed specifically at reducing aggression do not have the expected impact in the long term. In relation to the above, it is also worth highlighting that no significant differences were found in emotional control skills or in empathy, which seems to suggest that the specific effects on interpersonal emotions are attenuated over time and, therefore, that these components require reinforcements during the intervention.

In general, significant effects on conduct problems in the long term are coherent with other multicomponent programs that have also demonstrated a long-term preventive effect on externalising problems (Eddy et al., 2003; Hektner, August, Bloomquist, Lee & Kimes-Dougan, 2014; Webster-Stratton, Reid & Hammond, 2001) and delinquency (Conduct Problems Prevention Research Group, 2010; Tremblay, Pagani-Kurtz, Masse, Vitaro & Pihl, 1995).

On another hand, results demonstrate that the program is capable of favourably affecting prosocial and communication skills and of decreasing involvement with antisocial friends during adolescence. Given the relevance of these factors in chronification models of conduct problems (Dodge et al., 2010), this result can also be considered favourable for the prevention of persistent antisocial behaviour problems.

Evidence is also found of significant effects when examining the effects on drug use specifically. Participation in the program is associated with more unfavourable attitudes toward drugs and a lower intention of tobacco and alcohol use. Significant effects are also observed in the prevention of tobacco use, with a lower frequency of use in adolescents that participated in the program, both over their lifetime and over the last month. As regards alcohol, apparently the frequency of use remains unaffected (which, in fact, is high in the general population of adolescents at these ages; Plan Nacional sobre Drogas, 2013), but quantity of use is affected, with fewer drinks consumed and episodes of drunkenness in the intervention group. These results are especially worth emphasising, given that the increase in quantity of alcohol consumption is a parameter of special concern in western societies, according to epidemiological studies carried out over the last decade (ESPAD, 2011; Johnston, O'Malley, Miech, Bachman & Schulenberg, 2015). No significant effects are found as regards use of cannabis; however, given that the consumption of cannabis, in general, has a later onset than tobacco and alcohol use, an evaluation in an even longer term would be required to properly assess the effect on use patterns of this substance. In fact, the use of cannabis has been associated with the use of alcohol and tobacco among youth in Spain (Míguez Varela & Becoña, 2015), wherefore it would be relevant to examine whether, in broader evaluations, effects also arise in relation to cannabis. In general, the results on drug use are coherent with some previous studies (Eddy et al., 2003; Zonnevyille et al., 2007) which have also provided evidence of the effects on drug use, and specifically on the use of alcohol (Eddy et al., 2003), of multicomponent programs that address externalising conduct problems.

Therefore, this study contributes toward consolidating the usefulness of multicomponent programs based on developmental psychopathology models for exerting effects on attitudes and behaviours of youth when these approach adolescence. The program object of this evaluation, which includes an integral intervention in coordination with parents, teachers and children themselves, has effects on numerous indicators of psychosocial adjustment, including drug use.

In addition to the implications that these results may have for orientating indicated prevention aimed at children, they also provide support for the models that serve as the basis of these programs. As other authors have pointed out (LeMarquand, Tremblay & Vitaro, 2001), verifying the efficacy of the intervention programs allows for validating the basic principles as to the source and maintenance of problems targeted by the intervention. In our case, the effects of the intervention have backed the importance of conduct problems in the development of drug use.

This way, this study contributes new data in support of the efficacy of a type of program whose long-term impact requires systematic examination. Furthermore, the use of several informants strengthens the effects found. The study, as a whole, entails some limitations to be overcome by future research. On one hand, the limited sample size (common in these types of studies with high-risk children; Zonnevylle-Bender et al., 2007) weakens the statistical power of the analyses carried out. In this regard, the implementation of studies at several sites would allow for broadening the scope of the evaluation of efficacy; furthermore, this would allow for including the study of moderators of efficacy to understand which of the characteristics of the children, their environment or the application conditions would maximise the intervention's positive effects. Variables like sex, socioeconomic status of the family, severity of initial conduct problems, comorbidities, as well as the fidelity and integrity of the implementation are some elements that require study; these factors have been identified in recent decades as factors affecting the success of parent training programs (Maughan, Christiansen, Jenson, Olympia & Clark, 2005; Robles & Romero, 2011) and could also be analysed as moderators of these types of programs. Particularly, the role of contextual conditions as moderating variables deserves a systematic analysis, given the relevance in studies on addictive behaviours of factors related with the macrosocial (Buil, Solé Moratilla & García Ruiz, 2015) and family environments

(Hernández-Serrano, Font-Mayolas & Gras, 2015). Increasing the sample size will also allow for breaking down the mechanisms of influence on the program and for evaluating which of the program components are critical for its positive impact.

Given the costs associated with this type of program, another aspect worthy of analysis is its efficiency in terms of costs and benefits. Some previous reviews have provided support for the efficiency of multicomponent programs (Foster et al., 2007), though this aspect should be analysed systematically as long-term studies are implemented.

For the time being, evidence from this study provides support for including early-onset conduct problem reduction programs as drug abuse prevention programs (Glantz, 2002). It has been claimed, in this regard, that a multicomponent intervention could have a cascade effect, generating a chain of positive changes between the individual and the environment (Patterson, Forgatch & Desarmo, 2010), capable of substantially altering the individual's development path and, in particular, the risk of involvement in drug abuse. Intervention at early ages, on another hand, is compatible with neuroscientific research that provides support for the importance in development programs of the cognitive functions of self-management and self-control when the corresponding neural systems still have high plasticity and are responsive to environmental inputs (see Fishbein & Tarter, 2009). In fact, evidence that is now being generated on the relevance of conduct problems have affirmed that conduct problems could offer "the greatest" opportunity for prevention in the field of mental health (Harley, Murtagh & Cannon, 2008).

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

References

Achenbach, T. M. (1991a). *Manual for the Teacher's Report Form and 1991 Profile.* Burlington: University of Vermont.

Achenbach, T. M. (1991b). *Manual for the Child Behavior Checklist and 1991 Profile.* Burlington: University of Vermont.

Anselmi, L., Barros, F. C., Teodoro, M. L., Piccinini, C. A., Menezes, A. M. B., Araujo, C. L. & Rohde, L. A. (2008). Continuity of behavioral and emotional problems from pre-school years to pre-adolescence in a developing country. *Journal of Child Psychology and Psychiatry, 49,* 499-507.

Armsden, G. C. & Greenberg, M. T. (1987). The Inventory of Parent and Peer Attachment: Relationships to well-being in adolescence. *Journal of Youth and Adolescence, 16,* 427-454.

Barkley, R.A. (1997). *Defiant Children: A Clinician's Manual for Assessment and Parent Training* (2nd ed.). New York: Guilford.

Berry, J. W., Phinney, J. S., Sam, D. & Vedder, P. (Eds.) (2006). *Immigrant youth in cultural Transition: Acculturation, identity and adaptation across national contexts.* Hillsdale: Erlbaum.

Boxmeyer, C. L., Lochman, J. E., Powell, N. P. & Powe, C. E. (2015). Preventing conduct disorders and related problems. In L. M. Scheier (Ed.), *Handbook of Adolescent Drug Use Prevention: Research, Intervention Strategies, and Practice* (pp. 125-134). Washington, DC: American Psychological Association.

Buil, P., Solé Moratilla, M. J. & García Ruiz, P. (2015). Online gambling advertising in Spain: A study on the protection of minors. *Adicciones, 27,* 198-204.

Cicchetti, D. & Cohen, D. J. (2006). *Developmental Psychopathology.* New York: Wiley.

Conduct Problems Prevention Research Group (1995). *Social Competence Scale (Parent Version).* University Park, PA: Pennsylvania State University.

Conduct Problem Prevention Research Group (2004). The effects of the Fast Track program on serious problem outcomes at the end of elementary school. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 36,* 1141-1159.

Conduct Problems Prevention Research Group (2010). Fast Track intervention effects on youth arrests and delinquency. *Journal of Experimental Criminology, 6,* 131-157.

Del Barrio, V., Aluja, A., & García, L. F. (2004). Relationship between empathy and the Big Five personality traits in a sample of Spanish adolescents. *Social Behavior and Personality, 32,* 677-682.

Dodge, K. A. & Coie, J. D. (1987). Social information processing factors in reactive and proactive aggression in children's peer groups. *Journal of Personality and Social Psychology, 53,* 1146-1158.

Dodge, K. A., Malone, P. S., Lansford, J. E., Miller, S., Pettit, G. S. & Bates, J. E. (2010). *A dynamic cascade model of the development of substance use onset.* New York: Wiley.

Eddy, J. M., Reid, J. B., Stoolmiller, M. & Petrow, R. A. (2003). Outcomes during middle school for an elementary school-based preventive intervention for conduct problems: Follow-up results from a randomized trial. *Behavior Therapy, 34,* 535-582.

EMCDDA (2009). *Preventing later substance use disorders in at-risk children and adolescents: A review of the theory and evidence base of indicated prevention.* Lisbon: European Monitoring Center for Drug and Drug Addiction.

ESPAD (2011). *The 2011 ESPAD Report: Substance use among students in 36 European countries*. Stockholm: The Swedish Council for Information on Alcohol and Other Drugs.

Fishbein, D. & Tarter, R. (2009). Infusing neuroscience into the study and prevention of drug misuse and co-ocurring aggressive behavior. *Substance Use and Misuse, 44*, 1204-1235.

Foster, E. M., Olchowski, A. E. & Webster-Stratton, C. H. (2007). Is stacking intervention components cost-effective? An analysis of the Incredible Years program. Journal of the American Academy of Child and Adolescent Psychiatry, 46, 1414-1424.

Foxcroft, D. R. (2014). "Form ever follows function. This is the law". A prevention taxonomy based on a functional typology. *Adicciones, 26,* 10-14.

Glantz, M. D. (2002). Introduction to the special issue on the impact of childhood psychopathology interventions on subsequent substance abuse: Pieces of the puzzle. *Journal of Consulting and Clinical Psychology, 70,* 1203-1206.

Gordon, R. S. (1983). An operational classification of disease prevention. *Public Health Reports, 98*, 107-109.

Granic, I. & Patterson, G. R. (2006). Toward a comprehensive model of antisocial development: A dynamic systems approach. *Psychological Review, 113,* 101-131.

Haller, M., Handley, E., Chassin, L. & Bountress (2010). Developmental cascades: Linking adolescent substance use, affiliation with substance use promoting peers, and academic achievement to adult substance use disorders. *Development and Psychopathology, 22,* 899-915.

Harley, M., Murtagh, A. & Cannon, M. (2008). Conduct disorder: Psychiatry's greatest opportunity for prevention. *Psychological Medicine, 38,* 929-931.

Hawkins, E. H. (2009). A tale of two systems: Co-occurring mental health and substance abuse disorders treatment for adolescents. *Annual Review of Psychology, 60,* 197-227.

Hektner, J. M., August, G. J., Bloomquist, M. L., Lee, S. Klimes-Dougan, B. (2014). A 10-year randomized controlled trial of the Early Risers conduct problems preventive intervention: Effects on externalizing and internalizing in late high school. *Journal of Consulting and Clinical Psychology, 82,* 355-360.

Hernández-Serrano, O., Font-Mayolas, S. & Gras, M. E. (2015). Polydrug use and its relationship with the familiar and social context amongst young college students. *Adicciones, 27,* 205-213.

Hofstra, M. B., Van der Ende, J. & Verhulst, F. C. (2000). Continuity and change of psychopathology from childhood into adulthood: A 14-year follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 39,* 850-858.

Hser, Y. I., Grella, C. E., Collins, C. & Teruya, C. (2003). Drug-use initiation and conduct disorder among adolescents in drug treatment. *Journal of Adolescence, 26,* 331-345.

Johnston, L. D., O'Malley, P. M., Miech, R. A., Bachman, J. G., & Schulenberg, J. E. (2015). *Monitoring the Future National Survey results on drug use: 1975-2014: Overview, key findings on adolescent drug use*. Ann Arbor: Institute for Social Research, The University of Michigan.

Larson, J. & Lochman, J. E. (2002). *Helping schoolchildren cope with anger. A cognitive-behavioral intervention*. New York: Guilford.

LeMarquand, D., Tremblay, R. E. & Vitaro, F. (2001). The prevention of conduct disorder: A review of successful and unsuccessful experiments. In J. Hill and B. Maughan (Eds.), *Conduct Disorders in Childhood and Adolescence* (pp. 449-478). Cambridge: Cambridge University Press.

López-Romero, L., Romero, E., & Andershed, H. (2015). Conduct problems in childhood and adolescence: Developmental trajectories, predictors and outcomes in a six-year follow-up. *Child Psychiatry and Human Development, 46,* 762–773

Luengo, M. A., Otero, J. M., Romero, E., Gómez-Fraguela, X. A. & Tavares, E. T. (1999). Análisis de items para la evaluación de la conducta antisocial: Un estudio transcultural. *Revista Iberoamericana de Diagnóstico y Evaluación Psicológica, 1*, 21-36.

Luengo, M. A., Romero, E., Gómez-Fraguela, J. A., Garra, A. & Lence, M. (1999). *La prevención del consumo de drogas y la conducta antisocial en la escuela: Análisis y evaluación de un Programa*. Madrid: Ministerio de Educación y Cultura, Ministerio de Sanidad y Consumo y Ministerio del Interior.

Luengo, M. A., Villar, P., Sobral., J., Romero, E. & Gómez-Fraguela, X. A. (2009). El consumo de drogas en los adolescentes inmigrantes: Implicaciones para la prevención. *Revista Española de Drogodependencias, 3,* 420-447.

Martel, M. M., Pierce, L., Nigg, J. T., Jester, J. M., Adams. K., Puttler, L. I.,... Zucker, R. A. (2009). Temperament pathways to childhood disruptive behavior and adolescent substance abuse: Testing a cascade model. *Journal of Abnormal Child Psychology, 37,* 363-373.

Maughan, D. R., Christiansen, E., Jenson, W. R., Olympia, D., & Clark, E. (2005). Behavioral parent training as a treatment for externalizing behaviors and disruptive behavior disorders: A meta-analysis. *School Psychology Review, 34*, 267-286.

Míguez Varela, M. C. & Becoña, E. (2015). Do cigarette smoking and alcohol consumption associate with cannabis use and problem gambling among Spanish adolescents? *Adicciones, 27,* 8-16.

NIDA (2003). *Preventing drug use among children and adolescents: A research-based guide*. Bethesda, MD: US Department of Health and Human Services.

Patterson, G. R., Forgatch, M. S. & Desarmo, D. S. (2010). Cascading effects following intervention. *Development and Psychopathology, 22*, 949-970.

Plan Nacional sobre Drogas (2013). *Encuesta Escolar sobre Uso de Drogas en Estudiantes de Enseñanzas Secundarias (ESTUDES) 2012-2013*. Madrid: Plan Nacional sobre Drogas.

Robles, Z. (2009). *Intervención sobre problemas de conducta de inicio temprano. Evaluación de un programa de entrenamiento para padres*. Tesis doctoral. Universidad de Santiago de Compostela.

Robles, Z. y Romero, E. (2011). Programas de entrenamiento para padres de niños con problemas de conducta: Una revisión de su eficacia. *Anales de Psicología, 27,* 86-101.

Romero, E., Robles, Z., & Lorenzo, E. (2006). Prácticas parentales, atmósfera familiar y problemas de conducta externalizante en la infancia. *Revista de Psiquiatría, 33,* 84-92.

Romero, E., Villar, P., Luengo, M. A. & Gómez-Fraguela, J. A. (2009). EmPeCemos: Un programa multicomponente para la prevención indicada de los problemas de conducta y el abuso de drogas. *Revista Española de Drogodependencias, 4,* 420-447

Romero, E., Villar, P., Luengo, M. A., Gómez-Fraguela, X. A. & Robles, Z. (2014). *EmPeCemos. Programa para la Intervención sobre los Problemas de Conducta infantiles*. Madrid: TEA.

Romero, E., Villar, P. & Gómez-Fraguela, X. A. (2010). Intervening on family, school and children for prevention of early-onset conduct problems. *European Journal of Public Health, 20* (Supplement 1: Proceedings from the 3rd European Public Health Conference), 90.

Salvo, N., Bennett, K., Cheung, A., Chen, Yo, Rice, M., Rush, B.,... & Bowlby, A. (2012). Prevention of substance use in children/adolescents with mental disorders: a systematic review. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 21*, 245-252.

Scheier, L. M. (Ed.) (2015). *Handbook of adolescent drug use prevention: Research, intervention Strategies, and practice*. Washington, DC: American Psychological Association.

Sitnick, S. L., Shaw, D. S. & Hyde, L. W. (2014). Precursors of adolescent substance use from early childhood and early adolescence: Testing a developmental cascade model. *Development and Psychopathology,* 26, 125-140.

Sobral, J., Gómez-Fraguela, X. A., Romero, E., Luengo, M. A. & Villar, P. (2012). Riesgo y protección de desviación social en adolescentes inmigrantes: Personalidad, familia y aculturación. *Anales de Psicología, 28,* 664-674.

Thornberry, T. P., Lizotte, A. J., Krohn, M. D., Farnworth, M. & Jang, S. J. (1994). Delinquent peers, beliefs, and delinquent behavior: A longitudinal test of interactional theory. *Criminology, 32,* 47-83.

Tremblay, R. E., Pagani-Kurtz, L., Masse, L. C.,Vitaro, F. & Pihl, R. O. (1995). A bimodal preventive intervention for disruptive kindergarten boys: Its impact through mid-adolescence. *Journal of Consulting and Clinical Psychology, 63,* 560-568.

Webster-Stratton, C. & Hammond, M. (1997). Treating children with early-onset conduct problems: A comparison of child and parent training interventions. *Journal of Consulting and Clinical Psychology, 65,* 93-109.

Webster-Stratton, C., Reid, M. J. & Hammond, M. (2001). Preventing conduct problems, promoting social competence: A parent and teacher training partnership in Head Start. *Journal of Clinical Child Psychology, 30,* 283-302.

Zonnevylle-Bender, M. J. S., Matthys, W., Van De Wiel, N. M. H. & Lochman, J. E. (2007). Preventive effects of treatment of disruptive behavior disorder in middle childhood on substance use and delinquent behavior. *Journal of the American Academy of Child and Adolescent Psychiatry, 46,* 33-39.

Factors associated with substance use among Spanish military personnel involved in "Bosnia-Herzegovina"

Factores asociados al consumo de drogas en una muestra de militares españoles desplegados en "Bosnia-Herzegovina"

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Abstract

The use of both legal and illegal drugs has rarely been investigated among the Spanish military population involved in multinational military operations. The aim of the current study was to examine the consumption of drugs by Spanish military personnel in Bosnia-Herzegovina, and the variables associated with such substance use. A total of 605 military personnel participated in the cross-sectional study. The participants' mean age was 25.9 years (*SD* = 5.9), and 93.9% of the sample was male. The majority of the participants were enlisted personnel (83.5%). The most widely used drugs were tobacco (54.2%), and alcohol (39.9%). With respect to illegal drugs, the results showed that the drug with the highest prevalence of "use at some point during a lifetime" was cannabis (36.2%), followed by cocaine (14.9%) and amphetamines (12.1%). The most important variable associated with a decrease in the consumption of illegal drugs was social support. Conversely, participants with friends who have used illegal drugs had an increased likelihood of drug consumption. Given that the use of drugs can adversely affect soldiers' performance, preventive measures should be applied in multinational military operations.

Keywords: Military personnel; Multinational military operations; Drug use; Risk factors; Protective factors.

Resumen

El consumo de drogas legales e ilegales ha sido muy poco investigado en población militar española destinada en zonas de operaciones multinacionales. El objetivo de la investigación fue evaluar el nivel de consumo de drogas en militares españoles que realizaban misiones en Bosnia-Herzegovina, e identificar las posibles variables asociadas con dicho consumo. En el estudio transversal participaron 605 militares. La edad media de los participantes fue de 25,9 años (*DT* = 5,9) y el 93,9% de la muestra eran hombres. La mayoría de los participantes pertenecían a las escalas de tropa y marinería (83,5%). Las drogas más usadas fueron el tabaco (54,2%), y el alcohol (39,9%). En relación a las drogas ilegales, los resultados muestran que la droga con una mayor prevalencia de consumo "alguna vez en su vida" fue el cannabis (36,2%), seguida de la cocaína (14,9%) y las anfetaminas (12,1%). La variable más relevante asociada con una disminución en el consumo de drogas ilegales ha sido el apoyo social. En cambio, los participantes quienes tenían amigos consumidores de drogas ilegales incrementaban la probabilidad de consumo de drogas. Se resalta la importancia de la prevención en zonas de operaciones multinacionales para evitar el efecto negativo que podría tener el consumo de drogas en el desempeño adecuado de las misiones encomendadas.

Palabras clave: Personal militar; Zonas de operaciones multinacionales; Consumo de drogas; Factores de riesgo; Factores de protección.

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Drug use is a social problem that affects a variety of groups, some of them more researched than others. For example, investigations or reports on drug use among adult or adolescent civilians are numerous both nationally and internationally (Melchior, Chastang, Goldberg & Fombonne, 2008; Miquel et al., 2015; Motos Sellés, Cortés Tomás, Giménez Costa & Cadaveira Mahía, 2015; Mounteney et al., 2016; Observatorio Español sobre Drogas, 2013; Observatorio Español de la Droga y las Toxicomanías, 2015; Observatorio Europeo de las Drogas y las Toxicomanías, 2014). On the other hand, there are other more specific groups that have been less researched, the military population among them. As far as we are aware, studies carried out in the Spanish armed forces are far and few between, and given the aim of protecting the confidentiality of critical information in this group, the results they yield are not normally accompanied by precise numerical data (e.g., review the work done by Donoso Rodríguez, 2012). Martínez, Alonso, Taranco and Gutiérrez (2010) carried out a study on Spanish national territory into illicit drug use among non-deployed members of the armed forces in the army, navy and air force. The investigation began in 2002 and ended in 2007. In general, they found that 9% of the military currently used cannabis, 2% hallucinogenic drugs, 3.5% amphetamine and 8% cocaine. The prevalence of drug use declined over the years, with the exception of 2003, when there was an increase in consumption compared to 2002. For example, while 8.2% used cocaine in 2002, which came down to 4.5% in 2007, this progressive decrease was countered in 2003, which saw consumption of 10.7%. In a further study, Donoso Rodríguez (2012) assessed the prevalence of current use of legal (alcohol and tobacco) and illegal drugs (cannabis, cocaine, opiates, hallucinogens and amphetamines) in both a sample of non-deployed professional army soldiers from 1997 to 2007 and a group of non-deployed army officers from 2002 to 2008. This author found that the most heavily used substances in the professional army were alcohol and tobacco, with cannabis the most commonly used illicit drug, followed by cocaine and amphetamines. At the same time, however, it should be noted that a high percentage of the troops declared that they had not used any illegal psychoactive substance. Over the years of the study, there was a decrease in the use of legal and illegal drugs (cannabis, cocaine and amphetamines). Among the officers, the most frequently used substances were also legal drugs (alcohol and tobacco), and the consumption of illicit drugs was very low. Substance use has remained stable over the years and is similar to the troops.

Some studies suggest that drug use could differ between military personnel and the civilian population. For example, Teachman, Anderson, and Tedrow (2015) noted that there was an increase in alcohol consumption among male soldiers who enlisted in the military compared to those who did not enroll. Opposite results occur when it comes to the women, where the likelihood of alcohol consumption decreased in those women who enlisted in the military. These data are of great interest because they seem to indicate that there could be an interaction between the variable of being enlisted and sex. It is important to highlight the male-dominated nature of the Spanish military population, with 83.5% of the professional military personnel in the army and navy being men, a proportion that decreases to 73.7% when it comes to service personnel in the armed forces (Unidad de Estadística del Órgano Central, 2016).

In line with this possible discrepancy in drug consumption between military and civilian populations, the Household Survey on Alcohol and Drugs in Spain (EDADES) found that 6.6% of the civil population in Spain (aged 15 to 64) has consumed cannabis in the last 30 days, with 0.1% consuming hallucinogens, 0.3% amphetamines and 1.1% cocaine (Observatorio Español de la Droga y las Toxicomanías, 2015). These levels of illicit drug use are lower than those obtained in the study by Martínez et al. (2010). While it is true that the two studies do not use identical measures of consumption, they are very similar (current consumption and consumption in the last 30 days).

At the same time, there are specific situations that form part of military life, such as the participation in international missions in areas of multinational operations, with or without exposure to combat, and which may be associated with an increase in, or intensive consumption of traditional drugs such as alcohol (Cucciare et al., 2015; Jacobson et al., 2008). Thus, Kelsall et al. (2015) conducted a meta-analytical study comparing the consumption of alcohol or other substances among military personnel who participated in the Gulf War or in the Iraq-Afghanistan War to that of colleagues who did not take part in such conflicts. Military personnel who participated in the above-mentioned conflicts had a higher risk of alcohol consumption (OR of 1.3 in the Gulf War, OR of 1.4 in the Iraq-Afghanistan War) or consumption of other substances (OR of 1.1 in the Iraq-Afghanistan War).

Since research carried out among the military personnel of the Spanish armed forces is scarce, especially in areas of multinational operations, it would be important to have accurate information on the prevalence of drug use in this group during an international mission. Likewise, it would be of great interest to evaluate the possible factors associated with such substance use in this context, which have previously proved significant in other groups (e.g., Brook, Saar, Zhang & Brook, 2009; Coomber et al., 2011; Rudzinski et al., 2014; Schnohr et al., 2004; Sordo et al., 2015).

As a result, the aim of this study is to assess the use of legal and illegal drugs in a population of Spanish military personnel destined for the multinational operations area of Bosnia-Herzegovina, as well as the possible variables associated with such consumption.

Method

Participants and procedure

The sample consisted of 605 professional soldiers belonging to the Spanish armed forces (army and marine infantry), all destined for operational units located in the multinational operations zone in Bosnia-Herzegovina (Mostar-Spain, Mostar- Airport, Duzi detachment in Trebinje, and Sarajevo and Raylovac bases). The total number of military personnel making up the contingent during the time of the investigation was 1212. The inclusion criterion was that the participants were not involved in tasks typical of their profession during the implementation of the research. That is to say, the incidental sample consisted of all the military personnel making up the contingent with the exception of those who were, at the time the questionnaires were completed, on specific assignments such as escort or guard duty, surveillance, etc. As a result, 49.9% of all the troops deployed in the contingent were available, and all of them voluntarily agreed to participate.

The study was transversal. The evaluation booklet was self-administered collectively every Wednesday from January to April 2003 at 11:00 a.m. in the barrack messes. The same researcher who started the session was always present in the hall, giving the instructions aloud to complete the booklet and clarifying any doubts arising before the participants began to complete it. The session lasted approximately 60 minutes. He warned of the importance of not leaving any question or item unanswered. Finally, the anonymity of the participants and the confidentiality of the information obtained were guaranteed. All the military personnel present at the time the survey was carried out participated voluntarily in the research and received no compensation.

Variables

A booklet was provided in which information could be recorded on sociodemographic characteristics (age, sex, level of education, who they live with, locality of origin, etc.), habits of legal drug use among relatives (tobacco consumption in parents and siblings), illicit drug use of among friends , and the use of different drugs by the respondents themselves (alcohol, tobacco, cannabis, amphetamines, cocaine and other substances). Specifically, regular alcohol consumption was recorded (do you usually drink alcohol?), as was current smoking (do you smoke at present?), and whether illegal drugs have ever been used during the respondents lifetime (for example, have you ever used cocaine?). Likewise, questions specific to the military context were included, such as the respondent's type of unit (which force, role, and headquarters /general staff) or military rank (enlisted personnel and officers).

The protection variables were measured through a version of the Risk and Protection Factors Questionnaire (CFR-P, Martínez-González, Trujillo-Mendoza & Robles-Lozano, 2007) adapted for use with the study population. This measurement instrument was included in the above mentioned booklet, and consists of 35 items evaluating variables of protection against the consumption of legal and illegal drugs. The response format is a five-point Likert type scale, where 1 equals no protection and 5 maximum protection. The psychometric properties of the questionnaire were evaluated because the sample studied was different in composition and variability to the benchmark (Wilkinson and APA Task Force on Statistical Inference, 1999). Exploratory factor analysis was performed to study the dimensional structure of the evaluation instrument. The findings showed the existence of two dimensions of protection, which were coping skills (23 items) and social support (12 items). The internal consistency for the coping skill dimension, as measured by Cronbach's alpha coefficient, was 0.86 and for social support 0.68.

Statistical analysis

The data were analyzed descriptively by calculating the arithmetic means and standard deviations for variables continuous, and the frequencies for the categorical variables.

Student's t-test was used for hypothesis testing on two independent sample means of quantitative variables. If the assumption of equal population variances (using Levene's test) was not given, the Welch approximation was applied to perform the contrast on mean differences. Pearson's Chi-square analysis was applied for qualitative variables to contrast the prevalence of consumption obtained for the psychoactive substances in question. All variables yielding statistically significant differences with a p-value <0.05 were included as predictors in the various multiple binary logistic regression analyses performed for each of the legal and illegal drugs. The prevalence Odds Ratio (OR) was the indicator on which the multivariate analysis was focused. When the predictive variable introduced in the model is quantitative, for example age (completed years), and an OR greater than 1 is obtained with respect to the criterion variable, for example alcohol consumption, it means that the probability of alcohol consumption of a 35-year-old is higher than one who is 34 years old. In contrast, when the OR is less than 1, the probability of alcohol consumption of a 35-year-old individual is lower than that of a 34-year-old. In the selection of variables, the stepwise regression method was used (the elimination criterion was based on the probability of the Wald interval). All analyses were performed with the SPSS 20.0 statistical package, with the exception of the calculation of the 95% confidence intervals for prevalence of drug use, which followed Newcombe's test (1998).

Results

Sample characteristics

The mean age of the participants was 25.9 years (SD = 5.9), with a range of 18 to 51 years. Men made up 93.9%

of the sample, 69.8% of which had attended secondary school. The majority of the participants came from the forces (54.7%) and 83.5% of the personnel were enlisted personnel (Table 1).

Prevalence of legal and illegal drug use

Of the total sample, 39.9% regularly drink alcohol and 54.2% currently smoke. With regard to illicit drugs, 36.2% have at some point in their lives tried cannabis, 12.1% amphetamines, and 14.9% cocaine. Only 8% of participants have ever tried substances other than those indicated (Table 2).

It is worth pointing out that the parents of the participants smoke in 41.7% of cases, mothers in 21.9%, and siblings in 54.8%. The consumption of illegal drugs by friends is 60.8% (Table 1).

Association between variables of interest and drug use

The variables that were statistically significant in relation to habitual consumption of alcohol were: level of education, who you live with, military rank, father smoking tobacco, friends consuming illicit drugs, and age. The variables predicting habitual alcohol consumption were having a father who smoked and age (Table 3).

The variables that were statistically significant in relation to the current consumption of tobacco were: educational level, military rank , father smoking tobacco, and age. The variables level of education and having a father who smokes make up the predictive model for current tobacco consumption (Table 3).

The variables that were statistically significant in relation to cannabis use were: place of origin, level of education, who you live with, military unit, military rank, mother smoking tobacco, father smoking tobacco, friends consuming illicit drugs, age, coping and social support. The variables significantly predicting cannabis use were: place of origin, military unit, father smoking tobacco, friends consuming illegal drugs, age, and social support (Table 3).

The variables that were statistically significant in relation to the consumption of amphetamines were: level of education, who you live with, military unit, mother smoking tobacco, friends consuming illicit drugs, age, and social support. In the consumption of amphetamines, the predictor variables were friends consuming illegal drugs, age, and social support (Table 3).

The variables that were statistically significant in relation to cocaine use were: level of education, who you live with, military unit, military rank, mother smoking tobacco, father smoking tobacco, friends consuming illicit drugs, age, and social support. The results of the significant predictor variables comprising the model for cocaine use were: military unit, military rank, friends consuming drugs and social support (Table 3).

The variables that were statistically significant in relation to the consumption of other substances were: military scale, mother smoking tobacco, friends consuming illicit drugs, age, coping skills, and social support. The variables that

Table 1. *Characteristics of the sample and use of drugs among family and friends*

Sex	% (n)
Male	93.9 (568)
Female	6.1 (37)
Level of education	% (n)
Primary school	21 (127)
Secondary school	69.8 (420)
University	9.1 (55)
Who you live with	% (n)
Parents	40.2 (243)
Shared household	24.5 (148)
Own family	25 (151)
Alone	10.3 (62)
Place of origen	% (n)
Rural	75 (454)
Urban	25 (151)
Military unit	% (n)
Forces	54.7 (331)
Forces support services	37 (224)
Headquarters	8.3 (50)

Military rank	% (n)
Enlisted	83.5 (505)
Officer	16.5 (100)
Father smokes	% (n)
Smoker	41.7 (251)
Mother smokes	% (n)
Smoker	21.9 (132)
Siblings smoke	% (n)
Smoker	54.8 (328)
Friends use illicit drugs	% (n)
User	60.8 (367)

Table 2. *Prevalence of legal and illegal drug use*

				95% Confidence Interval	
		Prevalence (%)	n	Lower limit	Higher limit
Regularly consumes alcohol	Yes	39.9	241	36.1	43.9
Currently smokes	Yes	54.2	328	50.2	58.1
Uses cannabis	Yes	36.2	219	32.5	40.1
Uses amphetamines	Yes	12.1	73	9.7	14.9
Uses cocaine	Yes	14.9	90	12.3	17.9
Uses other substances	Yes	8	48	6	10.4

Table 3. *Binary logistic regression analysis of variables predicting legal and illegal drug use*

		95% Confidence Interval	
	Odds Ratio	Lower limit	Higher limit
Regular drinking			
Father smokes (rc. doesn't smoke)	1.5	1.0	2.1
Friends use illicit drugs (rc. don't use)	1.4	1.0	2.0
Age[a]	0.96	0.93	0.99
Currently smokes			
Secondary school (rc. primary)	0.9	0.6	1.3
University (rc. primary)	0.4	0.2	0.8
Father smokes (rc. doesn't smoke)	1.4	1.0	2.0
Cannabis use			
Urban (rc. rural)	0.6	0.4	0.9
Forces support services (rc. forces)	0.6	0.4	0.9
Headquarters (rc. forces)	1.2	0.6	2.3
Father smokes (rc. doesn't smoke)	1.6	1.1	2.2
Friends use illicit drugs (rc. don't use)	2.3	1.6	3.4
Age	0.9	0.9	1.0
Social support	0.6	0.4	0.9
Amphetamine use			
Friends use illicit drugs (rc. don't use)	5.5	2.8	10.7
Age	0.8	0.7	0.9
Social support	0.4	0.2	0.6
Cocaine use			
Secondary school (rc. primary)	0.6	0.3	1.0
University (rc. primary)	0.2	0.0	1.3
Forces support services (rc. forces)	0.4	0.2	0.7
Headquarters (rc. forces)	0.1	0.0	0.9
Mother smokes (rc. doesn't smoke)	1.7	1.0	2.9
Friends use illicit drugs (rc. don't use)	2.8	4.9	8.7
Social support	0.4	0.2	0.7
Use of other substances			
Friends use illicit drugs (rc. don't use)	8.7	3.8	19.9
Social support	0.4	0.2	0.7

Notes. rc. = reference category for the predictor variable; a = two decimal places are reported to avoid potentially incorrect interpretation when rounding a single decimal place.

predict the consumption of other substances were friends consuming illicit drugs, and social support (Table 3).

Discussion

In the present study, smoking was the most common example of substance use among the Spanish military population in the multinational operations zone of Bosnia-Herzegovina. Drinking was the second most common substance use, followed by cannabis consumption. Social support was an important predictor variable of illicit drug use; therefore, greater social support was associated with a lower probability of such use. Another relevant variable that predicted drug use was having friends who used illicit drugs, i.e., soldiers with friends who used illicit drugs had an increased likelihood of using those drugs.

As mentioned above, the most readily consumed drugs in the multinational operations area were tobacco (54.2% currently smoke) and alcohol (39.9% regularly drink). With regard to the latter, it is important to mention that it appears that alcohol consumption increases in the military population deployed in the area of operations in accordance with the conclusions drawn from international studies (Jacobson et al., 2008; Kelsall et al. 2015). The results obtained showing greater consumption of legal compared to illegal drugs coincide with other investigations carried out with a non-deployed Spanish military population (Donoso Rodríguez, 2012). If we compare these data with those observed in the Household Survey on Alcohol and Drugs in Spain (EDADES), selecting for this purpose the civil population group and level of consumption closest to that used in the current study, we find that 7.2% of the male population aged 25 to 34 consume alcohol daily. With regard to smoking, 37.9% of the general male population aged 25-34 years have used this drug daily in the last 30 days (Observatorio Español de la Droga y las Toxicomanías, 2015). Consequently, it could be tentatively concluded that tobacco and alcohol consumption is higher in the military population deployed in the area of operations compared to the Spanish civilian population. This assertion would need to be confirmed in future studies where similar consumption criteria are employed.

With respect to illicit drugs, the most widely consumed was cannabis, with 36.2% of the military personnel having used it at some point in their lives. The second most used was cocaine with 14.9%, followed by amphetamines with 12.1%. Other substances were used by 8% of the participating military. In a study by Martínez et al. (2010) with a non-deployed Spanish military population, the order of the most commonly consumed illicit drugs found in their sample was similar to that obtained in the present study (9% currently consume cannabis, 8% cocaine and 3.5% amphetamines). The prevalence of illicit drug use in the study by Martínez et al. (2010) was lower than that found in the area of operations, although these values are not completely comparable because each study used a different measure of consumption: 'current use' was used in the research by Martínez et al. (2010) and 'have used at some point' in the present study. Another aspect to be highlighted in the study by Martínez et al. (2010) is that the prevalence of drug use in the Spanish military population was found to have been decreasing over the years (2002-2007), except for the year in which the data were obtained for the present study; a year in which there was an increase in the consumption of illicit drugs compared to the previous year. In the EDADES survey, prevalences of cannabis and cocaine use at some point in a lifetime were higher in the Spanish civilian population of similar age and sex (males aged 25 to 34 years) than in the deployed military population, On the other hand, the consumption of amphetamines was inferior to that yielded by the present sample. In the Spanish civilian population, 50.5% consumed cannabis, 9.4% amphetamines and 22.1% cocaine (data provided by the Government Delegation for the National Plan on Drugs according to the study published by the Observatorio Español de la Droga y las Toxicomanías n in 2015).

Participants whose parents were smokers were more likely to consume alcohol; conversely, the probability of use decreased among older military personnel. These results coincide with those obtained by other authors (Engels, Knibbe, de Vries, Drop and van Breukelen, 1999), which indicates that the paternal model plays a relevant role in greater consumption of drugs. It is true that in the longitudinal study of Engels et al. (1999) the participants were adolescents (the sample had a mean age of 12.4 years in the first data collection and an average of 17.4 in the last), so it would be interesting to confirm in future investigations if this factor increases drinking among the military population. With regard to the age variable, similar results were obtained in a study by Iversen et al. (2007) of the military population, with alcohol consumption being lower in the older group.

The variable that was associated with increased smoking was to have parents who were smokers, and the variable related to a lower likelihood of use was having a university education. That is to say, participants who had studied at university were less likely to smoke than those with only primary education. As with alcohol consumption, in a longitudinal study by Brook et al. (2009) with a non-military population, it was found that the father's smoking was associated with an increase in one's own tobacco consumption. Another important variable, in this case associated with protection, is to have a higher education. Similar results were found in a civilian study where participants with a higher educational level were less likely to smoke (Schnohr et al., 2004). Therefore, educational level is a relevant factor to take into account; in the present study only 9.1% of the participants had higher studies.

Cannabis use was less likely when participants lived in urban settings, belonged to the forces support group, were older and had more social support. An increase in consumption occurred when parents smoked or their friends used illicit drugs. These results are consistent with the findings of Coomber et al. (2011), who found that living in urban settings reduced the likelihood of cannabis use. Of the variables specifically related to the military context, the participants who belonged to the forces support group had a lower probability of consumption compared to those belonging to the forces group. In addition, it is again observed that parents who smoke or are older are variables associated with drug use, the former with an increase and the second with a decrease in the use of cannabis. The report prepared by the Observatorio Español de la Droga y las Toxicomanías (2015) found a similar trend in the Spanish civilian population with cannabis consumption being less widespread among older people. Another factor that seems to be important is the consumption of illicit drugs by friends, confirming peer group influence in the use of the drug, as has been revealed in other studies with non-military population (Rudzinski et al., 2014). Social support was another relevant variable, as increased social support was associated with a decrease in the likelihood of cannabis use. Similar results have been found with civilian populations where social support was inversely linked to the use of cannabis (Chauchard, Septfons, & Chabrol, 2013).

The likelihood of amphetamine use was greater among those participants whose friends used illicit drugs, and lower in older soldiers or with more social support. Similar results have been found in other groups (Observatorio Español de la Droga y las Toxicomanías, 2015; Rice, Milburn, Rotheram-Borus, Mallett & Rosenthal, 2005).

Some military-specific variables were associated with cocaine use. Apparently, participants with a forces support function are less likely to consume this drug than those belonging to the forces group. Similar results were obtained when comparing the group belonging to headquarters with the forces group, with a lower consumption reported among headquarters personnel. In the study conducted by Donoso Rodríguez (2012), a lower consumption was also found among officers. Perhaps these results are due to the fact that force-trained personnel have been trained to behave in a somewhat more reckless manner in order to meet the challenges posed by critical missions and thus have a more uninhibited attitude than headquarters personnel and support services, which are dedicated almost exclusively to decision making and logistical tasks; uninhibited behavior and attitudes that could be generalized to other aspects of life, such as in this case breaking the non-use of illicit drugs rule. A variable that was associated with an increase in cocaine consumption was having friends who used illicit drugs, while having greater social support was linked to a decrease in their use. Other studies with non-military populations have also obtained an association of these variables with cocaine use (Bohnert, German, Knowltonc & Latkinc, 2010).

In relation to the consumption of other substances, the predictor variables were the two that have been relevant to all illicit drug use: having friends who use illegal drugs increases the likelihood of using other substances, and greater social support decreases consumption.

The present study has several limitations, among them: a) participants from only a single area of multinational operations were included since the demands of the different deployment areas could require different professional and psychological resources; b) the reliability value for the social support scale is very close to the recommended minimum; c) the transversal design does not allow the assessment of changes in consumption; d) drug use was only measured subjectively. Therefore, it would be advisable in future investigations to evaluate military personnel assigned to different areas of multinational operations and compare them with the non-deployed Spanish military population using similar consumption measures. It would also be desirable to apply longitudinal designs in order to enable the assessment of drug use at different times and also to accompany subjective evaluations with other objective measures that can provide unequivocal information regarding consumption using, for example, blood and urine tests.

In conclusion, there is drug use in the area of multinational operations, and this use appears to increase when friends also take illicit drugs, but decreases with greater social support. Therefore it would be important to implement preventive measures taking into account that such consumption could affect the adequate performance of the missions with which they are entrusted. For example, it would be necessary to increase the availability of healthy leisure and free time activities, especially if one takes into account the number of free hours available outside the hours dedicated to professional tasks.

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Conflict of interests

There are no conflicts of interest.

References

Bohnert, A. S. B., German, D., Knowltonc, A. R. & Latkinc, C. A. (2010). Friendship networks of inner-city adults: A latent class analysis and multi-level regression of supporter types and the association of supporter latent class membership with supporter and recipient drug use. *Drug and Alcohol Dependence, 107*, 134–140. doi:10.1016/j.drugalcdep.2009.09.012.

Brook, J. S., Saar, N. S., Zhang, C. & Brook, D. W. (2009). Familial and non-familial smoking: Effects on smoking and nicotine dependence. *Drug and Alcohol Dependence, 101*, 62-68. doi:10.1016/j.drugalcdep.2008.11.003.

Chauchard, E., Septfons, A. & Chabrol, H. (2013). Motivations et stratégies lors d'arrêt spontané de la consommation de cannabis: quel impact sur les rechutes? *L'Encéphale, 39*, 385-392. doi:10.1016/j.encep.2013.03.008.

Coomber, K., Toumbourou, J. W., Miller, P., Staiger, P. K., Hemphill, S. A. & Catalano, R. F. (2011). Rural adolescent alcohol, tobacco, and illicit drug use: A comparison of students in Victoria, Australia, and Washington state, United States. *The Journal of Rural Health, 27*, 409-415. doi:10.1111/j.1748-0361.2010.00360.x.

Cucciare, M. A., Sadler, A. G., Mengeling, M. A., Torner, J. C., Curran, G. M., Han, X. & Booth, B. M. (2015). Associations between deployment, military rank, and binge drinking in active duty and reserve/national guard US servicewomen. *Drug and Alcohol Dependence, 153*, 37-42. doi:10.1016/j.drugalcdep.2015.06.013.

Donoso Rodríguez, D. (2012). Epidemiología en drogas. Análisis de tendencias de consumo de sustancias psicotrópicas en el ejército de tierra (1997-2007). En D. Donoso Rodríguez (Ed.), *Psicología en las Fuerzas Armadas* (pp. 207-228). Madrid, España: Ministerio de Defensa.

Engels, R. C. M. E., Knibbe, R. A., de Vries, H., Drop, M. J. & van Breukelen, G. J. P. (1999). Influences of parental and best friends' smoking and drinking on adolescent use: A longitudinal study. *Journal of Applied Social Psychology, 29*, 337-361. doi:10.1111/j.1559-1816.1999.tb01390.x.

Iversen, A., Waterdrinker, A., Fear, N., Greenberg, N., Barker, C., Hotopf, M., … Wessely, S. (2007). Factors associated with heavy alcohol consumption in the U.K. armed forces: Data from a health survey of Gulf, Bosnia, and era veterans. *Military Medicine, 172*, 956-961. doi:10.7205/MILMED.172.9.956.

Jacobson, I. G., Ryan, M. A. K., Hooper, T. I., Smith, T. C., Amoroso, P. J., Boyko, E. J., … Bell, N. S. (2008). Alcohol use and alcohol-related problems before and after military combat deployment. *JAMA, 300*, 663-675. doi:10.1001/jama.300.6.663.

Kelsall, H. L., Wijesinghe, M. S. L., Creamer, M. C., McKenzie, D. P., Forbes, A. B., Page, M. J. & Sim, M. R. (2015). Alcohol use and substance use disorders in Gulf War, Afghanistan, and Iraq War veterans compared with nondeployed military personnel. *Epidemiologic Reviews, 37*, 38-54. doi:10.1093/epirev/mxu014.

Martínez, M., Alonso, V., Taranco, M. & Gutiérrez, C. (2010). Encuesta sobre drogas a los militares de tropa y marinería de las Fuerzas Armadas españolas. *Sanidad Militar, 66*, 70-82.

Martínez-González, J. M., Trujillo-Mendoza, H. M. & Robles-Lozano, L. (2007). *Factores de riesgo, protección y representaciones sociales sobre el consumo de drogas: implicaciones para la prevención*. Sevilla, España: Consejería para la Igualdad y el Bienestar Social de la Junta de Andalucía.

Melchior, M., Chastang, J.-F., Goldberg, P. & Fombonne, E. (2008). High prevalence rates of tobacco, alcohol and drug use in adolescents and young adults in France: Results from the GAZEL youth study. *Addictive Behaviors, 33*, 122–133. doi:10.1016/j.addbeh.2007.09.009-

Miquel, L., Rodamilans, M., Giménez, R., Cambras, T., Canudas, A. M. & Gual, A. (2015). Evaluación del consumo de riesgo de alcohol en estudiantes universitarios de la Facultad de Farmacia. *Adicciones, 27*, 190-197. doi:10.20882/adicciones.705.

Motos Sellés, P., Cortés Tomás, M.T., Giménez Costa, J. A. & Cadaveira Mahía, F. (2015). Predictores del consumo semanal de alcohol y sus consecuencias asociadas en universitarios consumidores intensivos de alcohol. *Adicciones, 27*, 119-131. doi:10.20882/adicciones.700.

Mounteney, J., Griffiths, P., Sedefov, R., Noor, A., Vicente, J. & Simon, R. (2016). The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. *Addiction, 111*, 34-48. doi:10.1111/add.13056.

Newcombe, R. G. (1998). Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. *Statistics in Medicine, 17*, 857-872. doi:10.1002/(SICI)1097-0258(19980430)17:83.0.CO;2-E.

Observatorio Español sobre Drogas (2013). *Encuesta escolar sobre uso de drogas en estudiantes de Enseñanzas Secundarias (ESTUDES) 2012-2013*. Madrid, España: Ministerio de Sanidad, Servicios Sociales e Igualdad.

Observatorio Español de la Droga y las Toxicomanías (2015). *Informe 2015. Alcohol, tabaco y drogas ilegales en España*. Madrid, España: Ministerio de Sanidad, Servicios Sociales e Igualdad.

Observatorio Europeo de las Drogas y las Toxicomanías (2014). *Informe europeo sobre drogas. Tendencias y novedades*. Luxemburgo, Luxemburgo: Observatorio Europeo de las Drogas y las Toxicomanías.

Rice, E., Milburn, N. G., Rotheram-Borus, M. J., Mallett, S. & Rosenthal, D. (2005). The effects of peer group network properties on drug use among homeless youth. *The American Behavioral Scientist, 48*, 1102–1123. doi:10.1177/0002764204274194.

Rudzinski, K., Dawe, M., McGuire, F., Shuper, P. A., Rehm, J. & Fischer, B. (2014). Reflections regarding future can-

nabis use among high-frequency users in a Canadian university student population. *Journal of Research on Adolescence, 24*, 598–607. doi:10.1111/jora.12087.

Schnohr, C., Højbjerre, L., Riegels, M., Ledet, L., Larsen, T., Schultz-Larsen, K., … Grønbaek, M. (2004). Does educational level influence the effects of smoking, alcohol, physical activity, and obesity on mortality? A prospective population study. *Scandinavian Journal of Public Health, 32*, 250-256. doi:10.1080/14034940310019489.

Sordo, L., Indave, B. I., Pulido, J., Molist, G., Rosales-Statkus, M. E., Ruiz-García, M. & Barrio, G. (2015). Epidemiología del abuso de alcohol entre la población inmigrante en España. *Adicciones, 27*, 132-140. doi:10.20882/adicciones.697.

Teachman, J., Aderson, C. & Tedrow, L. M. (2015). Military service and alcohol use in the United States. *Armed Forces & Society, 41*, 460-476. doi:0.1177/0095327X14543848.

Unidad de Estadística del Órgano Central (2016). *Estadística del personal militar de complemento, militar de tropa y marinería y reservista voluntario 2015*. Madrid, España: Ministerio de Defensa.

Wilkinson, L. & APA Task Force on Statistical Inference. (1999). Statistical methods in psychology journal: Guidelines and explanations. *American Psychologist, 54*, 594-604. doi:10.1037/0003066X.54.8.594.

Intimate partner violence among female drug users admitted to the general hospital: screening and prevalence

Violencia de género en mujeres con consumo de sustancias ingresadas en el hospital general: cribado y prevalencia

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Abstract

Intimate partner violence (IPV) is a public health problem worldwide. Several factors have been found to be associated with an increased prevalence of IPV, such as substance use. A cross-sectional study was conducted with the aim of determining the prevalence of IPV among women entering Hospital del Mar (Barcelona) for any medical/surgical reason, and who had a diagnosis of substance use disorder. Secondly, it was intended to psychometrically validate the Spanish version of the *Hurt, Insulted, Threatened with Harm, Screamed* (HITS) questionnaire. All patients were assessed by two IPV questionnaires, the *Composite Abuse Scale* (CAS) and HITS. Out of 52 patients interviewed, 46 answered both questionnaires. According to the CAS questionnaire, 23 patients (50%) experienced IPV at some point in their lives and 11 (23.9%) in the last year. Cannabis consumption was also associated with an increased severity of IPV (95% CI 3.5-28.9, $p = .013$).According to the HITS questionnaire, there was a IPV prevalence of 39.1% (18 patients) in the last 12 months. HITS had a specificity of 100% and a sensitivity of 78% relative to the CAS questionnaire. A cut-off score x∈ [6,7], derived through ROC analysis, correctly discriminated 91% of the victims and 100% of the non-victims. The results obtained showed that the prevalence of IPV was very high among women who suffered from more than one substance use disorder. Therefore, it is highly recommended to systematically screen for IPV victimization by putting the HITS questionnaire into practice.

Key Words: Liaison psychiatry; Intimate partner violence; Screening test; Substance use disorder; Validation.

Resumen

La violencia de género (VG) es un problema de salud pública a escala mundial. Existen determinados factores asociados a un aumento de la prevalencia, como el consumo de sustancias. Se realizó un estudio transversal con el objetivo de determinar la prevalencia de VG en las mujeres que ingresaron en el Hospital del Mar (Barcelona) por cualquier motivo médico/quirúrgico y con el diagnóstico de trastorno por consumo de sustancias. Secundariamente, se pretendió validar la versión en español del cuestionario *Hurt, Insulted, Threatened with Harm, Screamed* (HITS). Se evaluaron a todas las pacientes mediante dos cuestionarios de detección de VG, el *Composite Abuse Scale* (CAS) y el HITS. De las 52 pacientes entrevistadas durante el período de estudio, 46 respondieron ambos cuestionarios. Según el cuestionario CAS, 23 pacientes (50%) presentaron VG alguna vez en la vida y 11 (23,9%) en el último año. El consumo de cannabis se asoció a una mayor gravedad de la VG (IC95% 3,5-28,9, $p = .013$). La prevalencia de VG, según el HITS, fue de 39,1% (18 pacientes) en los últimos 12 meses. El HITS mostró en relación al CAS una especificidad del 100% y una sensibilidad del 78%. Un punto de corte x∈ [6,7], obtenido mediante el análisis ROC, fue el que mejor discriminó al 91% de las víctimas y al 100% de las no-víctimas. Los resultados obtenidos demostraron una elevada prevalencia de VG entre las mujeres consumidoras de más de una sustancia de abuso. Por ese motivo, se recomienda incorporar el cribado sistemático mediante el cuestionario HITS.

Palabras clave: Psiquiatría de enlace; Violencia de género; Cribado; Trastorno por consumo de sustancias; Validación.

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Intimate partner violence (IPV) is an important public health issue due to its negative effects and high prevalence. The concept of IPV includes actual or threatened physical, sexual or psychological violence by a current or former partner, who can be of the same or opposite sex (WHO, 2013). In this study, however, the term IPV will be used to refer to violence against women. Although some studies show similar levels of victimization and perpetration, violence against women has more serious consequences (e.g. death) (Desmarais, Reeves, Nicholls, Telford & Fiebert, 2012; Langhinrichsen-Rohling, McCullars & Misra, 2012). According to Devries et al. (2013), 30% of women worldwide have experienced physical and/or sexual violence by their partners at some point in their lives. In Spain, 12.5% of women over 16 report being the victim of physical or sexual violence by their current or former partners over the course of their lives (Ministerio de Sanidad y Políticas Sociales, 2015).

A systematic review of the research on risk factors associated with IPV has shown that a family history of violence or abuse in childhood, belonging to an ethnic minority, having low income or IQ are all linked to suffering IPV (Capaldi, Knoble, Shortt & Kim, 2012). IPV can have major consequences, resulting in injuries and serious mental health problems among the victims of IPV and the children who witness it. Victims of IPV are at greater risk of suffering gastrointestinal or gynaecological problems (including sexually transmitted diseases and pregnancy difficulties), severe or chronic pain and a greater risk of committing suicide than women who are not victims of IPV (Campbell, 2002; Hussain et al., 2015). Similarly, certain mental health problems such as depression, anxiety disorder, posttraumatic stress and substance use disorder have been associated with IPV (Gilchrist, Blázquez & Torrens, 2012; Reingle, Jennings, Connell, Businelle & Chartier, 2014). Furthermore, more than a third of murdered women are killed by their partners (Stöckl et al., 2013). Thus, apart from the legal and judicial issues, IPV is the cause of major health problems, and from this perspective healthcare personnel consequently play an important role in its prevention and detection.

While many studies point to a significant and greater prevalence (25-75%) of all types of violence and its severity among women who are dependent on alcohol or other substances (El-Bassel, Gilbert, Witte, Wu & Chang, 2011; Feingold, Washburn, Tiberio & Capaldi, 2015; Weaver, Gilbert, El-Bassel, Resnick & Noursi, 2015), none have been carried out in Spain on the prevalence of IPV among hospitalised women who consume drugs. The objective of the present study was therefore twofold: 1) to detect the prevalence of IPV among women with substance use disorder who were admitted to a general hospital for any health problems, whether related to their addiction or not, and 2) to validate the Spanish version of the *Hurt, Insulted, Threatened with Harm and Screamed* (HITS) questionnaire (Sherin, Sinacore, Li, Zitter & Shakil, 1998) among women substance users. HITS is a screening tool requiring very little administrative time which can be useful in everyday clinical practice.

Methods

Participants

The patients assessed in this study were all the women attended by the liaison addiction psychiatry team in the periods November 2013-February 2014 (n=18), May-June 2014 (n=3) and September 2014-February 2015 (n=25) in the Instituto de Neuropsiquiatría y Adicciones (INAD) of the Parc de Salut Mar de Barcelona, or hospitalised in the detoxification unit of the Hospital del Mar.

The inclusion criteria were 1) having had an intimate partner at some point in their lives, 2) being over 18 years of age, 3) being diagnosed with a SUD (DSM-5) with or without any associated medical-surgical pathology. Exclusion criteria were: 1) severe cognitive disorders, 2) severe intoxication or withdrawal symptoms, and 3) a language barrier when assessment was carried out. All women meeting the inclusion criteria were informed about the characteristics of the research and the confidentiality with their personal details would be treated. They were asked to sign a letter of informed consent in order to join the study. The study was approved by the Clinical Research Ethics Committee of the Parc de Salut Mar (CEIC-PSMAR).

During the course of the study, 52 patients were admitted to hospital, of which 4 (7.7%) declined to take part in the study (response rate: 92.3%) and 2 were excluded on the grounds of severe cognitive disorder. Of the 46 patients studied, 24 (52.2%) were treated in the detoxification unit, while 22 (47.8%) came through in-hospital consultation. No significant differences were found regarding sociodemographic or clinical characteristics of the sample across the three recruitment periods.

Assessment instruments

All participants were asked to complete an ad hoc questionnaire for sociodemographic and clinical data (age, sex, marital status, origin, employment situation, years of schooling, address, social environment of substance use, criminal record, family history of addiction or psychiatric disorders, as well as the characteristics of substance use, reason for hospitalisation or other diagnoses) by the INAD addiction unit's regular in-hospital consultation team.

IPV assessment was carried out with the Spanish-language version of the Composite Abuse Scale (CAS) (Tirado-Muñoz, Gilchrist, Lligoña & Torrens, 2015). Participants were asked to report the frequency with which abuse occurred over the last year, either with their current or last previous partner. The CAS questionnaire consists of a total of 30 items classified in 4 subscales: severe combined abuse (8 items, 0-40 points), physical abuse (7 items, 0-35 points), emotional abuse (11 items, 0-55 points) and harassment (4 items,

0-20 points). Questions were answered with the frequency of occurrence: never (0 points), once only (1 point), several times (2 points), monthly (3 points), weekly (4 points), daily (5 points). It takes approximately 15-20 minutes to carry out the questionnaire. A total score of ≥7 indicate IPV, with the highest scores reflecting the severity of violence. Within the subscales of the different types of abuse, the cut-off scores used were: severe combined abuse (1 point), physical abuse (1 point), emotional abuse (3 points) and harassment (2 points). The questionnaire showed good internal consistency (Cronbach's alpha >0.85) for the 4 subscales and corrected item-total correlations of >0.5 (Hegarty, Sheehan & Schonfeld, 1999).

The HITS questionnaire (Sherin et al., 1998) consists of 4 questions: (1) "How often does your partner physically hurt you?", (2) "How often does your partner insult you or talk down to you?", (3) "How often does your partner threaten you with harm?", (4) "How often does your partner scream or curse at you?" These questions are answered with the frequency of the respective abuse, from never (1 point) to frequently (5 points). The total score can range from 4 to 20 points, with 10 points or higher being considered an indicator of IPV. This questionnaire can be administered in 1 minute.

In contrast to CAS, HITS only assesses IPV in relation to the current partner. The questionnaire was rendered in Spanish by a process of translation and back translation. The

Table 1. *Sociodemographic and clinical characteristics of the sample*

	Participants	**IPV CAS N=46**		
	N=46	**YES (n=23)**	**NO (n=23)**	*p*
	n (%)	n (%)	n (%)	
Sociodemographic				
Age [mean±SD] (years)	46.6 ±10.6	43.70 ±10	49.48±10.6	0.06
Marital status				0.63*
Married	25 (54.3)	12 (52.2)	13 (56.5)	
Origin				1*
Foreigner	6 (13)	3 (13)	3 (13)	
Employment situation				0.59*
Unemployed or pension	22 (47.8)	12 (52.2)	10 (43.5)	
Years of schooling	10.6 ±4.4	11.14±4.7	10.17±4.1	0.47
Social user environment	22 (48.9)	12 (54.5)	10 (43.5)	0.46
Criminal record	11 (23.9)	6 (26.1)	5 (22.7)	0.56*
Fam. hist.* of addiction	26 (60)	14 (63.6)	12 (54.5)	0.54
Fam. hist.* of psychiatric treament	10 (22.7)	4 (18.2)	6 (27.3)	0.47
Place of admission				0.24
Detoxification unit	24 (52.2)	14 (60.9)	10 (43.5)	
In-hospital consultation	22 (47.8)	9 (39.1)	13 (56.5)	
Other diagnoses				
Depressive disorder	11 (24.4)	5 (22.7)	6 (26.1)	0.79
Personality disorder	12 (27.3)	8 (38.1)	4 (17.4)	0. 12
Infected with HIV	10 (22.2)	7 (31.8)	3 (13)	0.16*
Infected with HCV	10 (21.7)	8 (34.8)	2 (8.7)	0.09*
Chronic liver disease	16 (35.6)	6 (27.3)	10 (43.5)	0.13*
Primary substance				
Heroin	7 (15.2)	4 (17.4)	3 (13.0)	1.00*
Alcohol	24 (52.2)	9 (39.1)	15 (65.2)	0.07
Nicotine	1 (2.2)	1 (4.3)	0 (0)	1.00*
Hypnosedatives	3 (6.5)	2 (8.7)	1 (4.3)	1.00*
Cocaine	7 (15.2)	5 (21.7)	2 (8.7)	0.41*
Cannabis	2 (4.3)	1 (4.3)	1 (4.3)	1.00*

Note. IPV: intimate partner volence; CAS: Composite Abuse Scale; SD: standard deviation; Fam. Hist.: family history; HIV: Human immunodeficiency virus; HCV: hepatitis C virus. *Fisher's exact test.

Spanish version has not been validated with women substance users. The CAS and HITS questionnaires were administered by an independent researcher of the regular addiction consultation team.

Procedure

The addiction consultation team receives daily requests for evaluation and intervention from Hospital del Mar patients with a concomitant substance use disorders. As part of standard procedure, sociodemographic and clinical data are gathered, along with details of substance use with the above mentioned ad hoc questionnaire. If during the course of a consultation with a patient the inclusion criteria were met, the independent researchers were informed and they completed data collection for the study. If an IPV victim asked for help during the interview, the hospital's help system was explained to her and the corresponding social worker was informed of the situation so that the resources for helping the victims could be accessed.

Data analysis

A descriptive analysis of the sample was carried out. Chi square and Fisher's exact tests were used for the qualitative variables, while the Student T-test was applied to the quantitative variables. The sample was divided into those who had and those who had not been the victims of IPV according to the CAS. This was followed by a calculation of Cohen's kappa coefficient to determine the level of concordance between the two questionnaires, as well as the sensitivity, specificity, the positive predictive value (PPV) and negative predictive value (NPV) of the HITS questionnaire with respect to the CAS, which served as the gold standard. Finally, an analysis of the receiver operating curve (ROC) was carried out to establish the cut-off value for optimal sensitivity and specificity on the HITS scale, and also evaluate the discriminatory power of HITS compared to CAS. Results were evaluated using a significance level of $p<.05$. All the uni- and bivariant analyses were carried out with SSPS (version 20).

Results

Sociodemographic and clinical characteristics

Mean age was 46.6 (*SD*=10.6). Twenty-five patients (54.3%) were married or had a current partner (10 single, 9 separated, 2 widows). In terms of employment, 23.9% of these patients were unemployed, 23.9% were recipients of benefits other than invalidity, and only 17.4% were in work. Table 1 shows the sociodemographic and clinical details of the sample. The most frequent admission diagnoses were: alcohol use disorder (n=10, 21.7%) and cocaine use disorder (n=7, 15.2%). Chronic liver disease was a secondary diagnosis in 35.6% of participants, while personality disorder was diagnosed in 27.3% of cases (see Table 1).

Toxicological history

The majority of patients (n=36, 78.3%) consumed alcohol, and this was also the primary drug used in 24 (52.2%) cases. The other most frequently used substances, besides nicotine, were cocaine (43.5%) and cannabis (30.4%), with cocaine being the primary drug in 7 cases (15.2%) (see Table 1 and 2). The majority of participants were polydrug users, with a mean number of drugs used of 2.9 (*SD*=1.7). Table 2 also shows the substance use characteristics (onset age, longest period of abstinence, and consumption over the previous 30 days).

Prevalence of IPV measured by CAS

CAS results show that 23 patients (50%) had experienced IPV at some point in their lives, with 23.9% reporting it within the last year. Of these, 16 patients (34.8%) suffered severe combined abuse, 21 (45.7%) physical abuse, 22 (47.8%) emotional abuse and 16 women (34.8%) were

Table 2. *Prevalence of IPV and consumption patterns by substance*

	Participants	IPV CAS		Mean onset age			Longest period of abstinence (months)		Days of use in last month		Mean CAS*score
	N=46	YES (n=23)	NO (n=23)	P	Media	SD	Media	SD	Media	SD	
	n (%)	n (%)	n (%)								
Substances used											
Heroin	14 (30.4)	10(43.5)	4 (17.4)	0.06	22.8	8.3	76.5	99.3	9.5	13.7	24.93
Alcohol	36 (78.3)	17 (73.9)	19 (82.6)	0.47	17.44	5.2	9.33	18.9	19.5	12.7	14.75
Nicotine	34 (73.9)	19 (82.6)	15 (65.2)	0.18	15.32	3.5	14.16	58.1	19.8	14.2	17.68
Hypnosedatives	12 (26.1)	7 (30.4)	5 (21.7)	0.5	25.75	9.3	0.17	0.6	25.8	10	19.17
Cocaine	20 (43.5)	14 (60.9)	6 (26.1)	**0.02***	21.8	6.5	43.6	56.9	14.6	15.0	24.85
Cannabis	14 (30.4)	11 (47.8)	3 (13)	**0.01****	17.5	7.5	14	22.1	17.5	15.0	26.93

Note. IPV: intimate partner violence; CAS: Composite Abuse Scale; SD: standard deviation. *p<.05 **p<0.01

subjected to harassment. No significant differences were found in the sociodemographic or clinical characteristics on the basis of having suffered IPV or not in the past year, although a greater number of women victims of violence were HCV positive. There were no significant differences in IPV victimisation with regard to any particular drug (see Table 1).

The substances most clearly linked to the presence of IPV were cannabis (p = .01) and cocaine (p = .02), with women cannabis users scoring the most points on the CAS questionnaire (mean 26.93) (CI 95% 3.5-28.9, p = .013) (see Table 2).

HITS questionnaire validation

An analysis of the HITS questionnaire shows that the prevalence of IPV was 39.1% (18 patients) in the last 12 months. In our study, the HITS questionnaire yielded a specificity of 100% with regard to CAS and a sensitivity of 78% (5 cases reported as IPV victims by CAS were not detected by HITS). Furthermore, HITS displayed a PPV of 100% and an NPV of 82%. With a Cohen's kappa of 0.78 (p = .000), both questionnaires can be said to be concordant. The ROC analysis for HITS with regard to CAS yielded an area under the curve (AUC) of 0.97 (CI 95% [0.92-1], p = .000). The cut point of x∈[6.7] optimised sensitivity and specificity, correctly discriminating 91% of the victims and 100% of the non-victims (see Figure 1).

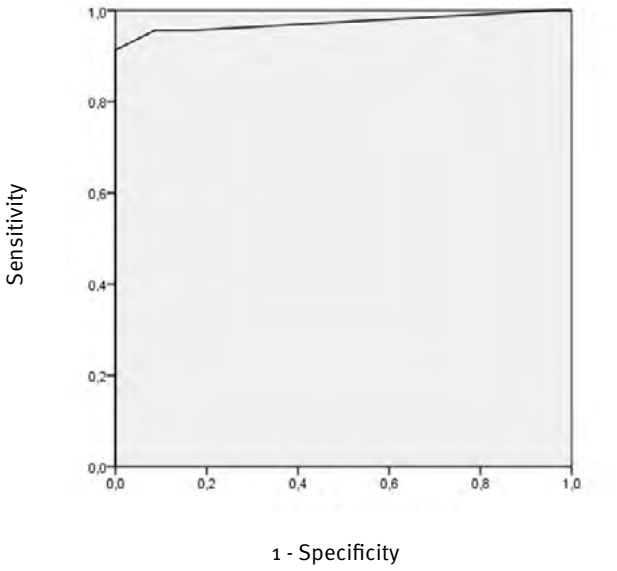

Figure 1. ROC curve for detecting IPV using the Hurt, Insulted, Threatened with harm, and Screamed at (HITS) questionnaire in comparison to the Composite Abuse Scale (CAS).

Discussion

A high level of IPV is found among women admitted to general hospital with substance use disorder and attended by the liaison addiction psychiatry unit. Of the patients interviewed as part of this study 50% had experienced IPV at some point during their lives, 23.9% in the past year. This percentage is similar to that of other studies, in which the prevalence of IPV among women substance users is estimated at 25-75% (El-Bassel et al., 2011; Gilchrist et al., 2012), which is clearly higher than in the general population, where it stands at 12.5% in the case of Spain (Ministerio de Sanidad & Políticas Sociales, 2015).

With regard to the substance use disorders most commonly associated with being abused, alcohol has been closely linked to IPV (Devries et al., 2014; Kraanen, Vedel, Scholing & Emmelkamp, 2014); nevertheless, alcohol and cocaine use disorders among women users are those considered most likely to lead to becoming a victim of IPV (Kraanen et al., 2014). In addition, according to the results of the *National Epidemiologic Survey on Alcohol and Related Conditions* (NESARC), opioid and cannabis use disorders are also linked to suffering IPV (Reingle et al., 2014; Smith, Homish, Leonard & Cornelius, 2012).

In a recent meta-analysis of longitudinal studies, the existence of a bidirectional relationship between alcohol consumption and IPV was revealed (OR: 1.80, CI 95% [1.58-2.06]) (Devries et al., 2014), an association which was also detected, although not to a significant degree, in the present study. The lack of longitudinal studies investigating this relationship prevents us from determining causality in the use of other substances or discriminating whether this link is always bidirectional.

Few studies control for the confounding factor in IPV of whether the victim was an alcohol user. A research carried out in the USA has shown that partners with the same consumption pattern ran a lower risk of suffering abuse. Habitual substance use is therefore a predictive factor in IPV, though it appears that the presence of conflicts within the relationship is a better predictor of IPV than alcohol use itself (Leadley, Clark & Caetano, 2000).

Different mechanisms have been proposed to explain the relationship between substance use disorders and falling victim to IPV. It has been posited by some that the problems associated with substance use lead to a stressful situation within the couple which then results in IPV; others in turn suggest that victims of partner violence use substances to counteract the stress, anxiety and pain caused by being abused (Kraanen et al., 2014). It is possible that substance use among women in methadone maintenance programmes may be a form of self-medication to be able to cope with the negative effects of experiencing IPV (El-Bassel, Gilbert, Wu, Go & Hill, 2005).

IPV among women substance users is associated with mental health problems (Cohen, Field, Campbell & Hien,

2013; Gilchrist et al., 2012) and can increase the risk of being infected with HIV or HCV via unsafe sexual behaviour and injection (Wagner et al., 2009). Given the devastating physical and psychological effects of IPV on women, the need to detect this abuse is considered vital, even among women not seeking treatment for substance use but attended by hospital services on other grounds.

A further important finding of this study, although not significant, is the link between being a victim of IPV and HCV positive. This confirms the results of previous studies which have assessed the prevalence of HCV among women substance users (Gilbert et al., 2000), finding a strong association between being HCV positive and being a victim of IPV. This should be taken into account when prescribing new treatment options for women substance users since the risk of HCV reinfection is high among women victims of IPV.

Given the lack of IPV screening tools in Spanish, the finding that the Spanish version of HITS is a useful screening tool for IPV in this population is highly relevant. Far less time is needed to administer HITS than CAS, which makes it a good alternative for detecting IPV in healthcare environments. A study of the validity and reliability of HITS in the Spanish population yielded similar results to ours. A cut point of 5.5 best discriminated women victims of IPV (Chen, Rovi, Vega, Jacobs & Johnson, 2005). HITS was also compared to a Spanish-language version of WAST, another questionnaire used for detecting IPV. Finally, it can be said that more studies are necessary to test for internal consistency and to assess cut point adjustments for improving the discriminatory power of HITS.

In conclusion, the results obtained in this study confirm that women substance users constitute a high-risk group for IPV in our environment. Systematic screening using the HITS questionnaire is therefore recommended for all women diagnosed with more than one substance use disorder admitted to general hospital for any reason. Detection of substance use as a modifiable risk factor should be a starting point for future IPV intervention and prevention strategies and a manualized cognitive-behavioural treatment which has proved efficacious in the reduction of IPV among women substance users is available (Tirado-Muñoz et al., 2015).

Finally, some limitations of the study need to be pointed out. The number of women attended by in-hospital consultation was limited. Nevertheless, the sample non-response percentage of 7.7% was lower in comparison to that of other studies carried out with women with substance use disorders and IPV (Kraanen et al., 2014). Given the limited sample size, the results of the study need to be interpreted with caution and should not be extrapolated to populations from other geographical areas.

Because the study was carried out over different time periods for reasons of research staff availability, a possible time-related bias cannot be ruled out.

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Conflict of interests

The authors declare that they have no conflict of interests.

References

Campbell, J. C. (2002). Health consequences of intimate partner violence. *Lancet*, *359*, 1331-1336. doi:10.1016/S0140-6736(02)08336-8

Capaldi, D. M., Knoble, N. B., Shortt, J. W. & Kim, H. K. (2012). A Systematic Review of Risk Factors for Intimate Partner Violence. *Partner Abuse*, *3*, 231-280. doi:10.1891/1946-6560.3.2.231

Chen, P. H., Rovi, S., Vega, M., Jacobs, A. & Johnson, M. S. (2005). Screening for domestic violence in a predominantly Hispanic clinical setting. *Family Practice*, *22*, 617-623. doi:10.1093/fampra/cmi075

Cohen, L. R., Field, C., Campbell, A. N. & Hien, D. A. (2013). Intimate partner violence outcomes in women with PTSD and substance use: A secondary analysis of NIDA Clinical Trials Network «Women and Trauma» Multi-site study. *Addictive Behaviors*, *38*, 2325-2332. doi:10.1016/j.addbeh.2013.03.006

Desmarais, S. L., Reeves, K. A, Nicholls, T. L., Telford, R. P. & Fiebert, M. S. (2012). Prevalence of Physical Violence in Intimate Relationships: Part 1. Rates of Male and Female Victimization. *Partner Abuse, 3*, 140-169.

Devries, K. M., Mak, J. Y., García-Moreno, C., Petzold, M., Child, J. C., Falder, G., … Watts, C. H. (2013). Global health. The global prevalence of intimate partner violence against women. *Science, 340*, 1527–1528. doi: 10.1126/science.1240937

Devries, K. M., Child, J. C., Bacchus, L. J., Mak, J., Falder, G., Graham, K., … Heise, L. (2014). Intimate partner violence victimization and alcohol consumption in women: a systematic review and meta-analysis. *Addiction (Abingdon, England)*, *109*, 379-391. doi:10.1111/add.12393

El-Bassel, N., Gilbert, L., Wu, E., Go, H. & Hill, J. (2005). Relationship between drug abuse and intimate partner violence: a longitudinal study among women receiving methadone. *American Journal of Public Health*, *95*, 465-470. doi:10.2105/AJPH.2003.023200

El-Bassel, N., Gilbert, L., Witte, S., Wu, E. & Chang, M. (2011). Intimate partner violence and HIV among drug-involved women: Contexts linking these two epide-

mics—challenges and implications for prevention and treatment. *Substance Use & Misuse*, *46*, 295–306. doi:10.3109/10826084.2011.523296.

Feingold, A., Washburn, I. J., Tiberio, S. S. & Capaldi, D. M. (2015). Changes in the Association of Heavy Drinking and Drug Use with Intimate Partner Violence in Early Adulthood. *Journal of Family Violence*, *30*, 27–34. doi:10.1007/s10896-014-9658-6

Gilbert, L., El-Bassel, N., Rajah, V., Foleno, A., Fontdevila, J., Frye, V. & Richman, B. L. (2000). The converging epidemics of mood-altering-drug use, HIV, HCV, and partner violence: a conundrum for methadone maintenance treatment. *Mount Sinai Journal of Medicine*, *67*, 452-464.

Gilchrist, G., Blázquez, A. & Torrens, M. (2012). Exploring the relationship between intimate partner violence, childhood abuse and psychiatric disorders among female drug users in Barcelona. *Advances in Dual Diagnosis*, *5*, 46-58. doi:10.1108/17570971211241895

Hegarty, K., Sheehan, M. & Schonfeld, C. (1999). A multidimensional definition of partner abuse: development and preliminary validation of the Composite Abuse Scale. *Journal of Family Violence*, *14*, 399-414.

Hussain, N., Sprague, S., Madden, K., Hussain, F. N., Pindiprolu, B. & Bhandari, M. (2015). A comparison of the types of screening tool administration methods used for the detection of intimate partner violence: a systematic review and meta-analysis. *Trauma, Violence & Abuse*, *16*, 60-69. doi:10.1177/1524838013515759

Kraanen, F. L., Vedel, E., Scholing, A. & Emmelkamp, P. M. G. (2014). Prediction of intimate partner violence by type of substance use disorder. *Journal of Substance Abuse Treatment*, *46*, 532-539. doi:10.1016/j.jsat.2013.10.010

Langhinrichsen-Rohling, J., McCullars, A. & Misra, T. (2012). Motivations for Men and Women's Intimate Partner Violence Perpetration: A Comprehensive Review. *Partner Abuse*, *3*, 1-33. doi:10.1891/1946-6560.3.4.e10

Leadley, K., Clark, C. & Caetano R. (2010). Couples' drinking patterns,intimate partner violence, and alcohol-related partnership problems. *Journal Substance Abuse*, *11*, 253–263.

Ministerio de Sanidad y Políticas Sociales. (2015). Macroencuesta Violencia contra la Mujer 2015. Retrieved from: http://www.msssi.gob.es/gabinetePrensa/notaPrensa/pdf/30.03300315160154508.pdf

Reingle, J. M., Jennings, W. G., Connell, N. M., Businelle, M. S. & Chartier, K. (2014). On the pervasiveness of event-specific alcohol use, general substance use, and mental health problems as risk factors for intimate partner violence. *Journal of Interpersonal Violence*, *29*, 2951-2970. doi:10.1177/0886260514527172

Sherin, K. M., Sinacore, J. M., Li, X. Q., Zitter, R. E. & Shakil, A. (1998). HITS: a short domestic violence screening tool for use in a family practice setting. *Family Medicine*, *30*, 508-512.

Smith, P.H., Homish, G.G., Leonard, K.E. & Cornelius, J.R. (2012). Intimate partner violence and specific substance use disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychology of Addictive Behaviors*, *26*, 236-245. doi:10.1037/a0024855.

Stöckl, H., Devries, K., Rotstein, A., Abrahams, N., Campbell, J., Watts, C. & Moreno, C. G. (2013). The global prevalence of intimate partner homicide: a systematic review. *Lancet*, *382*, 859-865. doi:10.1016/S0140-6736(13)61030-2

Tirado-Muñoz, J., Gilchrist, G., Lligoña, E., Gilbert, L. & Torrens, M. (2015). A group intervention to reduce intimate partner violence among female drug users. Results from a randomized controlled pilot trial in a community substance-abuse center. *Adicciones*, *27*, 168-178.

Wagner, K. D., Hudson, S. M., Latka, M. H., Strathdee, S. A., Thiede, H., MacKesy-Amiti, M. E. & Garfein, R. S. (2009). The effect of intimate partner violence on receptive syringe sharing among young female injection drug users: An analysis of mediation effects. *AIDS and Behavior*, *13*, 217-224. doi:10.1007/s10461-007-9309-5

Weaver, T. L., Gilbert, L., El-Bassel, N., Resnick, H. S. & Noursi, S. (2015). Identifying and intervening with substance-using women exposed to intimate partner violence: phenomenology, comorbidities, and integrated approaches within primary care and other agency settings. *Journal of Women's Health (Larchmt)*, *24*, 51-56. doi:10.1089/jwh.2014.4866

World Health Organization. (2013). Responding to intimate partner violence and sexual violence against women: WHO clinical and policy guidelines. Retrieved from: http://apps.who.int/iris/bitstream/10665/85240/1/9789241548595_eng.pdf?ua=1

Problem video game playing is related to emotional distress in adolescents

El uso problemático de videojuegos está relacionado con problemas emocionales en adolescentes

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Abstract

Problem use of video games is an increasing risk behaviour. High exposure of adolescents to video games has been linked to a variety of disorders, but the relationship between problem video game playing and emotional welfare is unknown. The aim of the study is to analyse problem video game playing in a sample of adolescents and to determine whether there are differences between online and offline players, in addition to examining its relationship with anxiety and depressive symptomatology. A sample of adolescents (N = 380) completed self-reports measuring video game use and symptoms of anxiety and depression. We found that 7.4% of females and 30% of males can be considered as playing at problem levels. Online players were almost 12 times more likely to play at high frequency than offline players ($x^2_{(1, 267)}$ = 72.72, p < .001, OR = 11.63, 95% CI [6.31, 21.43]). Males play more frequently, and play more online ($x^2_{(1, 267)}$ = 50.85, p < .001, OR = 6.74, 95% CI [3.90, 11.64]), with a clear relationship between problem video game playing and anxiety (r = .24; p < .001). In females, there is a relationship between problem video game playing and depression (r = .19; p < .05). Our findings contribute to a better understanding of the psychological variables involved in problem video game playing. The implementation of strategies is suggested in order to prevent pathological gaming and associated problems.

Key words: Video Game; Anxiety; Depression; Adolescents; Problem Video Game Playing.

Resumen

El uso problemático de los videojuegos es una conducta de riesgo cada vez más frecuente. La alta exposición de los adolescentes a los videojuegos se ha relacionado con una variedad de trastornos, pero se desconoce la relación entre el uso problemático de videojuegos y el bienestar emocional. El objetivo del estudio es analizar el uso problemático de videojuegos en una muestra de adolescentes y determinar si existen diferencias entre jugadores online y offline, además de examinar su correlación con sintomatología ansiosa y depresiva. Una muestra de adolescentes (N = 380) completó autoinformes que medían el uso de videojuegos y sintomatología ansiosa y depresiva. El 7,4% de las chicas y el 30% de los chicos pueden considerarse jugadores problemáticos. Jugadores online tienen casi 12 veces más probabilidad de jugar con alta frecuencia en comparación con jugadores offline ($x^2_{(1, 267)}$= 72,72, p < ,001, RM = 11,63, 95% IC [6,31, 21,43]). Los chicos juegan con mayor frecuencia y lo hacen en mayor medida online ($x^2_{(1, 267)}$= 50,85, p < ,001, RM= 6,74, 95% IC [3,90, 11,64]), con una clara relación entre el uso problemático de los videojuegos y la ansiedad (r =.24; p < ,001). En las chicas existe relación entre el uso problemático de videojuegos y bajo estado de ánimo (r = ,19; p < ,05). Los hallazgos contribuyen a una mejor comprensión de las variables psicológicas relacionadas con el uso problemático de videojuegos, consolidando la idea de instaurar programas educativos para prevenir el abuso de los videojuegos y sus problemas asociados.

Palabras clave: Videojuegos; Ansiedad; Depresión; Adolescentes; Juego problemático.

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The increased presence and use of information and communication technologies in today's society occurs primarily amongst children and adolescents (Lorenci, 2012). Internet Gaming Disorder (IGD) is one of the new conditions for further study included in the fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5; APA, 2013), defined as a "persistent and recurrent use of the Internet to engage in games, often with other players, leading to clinically impairment or distress as indicated by five (or more) of the following in a twelve- month period: preoccupation, withdrawal, tolerance, loss of control, loss of interest in previous hobbies, continued use despite knowledge of psychosocial problems, deception, escape and conflict with relationships, and job or school (p. 795)". The individuals presenting this problem typically face serious impairment in significant areas such as school, work or relationships (APA, 2013). Chamarro et al. (2014) claim that the use of video games becomes problematic when their healthy use generates psychological dependence: avoidance of problems, mood modification, loss of control, and targeting.

A growing number of studies highlight the differences between online and offline gaming. Unlike traditional video games, online video games integrate play within an Internet-based social context, creating a distinctive environment for social play (Kowert & Oldmeadow, 2013). The social elements contained within this environment constitute a primary reason for continued play frequency and extended duration (Caplan, Williams, & Yee, 2010). Online video games are more likely than offline games to be associated with problem use (Porter, Starcevic, Berle, & Fenech, 2010), and it has been suggested that online gaming way have a greater addictive potential (Ng & Wiemer-Hastings, 2005).

Prevalence rates of problematic Internet use in Spanish studies vary between 3.7% and 9.9% (Muñoz-Rivas, Fernández, & Gámez-Guadix, 2010). In 2014, online gambling platforms registered an average of 130,000 new players per month (Buil, Moratilla, & Ruiz, 2015). Similarly, it has been reported that 6.1% (Chamarro et al., 2014) to 8.2% (Oliva, 2012) of Spanish adolescents may be addicted to video games, with higher pathological gaming in boys as compared to girls (Labrador & Villadangos, 2010; Oliva, 2012).

Some social factors might explain the acquisition of gaming behaviours: high availability, easy accessibility, great social acceptance, high diffusion and lax legal restrictions (Blanco, González, & Martos, 2015). Pathological gaming has been linked to the expectation of positive moods or relieving negative moods (Shead, Callan, & Hodgins, 2008) and some evidence has been found on the mediation of emotional regulation in the emergence of a compulsive use of video games (Haagsma, Caplan, Peters, & Pieterse, 2013). Some studies have revealed the mediation of emotional regulation in the development of pathological gaming problems (Estévez, Herrero, Sarabia, & Jáuregui, 2014; Schreiber, Grant, & Odlaug, 2012), and it has been suggested that the abuse of video games could influence negatively on anxiety and depressive symptoms (Martínez, Betancourt, & González, 2013; Tortolero et al., 2014) – although most studies focus on aggressive games. Lafrenière, Vallerand, Donahue, and Lavigne (2009) found that gamers who were obsessively involved showed negative affective experiences; consistently, other have reported that problematic use of video games is associated with elevated levels of anxiety and depression (Mentzoni et al., 2011). In this regard, a study by Vazquez et al. (2013) with Spanish adolescents found a prevalence of negative mood in 14.9% of boys and 16.9% of girls, reaching 20.7% in high school ages.

Further, problem use of videogames seems to be associated with interference and misalignment in lifestyle – with important consequences for adolescents (Beranuy, Chamarro, Graner, & Carbonell, 2009). Some of the negative social effects of abusing video games include weak affective relationships with parents and people their own age, and the strengthening of social racial or sexual stereotypes (Dickerman, Christensen, & Kerl-McClain, 2008).

The relationship between video game abuse and anxiety and depression in Spanish adolescents is still to be established. The first aim of this paper is to analyze problem video game playing in a sample of adolescents and to determine whether differences exist between online and offline players. Second, it is intended to give evidence about the association between video game use and anxiety and depression symptomatology in Spanish adolescents. Our hypotheses, based on previous studies, are that there is a high problem video game playing prevalence, with differences between online and offline players; and that the use of video games at problem level is associated with higher anxiety and higher depression.

Method

Participants

The research team contacted a convenience sample of 35 schools in five Spanish cities in the province of Alicante, and all the schools that agreed to participate were included in the study. The sample was formed by 380 students from three public schools (all participants invited to participate in the study agreed to do so). Participants were aged 12 to 17 ($M = 14.9$, $SD = 1.46$); 14.7% were aged 12-13, 48.2% were aged 14.15 and 37.1% were aged 16-17, and were equally distributed between males and females, with no gender differences across age groups. The majority (92.6%) had Spanish nationality; 7.4% were distribu-

ted across 18 additional nationalities, and the nationality of one participant was unreported. In compliance with school requirements, no data were collected regarding ethnic group or socio-economic levels, but the vast majority of participants were White (Caucasian) middleclass students.

Instruments

Socio-demographics were assessed with items including age, gender, and nationality. Use of video games was measured with the Spanish version of the Problem Video Game Playing scale (PVP; Tejeiro & Moran, 2002). The PVP scale is a nine-item dichotomous questionnaire based on the DSM-IV (APA, 1994) criteria for substance dependence and for pathological gaming, as well as the literature on addictions. The original items in Spanish were utilized, but the reference to 'stealing' was deleted from item 8 in order to increase the similarity between this item and the DSM-5 criteria for IGD and substance use disorder. Different studies in a variety of countries and settings have confirmed that the PVP is one-dimensional, has a good internal consistency (Cronbach's alpha .69 to .91), and strong convergent and criterion validity (e.g., López-Fernández, Honrubia-Serrano, Baguley, & Griffiths, 2014). In this study, the PVP's internal consistency coefficient was low (Cronbach's α = .58); no item could be excluded in either subsample because that would have a negative effect on alpha.

Several cutoff points have been suggested for the PVP: three (Arab et al., 2007), four (Tejeiro, Gómez-Vallecillo, Pelegrina, Wallace, & Emberley, 2012), five (Adiele & Olatokun, 2014) and six (López-Fernández et al., 2014). The cutoff point in this study was four, which is the lower bound of the range suggested by the DSM-5 to consider a substance use disorder as of moderate severity.

Anxiety and depression were measured with the Goldberg, Bridges, Duncan-Jones, and Grayson (1988) scales. Derived by latent trait analysis from a standardized psychiatric research interview, these scales provide dimensional measures of the severity of each disorder. Each scale is formed by nine items (dichotomous response; one point for each affirmative answer), but the full set of questions needs to be administered only if the first four items have registered at least two positive answers (in the scale of anxiety) or at least one positive answer (in the scale of depression). The cutoffs are located in four or more for anxiety and in two or more for depression, with higher scores indicating higher severity. The authors indicate that an individual with a score at the cutoff for either scale has a 50% chance of having a clinically important disturbance, and above these scores the probability rises sharply. The total score has a specificity of .84 and a sensitivity of .75. In our study, Cronbach´s alpha values were moderate at α = .71 for the anxiety scale and α = .66 for the depression scale.

Procedure

After approval of the study by an ethics committee at Universidad Miguel Hernández as well as by the school boards – ensuring that the study does not involve risk to participants and respects human rights –, adolescents and their parents were informed about its objectives and provided written informed assent and consent, respectively. All measures to ensure confidentiality and anonymity were implemented and explained to the participants. After some short oral instructions, the surveys were administered by two members of the research team to groups of around 30 participants in their regular classrooms during school hours. Completion of the questionnaires required 10 to 20 minutes.

Data analysis

The SPSS version 21.0 statistical package and Amos version 21.0 were utilized for data analyses. Chi-square tests were used for nominal variables and the effect size was measured with odds ratio and ϕ for binary variables, and with Cramer's V or ϕ_c for categorical non-dichotomous variables. Normality (Shapiro-Wilk) and homoscedasticity (Levene's) tests were conducted for each variable and, according to the results, either parametric (Student's *t*) or nonparametric (Mann-Whitney's *U*) tests were conducted; the effect size was measured with Cohen's *d* for Gaussian variables and with *r* for non-Gaussian variables (Fritz, Morris, & Richler, 2012).

Results

Use of Video Games

The vast majority of participants had played video games in the past year (86.1%), with 36.1% being frequent players (daily or almost daily). Males were 4.6 times more likely than females to play frequently; 52.6% males, 19.5% females, $x^2_{(1, 380)} = 45.30$, $p < .001$, OR = 4.60, 95% CI [2.91, 7.27]; no differences in high frequency were found across age groups. Most participants played only or mostly offline (42.4%), with the remaining fairly distributed between online gaming (27.9%) and both types (29.5%); males played online (63.3%) significantly more than females (20.4%); $x^2_{(1, 267)} = 50.85$, $p < .001$, OR = 6.74, 95% CI [3.90, 11.64]; age groups did not differ in online vs. offline playing (39.1% of online gamers in 11-13 years-old, 36.3% in 14-15, and 44.3% in 16-17). Online players were almost 12 times more likely to play at high frequency (62.3%) than offline players (12.4%); $x^2_{(1, 267)} = 72.72$, $p < .001$, OR = 11.63, 95% CI [6.31, 21.43]. A logistic regression with high frequency as dependent variable found that greater likelihood persisted even when gender and age were controlled for, OR = 9.27, 95% CI [4.83, 17.80]. Table 1 shows participant's scores.

Males scored significantly higher than females in the PVP (U = 10957, $p < .001$, r = .35). No difference was found across the age groups. With a cutoff point of four, 7.4% of

Table 1. *Scores in the Problem Video game Playing questionnaire (PVP) and Goldberg et al.'s (1988) scales.*

		Males (n = 189)	Females (n = 191)	Total (N = 380)
PVP		2.48 (1.81)**	1.27 (1.81)	1.88 (1.67)
	Online players	3.56 (1.56)**	1.78 (1.25)	2.67 (1.81)**
	Offline players	1.32 (1.02)	1.14 (0.83)	1.23 (1.29)
Anxiety		2.56 (1.88)	4.01 (2.42)**	3.29 (2.29)
Depression		1.61 (1.61)	2.23 (2.00)*	1.92 (1.84)

Note. * $p < ,05$; ** $p < ,001$

Table 2. *Significance of differences between problem and non-problem gamers in scores above the cutoff points for anxiety and depression.*

	χ^2	*d.f.*	*p*	*OR* (CI 95%)
Anxiety	1.57	1	< .001	3.15 (1.64-6.04)
Depression	0.92	1	.09	1.83 (0.97-3.45)

females and 30% of males can be considered as playing at problem levels; OR = 5.39, 95% CI [2.88, 10.08]. The score for online gamers was significantly higher than the score for offline gamers ($U = 4441.5$, $p < .001$, $r = .42$); 33% of online gamers and 6.8% of offline gamers (16.5% of total gamers) scored above the cutoff point of four, with 75% of all problem gamers playing online.

Anxiety and Depression

Of all participants, 53.4% scored above the cutoff point for anxiety; females scored higher than males ($U = 11592$, $p < .001$, $r = .31$). For depression, 47.6% of participants scored above the cutoff point; females also scored higher than males ($U = 14804.5$, $p = .003$, $r = .15$). Table 1 shows the scores for each of the scales.

Spearman's correlations revealed that, for females, only the correlation between the PVP total score and score in depression was significant ($r = .19$; $p < .05$), but this relationship lost significance when partial correlation controlling for online vs. offline gaming was calculated. For males, PVP total score correlated significantly with depression ($r = .21$; $p < .05$) and anxiety ($r = .24$; $p < .001$) scores, even when partial correlation controlling for online vs. offline gaming was calculated ($r = .30$, $p = .001$ for both anxiety and depression).

Amongst males, problem gamers were three times more likely than non-problem gamers to score above the cutoff point in the anxiety scale (OR = 3.15, 95% CI [1.64, 6.04]) and almost twice as likely to score above the cutoff point in the depression scale (OR = 1.83, 95% CI [0.97, 3.45]), although the later was not statistically significant; see Table 2. Also, male problem gamers scored significantly higher in anxiety ($U = 2769$, $p = .006$, $r = .20$) and in depression ($U = 2996.5$, $p = .029$, $r = .16$) as compared to male non-problem gamers. No significant difference of any sort was found for females.

Discussion

Our aim was to measure problem video game playing, anxiety and depression in a sample of Spanish adolescents and to analyze their relationships. We found that 86.1% of adolescents had played video games in the past year; this result is consistent with those of Beltrán, Beltrán, Moreno, Cervelló, & Montero (2012), although our study draws attention to the higher percentage of frequent players (36.1%, daily or almost daily). As in previous studies (Chamarro et al., 2014; Chóliz & Marco, 2011; Labrador & Villadangos, 2010), males were more likely than females to play frequently and also to be online players, thus posing a greater addictive potential (Ng & Wiemer-Hastings, 2005).

The individuals presenting Internet Gaming Disorder typically face serious impairment in significant areas (APA, 2013). Anxiety and depression symptoms and disorders are the most prevalent psychological problems in adolescents (Skrove, Romundstad, & Indredavik, 2013), especially in females (Rosa-Alcázar, Parada-Navas, & Rosa-Alcázar, 2014). As hypothesized, we found a clear relationship between problem video game playing and anxiety (and to a lesser degree also with depression), but only in males. In females, only a weak relationship was found between problem video game playing and depression, and it lost significance when online vs. offline gaming was controlled for.

Mehroof and Griffiths (2010) established that trait and state anxiety display significant associations with gaming addiction, and some traits as neuroticism, sensation seeking, and aggression, might lead individuals to pathological gaming (Gyollai et al., 2014). It seems reasonable to assume that interventions should then begin with the detection of these personality traits, to prevent problem video game playing development. Usually the game is not played to obtain a benefit or a reward, but for the pleasure or intrinsic interest (Chóliz & Marco, 2011), facilitated by the games' structural and functional features (Lee & LaRose, 2007). Adolescent video gamers get short-term rewards, but in turn present anxiety and depression symptoms, which may lead to the increased use of video games as a strategy to avoid or escape situations, everyday experiences of stress, and exhaustion (Muros, Aragón, & Bustos, 2013), but future studies should clarify the direction of this relationship.

Despite some clear limitations, such as the opportunistic and convenience sample and the self-report method, and relatively poor psychometric properties of some of the scales used, our study provides the first empirical evidence of the association between excessive use of video games and anxiety and depression amongst Spanish adolescent. Furthermore, for adolescents with certain risk profiles, the misuse of video games may cause social, family and school problems. The early detection of the problem use of video games, especially among adolescents at risk of emotional problems, is therefore necessary in order to prevent and minimize other negative outcomes such as emotional disorders related to anxiety and depression.

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Conflicts of interest

There are no conflicts of interest.

References

Adiele, I. & Olatokun, W. (2014). Prevalence and determinants of Internet addiction among adolescents. *Computers in Human Behaviour, 31*, 100-110. doi:10.1016/j.chb.2013.10.028.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders, Fourth Edition.* Arlington, VA: American Psychiatric Association.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, Fifth Edition.* Arlington, VA: American Psychiatric Association.

Arab, E., Sommer, K., Herskovic, V., Sommer, S., Sandoval, C. & Poblete, C. (2007). Evaluación del uso del video juego en escolares de la Región Metropolitana. *Revista Chilena de Psiquiatría y Neurología de la Infancia y la Adolescencia, 18*, 7-11.

Beltrán, V. J., Beltrán, J. I., Moreno, J. A., Cervelló, E. & Montero, C. (2012). El uso de videojuegos activos entre los adolescentes. *CCD. Cultura_Ciencia_Deporte, 7*, 19-24. doi:10.12800/ccd.v7i19.20.

Beranuy, M., Chamarro, A., Graner, C. & Carbonell, X. (2009). Validación de dos escalas breves para evaluar la adicción a Internet y el abuso de móvil. *Psicothema, 21*, 480-485.

Blanco, P., González, M. & Martos, C. (2015). El juego como adicción social: crónica de una patología anunciada. *Alternativas: Cuadernos de Trabajo Social, 22*, 9-22.

Buil, P., Moratilla, M. J. S. & Ruiz, P. G. (2015). La regulación publicitaria de los juegos de azar online en España. Una reflexión sobre la protección del menor. *Adicciones, 27*, 198-204.

Caplan, S., Williams, D. & Yee, N. (2010). Problematic Internet use and psychosocial well-being among MMO players. *Computers in Human Behaviour, 25*, 1312–1319.

Chamarro, A., Carbonell, X., Manresa, J. M., Muñoz-Miralles, R., Ortega-González, R., López-Morron, M. R., …, Toran-Montserrat, P. (2014). El Cuestionario de Experiencias Relacionadas con los Videojuegos (CERV): Un instrumento para detectar el uso problemático de videojuegos en adolescentes españoles. *Adicciones, 26*, 303-311.

Chóliz, M. & Marco, C. (2011). Patrón de uso y dependencia de videojuegos en infancia y adolescencia. *Anales de Psicología, 27*, 418-426.

Dickerman, C., Christensen, J. & Kerl-McClain, S. B. (2008). Big breasts and bad guys: Depictions of gender and race in video games. *Journal of Creativity in Mental Health, 3*, 20-29. doi:10.1080/15401380801995076.

Estévez, A., Herrero, D., Sarabia, I. & Jáuregui, P. (2014). Mediating role of emotional regulation between impulsive behaviour in gambling, Internet and videogame abuse, and dysfunctional symptomatology in young adults and adolescents. *Adicciones, 26*, 282-290.

Fritz, C. O., Morris, P. E. & Richler, J. J. (2012). Effect size estimates: current use, calculations, and interpretation. *Journal of Experimental Psychology: General, 141*, 2-18. doi:10.1037/a0024338.

Goldberg, D., Bridges, K., Duncan-Jones, P. & Grayson, D. (1988). Detecting anxiety and depression in general medical settings. *British Medical Journal, 297*, 897-899. doi:10.1136/bmj.297.6653.897.

Gyollai, A. D., Griffiths, M., Barta, C., Vereczkei, A., Urban, R., Kun, B., …, Demetrovics, Z. (2014). The genetics of problem and pathological gambling: a systematic review. *Current Pharmaceutical Design, 20*, 3993-3999. doi: 10.2174/13816128113199990626.

Haagsma, M. C., Caplan, S. E., Peters, O. & Pieterse, M. E. (2013). A cognitive-behavioural model of problematic online gaming in adolescents aged 12-22 years. *Computers in Human Behaviour, 29*, 202-209. doi:10.1016/j.chb.2012.08.006.

Kowert, R. & Oldmeadow, J. A. (2013). Social reputation: Exploring the relationship between online video game involvement and social competence. *Computers in Human Behaviour, 29*, 1872–1878. doi:10.1016/j.chb.2013.03.003.

Labrador, F. J. & Villadangos, S. M. (2010). Menores y nuevas tecnologías: conductas indicadoras de posible problema de adicción. *Psicothema, 22*, 180-188.

Lafrenière, M. C., Vallerand, R. J., Donahue, E. G. & Lavigne, G. L. (2009). On the costs and benefits of gaming: the role of passion. *CyberPsychology & Behaviour, 12*, 285-290. doi:10.1089/cpb.2008.0234.

Lee, D. & LaRose, R. (2007). A socio-cognitive model of video game usage. *Journal of Broadcasting & Electronic Media, 51*, 632-650. doi:10.1080/08838150701626511.

López-Fernández, O., Honrubia-Serrano, L. M., Baguley, T. & Griffiths, M. D. (2014). Pathological video game playing in Spanish and British adolescents: Towards the exploration of Internet Gaming Disorder symptomatology. *Computers in Human Behaviour, 41*, 304-312. doi:10.1016/j.chb.2014.10.011.

Lorenci, M. (2012). *Anuario SGAE de las Artes Escénicas, musicales y audiovisuales*. Fundación Autor: Madrid.

Martínez, P., Betancourt, D. & González, A. (2013). Uso de videojuegos, agresión, sintomatología depresiva y violencia intrafamiliar en adolescentes y adultos jóvenes. *Revista Colombiana de Ciencias Sociales, 4*, 167-180.

Mehroof, M. & Griffiths, M. D. (2010). Online gaming addiction: the role of sensation seeking, self-control, neuroticism, aggression, state anxiety, and trait anxiety. *Cyberpsychology, Behaviour, and Social Networking, 13*, 313-316. doi:10.1089/cyber.2009.0229.

Mentzoni, R. A., Brunborg, G. S., Molde, H., Myrseth, H., Skouveroe, K. J. M., Hetland, J. & Pallesen, S. (2011). Problematic video game use: estimated prevalence and associations with mental and physical health. *Cyberpsychology, Behaviour, and Social Networking, 14*, 591-596. doi:10.1089/cyber.2010.0260.

Muñoz-Rivas, M. J., Fernández, L. & Gámez-Guadix, M. (2010). Analysis of the indicators of pathological Internet use in Spanish university students. *The Spanish Journal of Psychology, 13*, 131-137. doi:10.1017/s1138741600002365.

Muros, B., Aragón, Y. & Bustos, A. (2013). La ocupación del tiempo libre de jóvenes en el uso de videojuegos y redes. *Comunicar, 20*, 31-39. doi:10.3916/c40-2013-02-03.

Ng, B. D. & Wiemer-Hastings, P. (2005). Addiction to the internet and online gaming. *Cyberpsychology & Behaviour, 8*, 110-113. doi:10.1089/cpb.2005.8.110.

Oliva, A. (2012). *Uso y riesgo de adicciones a las nuevas tecnologías entre adolescentes y jóvenes andaluces*. Sevilla: Aguaclara.

Porter, G., Starcevic, V., Berle, D. & Fenech, P. (2010). Recognizing problem video game use. *Australian and New Zealand Journal of Psychiatry, 44*, 120–128.

Rosa-Alcázar, A. I., Parada-Navas, J. L. & Rosa-Alcázar, A. (2014). Síntomas psicopatológicos en adolescentes españoles: relación con los estilos parentales percibidos y la autoestima. *Anales de Psicología, 30*, 133-142. doi:10.6018/analesps.30.1.165371.

Schreiber, L. N., Grant, J. E. & Odlaug, B. L. (2012). Emotion regulation and impulsivity in young adults. *Journal of Psychiatric Research, 46*, 651-658. doi:10.1016/j.jpsychires.2012.02.005.

Shead, N., Callan, M. J. & Hodgins, D. C. (2008). Probability discounting among gamblers: Differences across problem gambling severity and affect-regulation expectancies. *Personality and Individual Differences, 45*, 536-541. doi:10.1016/j.paid.2008.06.008.

Skrove, M., Romundstad, P. & Indredavik, M. S. (2013). Resilience, lifestyle and symptoms of anxiety and depression in adolescence: the Young-HUNT study. *Social Psychiatry and Psychiatric Epidemiology, 48*, 407-416. doi:10.1007/s00127-012-0561-2.

Tejeiro, R., Gómez-Vallecillo, J., Pelegrina, M., Wallace, A. & Emberley, E. (2012). Risk factors associated with the abuse of video games in adolescents. *Psychology, 3*, 310-314. doi:10.4236/psych.2012.34044.

Tejeiro, R. & Moran, R. B. (2002). Measuring video game pathological playing in adolescents. *Addiction, 97*, 1601-1606. doi:10.1046/j.1360-0443.2002.00218.x.

Tortolero, S. R., Peskin, M. F., Baumler, E. R., Cuccaro, P. M., Elliott, M. N., Davies, S. L., …, Schuster, M. A. (2014). Daily violent video game playing and depression in preadolescent youth. *Cyberpsychology, Behaviour, and Social Networking, 17*, 609-615. doi:10.1089/cyber.2014.0091.

Vázquez, M. E., Muñoz, M. F., Fierro, A., Alfaro, M., Rodríguez, L. & Bustamante, P. (2013). Estado de ánimo de los adolescentes y su relación con conductas de riesgo y otras variables. *Revista Pediatría de Atención Primaria, 15*, 219. doi:10.4321/s1139-76322013000400003.

Bipolar disorder and substance use disorders. Madrid study on the prevalence of dual disorders/pathology

Trastorno bipolar y trastorno por uso de sustancias. Estudio Madrid sobre prevalencia de patología dual

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Abstract

Given its prevalence and impact on public health, the comorbidity of bipolar and substance use disorders is one of the most relevant of dual diagnoses. The objective was to evaluate the characteristics of patients from community mental health and substance abuse centres in Madrid. The sample consisted of 837 outpatients from mental health and substance abuse centres. We used the Mini International Neuropsychiatric Interview (MINI) and Personality Disorder Questionnaire (PDQ4+) to evaluate axis I and II disorders. Of these patients, 174 had a lifetime bipolar disorder, 83 had bipolar disorder type I and 91 had type II. Most patients had dual pathology. Of the 208 participants from the mental health centres, 21 had bipolar disorder and 13 (61.9%) were considered dually-diagnosed patients, while 33.2% of non-bipolar patients had a dual diagnoses (p = 0.03). Of the 629 participants from the substance abuse centres, 153 patients (24.3%) had a bipolar diagnosis. Bipolar dual patients had higher rates of alcohol and cocaine dependence than non-bipolar patients. Moreover, age at onset of alcohol use was earlier in bipolar dually-diagnosed patients than in other alcoholics. Bipolar dually-diagnosed patients had higher personality and anxiety disorder comorbidities and greater suicide risk. Thus, alcohol and cocaine are the drugs most associated with bipolar disorder. Given the nature of the study, the type of relationship between these disorders cannot be determined.

Keywords: Dual diagnosis, prevalence, bipolar disorder, alcohol, cocaine, cannabis, opioids.

Resumen

La comorbilidad entre trastorno bipolar y trastorno por uso de sustancias (TUS) es de las más relevantes dentro del espectro de la patología dual por su prevalencia y sus repercusiones evolutivas y sociosanitarias. Nuestro objetivo fue estudiar las características de los pacientes con diagnóstico de trastorno bipolar y trastorno por uso de sustancias procedentes del Estudio Madrid sobre prevalencia de patología dual en sujetos en tratamiento en el servicio sanitario público. La muestra procede de pacientes en tratamiento en las redes públicas de salud mental y de tratamiento para las adicciones de la Comunidad de Madrid. Los sujetos fueron evaluados con la entrevista Mini International Neuropsychiatric Interview (MINI) para el diagnóstico de los trastornos mentales y con la escala Personality Disorder Questionnaire (PDQ) para el diagnóstico de los trastornos de personalidad. De los 837 pacientes incluidos, 174 tenían un diagnóstico a lo largo de la vida de trastorno bipolar, 83 con trastorno bipolar tipo I y 91 del tipo II. La mayoría de ellos tenían algún diagnóstico de TUS. En la red de salud mental, de los 208 participantes, 21 tenían un diagnóstico de trastorno bipolar, de estos el 13 (61.9%) tenían un diagnóstico de TUS y se consideraron duales, mientras que en el resto de los pacientes de salud mental el 33.2% tenían un diagnóstico comórbido de TUS (p = 0.03). En los centros de drogas, de los 629 pacientes valorados, un 24.3% (n = 153) tenían un diagnóstico de trastorno bipolar. El subgrupo de pacientes con trastorno bipolar tenía mayor prevalencia de adicción al alcohol y a la cocaína que el resto de los pacientes. Además, la edad de inicio en el consumo de alcohol era más precoz entre los adictos bipolares que entre los adictos no bipolares. Los bipolares duales era un subgrupo con mayor comorbilidad con trastornos de personalidad, otros trastornos mentales como trastornos de ansiedad y mayor riesgo de suicidio. Estos datos apoyan que el alcohol principalmente y la cocaína son las drogas más relacionadas con la presencia de un trastorno bipolar, pero al ser un estudio transversal no se pueden extraer conclusiones etiológicas.

Palabras clave: Patología dual, prevalencia, trastorno bipolar, alcohol, cocaína, cannabis, opiáceos.

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Dual diagnosis is defined as the presence of an addiction disorder and a lifetime mental disorder. Important epidemiological studies of both the general population (Kessler, Nelson, McGonagle, Edlund, Frank & Leaf, 1996; Regier et al.,1990) and of clinical samples (Weaver et al., 2003) highlight that this concurrence is common. Comorbidity affects both clinical presentation and outcome, impacts the therapeutic approach due to less scientific evidence on the most suitable treatment, and is associated with lower adherence to treatment, higher use of health services and greater functional impairment (González-Pinto et al., 2006; González-Pinto, Reed, Novick, Bertsch & Haro, 2010; Lagerberg et al., 2010).

In the Epidemiologic Catchment Area (ECA) study of the general population, the axis I mental disorder most associated with drug use was bipolar disorder (Regier et al., 1990), confirmed by other studies of the general population, such as the National Comorbidity Survey (NCS) or the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and subsequent clinical studies (Kessler, Rubinow, Holmes, Abelson & Zhao, 1997; Grant et al., 2005; Merikangas et al., 2007; Cassidy, Ahearn, Carroll, 2001; Simon et al., 2004). Different explanations may account for this high prevalence, such as the self-medication hypothesis, shared vulnerability factors or substance use as a risk factor (Levin & Hennessy, 2004). Differences in reward processing have been described as impacting vulnerability to addiction (Singh et al., 2013). Clinical factors have also been considered, as patients show higher use during manic episodes, possibly in relation to these patients' search for pleasure and their disinhibited and impulsive conduct characteristic of a manic episode, while they show lesser use during depressive episodes (Levin & Hennessy, 2004; Trost et al., 2014). Greater impulsivity is considered characteristic of bipolar disorders (Powers et al., 2013). Therefore, it is convenient to study the prevalence of lifetime and current addictions among this group, given that these can be quite variable, depending on the patient's clinical status (McElroy et al., 2001). It is possible that the abovementioned explanatory models are not mutually exclusive, due to the existence of data supporting the different hypotheses and the applicability of different explanations to a given patient.

In general, results show that bipolar patients have higher substance use for all substances, but some drugs may have differential effects on emotional regulation and may be more related to provoking changes in these patients' mood; these patients may be more likely to use these due to possible positive short-term effects on their mood (Merikangas et al., 2008). However, it is unclear whether bipolar patients have a preference for certain drugs, or whether there is a higher prevalence of certain addictions, or whether changes exist in usage patterns depending on one's emotional state.

The purpose of this study was to evaluate the relationship between drug dependency and bipolar disorder diagnosis in a sample of outpatients receiving treatment through the mental health and drug abuse network of the Community of Madrid, as part of study on the prevalence of dual diagnosis in this Community, described in other articles (Arias et al., 2013a).

Methodology

Sample

Patients were selected consecutively by their own therapists at the Drug Addiction Treatment Centres (DATCs) of the Community of Madrid and the Madrid City Council and in the Mental Health Centres (MHCs) of the Community of Madrid. Therefore, both first-time patients and returning patients seeking treatment were included. Participants were comprised of 81 interviewers (psychiatrists, psychologists or general practitioners broadly experienced with addictions) from 64 drug treatment centres and 17 mental health centres from the Community of Madrid. All interviewers underwent training on the administration of the structured interview. Participants signed an informed consent form. The Ethical Research Committee of the Gregorio Marañón Hospital in Madrid approved the study. The participation percentage was 87.2%.

Methods

The structured Mini International Neuropsychiatric Interview (MINI) was used to detect the presence of mental disorders, enabling diagnosis in accordance with DSM-IV and CIE-10 criteria (Sheehan et al., 1997). This interview allows for exploring the main axis I current and lifetime psychiatric disorders. It is comparable with longer interviews, such as the SCID-I and the CIDI, with acceptably high degrees of validity and reliability, yet requires less time to complete and briefer training periods for clinical interviewers (Sheehan et al., 1998; Amorim, Lecrubier, Weiller, Hergueta & Sheehan, 1998; Lecrubier et al., 1997). Lifetime mental disorders that were not evaluated by this instrument were explored during the clinical interview. Bipolar disorder type I was established if the MINI interview met requirements of at least one manic episode currently or in the past, and bipolar disorder type II was established if requirements were met of at least one current or past hypomanic episode and major depressive disorder but without meeting criteria of manic episodes.

The PDQ4+ (Personality Disorder Questionnaire) (Spanish adaptation by Calvo, Caseras, Gutierrez y Torrubia, 2002) was used for diagnosing personality disorders. This instrument combines the speed and convenience of a self-administered questionnaire with the control of effects of mood state inherent to an interview. It is a solid diagnostic tool aligned with DSM-IV criteria when the clinical significance scale is administered.

Statistical analysis

The following descriptive parameters were calculated for all variables: mean and standard deviation for statistics adjusted to a normal distribution (Shapiro-Wilk test) and the median and interquartile range for statistics not adjusted to a normal distribution. Qualitative variables were expressed as relative frequencies in percentage. Both groups were compared using the chi-squared test ($\chi 2$) or Fisher's exact test, as applicable, for categorical variables and using the Student's t-distribution or Mann-Whitney U for quantitative variables. The main variable is calculated at the 95% confidence interval level. Tests are considered significant if $p < 0.05$.

To evaluate factors that may influence predicting the presence of a bipolar disorder, a multivariate logistic regression model is used including all of those factors that may affect the dependent variable. Model selection criteria include parameters with $p < 0.1$ to enter and those with $p < 0.05$ to exit, although all confounding factors that modify their β or that of other parameters by over 20% are used. Furthermore, the corresponding interactions are tested, including only significant ones. When the presence of linearity or colinearity are detected, stratified data are displayed, adjusted for the main possible confounders. Statistical analysis is generated using SPSS v.17 software.

Table 1. *Characteristics of patients diagnosed with lifetime bipolar disorder (n = 174)*

Age (years)	36.4 (SD = 9.2)
Male	126 (72.8%)
Unmarried	106 (61.6 %)
Married	38 (22.1%)
Other	28 (16.3%)
Primary education	78 (45.6%)
Secondary education	69 (40.4%)
University degree	23 (13.5%)
Employed	80 (46.2%)
Unemployed	55 (31.8%)
Other	38 (21.0%)
Living with family of origin	85 (48.9%)
Living with own family	43 (24.7%)
Living alone	29 (16.7%)
Other	17 (9.8%)
Treatment centre:	
Mental Health (n = 208)	21 (10.1% of the total of MHCs)
Drug Addiction Treatment Centres (n = 629)	153 (24.3% of the total of DATCs)
Medical pathology	57 (32.9%)
Bipolar disorder subtypes:	
Type I	83 (47.7%)
Type II	91 (52.3%)

Note. SD = Standard Deviation

Results

Patients included totalled 837: 208 (24.9%) were from MHCs and 629 (75.1%) from DATCs. Of the 837 patients evaluated, 710 were diagnosed with some type of lifetime substance use disorder (SUD) (including alcohol, excluding tobacco). There were 127 participants (15.2%) without SUDs. Of the total sample, 174 patients were diagnosed a lifetime bipolar disorder (BD) (20.8% of the total sample), 83 were diagnosed a type I BD and 91 were diagnosed a type II BD.

Sociodemographic characteristics.

Table 1 displays the sociodemographic characteristics of bipolar patients. They were younger than the rest of the sample (36.4 years of age, SD = 9.2 compared with 38.9 years of age, SD = 10.4, p = 0.004) with a male majority, though this differed depending on whether they came from MHCs or DATCs.

Prevalence of both current and lifetime substance use disorders (SUDs) in the sample of bipolar patients *(Table 2)*

Given the majority of patients from DATCs, a high percentage of SUDs existed amongst bipolar patients. There were differences in the prevalence of abuse or dependence on alcohol, cocaine, cannabis and tobacco among bipolar and non-bipolar groups. There were no differences as to dependency on opioids. In addition, age at onset of alcohol use was lower in the group of bipolar patients than in non-bipolar addicts. Furthermore, there was a higher prevalence of a history of intravenous opioid use among these bipolar patients.

Personality Disorder (PD) diagnoses

There was a predominance of PD diagnoses among the bipolar disorder group compared with the non-bipolar disorder group (n = 113, 64.9% vs. n = 301, 45.4%, respectively, p = 0.001), with significant differences for all of the personality disorders evaluated. Likewise, when grouped by different clusters, there existed predominance of cluster A, B and C in the BD group.

Logistic regression model

A predictive logistic regression model was carried out for the presence of BD (Table 3). When adjusted for age, gender and other drugs, only addiction to cocaine as a risk factor (OR = 1.65, p = 0.01) and addiction to alcohol as a risk factor (OR = 2.2, p = 0.001) remained as predictive variables in the model. Given that this regression model showed problems of colinearity due to the relationship between the different addictions, a stratified analysis was performed to detect the presence or non-presence of addiction to alcohol and cocaine. The relationship between alcohol and BD remained statistically significant both in cocaine addiction as well as in non-addicts to cocaine. Similar results were ob-

Table 2. *Substance use disorder and personality disorder in the sample of bipolar patients (n = 174)*

Drug	Bipolar	Non-bipolar
Alcohol or SUD currently*	143 (82.2%)	438 (66.1%)
Lifetime*	165 (94.8%)	545 (82.2%)
Alcohol currently*	92 (52.9%)	255 (38.5%)
Lifetime*	134 (77.0%)	394 (59.4%)
SUD currently (w/out alcohol)*	121 (69.5%)	355 (53.5%)
Lifetime*	145 (83.3%)	470 (70.9%)
Cocaine currently*	94 (54.0%)	271 (40.9%)
Lifetime*	121 (69.5%)	367 (55.4%)
Opioids currently+	18 (10.3%)	82 (12.4%)
Lifetime+	45 (25.9%)	167 (25.2%)
Cannabis currently**	39 (22.4%)	94 (14.2%)
Lifetime**	90 (51.7%)	263 (39.7%)
Sedatives currently+	8 (4.6%)	29 (4.4%)
Lifetime****	32 (18.4%)	87 (13.1%)
Tobacco lifetime*	118 (67.8%)	372 (56.1%)
Single SUD diagnosis lifetime	34 (19.5%)	135 (20.4%)
Multiple SUD diagnosis	131 (75.3%)	410 (61.8%)
Intravenous opioid use (n = 44)**	35 (79.5%)	102 (60.4%)
Age at onset of use:		
Alcohol***	15.3 (SD = 4.2)	16.5 (SD = 6.1)
Cocaine+	20.3 (SD = 6.2)	21.2 (SD = 6.5)
Cannabis****	15.5 (SD = 3.5)	16.4 (SD = 4.5)
Opioids+	18.8 (SD = 6.1)	20.0 (SD = 5.6)
Personality disorders*	113 (64.9%)	301 (45.4%)

Note. SUD = Substance Use Disorder. SD = Standard Deviation.
+=Not significant in comparison with the non-bipolar group. *= p < 0.001. **= p < 0.01. ***= p < 0.05. ****= p < 0.08.

Table 3. *Predictive logistic regression model for the presence of bipolar disorder*

Variable	β coefficient	OR	P
Age	0.02	0.98	0.05
Gender (female)	0.56	1.74	0.01
Lifetime cocaine	0.50	1.65	0.01
Lifetime alcohol	0.78	2.2	0.0001

Note. Chi-squared of the model = 34.9, gl = 4, p = 0.001.

tained as regards cocaine addiction when stratified for the presence of alcohol, though these differences were not statistically significant, but without differences between alcohol addicts and non-addicts to alcohol.

Comparison between bipolar disorders type I and type II

Objective differences between these groups were not found. The slightly higher percentage of addictions in the bipolar type I group was statistically no significant.

Characteristics of bipolar patients addicted to alcohol

Of the 174 bipolar patients, 92 were diagnosed a current alcohol use disorder and 134 a lifetime disorder. There was a predomination of males (79.1%) in this subgroup compared with non-addicts to alcohol (65.9%, p = 0.05), a higher prevalence of cocaine dependency and a greater frequency of personality disorders in cluster A. There were only 20 patients with a lifetime dependency on alcohol without other concomitant SUDs, with a majority of females in this small group (11 females, 55% and 9 males, 45%). Meanwhile, there was a majority of males in the alcohol dependency group with other addictions (95 males, 84.1% and 18 females, 15.9%, p = 0.02 compared with bipolar patients not addicted to alcohol).

Characteristics of bipolar patients addicted to cocaine

There were 94 patients with a current dependency and 121 with a lifetime dependency on cocaine. There were predominantly more males compared with other bipolars (p = 0.03), lower education level (p = 0.05), higher unemployment rate (p = 0.05), greater use of opioids and sedatives and a higher prevalence of personality disorders in cluster B (53.2% vs. 37.5%, p = 0.04).

Bipolar patients in the mental health network

Of the 208 patients from the mental health network, 21 were diagnosed with BD. Of these, 13 (61.9%) were dua-

Table 4. *Bipolar disorders (n = 21) in the mental health network (n = 208) and bipolar disorders (n = 153) in the drug addiction treatment network (n = 629)*

	Mental health network	Drug addiction treatment network
Age	42.7 years (SD = 13.3)+	35.6 years (SD = 8.2)**
Males (total of bipolars) Females	8 (38.1%)+ 13 (61.9%)	118 (77.6%)* 34 (22.4%)
Males (dually-diagnosed bipolars) Females	7 (53.8% 6 (46.2%)	
Alcohol or SUD currently Lifetime	8 (38.1%)+ 13 (61.9%)+	
Alcohol currently Lifetime	5 (23.8%)+ 10 (47.6%)*	87 (56.9%)** 124 (81.0%)**
SUD currently (w/out alcohol)+ Lifetime+	5 (23.8%)+ 8 (38.1%)+	116 (75.8%)+
Cocaine currently Lifetime	4 (19.0%)* 4 (19.0%)+	90 (58.8%)+ 117 (76.5%)+
Opioids currently Lifetime	0 0	18 (11.8%)+ 45 (29.4%)+
Cannabis currently Lifetime	3 (14.3%)+ 5 (23.8%)+	36 (23.5%)+ 85 (55.6%)+
Sedatives currently Lifetime	0 1 (4.8%)	8 (5.2%)+ 31 (20.3%)+
Personality disorders*	16 (76.2%)*	97 (63.4%)***
Anxiety disorders		98 (64.1%)***
Bipolar disorder subtype Type I Type II	 9 (4.3% of Mental Health patients) 11 (5.3%)	 74 (11.8% of drug addiction treatment patients) 80 (12.7%)
Age at onset of use: Alcohol Cannabis	 16.4 (SD = 3.2)+	 15.2 (SD = 4.2)* 15.3 (SD = 3.3)****

Note. SUD = Substance Use Disorder. SD = Standard Deviation.
+=Not significant in comparison with the non-bipolar group. *= p < 0.05. **=p ‹ 0.01. ***= p < 0.001. ****= p < 0.07.

lly-diagnosed (compared with 62, 33.2% in the non-bipolar patients, p = 0.03). There were predominantly more females in the bipolar subgroup but without differences in comparison with the remaining patients from the MHCs. However, there were slightly more males among dually-diagnosed patients (of the 13 dual diagnosis patients, 7 were male (53.8%) and 6 were female). As occurs in the general sample, the drugs most associated with this diagnosis were alcohol and cocaine, and there was a greater number of patients with PD (Table 4).

Bipolar patients in the drug addiction treatment network

Of the 629 subjects from the drug addiction treatment network, 153 were bipolar (24.3%). Although there were more males in this subgroup, the percentage of females was higher than in the rest of the sample from the drug addiction treatment centres. The presence of BD was associated with alcohol dependency and with a higher frequency of PD and diagnoses of anxiety disorders (Table 4).

When comparing bipolar patients from the drug addiction treatment and mental health networks, there were more males in the drug addiction treatment network (p = 0.001), with a worse employment status and higher unemployment rate (p = 0.001), more patients with a comorbid medical pathology (p = 0.05) and more diagnoses of disorders due to the use of alcohol, cocaine and cannabis. There were no differences as to prevalence of comorbid PD.

Bipolar disorder and risk of suicide

Patients with BD had a higher prevalence of risk of suicide as assessed by the MINI than the rest of the patients (p = 0.001) and the rest of the dually-diagnosed patients (p = 0.006). When stratified for the presence of lifetime disorders due to the use of alcohol, cocaine and cannabis, the prevalence of the risk of suicide was always higher in the group of bipolar patients compared with non-bipolar patients, but in the presence of any SUD the prevalence of risk of suicide was even higher. The risk of suicide in these bipolar patients was associated with the presence of a greater number of PDs

(2.9, SD = 2.8 vs. 1.9, SD = 2.7, p = 0.01), higher number of axis I diagnoses (3.6, SD = 1.9 vs. 2.4, SD = 1.5, p = 0.001), higher number of SUD diagnoses (2.9, SD = 1.6 vs. 2.4, SD = 1.4) and tending toward a younger age of onset of tobacco use (13.6 years of age, SD = 3.1 vs. 15.1, SD = 6.0, p = 0.08) than bipolar patients without risk of suicide.

Discussion

There exists an association between BD and SUDs, mainly an association with alcohol and cocaine, in the sample of patients in treatment. A high percentage of bipolar patients in treatment through the mental health network -up to 62%- were diagnosed with SUDs during their lifetime. Other clinical samples have yielded similar figures, such as a prevalence of SUDs of 54% (Yatham, Kauer-Sant'Anna, Bond, Lam & Torres, 2009), 59% in a sample of manic patients (Frank, Boland, Novick, Bizzarri & Rucci, 2007) or 72% of SUDs during one's lifetime in hospitalized bipolar patients (Bauer et al., 2005). On another hand, up to a quarter of addicts seeking treatment at drug treatment centres have a bipolar disorder. This is similar to other clinical samples (Nallet et al., 2013; Van Zaane, Van den Berg, Draisma, Nolen & Van den Brink, 2012).

Sociodemographic characteristics coincide with those of dually-diagnosed patients, with predominantly younger males (Tondo et al., 1999; Sonne & Brady, 1999). However, this male majority is less prominent in the mental health network and there is a significantly higher number of females in the drug addiction treatment network with this type of dual pathology than with the remaining diagnoses. Therefore, we may consider that the usual differences common to gender as regards dual pathology are mitigated in the case of dual bipolar patients (Frye et al., 2003).

The drugs most associated with bipolar disorder were dependence on alcohol, cocaine and cannabis, by order of magnitude of the difference compared with non-bipolar patients. These drugs are frequently described in relationship with BD (Cerullo & Strakowski, 2007; Merikangas et al., 2008; Salloum et al., 2005). In addition, as regards alcohol, the age at onset of alcohol use of patients with BD is younger, possibly suggesting a causal role for alcohol use. However, the transversal nature of this study does not allow for establishing other ethological relationships. Both alcohol and cocaine use have been considered substances that may induce pathological affective states, but these substances may also help short-term regulation of negative emotional states, though with a more prejudicial long-term impact. Likewise, the use of these substances increases during manic episodes due to the elation and disinhibition characteristic of these. Therefore, the combination of cocaine and alcohol appears to have a special link with bipolar disorder due to their specific effects on affective states (Pacini et al., 2010) and it has been suggested that they are associated with different clinical symptoms (Mitchell, Brown & Rush, 2007). Other researchers suggest that a prolonged exposure to alcohol of some bipolar patients with mild disorders would result in more clinically relevant symptoms of the illness (Cerullo & Strakowski, 2007). Other authors observe relationships between the types of clinical symptoms of mania and the specific use of drugs such as alcohol or cannabis (Güclü, Şenormanci, Aydin, Erkiran & Köktürk, 2014) or a differential use of drugs such as cocaine, alcohol or cannabis depending on the type of bipolar disorder (mixed, hypomanic, mania or depression) (Maremmani et al., 2012). The strong association between bipolar disorder and alcohol dependence has also been related with the possible existence of genetic factors common to both (Carmiol et al., 2015).

In another study we carried out with the subgroup of psychotic patients, we found a relationship between psychosis and addiction to cannabis (Arias et al., 2013b). Together with the data from the current study, there appears to be a certain specificity between different substances and different diagnoses of mental disorders.

The high prevalence of PD diagnoses in these dually-diagnosed patients support other studies that highlight a high comorbidity in dually-diagnosed bipolar patients, but also raises the question as to whether there may be problems in the differential diagnosis between PD, the symptoms inherent to SUDs and BP, as pointed out by some authors (Levin & Hennessy, 2004; Stewart & El-Mallakh, 2007). It is possible that too many patients of this sample are diagnosed with a BD for having diagnosed as such those with changes in mood that are inherent to their SUDs or BD. Likewise, it is possible that too many patients of this sample are diagnosed with a PD due to the instrument used. In any case, the use of structured interviews may minimize this bias and, likewise, it has also been pointed out that, in recognition of the difficulty inherent to diagnosing these types of symptoms and the need for achieving a suitable diagnosis to differentiate affective and behavioural symptoms of BDs, PDs and SUDs, comorbidity between these symptoms is frequent with other PDs or axis I disorders, such as anxiety disorders (Bauer et al., 2005; Merikangas et al., 2007; Mantere et al., 2006; Merikangas et al., 2011; Mazza et al., 2009). Therefore, comorbidity of BD with PD, such as a borderline personality disorder, is associated with a greater risk of SUD (Hidalgo-Mazzei, Walsh, Rosenstein & Zimmerman, 2015).

Literature does not clarify which BD subtype is more related with SUDs. Some authors point out that patients with type I BD usually have more addictive behaviours (Merikangas et al., 2008) but other authors mention that addicted patients are more likely to have hypomanic or mixed symptoms (Do & Mezuk, 2013; Himmelhoch, Mulla, Neil, Detre & Kupfer, 1976; Keller et al., 1986; Mazza et al., 2009). Our study did not find differences in the prevalence of different SUDs, though the prevalence of SUD was slightly higher in type I BD. Given the small number of bipolar patients from

the mental health network, we cannot draw conclusions as to differences between bipolar disorder subtypes across both treatment networks.

Our data suggest that this subgroup of bipolar patients with addictions have a higher risk of suicide than other patients with mental disorders or addicts undergoing treatment, highlighting the greater clinical seriousness of this subgroup of dually-diagnosed patients. The increased risk of suicide amongst dually-diagnosed patients has already been researched (Carrà, Bartoli, Crocamo, Brady & Clerici, 2014; Comtois, Russo, Roy-Byrne & Ries, 2004; González-Pinto et al., 2006). Furthermore, the patient subgroup with risk of suicide is associated with higher comorbidity with axis I, with other SUDs and a higher number of concomitant PDs, wherefore they comprise a patient subgroup that requires special follow-up and proper management of all of these comorbidities.

Another relevant aspect of this study is the different profiles of the dually-diagnosed bipolar patients across the two public treatment networks. The drug addiction treatment network had more bipolar patients with a higher addictive comorbidity and other axis I disorders, though, surprisingly, not with axis II disorders, with a predominance of males, lower employment rates and poorer medical conditions. The data presented in this project can be extrapolated to the bipolar population of the drug addiction treatment centres, though a larger sample size would be required to extrapolate said data to the mental health network.

A limitation of the study is its transversal nature, which does not allow for inferring causal relationships. Most of the patients have polydrug use, wherefore solid conclusions cannot be drawn as to the effect of any particular drug. The sample is comprised of patients undergoing treatment, wherefore the data cannot be extrapolated to the general population, and the existence of comorbidity with other disorders may favour seeking treatment. The use of the MINI as the diagnostic interview might not be the most suitable for this population, given that it does not distinguish between induced main symptoms as other diagnostic interviews do and might fail to perform a suitable differential diagnosis; it was chosen for the simplicity of its administration, given the high number of researchers involved. The sample from the mental health network is quite small. Given that most patients with bipolar disorder seek treatment through the latter network, it is possible that the characteristics of our sample fail to represent bipolar patients in treatment, but rather of addicts in treatment with comorbidity with a bipolar disorder.

One of the strengths is the considerable sample size, especially as regards patients from the drug addiction treatment network, wherefore we consider it to represent addicts that seek treatment at drug treatment centres. In addition, the use of the structured interview increases diagnostic reliability.

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

References

Amorim, P., Lecrubier, Y., Weiller, E., Hergueta, T. & Sheehan D. (1998). DSM-IV-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. *European Psychiatry, 13*, 26-34. doi: 10.1016/S0924-9338(97)86748-X

Arias, F., Szerman, N., Vega, P., Mesias, B., Basurte, I., Morant, C., ... Babín, F. (2013a). Estudio Madrid sobre prevalencia y características de los pacientes con patología dual en tratamiento en las redes de salud mental y de atención al drogodependiente. *Adicciones, 25,* 118-127.

Arias, F., Szerman, N., Vega, P., Mesias, B., Basurte, I., Morant, C., ... Babin, F. (2013b). Abuso o dependencia al cannabis y otros trastornos psiquiátricos. Estudio Madrid sobre prevalencia de patología dual. *Actas Españolas de Psiquiatría, 41,* 123-130.

Bauer, M.S., Altshuler, L., Evans, D.R., Beresford, T., Williford, W.O. & Hauger, R. (2005). Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. *Journal of Affective Disorders, 85,* 301-315.

Calvo, N., Caseras, X., Gutierrez, F. & Torrubia, R. (2002). Spanish version of the personality diagnostic questionnaire-4+ (PDQ-4+). *Actas Españolas de Psiquiatría, 30,* 7–13.

Carmiol, N., Peralta, J.M., Almasy, L., Contreras, J., Pacheco, A., Escamilla, M.A., ... Glahn, D.C. (2014). Shared genetic factors influence risk for bipolar disorder and alcohol use disorders. *European Psychiatry, 29,* 282-287. doi: 10.1016/j.eurpsy.2013.10.001

Carrà, G., Bartoli, F., Crocamo, C., Brady, K.T. & Clerici, M. (2014). Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review

and meta-analysis. *Journal of Affective Disorders, 167,* 125-135. doi: 10.1016/j.jad.2014.05.066

Cassidy, F., Ahearn, E.P. & Carroll, B.J. (2001). Substance abuse in bipolar disorder. *Bipolar Disorders, 3,* 181-188.

Cerullo, M.A. & Strakowski, S.M. (2007). The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Substance Abuse Treatment, Prevention, and Policy, 2,* 29.

Comtois, K.A., Russo, J.E., Roy-Byrne, P. & Ries, R.K. (2004). Clinicians' assessments of bipolar disorder and substance abuse as predictors of suicidal behavior in acutely hospitalized psychiatric inpatients. *Biological Psychiatry, 56*, 757-763.

Do, E.K. & Mezuk, B. (2013). Comorbidity between hypomania and substance use disorders. *Journal of Affective Disorders, 150,* 974-980. doi: 10.1016/j.jad.2013.05.023

Frank, E., Boland, E., Novick, D.M., Bizzarri, J.V. & Rucci, P. (2007). Association between illicit drug and alcohol use and first manic episode. *Pharmacology, Biochemistry and Behavior, 86,* 395-400.

Frye, M.A., Altshuler, L.L., McElroy, S.L., Suppes, T., Keck, P.E., Denicoff, K., ... Post, R.M. (2003). Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. *American Journal of Psychiatry, 160,* 883-889.

González-Pinto, A., Mosquera, F., Alonso, M., López, P., Ramírez, F., Vieta, E. & Baldessarini, R.J. (2006). Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disorders, 8,* 618–624.

González-Pinto, A., Reed, C., Novick, D., Bertsch, J. & Haro, J.M. (2010). Assessment of Medication Adherence in a cohort of patients with bipolar disorder. *Pharmacopsychiatry, 43,* 263– 270. doi: 10.1055/s-0030-1263169

Grant, B.F., Stinson, F.S., Hasin, D.S., Dawson, D.A., Chou, S.P., Ruan, W.J. & Huang, B. (2005). Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry, 66,* 1205-1215.

Güclü, O., Şenormancı, Ö., Aydın, E., Erkıran, M. & Köktürk, F. (2014). Phenomenological subtypes of mania and their relationships with substance use disorders. *Journal of Affective Disorders, 174,* 569-573. doi: 10.1016/j.jad.2014.11.016

Hidalgo-Mazzei, D., Walsh, E., Rosenstein, L. & Zimmerman, M. (2015). Comorbid Bipolar Disorder and Borderline Personality Disorder and Substance Use Disorder. *Journal of Nervous and Mental Disease, 203*, 54-57. doi: 10.1097/NMD.0000000000000235

Himmelhoch, J.M., Mulla, D., Neil, J.F., Detre, T.P. & Kupfer, D.J. (1976). Incidence and significance of mixed affective states in a bipolar population. *Archives of General Psychiatry, 33,*1062-1066.

Keller, M.B., Lavori, P.W., Coryell, W., Andreasen, N.C., Endicott, J., Clayton, P.J., ... Hirschfeld, R.M. (1986). Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. The *Journal of the American Medical Association, 255,* 3138-3142.

Kessler, R.C., Nelson, C.B., McGonagle, K.A., Edlund, M.J., Frank, R.G. & Leaf, P.J. (1996). The epidemiology of cooccurring addictive and mental disorders: Implications for prevention and service utilization. *American Journal of Orthopsychiatry, 66,* 17–31.

Kessler, R.C., Rubinow, D.R., Holmes, C., Abelson, J.M. & Zhao, S. (1997). The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychological Medicine, 27,* 1079-1089.

Lagerberg, T.V., Larsson, S., Sundet, K., Hansen, C.B., Hellvin, T., Andreassen, O.A. & Melle, I. (2010). Treatment delay and excessive substance use in bipolar disorder. *Journal of Nervous and Mental Disease, 198,* 628-633. doi: 10.1097/NMD.0b013e3181ef3ef4

Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, L.I. & Sheehan, K. (1997). The MINI International Neuropsychiatric Interview (MINI) A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry, 12,* 224-231.

Levin, F.R. & Hennessy, G. (2004). Bipolar disorder and substance abuse. *Biological Psychiatry, 56*, 738-748.

Mantere, O., Melartin, T.K., Suominen, K., Rytsälä, H.J., Valtonen, H.M., Arvilommi, P., Leppämäki, S. & Isometsä, E.T. (2006). Differences in Axis I and II comorbidity between bipolar I and II disorders and major depressive disorder. *Journal of Clinical Psychiatry, 67,* 584-593.

Maremmani, I., Maremmani, A.G., Rugani, F., Rovai, L., Pacini, M., Bacciardi, S., ... Akiskal, H.S. (2012). Clinical presentations of substance abuse in bipolar heroin addicts at time of treatment entry. *Annals of General Psychiatry, 11,* 23. doi: 10.1186/1744-859X-11-23

Mazza, M., Mandelli, L., Di Nicola, M., Harnic, D., Catalano, V., Tedeschi, D., ... Janiri, L. (2009). Clinical features, response to treatment and functional outcome of bipolar disorder patients with and without co-occurring substance use disorder: 1-year follow-up. *Journal of Affective Disorders, 115,* 27-35. doi: 10.1016/j.jad.2008.08.019

McElroy, S.L., Altshuler, L.L., Suppes, T., Keck, P.E. Jr, Frye, M.A., Denicoff, K.D., ... Post, R.M. (2001). Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *American Journal of Psychiatry, 158,* 420-426.

Merikangas, K.R., Akiskal, H.S., Angst, J., Greenberg, P.E., Hirschfeld, R.M., Petukhova, M. & Kessler, R.C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Archives of General Psychiatry, 64,* 543-552.

Merikangas, K.R., Herrell, R., Swendsen, J., Rössler, W., Ajdacic-Gross, V. & Angst, J. (2008). Specificity of bi-

polar spectrum conditions in the comorbidity of mood and substance use disorders: results from the Zurich cohort study. *Archives of General Psychiatry, 65,* 47-52. doi: 10.1001/archgenpsychiatry.2007.18

Merikangas, K.R., Jin, R., He, J.P., Kessler, R.C., Lee, S., Sampson, N.A., ... Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Archives of General Psychiatry, 68,* 241-251. doi: 10.1001/archgenpsychiatry.2011.12

Mitchell, J.D., Brown, E.S. & Rush, A.J. (2007). Comorbid disorders in patients with bipolar disorder and concomitant substance dependence. *Journal of Affective Disorders, 102,* 281-287.

Nallet, A., Weber, B., Favre, S., Gex-Fabry, M., Voide, R., Ferrero, F., ... Aubry, J.M. (2013). Screening for bipolar disorder among outpatients with substance use disorders. *European Psychiatry, 28,* 147-153.

Pacini, M., Maremmani, I., Vitali, M., Romeo, M., Santini, P., Vermeil, V. & Ceccanti, M. (2010). Cocaine Abuse in 448 Alcoholics: Evidence for a Bipolar Connection. *Addictive Disorders & their Treatment, 9,* 164–171.

Powers, R.L., Russo, M., Mahon, K., Brand, J., Braga, R.J., Malhotra, A.K. & Burdick, K.E. (2013). Impulsivity in bipolar disorder: relationships with neurocognitive dysfunction and substance use history. *Bipolar Disorders, 15,* 876-884. doi: 10.1111/bdi.12124

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L. & Goodwin, F.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: Result from the Epidemiologic Catchment Area (ECA) Study. The *Journal of the American Medical Association, 264,* 2511–2518.

Salloum, I.M., Cornelius, J.R., Douaihy, A., Kirisci, L., Daley, D.C. & Kelly, T.M. (2005). Patient characteristics and treatment implications of marijuana abuse among bipolar alcoholics: results from a double blind, placebo-controlled study. *Addictive Behaviors, 30,* 1702-1708.

Sheehan, D.V., Lecrubier, Y., Harnett-Sheehan, K., Janavs, J., Weiller, E. & Bonora, L.I. (1997). Reliability and validity of the MINI International Neuropsychiatric Interview (MINI): According to the SCID-P. *European Psychiatry, 12,* 232-241.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., ... Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59,* 22-33.

Simon, N.M., Otto, M.W., Weiss, R.D., Bauer, M.S., Miyahara, S., Wisniewski, S.R., ... Pollack, M.H. (2004). Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. *Journal of Clinical Psychopharmacology, 24,* 512-520.

Singh, M.K., Chang, K.D., Kelley, R.G., Cui, X., Sherdell, L., Howe, M.E., ... Reiss, A.L. (2013). Reward processing in adolescents with bipolar I disorder. *Journal of the American Academy Child & Adolescent Psychiatry, 52,* 68-83. doi: 10.1016/j.jaac.2012.10.004

Sonne, S.C. & Brady, K.T. (1999). Substance abuse and bipolar comorbidity. *Psychiatry Clinics of North America, 22,* 609-627.

Stewart, C. & El-Mallakh, R.S. (2007). Is bipolar disorder overdiagnosed among patients with substance abuse? *Bipolar Disorders, 9,* 646-648.

Tondo, L., Baldessarini, R.J., Hennen, J., Minnai, G.P., Salis, P., Scamonatti, L., ... Mannu, P. (1999). Suicide attempts in major affective disorder patients with comorbid substance use disorders. *Journal of Clinical Psychiatry, 2,* 63-69.

Trost, S., Diekhof, E.K., Zvonik, K., Lewandowski, M., Usher, J., Keil, M., ... Gruber, O. (2014). Disturbed anterior prefrontal control of the mesolimbic reward system and increased impulsivity in bipolar disorder. *Neuropsychopharmacology, 39,* 1914-1923. doi: 10.1038/npp.2014.39

Van Zaane, J., Van den Berg, B., Draisma, S., Nolen, W.A. & Van den Brink, W. (2012). Screening for bipolar disorders in patients with alcohol or substance use disorders: performance of the mood disorder questionnaire. *Drug and Alcohol Dependence, 124,* 235-241. doi: 10.1016/j.drugalcdep.2012.01.018

Weaver, T., Madden, P., Charles, V., Stimson, G., Renton, A. & Tyrer, P. (2003). Comorbidity of substance misuse and mental illness in community mental health and substance misuse services. *British Journal of Psychiatry, 183,* 304–313.

Yatham, L.N., Kauer-Sant'Anna, M., Bond, D.J., Lam, R.W. & Torres, I. (2009). Course and outcome after the first manic episode in patients with bipolar disorder: Prospective 12-month data from the systematic treatment optimization program for early mania project. *Canadian Journal of Psychiatry, 54,* 105-112.

The legalization of cannabis derivatives in Spain: Hypothesis on a potential emerging market

La legalización de los derivados del cannabis en España: Hipótesis sobre un potencial mercado emergente

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Abstract

First, this paper estimates the dimensions of the market for cannabis in Spain using data on the extent of consumption and the main patterns of use of consumers. Then the paper reviews the hypothetical production and distribution costs of these drugs in different production regimes under different legal conditions. The review shows that current prices of cannabis in the illegal market could be notably reduced if production and distribution of cannabis were decriminalized and even more if they were performed by legal enterprises. Thirdly, we examine the relationship between prices and consumption levels by analysing the price elasticity of demand. A fall in the prices of cannabis products will likely result in an increase in the number of users and in the total amount consumed. Lastly we consider several alternatives for the taxation of cannabis derivatives to counteract the likely fall in prices, and their pros and cons.

Keywords: drug policy; illicit drug markets; marijuana; cannabis legalization; prices; Spain.

Resumen

En este artículo se analiza en primer lugar la dimensión que tiene el mercado de cannabis en España en base a los datos disponibles sobre la extensión del consumo y las pautas de uso de los consumidores. A continuación se repasan y comparan los costes de producción y distribución del cannabis en distintos regímenes de producción y diversas condiciones jurídicas. Se observa cómo los precios del cannabis al detalle en el mercado ilegal son bastante altos y podrían reducirse considerablemente si se legalizasen la producción y la comercialización. En tercer lugar, se examina la relación que hay entre los precios y el consumo a través del análisis de la elasticidad del precio de la demanda. Se pone de manifiesto cómo una caída de los precios probablemente resulte en un aumento tanto en el número de usuarios como en la cantidad total consumida por estos. Por último, se consideran distintas alternativas de fiscalización destinadas a contrarrestar la caída de precios de los derivados del cannabis, mostrando sus fortalezas y debilidades.

Palabras clave: políticas sobre drogas; mercados de drogas ilícitas, marihuana, precios, legalización del cannabis, España.

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Cannabis derivatives are the most frequently used illicit drugs in the world. While consumption of these products is not at the same level as that of legal drugs such as tobacco, alcohol or caffeine, it is at least six times higher than that of any other illicit drug (Gowing et al., 2015; UNODC, 2015). Although cannabis derivatives are substances with a great variety of uses and therapeutic, religious and recreational significance, we are here concerned with them as commodities that are manufactured and distributed for monetary gain. They have their origin in an agricultural cheap product which can be grown in many regions of the world. However, in a situation of illegality, the costs of manufacture and distribution increase disproportionately, as is also the case with coca leaves or the poppy plant. Cost rise because manufacturers and distributors have to face risks at each stage of the manufacturing and sales process. Indeed, it can be said that the illicit drugs business has more of a services than manufacturing profile. Illegality also prevents economies of scale from operating which would bring down the costs of manufacturing, distribution and sales considerably (Hawken, 2013).

The first question that any government attempting to legalise cannabis derivatives should consider is to what extent it is willing to liberalize its production and marketing. In addition, there are various alternatives which could be applied in different ways and with greater or lesser restriction. Among the main policy options we would highlight the following: 1) *de facto* legalisation of retail sales in establishments similar to the Dutch *coffee shops*; 2) legalisation of small scale cultivation for personal use; 3) approval of shared cultivation in user clubs or associations; 4) establishment of a state monopoly on production and sale, administered via a licensing system similar to those that have existed for governing tobacco, alcohol and opium; and 5) allowing the free production and sale as consumer goods while prohibiting the sale to minors, as is the case today with alcohol and tobacco (Apfel, 2014; Brook & Wakabayashi, 2000; Gamella & Martín, 1992; Kilmer, Kruithof, Pardal, Caulkins & Rubin, 2013; MacCoun, 2014).

Such changes would have repercussions both within the country in question and on its international relations, particularly with those countries with which it maintains the closest trade, migratory and political links since it would affect the international treaties signed on the matter. The Dutch experience with *de facto* legalisation appears to indicate that the changes in the legal status of a substance affect neighbouring countries and their consumers, and that such changes are often of an international and transnational character (Decorte, 2007; Korf, 2002, 2011; MacCoun & Reuter, 1997, 2001; MacCoun, 2011; Monshouwer, van Laar & Vollebergh, 2011; van Ooyen-Houben & Keemans, 2015; van Ooyen-Houben, Bieleman & Korf, 2016).

It is also important to consider whether legalising the production and sale of cannabis would lead to a notable reduction of retail prices and an increase in availability. In addition, it is likely that products would become more standardised, adulteration would be diminished and both average levels of quality and potency would increase. The amount of information available to consumers about the products could also increase, while it is likely that different forms of commercialisation and advertising used by manufacturers and distributors would also multiply. All these factors could trigger increased consumption, especially in the mid-term (Caulkins, Kilmer & Kleiman, 2016; Caulkins, 2016a).

The marijuana and hashish trade is a business that currently generates large profits. Most of these products are consumed by intensive users, who are mostly found among the young adult population, aged between 18 and 25 (Caulkins et al., 2015; Caulkins et al, 2016; van Laar, Frijins, Trautmann & Lombi, 2013). From a commercial point of view, a business dedicated to the manufacture and distribution of cannabis would attempt to increase brand loyalty and expand its customer base among such intensive users, while at the same time aiming to attract new customers willing to try its products. To achieve this, such companies would likely develop and stimulate commodification and marketing processes for these products. Meanwhile, public administrations would take on new responsibilities, which would require appropriate regulation and budget provisions in order to address them. Such a situation would lead to new areas of conflict, legal action and complaints. Even if direct advertising of these products were banned, as is increasingly the case with tobacco, it is likely that indirect advertising and promotion of legal cannabis products would increase, potentially opening up new perspectives for these drugs or re-evaluating some which are already known.

We do not know what kind of social representations would occupy the collective imagination in a new societal context where these drugs were freely traded and legally available items of mass consumption. Nor do we know how these representations would influence the curiosity to try them, consume them on a regular basis or avoid them. But we should not rule out a scenario similar to that involving legally available psychoactive drugs in their various legal and commercial statuses, especially alcohol, something with which some North American states are currently experimenting.

If legalisation were to bring with it an increased number of users, especially those who took them with greater frequency or intensity, there would be a concomitant rise in the incidence and prevalence of problems associated with their use - including the risk of addiction - and therefore also in the costs to the individual, families and society attributed directly or indirectly to their consumption. This rise, both in the number of users and in problematic or harmful consumption patterns, is one of the central issues to be borne in mind in the discussion regarding legalisation and its consequences. (Caulkins, 2016a, 2016b; Hall & Lynskey, 2016; Hasin et al, 2015; WHO, 2016).

On the other hand, converting cannabis derivatives into products which can be bought and consumed legally could also have benefits for the consumer such as greater quality and standardisation of the product, improved health and safety control and more information regarding their contents. At the same time, however, we should not forget that there are legal products of mass consumption such as cigarettes or many popular drinks whose contents are a trade secret and not accessible to the consumer.

Legalisation could also lead to a decrease in police enforcement and criminal prosecution of dealers and traffickers, thus reducing the costs involved in these tasks. In addition, it is highly likely that trials connected with this trade and the number of people tried and imprisoned would also diminish. This could help to improve the Spanish legal and prison system, which is currently overloaded and hardly sustainable.

Despite this, neither the illegal market nor unlawful behaviour would disappear with legalisation. For example, the use of marijuana would continue to be prohibited for minors and so they would continue to obtain it illegally. The state would have to decide on the punishments to be imposed on people facilitating access or selling marijuana to minors. The trafficking and selling of drugs would continue to be investigated by the police and the penal system. Nevertheless, the policing, penal and prison system costs of such behaviour would certainly be much lower than those generated by with the current prohibitionist system. The savings involved could be partially dedicated to increasing and improving the treatment of problems linked to consumption, as well as improving the education of children and adolescents regarding the use of cannabis and other drugs, reducing the demand and consumption of these substances and limiting their excessive or problematic use as far as possible.

Furthermore, legalisation of cannabis would make it easier for public administrations to improve control of production and sales of the products. The state's main instrument for regulating prices and keeping them at a level which would prevent increased consumption is taxation. Revenues raised by taxation could also be dedicated to prevention and treatment, as well as to the implementation of other social policies. Conversely, taxes could handicap the fight against the illegal market if they keep prices for the legal products too high. There is currently no taxation model which has been successfully applied to the cannabis market. As will be seen, the choice of both tax base and rates to be applied to the production and consumption of cannabis are still decisions of an experimental nature with results which have not been entirely satisfactory.

Establishing the economic impact that government policies have or may have on the regulation, sale or use of cannabis is a complex undertaking. Beside the fact that it requires data that is often not available or does not exist, the model should cover variables such as production methods, prices, consumption patterns, the harm or loss it can cause, taxes and potential benefits. Working on the assumption that marijuana use involves risks and potential harm, and that both are proportional to the extent and forms of use, the number of intensive users and the levels of tetrahydrocannabinol (THC), the best public policy would be one that contributes to limiting and improving consumption, thus reducing the negative consequences, while at the same time making responsible and controlled consumption more possible. However, the recent legalisation of marijuana for recreational use in Uruguay and several North American states is highlighting the difficulties involved in implementing a taxation policy in this market, its limited effectiveness in combating the black market, as well as the moderate economic and social benefits of some of the tax revenue systems being tried out. Although it is still too early to evaluate the success of these experiments, the fact that some of them were substantially modified shortly after implementation suggests that economic considerations, alongside social criteria, must be kept foremost in mind when designing public policy on drugs (Kleiman & Ziskind, 2014).

This article analyses firstly the size of the cannabis market in Spain, on the basis of data available on the extent of use and consumption patterns of the different types of users. This will be followed by reviewing and comparing the costs of cannabis production and distribution in different production regimes and varying conditions of legality. The available data seems to show that retail prices of cannabis in the illegal market are quite high and could be considerably reduced were production and sales to be legalised. Thirdly, we will examine the relationship between price and consumption by analysing the price elasticity of demand, which indicates that a drop in prices would increase demand and aggregate consumption, and possibly also the number of users. Finally, the strengths and weaknesses of different taxation alternatives for marijuana are considered. For this purpose, we review the experiments that have been tried or are proposed in those North American states which have recently legalised cannabis for recreational use: Colorado, Washington, Oregon, Alaska and the District of Columbia.

The size of the cannabis market in Spain

Estimating the size of an illegal market is a complicated challenge. All estimates are rather problematic, so the data offered below should be considered as no more than hypothesis to be tested.

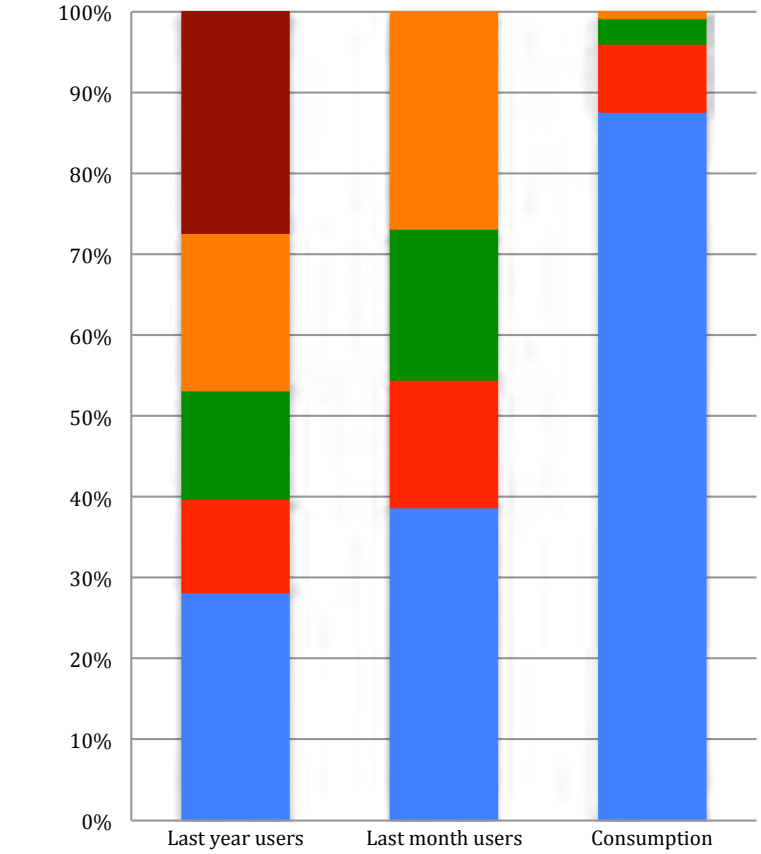
What is known is that recent studies in the USA and the European Union have shown cannabis to be mostly consumed among regular and experienced users who claim, in population-based surveys, to have used cannabis daily or almost daily in the past month. In addition, it has been shown that the quantity consumed rises with frequency of use, i.e. the greater the number of days on which this type of substance is

consumed, the greater the mean amount consumed in each episode of cannabis use. Those who use cannabis on a daily basis consume a much greater average daily quantity than those who do so less frequently. Therefore, when estimating consumption in any way, it is necessary to bear in mind the user profile in terms of the frequency with which they consume the substance, the normal dosage consumed, the routes of administration, etc. (Caulkins & Kilmer, 2013; Caulkins et al, 2015; Caulkins, Hawken, Kilmer & Kleiman, 2012; Kilmer, Caulkins, Midgette, et al., 2013; van Laar et al, 2013).

In our estimation we have applied the same procedure used by Caulkins and Kilmer (2013) to calculate the size of the cannabis market in the European Union. We have taken the data on the prevalence of cannabis use in the past month and frequency of use (measured in days of consumption) from the 2013 EDADES survey (Figure 1). The mean quantities consumed daily by each type of user was taken from a study in which an online questionnaire designed to gather this data was administered to 2,530 cannabis users in seven European Union countries (van Laar et al., 2013).

The amount of cannabis consumed in Spain in 2013 was around 388 tonnes[1], slightly lower than the 394 tonnes that Caulkins and Kilmer estimated for 2009. The greater part of this, which we estimate to account for 87% of the demand for these products, was consumed by those who use them on a daily or almost daily basis. Similar results are found in all EU countries where this has been studied (Caulkins & Kilmer, 2013).

According to the results of the study by Caulkins and Kilmer, Spain was the European Union country in which most cannabis was consumed in 2009. In that year, over a quarter of all cannabis derivatives used in the EU were con-



Note. PY: prevalence of use in the past year. PM: prevalence of use in the past month. 1-30: number of days used in the past month.
Source: Prepared by the authors based on data from EDADES 2013.

Figure 1. Relative size of different segments of the cannabis market in Spain, 2013

1 Since experts consider that surveys on drugs only reflect between 25% and 50% of real consumption, this amount would need to be multiplied by a correction factor of between 0.25 and 0.5 to obtain a quantity more in line with real use (Caulkins & Kilmer, 2013: 295-6). In this case, the amount consumed would be estimated at between 485 and 582 tonnes. In this article, the figures we offer do not take account of this difference between consumption declared by consumers and real consumption because it would vary according to the substance in question and would probably not be the same across all countries.

sumed there. Six countries accounted for 87% of total consumption: Spain, France, Italy, United Kingdom, Germany and the Netherlands. Nevertheless, significant differences could be observed between these countries, based on the relative importance of the most intensive users in each country. Three of the them (Spain, France and the Netherlands) have more than double the rate of intensive users (those who used the substance on more than 19 days in the past month) than the other three (Germany, UK and Italy), in which more than half the users only took the drug between once and three times a month. This could indicate the existence of two distinct cannabis consumption patterns in Europe: one where low intensity consumption is dominant, the other with a greater prevalence of users taking the drug on a daily or almost daily basis. Portugal would clearly be included in the group of Spain, France and the Netherlands, while two other countries, Belgium and Austria, would also be very close to this group.

The value of the cannabis market in Spain

What is the value and the dimension of the cannabis market in Spain? How much is spent in total purchasing this product? How much do all cannabis users spend together?

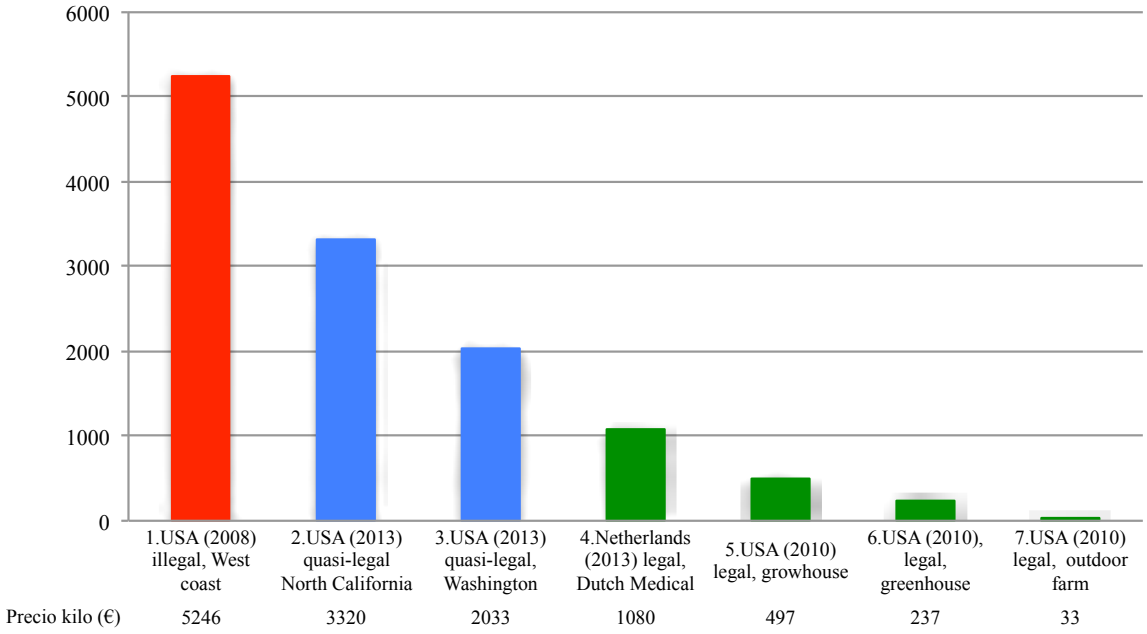
In their study of the European cannabis market, Caulkins and Kilmer (2013) calculated the approximate spending on cannabis in 22 EU countries in two different ways. Firstly, they multiplied the estimated quantity consumed by the average market retail price per gram of marijuana. The result of this calculation was a total spend of €1,931 million in Spain in 2009. The second calculation was made using the weighted average price data of monthly spending declared by the different types of users in the online survey of seven countries. This generated a total retail expenditure of €1,575 million, which would be equivalent to each user spending €55 per month and €659 per year.

Caulkins and Kilmer point out that the difference between the two figures may be due, among other reasons, to the fact that regular and intensive users usually buy large quantities, thus obtaining better prices and discounts. From this perspective, the divergence between the two estimates offers an approximate measure of the average size of discounts, which in Spain would be around 20%. This figure is in line with our own figures, which were obtained in our 2015 field study and in interviews with this type of user.

Cannabis prices in relation to their legal status

How far would cannabis prices drop if it were legalised? In an attempt to answer this question, we will review the analysis carried out by Caulkins (2014: 21-22) of several scenarios which we will attempt to sketch out with the available data. Figure 2 shows the results of comparing production costs and prices of a kilogram of *sinsemilla* marijuana under different production regimes and different legality status.

The first column in Figure 2, in red, represents the wholesale price per kilo of marijuana in the west of the USA in 2008, when the sale and use of cannabis was still illegal. Since then, prices have dropped considerably (Caulkins, 2014).



Note. *Sources:* 1. Caulkins, 2014; 2. Caulkins and Bond, 2012; 3. Caulkins, Andrzejewski and Dahlkemper, 2013; 4. Kilmer and Burgdorf, 2013; 5. Kilmer, Caulkins, Pacula, MacCoun, and Reuter, 2010; 6. Caulkins, 2010; 7. Caulkins, Hawken, Kilmer and Kleiman, 2012. Average annual exchange rates for the year in question were used to convert dollars to euros.

Figure 2. Wholesale price per kilogram of sinsemilla marijuana under different production regimes

The next two columns, in blue, show the drop in prices triggered by the partial lifting of prohibition for medicinal purposes, despite continued illegality at federal level. The green columns reflect production costs in different scenarios within legal production and trade regimes. The first of these shows the production costs of a Dutch pharmaceutical company which grows high quality cannabis for medicinal purposes on a small scale. The last three columns show estimated production costs of different cultivation alternatives within a regulated legal regime. Production costs could even be cheaper if we took the current hemp costs for a variety of industrial uses. In Canada, this type of hemp currently costs around €964 per hectare. Given these conditions, a kilogram of marijuana with a THC concentration similar to that of the *sinsemilla* variety could be produced for under €2 before taxes (Caulkins et al, 2012: 161). The production costs of a kilogram of tobacco are of a similar order and would be very similar for marijuana. In order to produce marijuana with high THC content it would not even be necessary to cultivate the *sinsemilla* variety since the industrial process could include enriching the marijuana with THC from other parts of the plant or from other plants – something which has not yet been tried in any of the states in which cannabis has been legalized for medicinal or recreational purposes.

How price changes affect consumption: the elasticity of demand

How would demand be affected by a fall in the prices of legal cannabis?

The effect of prices on consumption is termed "price elasticity of demand" in economics. This concept measures the change which takes place in the consumption of a good or service when the price is raised by one per cent and is calculated by observing the subsequent shifts in the product's demand curve.

The economists who have studied the elasticity of demand of cannabis have attempted to reveal how consumption changes in response to changes in both price and legislation. It should be noted that legalisation would also affect other determining factors of consumption that economic analyses do not take into consideration, such as the changes in cultural norms, informal sanctions (imposed for example by parents or other authority figures) or peer group pressure.

Research into the demand elasticity of cannabis has been carried out in countries like USA and Australia, but not in Spain. Pacula (2010) systematically reviewed all the literature on the subject, with a special focus on how changes in prices and legislation can affect the prevalence and frequency of use among the different types of user groups. As has been pointed out previously, consumption is largely concentrated among regular and intensive users (Gamella & Jiménez Rodrigo, 2003), so that any variation in the number of these would affect global consumption.

In all studies at international level, current users are concentrated in certain age groups. Spain is no exception and in the 2013 EDADES survey, 15.9% of those between 18 and 25 years of age claimed to have used cannabis in the past month, as against 7.7% of minors under 18 (15-17 years of age), and 5% of those above 25 (26-64 years of age).

Pacula points out that there is sufficient evidence in the literature that reductions in both prices and administrative or penal sanctions for marijuana use lead to (1) more people starting to use it, especially adolescents and young adults, (2) more regular users, and (3) their consumption being extended for longer periods. According to Pacula, any model that tries to project the impact that the legalisation of marijuana may have on the market also needs to take into account the changes in social norms and in the perception of harm, as well as the changes in monetary price and legal risks. Otherwise, the forecast effect of legalisation on consumption coud be underestimated(Pacula & Lundberg, 2014; Pacula, 2010).

There are many factors which make it difficult to calculate approximately by how much cannabis consumption could increase in Spain if its sale was legalised. First of all we do not know by how much prices would really fall. Secondly, the estimations of total demand elasticity carried out range from -0.4 to -1.5 and were calculated on modest price variations in a prohibition regime (Kilmer, Caulkins, Pacula, MacCoun & Reuter, 2010: 23; Pacula & Lundberg, 2014: 7). It is quite likely that the link between prices and consumption is rather different in a legal regime. In addition, there will certainly be other factors beyond price which would change in a legalised and normalised commercial environment. Many users would, for example, lose their fear of legal sanctions and their social and political implications (Kilmer et al., 2010: 23-24; MacCoun, 2010). It could also happen that perceptions of these drugs and their attractions would change, or that some of their risks or advantages would become more visible and undeniable if more verified data about their use were made available, as is currently the case with tobacco, sugar or alcohol.

Taxation of cannabis products

We stated previously that legalisation could contribute to a marked reduction in prices through the reduction of risks run by producers and distributors. Increases in productivity and a reduction in the average costs generated by the economies of scale can clearly be added to this, while a rise in the number of users and total consumption can also be expected. The fall in prices could be offset by the application of special taxes, thus providing revenues for the state which could in turn be given over to prevention and treatment as well as the implementation of other social policies. Taxes on marijuana should be of a sufficiently high rate to prevent an increase in consumption or a switch to other countries with

higher taxes, but they should be below the threshold which allows the legal trade to compete with the black market; these are difficult aims to achieve. In Washington, for example, the prices per gram of marijuana when it became available in legal establishments in 2014 ranged from $25 to $30. A considerable proportion of this price was determined by the excise taxes applied during this first stage: manufacturers, processors and retailers were taxed at 25% of the retail price. In July 2015, the taxation system was changed and a single 37% tax was applied on retail sales. At the same time, the number of licences for establishments selling the drug and the competition between them increased. As a result, marijuana prices fell to little more than $9 per gram in March 2016, very close to the prices in the illicit trade (Jensen & Roussell, 2016; The Daily News in Longview, 2-01-2016). In less than two years, the wholesale price of recreational marijuana fell by two thirds in Washington (Humphreys, 2016).

Two questions currently stand out in the debate on legalisation and taxation: at which rate should legal marijuana be taxed, and what exactly should be taxed? There are a variety of studies with interesting analyses and ideas on these topics (Caulkins et al, 2015; Kilmer et al, 2010; Kilmer, Caulkins, Midgette, et al, 2013), but the best information can be found in the reports and media articles about what is happening in those North American states which have so far legalised recreational use: Colorado, Washington, Alaska, Oregon and the District of Columbia. This last one has only legalised cultivation of up to six plants (three in the flowering stage) for residents because Congress has prevented the city of Washington from implementing a taxation system for regulating a legal market for marijuana. The experiences of the other states present interesting similarities and differences. In all these pioneering states the first act was to legalise the sale of marijuana for medicinal purposes, which was taxed at low rates. Its sale for recreational use was legalised in the next step, and this was taxed at higher rates. This gave rise to three competing markets: the illegal market, the legal market and the market for medicinal marijuana, some of which ended up being used fraudulently for recreational purposes. There were differences in the rates of taxation and the tax base applied in each state.

In November 2012 Colorado and Washington approved the legal sale of recreational marijuana. Products went on sale in early 2014 in Colorado and mid-2014 in Washington. Both states opted for an *ad valorem* tax on marijuana, i.e. a percentage of the final retail price of the product.

The main advantage of this system is that it is easy to apply and its implementation involves little cost. It does, however, suffer from certain disadvantages, chief among them its shortcomings in undermining the black market. Generally, when an industry begins operating, prices rise if demand outstrips supply. This occurred in both Washington and Colorado when marijuana was first sold legally for recreational purposes. Applying relatively high levels of special taxes on the products contributed to price increases, to the point where these could hardly compete with the market in illicit marijuana, which was thus able to sustain its sales. As a result, the sale of illicit marijuana managed to keep an important share of the market.

Furthermore, if producers manage to develop economies of scale, prices will fall and with them taxation revenues. An additional problem is that lower prices could lead to a rise in consumption among young people and that some of the lower priced marijuana might be diverted to illegal markets in other states at higher prices (Caulkins et al, 2015). This could be corrected by raising taxes, although this would have a negative effect on the emerging legal production sector. It appears that in the USA, pressure from the legal marijuana industry has resulted in changes in legislation and taxation in its favour, reducing taxes on its products (Jensen & Roussell, 2016; Subritzky, Pettigrew & Lenton, 2015)the cultivation, sale and use of recreational cannabis has been prohibited by law in most countries. The illegal sale in other states of marijuana purchased legally in Colorado has also been observed (Gurman, 2016; Hughes, 2016).

In November 2014, Oregon and Alaska passed legislation approving the production and sale of recreational cannabis. In October 2015 this type of marijuana became legally available in Oregon in dispensaries which had already been set up to sell it for medicinal use. It is hoped that in 2016 the first licences will be issued to open establishments which can sell marijuana exclusively for recreational use. These products have yet to go on sale in Alaska because its marijuana legislation is still under development. In contrast to Colorado and Washington, Oregon and Alaska have decided to apply weight-based rather than price-based excised taxes. In January 2016, Oregon began to apply a 25% tax on all transactions involving recreational marijuana taking place temporarily in the medicinal marijuana dispensaries. Once sales can be moved to the new establishments licensed for this purpose, a tax of between 17% and 20% is envisaged on these commercial operations.

Applying taxes by weight rather than price has the advantage of more stable revenues. In addition, it may hinder the development of mass production in the industry, thereby favouring the creation of more artisan products and of higher quality. On the other hand, this could entail the risk of a type of cannabis with a highly concentrated active ingredient being sold, something that has been observed in recent years in the illegal markets both in the USA and in the EU. For these reasons, some experts have proposed other systems which would tax the THC content or the proportion of the active ingredients THC and CBD (cannabidiol). Taxing the content of marijuana could favour the development of "softer" products with a lower psychoactive potential and which are less intoxicating. It is worth noting in this regard that various studies have highlighted the correlation between a greater risk of addiction and the potency

of the cannabis consumed (Freeman & Winstock, 2015). In the Netherlands, for example, a rise in THC concentrations of marijuana and hashish sold in the *coffee shops* coincided with an increased demand for treatment, although in recent years the demand for treatment has begun to go down (Hall, 2015; Liebregts, et al. 2013; MacCoun, 2011; Niesink, Rigter, Koeter & Brunt, 2015; Pijlman, Rigter, Hoek, Goldschmidt & Niesink, 2005). Other research has shown that the presence of CBD offsets some of the adverse effects of THC such as anxiety, panic attacks and some psychotic symptoms (Bhattacharyya et al., 2010; Englund et al., 2012; Leweke et al., 2012; Niesink & van Laar, 2013). However, a tax on active ingredients would most probably pose technical difficulties and involved higher costs since it would be necessary to create a system of random checks on the contents of the products offered for sale. This type of control has yet to be implemented anywhere.

Conclusions

The legal and political status of cannabis has changed in an unprecedented manner. In some western nations its production, distribution and sales are reaching a level of legalisation that will allow cannabis to be recognised as a psychoactive substance consumed on a large scale and tolerated in the same way as alcohol and tobacco, as well as to be included in the general pharmacopoeia. This transformation is generating a multitude of questions and uncertainties regarding the costs and benefits associated with cannabis becoming a legal, commercial and regulated product subject to taxation.

The legalisation of hemp derivatives provokes frequently conflicting reactions from polarised camps. Some see legalisation as an issue of social justice and a sort of panacea to treat a variety of illnesses or resolve problems of substance dependence. Others, meanwhile, can only see this age-old plant as a threat to the health of consumers and a source of social problems of all kinds. Nevertheless, defending the right to grow plants for personal consumption or the use of hemp derivatives among adults should not be incompatible with the promotion of responsible and moderate use of such products, or even the prevention of its consumption or the struggle to reduce its use among the most vulnerable members of society. These efforts could be sustained or even improved in a situation of legal normality and commercial legality of the products involved. Those promoting cannabis legalisation should also be more involved in working to prevent or reduce consumption, especially when immoderate, as well in reducing the harm it can cause - as do those in favour of tobacco control.

For some years, Spain has maintained a cannabis trading regime characterised by easy access, relatively low prices and rich and intense indirect advertising, with production and sales however remaining illegal. As a result, a market has consolidated around illicit hemp derivatives offering a wide range of Moroccan hashish and locally grown marijuana to a large number of consumers (Alvarez, Gamella & Parra, 2016; Gamella & Jiménez Rodrigo, 2004, 2005). Cannabis has become an attractive and desirable product for a notable sector of the Spanish population, mostly young people, who often underestimate the risks and dangers especially those involved in the most intensive and prolonged use.

In Spain cannabis consumption has remained decriminalised since the mid-1970. However, in 1982 a system of controls and punishments for possession and use of the drug in public places was introduced, based on administrative sanctions and fines (Mayán Santos, 2007). This system of penalties most likely contributed to the development of a disregard for the law and for the efforts at treatment and prevention of drugs which were realised in Spain among both cannabis users and public opinion in general.

This study has presented a series of politico-economic arguments relating to price, taxation and methods of regulation of the production and sale of cannabis. These aspects of the cannabis market should be taken into consideration in any reform of its legal status, as should the fact that cannabis prices in Spain are the lowest in the European Union, which goes some way towards explaining why Spain is one of the countries with the greatest number of both average and most experienced users. But there is still room for price reductions if production and distribution are decriminalised. Since lower cannabis prices could lead to a rise both in the number of consumers and the total quantity consumed, the discussion around the legalisation of cannabis production and trade needs to consider concrete measures to prevent sharp price cuts which could have serious effects on the demand for the products involved.

One of the crucial aspects regarding the legalisation of the hemp derivates market will therefore be its taxation. Taxes can serve to control prices and prevent a growth in demand as a consequence of possible price falls. The experiences of the pioneering states in marijuana legalisation for recreational use show that the taxation of cannabis is a complex issue for which generally accepted solutions have yet to be found. Finding a balance between satisfactory revenue and a tax level which will allow the legal market to progressively displace the illegal one requires more knowledge and a greater consensus among the different groups involved than is currently the case. The results of the first attempts to tax legal marijuana have not been as encouraging as was hoped. As might be expected after almost a century of the prohibition of these sought-after substances, the institutions created informally in response to illegality are more complex and flexible than imagined, and the new legal institutions have been extremely rigid and slow in their responses. Simply not enough is known about the consequences of legalising marijuana and all the good intentions and more or

less informed opinions do not suffice to develop either an efficient market or a satisfactory taxation system. Low rates of taxation are necessary so that an emerging market be capable of progressively replacing the illegal one. In consequence, it can be expected that, in its initial stages, the taxation of cannabis would not generate large revenues. It is furthermore quite likely that the greater part of this income would need to be invested in the regulation process itself, for example prevention and treatment programmes, management and control of production and sales, etc. At the same time, a significant decrease in the Spanish prison population and the concomitant reduction in public spending should not be expected. Indeed, the disappearance of administrative penalties for possession and use in public places would deprive the state of many million Euros of income from this dubious source. The repression of the illegal cannabis market and the persecution of traffickers would continue while a large illegal production industry exists in Spain and other countries which use Spain as a transit route for these products. At least in the short term, legalisation is thus highly unlikely to eradicate illegal cannabis growing in Spain or the illegal importing of cannabis derivatives from other countries such as Morocco.

It also remains to be seen how the legal and social experiments being carried out in various North American states, which will most likely also be tried in Europe, will affect the policies and positions of increasingly influential countries in other parts of the globalised world. It is impossible not to think of China, the Arab world, India or Russia in this respect. In several of these regions, cannabis use has ancient traditions which have continued to exist independently of the emergence of western counterculture in the 1960s and 70s which, however, also affects the younger generation of these countries in many ways.

The regulation or legalisation of cannabis derivatives is a complex issue which should be dealt with primarily from a public health perspective. This article has discussed several hypotheses informed with the currently available data which show the potential importance of socio-economic aspects in the planning, regulation and taxation of future cannabis control policies.

Conflict of interests

None of the authors of this study declare a conflict of interests.

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References

Alvarez, A., Gamella, J. F., & Parra, I. (2016). Cannabis cultivation in Spain. A profile of plantations, growers and production systems. *International Journal of Drug Policy, 37*, 70–81. doi: 10.1016/j.drugpo.2016.08.003.

Apfel, F. (2014). Cannabis – From prohibiton to regulation. "When the music changes so does the dance". ALICE RAP Policy Paper, 5. Retieved at http://www.alicerap.eu/resources/documents/doc_download/185-policy-paper-5-cannabis-from-prohibition-to-regulation.html.

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., … McGuire, P. K. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology, 35*, 764–774. doi:10.1038/npp.2009.184.

Brook, T. & Wakabayashi, B. T. (Eds.). (2000). *Opium regimes. China, Britain and Japan (1839-1952).* Berkeley, California: University of California Press.

Caulkins, J. P. (2010). *Estimated cost of production for legalized cannabis. WR-764-RC.* Retieved at http://www.rand.org/content/dam/rand/pubs/working_papers/2010/RAND_WR764.pdf.

Caulkins, J. P. (2014). Effects of prohibition, enforcement and interdiction on drug use. In LSE Expert Group on the Economics of Drug Policy (Ed.), *Ending the drug wars* (pp. 16–25). London: LSE Ideas. Retrieved at http://www.lse.ac.uk/IDEAS/publications/reports/pdf/LSE-IDEAS-DRUGS-REPORT-FINAL-WEB.pdf.

Caulkins, J. P. (2016a). Legalising drugs prudently: The importance of incentives and values. In LSE Expert Group on the Economics of Drug Policy (Ed.), *After the Drug Wars* (pp. 40–50). Retrieved athttp://www.lse.ac.uk/IDEAS/publications/reports/pdf/LSE-IDEAS-After-the-Drug-Wars.pdf.

Caulkins, J. P. (2016b). The real dangers of marijuana. *National Affairs*, 21–34. Retrieved at http://www.nationalaffairs.com/doclib/20151217_Caulkins_Indiv.pdf.

Caulkins, J., Andrzejewski, S. & Dahlkemper, L. (2013). *How much will the 25 / 25 / 25 tax scheme actually impact the price of cannabis? Supplement: Retail and processor markup. BOTEC Analysis Corp. I-502 Project #430-8a, final, June 28, 2013.* Retrieved at http://lcb.wa.gov/publications/Marijuana/BOTEC reports/8a_Impact_of_tax_schemes_Appendix_A_on_Markups-Final.pdf.

Caulkins, J. P. & Bond, B. M. (2012). Marijuana price gradients: Implications for exports and export-generated tax revenue for California after legalization. *Journal of Drug Issues, 42*, 28–45. doi: 10.1177/0022042612436650.

Caulkins, J. P., Hawken, A., Kilmer, B. & Kleiman, M. A. R. (2012). *Marijuana legalization. What everyone needs to know.* New York: Oxford University Press.

Caulkins, J. P. & Kilmer, B. (2013). Estimating the size of the EU cannabis market. In F. Trautmann, B. Kilmer & P.

Thurnbull (Eds.), *Further insights into aspects of the illicit EU drugs market* (pp. 289–323). Luxembourg: Publications Office of the European Union. Retrieved at http://ec.europa.eu/justice/anti-drugs/files/eu_market_full.pdf.

Caulkins, J. P., Kilmer, B. & Kleiman, M. A. R. (2016). *Marijuana legalization. What everyone needs to know* (second edition). New York: Oxford University Press.

Caulkins, J. P., Kilmer, B., Kleiman, M. A. R., MacCoun, R. J., Midgette, G., Oglesby, P., … Reuter, P. H. (2015). *Considering marijuana legalization. Insights for Vermont and other jurisdictions*. Santa Monica, California. Retrieved at http://www.rand.org/cohttp://www.rand.org/content/dam/rand/pubs/research_reports/RR800/RR864/RAND_RR864.pdf.

Decorte, T. (2007). Characteristics of the cannabis market in Belgium. In J. Fountain & D. J. Korf (Eds.), *Drugs in society: European perspectives* (pp. 28–38). Oxon, United Kingdom: Radcliffe Publishing.

Englund, a., Morrison, P. D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., … Kapur, S. (2012). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of Psychopharmacology, 27*, 19–27. doi: 10.1177/0269881112460109.

Freeman, T. P.& Winstock, A. R. (2015). Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychological Medicine. 45*, 3181–3189. doi: 10.1017/S0033291715001178.

Gamella, J. F. & Jiménez Rodrigo, M. L. (2003). *El consumo prolongado de cannabis. Pautas, tendencias y consecuencias*. Madrid: Fundación de Ayuda Contra la Drogadicción/ Junta de Andalucía, Comisionado para la Droga.

Gamella, J. F. & Jiménez Rodrigo, M. L. (2004). A brief history of cannabis policies in Spain (1968-2003). *Journal of Drug Issues, 34*, 623–659. doi:10.1177/002204260403400308.

Gamella, J. F. & Jiménez Rodrigo, M. L. (2005). Comercialización sin legalización: Políticas públicas y consumo/ comercio de cannabis en España (1968-2003). *Revista Española de Drogodependencias, 30*, 17–49.

Gamella, J. F. & Martín, E. (1992). Las rentas de Anfión: El monopolio español del opio en Filipinas (1844-1898) y su rechazo por la administración norteamericana. *Revista de Indias, 194*, 61–106.

Gowing, L. R., Ali, R. L., Allsop, S., Marsden, J., Turf, E. E., West, R. & Witton, J. (2015). Global statistics on addictive behaviours: 2014 status report. *Addiction, 110*, 904–919. doi:10.1111/add.12899.

Gurman, S. (2016). Drug traffickers are making millions shipping Colorado marijuana to other states. Retrieved at http://www.businessinsider.com/ap-drug-traffickers-seek-safe-haven-amid-legal-marijuana-2016-1.

Hall, W. (2015). What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction, 110*, 19–35. doi:10.1111/add.12703.

Hall, W. & Lynskey, M. (2016). Assessing the public health impacts of legalising recreational cannabis use in the USA. *Addiction*. doi.org/10.1111/add.13428

Hasin, D, Tulshi D, Kerridge B, Goldstein R, Chou P, Zhang H, et al. (2015) Prevalence of marijuana use disorders in the United States between 2001-2002 and 2012-2013. *The Journal of the American Medical Association Psychiatry, 72,* 1235–1242. doi:10.1001/jamapsychiatry.2015.1858.

Hawken, A. (2013). Economies of scale in the production of cannabis. Retrieved at http://www.liq.wa.gov/publications/Marijuana/BOTEC reports/5c-Economies-of-Scale-in-the-Production-of-Cannabis-Final-Revised.pdf.

Hughes, T. (2016). When smuggling Colo. pot, not even the sky's the limit. Retrieved at http://www.usatoday.com/story/news/2016/05/13/when-smuggling-colo-pot-not-even-skys-limit/83623226/.

Humphreys, K. (2016). So, something interesting happens to weed after it's legal. Retrieved at https://www.washingtonpost.com/news/wonk/wp/2016/05/04/the-price-of-legal-pot-is-collapsing/.

Jensen, E. L. & Roussell, A. (2016). Field observations of the developing legal recreational cannabis economy in Washington State. *International Journal of Drug Policy*. doi:10.1016/j.drugpo.2016.02.023.

Kilmer, B. & Burgdorf, J. (2013). Insights about cannabis production and distribution costs in the EU. In F. Trautmann, B. Kilmer & P. J. Turnbull (Eds.), *Further insights into aspects of the illicit EU drugs market* (pp. 389–402). Luxembourg: Publications Office of the European Union.

Kilmer, B., Caulkins, J. P., Midgette, G., Dahlkemper, L., MacCoun, R. J. & Pacula, R. L. (2013). *Before the grand opening. Measuring Washington State's marijuana market in the last year before legalized commercial sales*. Retrieved at http://www.rand.org/content/dam/rand/pubs/research_reports/RR400/RR466/RAND_RR466.pdf.

Kilmer, B., Caulkins, J. P., Pacula, R. L., MacCoun, R. J. & Reuter, P. H. (2010). *Altered State? Assessing how marijuana legalization in California could influence marijuana consumption and public budgets*. Santa Monica, California: RAND Corporation. Retrieved at http://www.rand.org/content/dam/rand/pubs/occasional_papers/2010/RAND_OP315.pdf.

Kilmer, B., Kruithof, K., Pardal, M., Caulkins, J. P. & Rubin, J. (2013). *Multinational overview of cannabis production regimes*. Cambridge: RAND Europe. Retrieved at http://www.rand.org/content/dam/rand/pubs/research_reports/RR500/RR510/RAND_RR510.pdf.

Kleiman, M. A. R., & Ziskind, J. (2014). Lawful access to cannabis: gains, losses and design criteria. In LSE Expert Group on the Economics of Drug Policy (Ed.), *Ending the drug wars* (pp. 77–82). London: LSE Ideas. Retrieved from: http://www.lse.ac.uk/IDEAS/publications/reports/pdf/LSE-IDEAS-DRUGS-REPORT-FINAL-WEB.pdf.

Korf, D. (2002). Dutch coffee shops and trends in cannabis use. *Addictive Behaviors, 27*, 851–866.

Korf, D. (2011). Marihuana behind and beyond coffeeshops. In T. Decorte, G. R. Potter & M. Bouchard (Eds.), *World wide weed: Global trends in cannabis cultivation and its control* (pp. 181–195). Famham, Surrey, UK: Ashgate.

Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., … Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry, 2*, 1–7. doi.org/10.1038/tp.2012.15.

Liebregts, N., van der Pol, P., Van Laar, M., de Graaf, R., van den Brink, W. & Korf, D. (2013). The role of study and work in cannabis use and dependence trajectories among young adult frequent cannabis users. *Frontiers in Psychiatry, 4*, 1–11. doi.org/10.3389/fpsyt.2013.00085.

MacCoun, R. J. (2010). *Estimating the non-price effects of legalization on cannabis consumption. WR-767-RC*. Retrieved at http://www.rand.org/content/dam/rand/pubs/working_papers/2010/RAND_WR767.pdf.

MacCoun, R. J. (2011). What can we learn from the Dutch cannabis coffeeshop system? *Addiction, 106*, 1899–1910. doi:10.1111/j.1360-0443.2011.03572.x.

MacCoun, R. J. (2014). The paths not (yet) taken: Lower risk alterntives to full market legalization of cannabis. In K. Tate, J. L. Taylor & M. Q. Sawyer (Eds.), *Something's in the air: Race, crime, and the legalization of marijuana* (pp. 40–53). New York: Routledge.

MacCoun, R. J. & Reuter, P. H. (1997). Interpreting Dutch cannabis policy: reasoning by analogy in the legalization debate. *Science, 278*, 47–52.

MacCoun, R. J. & Reuter, P. H. (2001). *Drug war heresies*. Cambridge, UK: Cambridge University Press.

Mayán Santos, M. E. (2007). La importancia de la cantidad y composición en los delitos relativos a drogas tóxicas, estupefacientes y sustancias psicotrópicas. *Revista Jurídica, 23*, 667–675.

Monshouwer, K., van Laar, M. & Vollebergh, W. A. (2011). Buying cannabis in "coffee shops." *Drug and Alcohol Review, 30*, 148–156. doi:10.1111/j.1465-3362.2010.00268.x.

Niesink, R. J. M., Rigter, S., Koeter, M. W. & Brunt, T. M. (2015). Potency trends of Δ9 -tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005-15. *Addiction, 110,* 1941-1959. doi:10.1111/add.13082.

Niesink, R. J. M. & van Laar, M. W. (2013). Does cannabidiol protect against adverse psychological effects of THC? *Frontiers in Psychiatry, 4*, 1–8. doi: 10.3389/fpsyt.2013.00130.

Pacula, R. L. (2010). *Examining the impact of marijuana legalization on marijuana consumption. Insights from the economics literature. RAND Corporation, WR-770-RC*. Retrieved at http://www.rand.org/pubs/working_papers/WR770.html

Pacula, R. L. & Lundberg, R. (2014). Why changes in price matter when thinking about marijuana policy: A review of the literature on the elasticity of demand. *Public Health Reviews, 35*, 1–18.

Pijlman, F. T. a, Rigter, S. M., Hoek, J., Goldschmidt, H. M. J. & Niesink, R. J. M. (2005). Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. *Addiction Biology, 10*, 171–180. doi:10.1080/13556210500123217.

Subritzky, T., Pettigrew, S. & Lenton, S. (2015). Issues in the implementation and evolution of the commercial recreational cannabis market in Colorado. *International Journal of Drug Policy, 27*, 1–12. doi:10.1016/j.drugpo.2015.12.001.

The Daily News in Longview, W. (2016). Local marijuana retailers contend with falling prices. Retrieved at http://tdn.com/news/local/local-marijuana-retailers-contend-with-falling-prices/article_72268328-fef1-5905-b2cd-e965add7a149.html.

UNODC (United Nations Office on Drugs and Crime). (2015). *World drug report, 2015*. New York: United Nations Publication, Sales No. E.15.XI.6. Recuperado de https://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf.

van Laar, M., Frijins, T., Trautmann, F. & Lombi, L. (2013). Cannabis market: User types, availability and consumption estimates. In F. Trautmann, B. Kilmer & P. Thurnbull (Eds.), *Further insights into aspects of the illicit EU drugs market* (pp. 73–182). Luxembourg: Publications Office of the European Union. Recuperado de http://ec.europa.eu/justice/anti-drugs/files/eu_market_full.pdf.

van Ooyen-Houben, M. & Keemans, E. (2015). Drug Policy: The "Dutch Model." *Crime and Justice, 44*, 165–226.

van Ooyen-Houben, M. M. J., Bieleman, B. & Korf, D. J. (2016). Tightening the Dutch coffee shop policy: Evaluation of the private club and the residence criterion. *International Journal of Drug Policy, 31,* 113–120. doi:10.1016/j.drugpo.2016.01.019.

WHO (World Health Organization). (2016). *The health and social effects of nonmedical cannabis use*. Retrieved at http://who.int/substance_abuse/publications/msbcannabis.pdf?ua=1.

Chemsex. An emergent phenomenon

Chemsex. *Un fenómeno emergente*

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Chemsex is the term given to the intentional use of psychoactive drugs in order to maintain sexual relations between men who have sex with men (MSM), usually for long periods of time and with multiple partners. This phenomenon has also been called *Party and Play* (*PnP*) in North America and *intensive sex partying* in Australia (Bourne et al., 2014). The intravenous (IV) use of these substances for similar purposes is known as *slamming* or *slamsex*. The drugs principally used are mephedrone, γ-hydroxybutyrate / γ-butyrolactone (GHB / GBL) and methamphetamine (McCall, Adams, Mason & Willis, 2015), although others have also been described (see Table 1). This definition, however, fails to explain other fundamental aspects of the phenomenon, such as the use of geosocial networking applications to locate or participate in "sessions". In fact, it has been reported that in comparison with MSMs who do not use such applications, those MSM who do use them tend to be younger, to have a better education and higher purchasing power, as well as more likely to engage in risky sexual behavior and present more STDs (Zou & Fan, 2016).

Since McCall and colleagues published the editorial *What is chemsex and why does it matter* in the BMJ in 2015, various observations about the phenomenon have appeared in the media in our country but there have been few scientific publications, which means that its dimension are still unknown. The most significant articles on the issue have appeared in the field of infectious diseases (Fernández-Dávila, 2016), indicating an increase in primary HIV infection in MSM and hepatitis C reinfection in this group, in addition to other STDs. It is among MSM that the greatest proportion of new HIV diagnoses in Europe was made in 2013, a total of 42% (Cornejo, Díaz, Díez & Valín, 2015). Similarly, a high rate of HCV reinfection has been reported among MSM in different European cities, reaching close to 25% (Ingiliz et al., 2016) with different independent risk factors: unprotected anal sex, sexual activity within a context of stimulant drug use, risky sexual practices or group sex (Vanhommerig et al, 2015), all features involved in *chemsex*.

With regard to the drugs used in *chemsex*, mephedrone stands out with a reported prevalence of use of up to 90% (Bourne et al., 2014). This substance, like other synthetic cathinones, has psychoactive and sympathomimetic effects similar to amphetamines, besides possessing entactogenic properties such as sensorial intensification, increase in sociability, disinhibition and sexual arousal. Its use is intended to enhance sexual stimulation and the duration of sessions (McCall, Adams, Mason & Willis, 2015). Its frequency in *slamsex* sessions has been observed at between 33% and 38% in some series (Bourne et al., 2015). This substance possesses great addictive potential. In intravenous use, the need to redose in increasingly shorter periods of time has been described, reaching 15-20 injections per day. In addition, this route of administration favors the appearance of induced psychotic symptoms. GHB is a CNS depressant that has a disinhibiting effect perceived as an aphrodisiac and a mild analgesic action. Its anesthetic effect favors the performance of aggressive sexual practices such as *fisting* because it relaxes the smooth muscle and decreases

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Table 1. *Psychoactive substances used in chemsex*

Psychoactive substance	Mephedrone and other synthetic cathinones: pentedrone, 4-MEC	Methamphetamine	GHB/GBL	Alkyl/butyl nitrites	MDMA	Cocaine	Ketamine
Street names	mephe, meow-meow, m-cat, bath salts.	Tina, crystal meth, ice, crank, speed.	Liquid ecstasy.	Poppers.	Ecstasy, molly. Sextasy (with sildenafil).	Coke, snow, blow.	Keta, vitamin K, Special K.
Intended effects	Stimulation, sexual arousal, euphoria, empathy feelings.	Stimulation, disinhibition, sexual arousal, increased confidence and self-esteem.	Sedation, anal sphincter relaxation. Euphoria, disinhibition, drunkenness, sexual stimulation.	Euphoria, socialization. Excitation and increase of power and increase of sexual pleasure.	Stimulation, feelings of empathy, acceptance and connection.	Activation, sexual arousal, hypervigilance.	Initial stimulation, relaxation, empathy, improvement of perception. Dissociation.
Adverse effects and complications	Dependence. Psychosis. Seizures, dystonias. Cardiac toxicity.	Psychotic symptoms. Hypertension. Dependence. Dry mouth and caries.	Drowsiness, loss of motor control (cumulative doses). Seizures. Delirium, Coma. Psychotic symptoms.	Retinal toxicity. Hypoxia. Hemolytic anemia.	Anxiety. Tachycardia, bruxism, "heat stroke". Affective symptoms and hangover.	Adrenergic hyperactiva tion. Vasospasm and ischemia. Paranoid ideation.	Mydriasis. Derealization. Accidents. Confusion. Hepatotoxicity. Neurotoxicity.

the pain threshold. Overdose with respiratory depression may be frequent, since it accumulates and its effect is potentiated in combination with other substances, and can thus lead to loss of consciousness, memory lapses and vulnerability to possible sexual abuse (Bourne et al., 2015). Methamphetamine is also common, especially with IV use. In this context, methamphetamine increases sexual confidence, duration, and intimacy. It also makes participation in high-risk behaviors such as group sex, sex with multiple partners, or aggressive sexual practices easier (Lea et al., 2016). Chronic methamphetamine use is associated with high dependence potential, mental health problems such as depression and/or psychosis, and transmission of blood borne viruses, mainly HIV (Darke, Kaye, McKetin & Duflou, 2008). Polydrug use in *chemsex* sessions is frequent, increasing the risks associated with the use of these drugs, in addition to the potential interactions between them and the antiretroviral treatments used by HIV-positive patients.

Given these data, we believe that epidemiological studies are needed to assess the phenomenon in Spain, not only in the field of infectious diseases, but also in relation to substance use and its impact on mental health. A multidisciplinary approach with these users, starting with a focus on reducing risks and damage, and leading to treatment for the consequences of substance use is now required in our country.

Conflicts of interest

The authors declare no conflicts of interest.

References

Bourne, A., Reid, D., Hickson, F., Torres Rueda, S. & Weatherburn, P. (2014). The Chemsex study: drug use in sexual settings among gay & bisexual men in Lambeth, Southwark & Lewisham. *London: Sigma Research, London School of Hygiene & Tropical Medicine.* Retrieved from http://www.sigmaresearch.org.uk/chemsex.

Bourne, A., Reid, D., Hickson, F., Torres-Rueda, S., Steinberg, P. & Weatherburn, P. (2015). "Chemsex" and harm reduction need among gay men in South London. *International Journal of Drug Policy, 26*, 1171-1176. doi:10.1016/j.drugpo.2015.07.013.

Cornejo, A., Díaz, A., Díez, M. & Valín, E. R. (2015). Vigilancia epidemiológica del VIH/sida. Situación en Europa & en España, 2013. *Boletín Epidemiológico Semanal, 22*, 249-256.

Darke, S., Kaye, S., McKetin, R. & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug and Alcohol Review, 27*, 253-262. doi:10.1080/09595230801923702.

Fernández-Dávila, P. (2016). "Sesión de sexo, morbo y vicio": una aproximación holística para entender la aparición del fenómeno ChemSex entre hombres gais, bisexuales y otros hombres que tienen sexo con hombres en España. *Revista Multidisciplinar del Sida, 4*, 41-65.

Ingiliz, P., Martin, T., Rodger, A., Stellbrink, H.J., Mauss, S., Boesecke, C. … the NEAT Study Group. (2016). Hepatitis C virus reinfection incidence and outcomes among HIV-positive MSM in Western Europe. *International Liver Congress, Abstract PS006.* Barcelona.

Lea, T., Mao, L., Hopwood, M., Prestage, G., Zablotska, I., de Wit, J. & Holt, M. (2016). Methamphetamine use among gay and bisexual men in Australia: Trends in recent and regular use from the Gay Community Periodic Surveys. *International Journal of Drug Policy, 29*, 66-72. doi:10.1016/j.drugpo.2016.01.003.

McCall, H., Adams, N., Mason, D. & Willis, J. (2015). What is chemsex and why does it matter? *British Medical Journal, 351*, h5790. doi:10.1136/bmj.h5790.

Vanhommerig, J.W., Lambers, F.A., Schinkel, J., Geskus, R.B., Arends, J.E., van de Laar, T.J., … Prins, M. (2015). Risk Factors for Sexual Transmission of Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: A Case-Control Study. *Open Forum Infectious Diseases, 2*. doi:10.1093/ofid/ofv115.

Zou, H., & Fan, S. (2016). Characteristics of Men Who Have Sex With Men Who Use Smartphone Geosocial Networking Applications and Implications for HIV Interventions: A Systematic Review and Meta-Analysis. *Archives of Sexual Behavior*. Advance online publication. doi:10.1007/s10508-016-0709-3.

Self-quitting in a Spanish sample. An exploratory study

Autoabandono del tabaco en una muestra española. Un estudio exploratorio

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The consumption of tobacco is a serious public health problem, mainly due to its relationship with cardiovascular disease and with different types of cancer (Bjartveit & Tverdal, 2009). In order to reduce the prevalence of smoking, different types of treatment, both pharmacological and psychological or a combination of both, have been tested but the degree of success of such treatments varies a lot depending on the different studies (Raich et al., 2015; Thomsen, Villebro, & Moller, 2014). Quitting the consumption of tobacco without professional help *(self-quitting,* in the English terminology) has received less attention, although it is the main method of smoking cessation used by most smokers who try to quit smoking, and it is estimated that 95% of smokers are successful with this method (Schater, 1990). Other scholars of the topic report more modest numbers, which range from 54 to 69% of smokers who have managed to quit smoking through self-quitting (Smith, Chapman, & Dunlop, 2015). The present study aims to perform an exploratory analysis of the variables that may help explain the success or failure of smoking cessation by means of self-quitting. This study obtained the favorable report of the Committee of Bioethics of the University of Almeria, whose of reference number is UALBIO2011/025.

The participants of the study were recruited through ads in press and radio and health centers. They were interviewed in order to record different variables related to the consumption of tobacco, such as age at onset, age at quitting, years of tobacco use, number of cigarettes per day, and nicotine dependence. We also assessed the presence of behavioral repertories related to personal self-regulation, such as self-control, understood as the ability to control interference derived from internal events, measured through of the Self-control Questionnaire of Rosenbaum, (Capafóns, 1989) and psychological inflexibility, or the inability to be in touch with functionally aversive private events, whether they be sensations, emotions, memories, thoughts, etc. and the performance of behaviors that change the form and/or frequency of these events, measured with the Acceptance and Action Questionnaire (AAQ-II), Spanish version of Ruiz, Langer, Luciano, Cangas, and Beltrán (2013). We assessed the carbon monoxide (CO) in exhaled air of the participants who stated they were abstinent, by means of a Bendfont co-Oximeter. Participants had to achieve an outcome equal to or lower than 5 bpm (particles per million) to be assigned to the group of former smokers.

We used the Kolmogorov-Smirnof *Z* and Student *t* statistics to contrast the arithmetic means.

We selected 137 participants, of whom 99 (72.2%) had been abstinent for a period of more than six months at the time of the interview (Former smokers); and 38 (27.7%) active smokers, who had ceased smoking for at least six months, by means of the self-quitting strategy (Relapsed smokers).

As shown in Table 1, of all the variables related to the history as a smoker used in the present study, only the mean age at quitting was significant, being higher in the case of those who remained abstinent (36.35 vs. 29.77 years). With regard to the measures of self-control and psychological

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Table 1. *Variables related to smoking.*

	Former smokers	Relapsed smokers	Kolmogorov-Smirnof Z (p)
Nr. of cigarettes/day: Mean (SD)	16.62 (10.21)	14.24 (5.23)	.86 (.447)
Age at first tobacco use: Mean (SD)	16.45 (2.80)	14.88 (5.50)	1.33 (.056)
Years as a smoker: Mean (SD)	19.29 (10.91)	14.99 (10.77)	1.28 (.76)
Age at quitting: Mean (SD)	36.35 (10.93)	29.77 (9.65)	1.63 (.01)*
Dependence (Fagerström): Mean (SD)	3.51 (2.37)	3.53 (2.10)	.484 (.973)

Nota. ***p* £ .05.

inflexibility, they were statistically different, as a function of the group of former smokers or relapsed smokers (27.72 vs. 19.97, t = 2.198, p £ .001, for self-control; and 23.46 vs. 25.36, t = -3.41, p £ .030, for psychological inflexibility, for former and relapsed smokers, respectively).

These results show that there were no differences in a large part of the habits related to tobacco consumption, except for age at quitting in smokers who use some kind of treatment, which coincides with the results obtained in other works (Gregor & Borrelli, 2012; Raich et al., 2015). It is possible that increased age leads to an increase in the aversive consequences derived from the consumption of tobacco and this would facilitate their quitting. In relation to self-control, the data obtained coincide with other contributions of authors about the benefit that programs of self-control can contribute to the treatment of smoking (Chiou, Wu, & Chang, 2013). Regarding psychological inflexibility, it could be a factor to take into account due to its predictive value in the success of self-quitting, coinciding with Roales-Nieto et al. (2016). In spite of this, it should be noted that the participants in the present study reported a low nicotine dependence, which could facilitate the initiation of self-quitting, in line with Linchestein and Cohen (1990). The data obtained may have some limitations due to the possible bias in the participants' information. On another hand, the selection of the participants was not random due to the difficulty to access them. Treatments that include the approach of self-control and psychological inflexibility could increase the rates of success in the psychological treatments of smoking.

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Conflict of interests

The authors declare the absence of conflicts of interest.

References

Bjartveit, K. & Tverdal, A. (2009a). Health consequences of sustained smoking cessation. *Tobacco Control, 18*, 197-205. doi:10.1136/tc.2008.026898.

Capafóns, A. (1989). Competencia aprendida-II- (La aproximación de Rosenbaum). Fiabilidad y validez de su medida. Crítica y recomendaciones. *Revista Española de Terapia del Comportamiento, 7*, 18-39.

Chiou, W., Wu, W. & Chang, M. (2013). Think abstractly, smoke less: A brief construal-level intervention can promote self-control, leading to reduced cigarette consumption among current smokers. *Addiction, 108*, 985-992. doi:10.1111/add.12100.

Gregor, K. & Borrelli, B. (2012). Barriers to quitting smoking among medically ill smokers. *Journal of Behavioral Medicine, 35*, 484-491. doi:10.1007/s10865-011-9376-y.

Lichtenstein, E. & Cohen, S. (1990). Prospective analysis of two modes of unaided smoking cessation. *Health Education Research, 5*, 63-72. doi:10.1093/her/5.1.63.

Raich, A., Martínez-Sánchez, J. M., Marquilles, E., Rubio, L., Fu, M. & Fernández, E. (2015). Smoking cessation after 12 months with multi-component therapy. *Adicciones, 27*, 37-46.

Roales-Nieto, J. G., San Pedro, E. M., García, R. C., Romero, B. M., López, F. J., Luciano, A. G., …López, M.H. (2016). Smoking self-quitting and psychological flexibility. *International Journal of Psychology and Psychological Therapy, 25*, 123-129.

Ruiz, F. J., Herrera, l. I. L., Luciano, C., Cangas, A. J. & Beltrn, I. (2013). Measuring experiential avoidance and psychological inflexibility: The Spanish version of the Acceptance and Action Questionnaire-II. *Psicothema, 25*, 123-129.

Schachter, S. (1990). 'Debunking myths about self-quitting: Evidence from 10 prospective studies of persons who attempt to quit smoking by themselves': Reply. *American Psychologist, 45*, 1389-1390. doi:10.1037/0003-066X.45.12.1389.

Smith, A. L., Chapman, S. & Dunlop, S. M. (2015). What do we know about unassisted smoking cessation in Austra-

lia? A systematic review, 2005-2012. *Tobacco Control, 24*, 18-27. doi:10.1136/tobaccocontrol-2013-051019.

Thomsen, T., Villebro, N. & Mller, A. M. (2014). Interventions for preoperative smoking cessation. *The Cochrane Database of Systematic Reviews,* (3), CD002294. doi:10.1002/14651858.CD002294.pub4.

Assessing the decision-making capacity of the addicted population to take part in research: myths, barriers, and benefits

Valoración de la capacidad para participar en investigación en población adicta: mitos, barreras y beneficios

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Obtaining informed consent in biomedical research is a fundamental ethical requirement in all national and international legal frameworks. To be valid, consent requires the researcher to ensure that his/her work is voluntary and that the patient is competent to make the decision to participate (Navío & Ventura, 2014). Spanish legislation on informed consent in research focuses on decision-making capacity and outlines those situations in which it is limited without, however, defining how this should be assessed. Emphasis is placed on the need to justify the inclusion of "vulnerable populations" in research, without specifying which (Real Decreto (Royal Decree) 1090/2015, 2015). There are no specific regulations governing the participation of patients with substance use disorders (SUDs).

As defined in international classifications, addiction is a disorder in which the person's control over their drug use deteriorates (American Psychiatric Association, 2014). Addicted people continue to use drugs despite the enormous negative consequences and even though they often voice the desire to stop. Some have interpreted the DSM-5 criteria that describe loss of control and compulsive behaviour in absolute terms (Charland, 2002). They argue that people with SUDs do not meet the standards required for giving voluntary consent, and that we should thus consider addicts unfit for participation in clinical trials unless proven otherwise.

In addition to the above considerations, there are other factors may affect the ability of addicted persons as a result of the direct effects of drug use, as well as a wide range of comorbidities that may reduce their concentration, thus limiting their understanding of informed consent.

Given the enormous burden on health and the economic and social costs generated by SUDs, there is great public interest in drug prevention and treatment (Carter & Hall, 2012). Research in this field will lead to more effective treatments to reduce the harm done to the individual and society. Addicted persons have the same rights to participate in and benefit from scientific research into their condition as any other person with any other disorder (Morán-Sánchez, Luna, Sánchez, Aguilera & Pérez-Cárceles, 2016). The potential benefits of addiction research, however, do not provide sufficient justification it if a vulnerable population is exploited. We must demonstrate that those who participate are able to consent freely, that this consent is obtained while respecting their autonomy, and that the risk/benefit balance is acceptable (Morera, 2000).

For all these reasons, assessing decision-making ability in addicts is vitally important. Available data are scarce. A study of what addiction research focuses on and the area it covers (Nogué & Miro, 2015) reveals that very little work has been done on how consent forms are understood (Morán-Sánchez et al., 2016). Studies with standardized instruments are required. Although there is no gold standard,

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the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) is the most widely used tool for formal assessment of the ability to consent to research (Appelbaum & Grisso, 2001). This semi-structured interview comprising 21 questions combines the description of information relating to a specific research project with an assessment of the subjects' abilities to understand and evaluate the information, their reasoning and decision making with regard to their participation in the research.

It should be paramount that the subjects grasp the basic ideas behind the project rather than merely repeating the information word for word. This includes understanding the degree to which they appreciate that their participation is voluntary, that withdrawal is possible without penalization, and that the objective of the research is not their own personal benefit but a generalizable one in the shape of knowledge. The threshold for considering a person capable of taking a decision should vary depending on its characteristics. Assessing this should involve a specific task and level of risk: an understanding of consent to participate in a simple study does not need to be as thorough than that required for a complex study involving greater risk. The literature recommends that decision-making be routinely evaluated in those studies with greater than minimum risk (Morán-Sánchez et al, 2016).

In 2013, a Spanish version of the MacCAT-CR was prepared by Baón, and a manual was subsequently published (Navío & Ventura, 2014) which takes into account the key points highlighted above and provides clinicians and researchers with a structured method to assist them in the informed consent process. However, it has not yet been widely used and assessments of decision-making capacity are still based on intuitive judgements. These tools could help reduce the vulnerability of addicted people participating in research, respecting their autonomy to decide when their capacity is preserved and establishing protective measures when it is not. Since we will occasionally come across people with wavering decision-making capacity, such measures may be very valuable.

Conflict of interests

The authors of this article declare no conflicts of interest.

References

American Psychiatric Association. (2014). *Manual Diagnóstico y Estadístico de los trastornos Mentales (DSM-5)* (5a.ed.). Madrid: Editorial Médica Panamericana.

Appelbaum, P.S. & Grisso, T. (2001). *MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research. Professional.* Sarasota, FL: Professional Resource.

Baón, B. (2013). *Adaptación y Validación Española de la Entrevista MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) y de un Cuestionario Breve para Evaluar la Capacidad de las Personas para Consentir Participar en Investigación* (tesis doctoral). Universidad Complutense de Madrid, Madrid. Retrieved from http://eprints.ucm.es/21253/1/T34444.pdf

Carter, A. & Hall, W. (2012). What is addiction? In Edwards G. (Ed.), *Addiction Neuroethics. The Promises and Perils of Neuroscience Research on Addiction* (pp. 19-34). New York, NY: Cambridge University Press.

Charland, L.C. (2002). Cynthia's dilemma: Consenting to heroin prescription. *The American Journal of Bioethics, 2*, 37-47. doi:10.1162/152651602317533686.

Morán-Sánchez, I., Luna, A., Sánchez, M., Aguilera, B. & Pérez-Cárceles, M.D. (2016). Decision-making Capacity for Research Participation among Addicted People: a cross-sectional study. *BMC Medical Ethics, 17*, 1-10. doi:10.1186/s12910-015-0086-9.

Morera, B. (2000). Aspectos bioéticos de la asistencia al drogodependiente. *Adicciones, 12*, 515-526. doi:10.20882/adicciones.662.

Navío, M. & Ventura, T. (2014). *Manual de Consulta en Valoración de la Capacidad.* Madrid: Editorial Médica Panamericana.

Nogué, S. & Miró, O. (2015). Núcleos y ámbitos de investigación sobre adicciones: necesidad de una visión más amplia. *Adicciones, 27*, 75-76. doi:10.20882/adicciones.195.

Real Decreto 1090/2015, de 4 de diciembre por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos. *Boletín Oficial del Estado.* Madrid, 24 de diciembre de 2015, núm.307, pp. 121923-121964.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

EL PROCESO DE REVISIÓN DEL MANUSCRITO

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

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

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

TREVICTA®
palmitato de paliperidona
suspensión inyectable de liberación prolongada

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

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

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

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

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

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

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

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

	Tiempo transcurrido desde la última dosis de TREVICTA		
	de la semana 12 a 13, incluida	de la semana 19 a la 24, incluida	desde la semana 25 y en adelante
Última dosis de TREVICTA (semana 0)	Dosis diaria de los comprimidos de paliperidona de liberación prolongada		
175 mg	3 mg	3 mg	3 mg
263 mg	3 mg	3 mg	6 mg
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

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

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

Dosis omitidas

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

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

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

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

Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia ni la seguridad en la población mayor de 65 años. En general, la dosis de TREVICTA recomendada en pacientes de edad avanzada con función renal normal es la misma que para los adultos más jóvenes con función renal normal. Dado que los pacientes de edad avanzada pueden presentar una reducción de la función renal, ver debajo en *Insuficiencia renal* las recomendaciones de dosificación para pacientes con insuficiencia renal. *Insuficiencia renal.* TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal (ver sección 5.2). En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se debe ajustar la dosis y se establizará el paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min). *Insuficiencia hepática.* No se ha estudiado el uso de TREVICTA en pacientes con insuficiencia hepática. Según la experiencia con paliperidona oral no es necesario ajustar la dosis en pacientes con insuficiencia hepática leve o moderada. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, por lo que se recomienda precaución en estos pacientes (ver sección 5.2). *Población pediátrica.* No se ha establecido la seguridad y eficacia de TREVICTA en niños y adolescentes menores de 18 años. No se dispone de datos. Forma de administración. TREVICTA está indicado para administración intramuscular únicamente. No se debe administrar por ninguna otra vía. Cada inyección se administrará sólo por un profesional sanitario, que administrará la dosis completa en una sola inyección. Se debe inyectar lenta y profundamente en el músculo deltoides o en el glúteo. Si aparecen molestias en el lugar de inyección, se considerará el cambio del glúteo al deltoides y viceversa en sucesivas inyecciones (ver sección 4.8). TREVICTA se debe administrar usando únicamente las agujas de pared fina que se facilitan en el envase de TREVICTA. Para la administración de TREVICTA no se utilizarán las agujas que se facilitan en el envase de la inyección mensual de palmitato de paliperidona ni otras agujas comercialmente disponibles (ver *Información reservada para médicos y profesionales sanitarios*). Se inspeccionará visualmente el contenido de la jeringa precargada para descartar la presencia de cuerpos extraños o decoloración antes de la administración. Es importante agitar enérgicamente la jeringa con la punta hacia arriba y la muñeca relajada durante al menos 15 segundos para garantizar una suspensión homogénea. TREVICTA debe ser administrado dentro de los 5 minutos siguientes a la agitación. Si transurren más de 5 minutos antes de la inyección, agitar otra vez enérgicamente durante al menos 15 segundos para resuspender el medicamento (ver *Información reservada para médicos o profesionales*). *Administración en el deltoides.* El tamaño especificado de la aguja para administración de TREVICTA en el músculo deltoides está determinado por el peso del paciente. • En pacientes de peso ≥90 kg, se debe utilizar la aguja de pared fina de 22 G 1 ½ (0,72 mm x 38,1 mm). • En pacientes de peso < 90 kg, se debe utilizar la aguja de pared fina de 22 G 1 (0,72 mm x 25,4 mm). Se debe administrar en el centro del músculo deltoides. Las inyecciones deltoideas se deben alternar entre los dos músculos deltoides. *Administración en el glúteo.* Para la administración de TREVICTA en el músculo glúteo, se utilizará la aguja de pared fina de 22 G 1½ (0,72 mm x 38,1 mm), sin tener en cuenta el peso corporal. La administración se debe hacer en el cuadrante superior externo del músculo glúteo. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. *Administración incompleta.* Para evitar la administración incompleta de TREVICTA, se debe agitar enérgicamente la jeringa precargada durante al menos 15 segundos en los 5 minutos que preceden a la administración para asegurar una suspensión homogénea (ver *Información reservada para médicos o profesionales sanitarios*). Sin embargo, si la dosis inyectada ha sido incompleta, la dosis restante de la jeringa no se debe reinyectar y no se debe administrar otra dosis debido la dificultad de calcular la proporción de la dosis que se administró realmente. Se vigilará estrechamente al paciente y se controlará clínicamente de forma apropiada hasta la siguiente inyección trimestral programada de TREVICTA. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en estados psicóticos graves o de agitación aguda. No se debe utilizar TREVICTA para controlar estados psicóticos graves o de agitación aguda en los que es necesario un control inmediato de los síntomas. Intervalo a QT. Se debe tener precaución al prescribir paliperidona a pacientes con enfermedad cardiovascular conocida o con antecedentes familiares de prolongación del QT y cuando se use a la vez que otros medicamentos que se espera que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos de Síndrome Neuroléptico Maligno (SNM) con paliperidona, que se caracteriza por hipertermia, rigidez muscular, inestabilidad autónoma, alteración de la consciencia y elevación de la creatinfosfoquinasa sérica. Otros síntomas clínicos incluyen mioglobinuria (rabdomiolisis) y fallo renal agudo. Si un paciente presenta signos o síntomas indicativos de SNM, se suspenderá la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Discinesia tardía. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, que se caracteriza por movimientos rítmicos involuntarios, predominantemente de la lengua y/o de la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la posibilidad de suspender la administración de todos los antipsicóticos, incluida la paliperidona. Se tendrá en cuenta la acción prolongada de TREVICTA. Leucopenia, neutropenia y agranulocitosis. Se han notificado acontecimientos de leucopenia, neutropenia y agranulocitosis en relación con paliperidona. Los pacientes con antecedentes de recuento de glóbulos blancos bajo clínicamente relevante o de leucopenia/neutropenia inducida por medicamentos se deben someter a vigilancia estrecha durante los primeros meses de tratamiento y se considerará la suspensión de TREVICTA ante el primer signo de leucopenia clínicamente relevante sin que intervengan otros factores causantes. A los pacientes con neutropenia clínicamente relevante se les monitorizará estrechamente a fin de detectar la aparición de fiebre u otros síntomas o signos de infección y, si se presentan estos síntomas, se administrará un tratamiento rápido. A los pacientes con neutropenia grave (recuento total de neutrófilos <1 x 10⁹/L) se les retirará la administración de TREVICTA y se les hará un seguimiento de los niveles de glóbulos blancos hasta su recuperación. Se tendrá en cuenta la acción prolongada de TREVICTA. Reacciones de hipersensibilidad. Se pueden producir reacciones de hipersensibilidad incluso en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.8). Hiperglucemia y diabetes mellitus. Se han notificado hiperglucemia, diabetes mellitus y exacerbación de una diabetes preexistente, incluso coma diabético y cetoacidosis con el uso de paliperidona. Se recomienda una vigilancia clínica adecuada, conforme a la práctica particular habitual. En los pacientes tratados con TREVICTA se vigilará la aparición de síntomas de hiperglucemia (como polidipsia, poliuria, polifagia y astenia) y los pacientes con diabetes mellitus deben ser monitorizados regularmente de un empeoramiento del control de la glucosa. Aumento de peso. Se han notificado casos de aumento significativos de peso relacionados con el uso de TREVICTA. El peso debe ser controlado con regularidad. Uso en pacientes con tumores dependientes de prolactina. Estudios de cultivo de tejidos indican que la prolactina puede estimular el crecimiento celular en tumores de mama humanos. Aunque hasta ahora no se ha demostrado una asociación clara con la administración de antipsicóticos en los estudios clínicos y epidemiológicos, se recomienda precaución en pacientes que tengan antecedentes clínicos relevantes. La paliperidona se debe utilizar con precaución en los pacientes con un tumor previsiblente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes, debido a su actividad bloqueante alfa-adrenérgica. En los ensayos clínicos de TREVICTA, el 0,3% de los pacientes notificaron reacciones adversas asociadas a hipotensión ortostática. TREVICTA se debe utilizar con precaución en pacientes con enfermedades cardiovasculares (p. ej., insuficiencia cardíaca, infarto o isquemia de miocardio, anomalías de la conducción), enfermedades cerebrovasculares o trastornos que predispongan al paciente a la hipotensión (p. ej., deshidratación o hipovolemia). Convulsiones. TREVICTA se debe utilizar con precaución en pacientes con antecedentes de convulsiones o de otros trastornos que puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona son más elevadas en pacientes con insuficiencia renal. En pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a < 80 ml/min), se ajustará la dosis y se estabilizará el paciente con palmitato de paliperidona inyectable mensual y después se hará la transición a TREVICTA. No se recomienda utilizar TREVICTA en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos de pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en estos pacientes. Pacientes de edad avanzada con demencia. TREVICTA no se ha estudiado en pacientes de edad avanzada con demencia. No se recomienda la administración de TREVICTA a pacientes de edad avanzada con demencia, debido al riesgo aumentado de mortalidad global y de reacciones adversas cerebrovasculares. La experiencia obtenida con risperidona que se describe a continuación se considera aplicable también a paliperidona. *Mortalidad global.* En un metanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, como risperidona, aripiprazol, olanzapina y quetiapina, tuvieron un aumento del riesgo de mortalidad en comparación con el placebo. En los tratados con risperidona, la mortalidad fue del 4% en comparación con el 3,1% de los pacientes que recibieron placebo. *Reacciones adversas cerebrovasculares.* En ensayos clínicos aleatorizados y controlados con placebo en los que pacientes con demencia recibieron tratamiento con algunos antipsicóticos atípicos como risperidona, aripiprazol y olanzapina se ha observado que el riesgo de reacciones adversas cerebrovasculares se multiplica por 3 aproximadamente. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y beneficios de prescribir TREVICTA a pacientes con enfermedad de Parkinson o con demencia con cuerpos de Lewy (DCL), porque ambos grupos tienen un mayor riesgo de Síndrome Neuroléptico Maligno y una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, embotamiento, inestabilidad postural y caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (entre ellos paliperidona) con efectos de bloqueo alfa-adrenérgico inducen priapismo. Se indicará al paciente que solicite asistencia médica urgente si el priapismo no se ha resuelto en el transurso de 4 horas. Regulación de la temperatura corporal. Se ha atribuido a los antipsicóticos la alteración de la capacidad del organismo de reducir la temperatura corporal central. Se recomienda tomar las medidas oportunas cuando se prescribe TREVICTA a pacientes que vayan a experimentar circunstancias que pueden contribuir a una elevación de la temperatura corporal central, p. ej., ejercicio intenso, exposición a calor extremo, tratamiento concomitante con medicamentos de actividad anticolinérgica o deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con el uso de antipsicóticos. Dado que los pacientes tratados con antipsicóticos presentan a menudo factores de riesgo adquirido de TEV, se identificarán todos los posibles factores de riesgo de TEV antes y en el transurso del tratamiento con TREVICTA, y se adoptarán medidas preventivas. Efecto anticolinérgico. En los estudios preclínicos con paliperidona se observó un efecto anticolinérgico. Si se produce este efecto en los seres humanos, puede aumentar los signos y síntomas de la sobredosis de determinados medicamentos o de trastornos como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de TREVICTA en un vaso sanguíneo. Síndrome del iris flácido intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1A-adrenérgico, como TREVICTA (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir TREVICTA con medicamentos que prolongan el intervalo QT, como antiarrítmicos de la clase IA (por ejemplo, quinidina o disopiramida) y antiarrítmicos de la clase III (por ejemplo, amiodarona o sotalol), algunos antihistamínicos, antibióticos (por ejemplo, fluoroquinolonas), algunos antipsicóticos y algunos antipalúdicos (por ejemplo, mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que TREVICTA afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos metabolizados por las isoenzimas del citocromo P-450. Dado que paliperidona actúa principalmente sobre el sistema nervioso central (SNC) (ver sección 4.8), se debe usar con precaución la combinación de TREVICTA con otros medicamentos que actúan sobre el sistema nervioso central, como los ansiolíticos, la mayoría de los antipsicóticos, los hipnóticos, los opiáceos etc. o el alcohol. La paliperidona puede antagonizar el efecto de la levodopa y de otros agonistas de la dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se prescribirá la dosis mínima eficaz de cada tratamiento. Debido a su capacidad de inducir hipotensión ortostática (ver sección 4.4), es posible observar un efecto aditivo cuando se administra TREVICTA con otros medicamentos que tienen esta capacidad, como otros antipsicóticos o los antidepresivos tricíclicos. Se recomienda precaución al combinar la paliperidona con otros medicamentos que disminuyen el umbral convulsivo (por ejemplo, fenotiazinas o butirofenonas, antidepresivos tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de los comprimidos de liberación prolongada de paliperidona en el estado estacionario (12 mg una vez al día) con comprimidos de liberación prolongada de valproato sódico (de 500 mg a 2.000 mg una vez al día), no afectó a la farmacocinética en el estado estacionario del valproato. No se han llevado a cabo estudios de interacción entre TREVICTA y el litio, sin embargo, no es probable que se produzcan una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a TREVICTA. Los estudios in vitro indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios in vitro ni in vivo de que esas isoenzimas desempeñen un papel importante en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración conjunta de paliperidona oral de liberación prolongada una vez al día con carbamazepina 200 mg dos veces al día produjo una reducción de aproximadamente un 37% de los valores medios de C_{max} y AUC en estado estacionario de paliperidona. Esta disminución se debe, en gran parte, a un aumento del 35% de la depuración renal de paliperidona, probablemente como consecuencia de la inducción de la gp-P renal por carbamazepina. Una disminución menor de la cantidad de principio activo excretado inalterado en la orina sugiere que hubo un efecto mínimo sobre el metabolismo de CYP a la biodisponibilidad de paliperidona durante la administración concomitante de carbamazepina. Con dosis más altas de carbamazepina podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al iniciar el tratamiento con carbamazepina se debe revisar, y aumentar si es necesario, la dosis de TREVICTA. Por el contrario, al suspender el uso de carbamazepina se debe volver a evaluar la dosis de TREVICTA y reducirse en caso necesario. Se tendrá en cuenta la acción prolongada de TREVICTA. La administración concomitante de una dosis única oral de paliperidona en forma de comprimidos de liberación prolongada de 12 mg con comprimidos de liberación prolongada de valproato sódico (dos comprimidos de 500 mg una vez al día) produjo un incremento de aproximadamente el 50% en los valores de C_{max} y AUC de paliperidona, probablemente debido al aumento de la de la absorción oral. Dado que no se han observado efectos sobre el aclaramiento sistémico, no es previsible una interacción clínicamente relevante entre los comprimidos de liberación prolongada de valproato sódico y la inyección intramuscular de TREVICTA. No se ha estudiado esta interacción con TREVICTA. Uso concomitante de TREVICTA con risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando TREVICTA sea administrado de forma conjunta con risperidona o con paliperidona oral durante periodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de TREVICTA con otros antipsicóticos son limitados. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona en mujeres embarazadas. El palmitato de paliperidona en inyección intramuscular y la paliperidona en administración oral no mostraron efectos teratogenos en estudios realizados en animales, pero se observaron otros tipos de toxicidad para la reproducción (ver sección 5.3). Los neonatos expuestos a paliperidona durante el tercer trimestre del embarazo tienen riesgo de sufrir reacciones adversas después del parto, entre ellas síntomas extrapiramidales y/o de abstinencia de intensidad y duración variables. Se han descrito casos de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultar respiratoria o trastornos de alimentación. En consecuencia, se recomienda una vigilancia estrecha del recién nacido. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque la exposición mediante a TREVICTA antes y durante el embarazo podría provocar reacciones adversas en los recién nacidos. Lactancia. La paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administre en dosis terapéuticas a mujeres lactantes. Debido a que se ha detectado paliperidona en el plasma hasta 18 meses después de administrar una dosis única de TREVICTA, se tendrá en cuenta la acción prolongada de TREVICTA, porque los lactantes podrían estar en riesgo incluso si la administración de TREVICTA es muy anterior a la lactancia. TREVICTA no se debe utilizar durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la visión, como sedación, somnolencia, síncope o visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a TREVICTA. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas del medicamento observadas con mayor frecuencia notificados en 2≥1% de los pacientes en dos ensayos clínicos controlados a doble ciego de TREVICTA, fueron aumento de peso, infección de las vías respiratorias altas, ansiedad, cefalea, insomnio y reacción en el lugar de inyección. Tabla de reacciones adversas. A continuación se recogen todas las RAM notificadas con paliperidona en función de la frecuencia estimado en los ensayos clínicos realizados con TREVICTA y con palmitato de paliperidona inyectable mensual. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1.000 a <1/100), *raras* (≥1/10.000 a <1/1.000), *muy raras* (<1/10.000) y *frecuencia no conocida* (no se puede estimar a partir de los datos disponibles).

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

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

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

Reacciones adversas observadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de la risperidona, de modo que los perfiles de reacciones adversas de estas sustancias (incluidas las formulaciones orales e inyectables) son relevantes entre sí. *Descripción de algunas reacciones adversas. Reacción anafiláctica.* Durante la experiencia poscomercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de palmitato de paliperidona mensual en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). *Reacciones en el lugar de la inyección.* En los ensayos clínicos de TREVICTA, el 5,3% de los pacientes notificaron reacciones adversas en el lugar de inyección. Ninguno de estos acontecimientos fue grave o motivó la suspensión del tratamiento. Según la clasificación realizada por los investigadores, síntomas como inducración, rubefacción e hinchazón no se presentaron a fuerzas leves en ≥95% de los evaluaciones. El dolor en el lugar de inyección valorado por el paciente en una escala analógica visual era escaso, y su intensidad disminuía con el tiempo. *Síntomas extrapiramidales (SEP).* En los ensayos clínicos de TREVICTA se notificaron acatisia, discinesia, distonía, parkinsonismo y temblor en el 3,9%, 0,8%, 0,5%, 3,6% y 1,4% de los pacientes, respectivamente. Los síntomas extrapiramidales (SEP) incluyeron los siguientes términos: parkinsonismo (mostrano extrapiramidal), síntomas extrapiramidales, fenómeno on-off, enfermedad de Parkinson, crisis parkinsoniana, hipersecreción salival, rigidez osteomuscular, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipocinesia, fobias en máscara, tirantez muscular, acinesia, rigidez nucal, rigidez muscular, marcha parkinsoniana, reflejo glabelar alterado y temblor parkinsoniano en reposo); acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (incluye discinesia, corea, trastornos del movimiento, espasmos musculares, coreoatetosis, atetosis y mioclonía), distonía (incluye distonía, espasmo cervical, espasmo facial, crisis oculógiras, distonía bucomandibular, risa sardónica, tetania, hipertonía, tortícolis, contracciones musculares involuntarias, contractura muscular, blefarospasmo, oculogiración, parálisis lingual, espasmo facial, faringoespasmo, miotonía, opistótonos, espasmo bucofaríngeo, pleurostótonos, espasmo lingual y trismus) y temblor. *Aumento de peso.* En el estudio a largo plazo de retirada aleatorizada, se notificaron aumentos anormales de ≥7% de peso corporal desde el momento inicial hasta el momento final del estudio, analizados a doble ciego, en el 10% de los pacientes del grupo de TREVICTA y el 11% de los pacientes del grupo de placebo. A la inversa, se notificaron reducciones anormales del peso corporal (≥7%) desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, en el 11% de los pacientes del grupo de TREVICTA y el 8% de los pacientes del grupo de placebo. Las variaciones medias del peso corporal desde el momento inicial hasta el momento final en un estudio doble ciego controlado con placebo, fueron de −0,94 kg y −1,28 kg en los grupos de TREVICTA y placebo, respectivamente. *Hiperprolactinemia.* Durante la fase de doble ciego del estudio a largo plazo de retirada aleatorizada, se observaron niveles de prolactina por encima del intervalo de referencia (>13,13 ng/ml en los varones y >26,72 ng/ml en las mujeres) en un porcentaje más elevado de varones y mujeres del grupo de TREVICTA que del grupo placebo (9% frente a 3% y 5% frente a 1%, respectivamente). En el grupo de TREVICTA, la variación media entre el momento inicial y el final en un estudio doble ciego controlado con placebo fue de +2,90 ng/ml para los varones (frente a -10,26 ng/ml en el grupo placebo) y de −7,48 ng/ml para las mujeres (frente a -32,93 ng/ml en el grupo placebo). Una mujer (2,4%) del grupo de TREVICTA tuvo una reacción adversa de amenorrea, mientras que no se observaron reacciones adversas potencialmente relacionadas con la prolactina en ninguna mujer del grupo placebo. No hubo reacciones adversas potencialmente relacionadas con la prolactina en ninguno de los grupos de varones. *Efecto de clase.* Con el uso de antipsicóticos pueden aparecer prolongación del intervalo QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicada, paro cardíaco y torsades de pointes. Se han notificado casos de TEV, entre ellos de embolia pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos. Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del QT y síntomas extrapiramidales. Se han descrito Torsades de pointes y fibrilación ventricular en un paciente expuesto a sobredosis de paliperidona oral. En caso de sobredosis aguda se debe tener en cuenta la posibilidad de que estén implicados varios fármacos. Tratamiento. Al evaluar las medidas terapéuticas y de recuperación, se tendrán en cuenta la naturaleza de liberación prolongada del medicamento, así como la prolongada vida media de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el trastorno circulatorio se deben tratar con las medidas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales graves, se debe administrar medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos y continuos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros fármacos antipsicóticos, código ATC: N05AX13. TREVICTA contiene una especie isomérica de paliperidona (+)y(−). *Mecanismo de acción.* Paliperidona es un agente bloqueante selectivo de los efectos de los monoaminas cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une estrechamente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D-2. Asimismo, paliperidona bloquea los receptores alfa 1 adrenérgicos y, en menor medida, los receptores histaminérgicos H-1 y los receptores alfa 2 adrenérgicos. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque se trata de un potente antagonista de D2, motivo por el que se cree que alivia los síntomas de la esquizofrenia, produce menos catalepsia y menos reducción de las funciones motoras que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede disminuir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. La eficacia de TREVICTA para el tratamiento de mantenimiento de la esquizofrenia en pacientes que han sido tratados adecuadamente durante al menos 4 meses con la formulación inyectable mensual de palmitato de paliperidona y las últimas dos dosis de la misma concentración se evaluó en un estudio a largo plazo de retirada aleatorizado, doble ciego y controlado con placebo y en un estudio de no inferioridad a largo plazo, doble ciego y controlado con fármaco activo. En ambos estudios, el criterio de valoración principal era la recaída. En el estudio a largo plazo de retirada aleatorizado, 526 pacientes adultos que cumplían los criterios DSM-IV de esquizofrenia se incorporaron en la fase abierta de transición y recibieron dosis flexibles de palmitato de paliperidona inyectable mensual administradas en el músculo deltoides o glúteo (50-150 mg) durante 17 semanas (los ajustes de dosis fueron en las semanas 5 y 9). Un total de 379 pacientes recibieron una dosis única de TREVICTA en el músculo deltoides o glúteo durante la fase de estabilización abierta (la dosis era 3,5 veces la última dosis de palmitato de paliperidona mensual). Los pacientes que se consideraban clínicamente estabilizados al final de la fase de estabilización de 12 semanas se aleatorizaron en proporción 1:1 para recibir TREVICTA o un placebo en una fase doble ciego de duración variable (la dosis de TREVICTA fue la misma que la última dosis recibida durante la fase de estabilización; esta dosis se mantuvo fija durante toda la fase de doble ciego). En este periodo, 305 pacientes sintomáticamente estables fueron aleatorizados para continuar el tratamiento con TREVICTA (n=160) o placebo (n=145) hasta que se produjese la recaída, la retirada prematura o el final del estudio. La variable principal de eficacia fue el tiempo hasta la primera recaída. Se pasó fin al estudio de acuerdo a un análisis intermedio preestablecido llevado a cabo cuando 233 pacientes habían sido aleatorizados y se habían observado 42 casos de recaída. Teniendo en cuenta el análisis final (N=305), 42 pacientes (29,0%) en el grupo de placebo y 14 pacientes (8,8%) en el grupo de TREVICTA habían experimentado un acontecimiento de recaída durante la fase de doble ciego. La razón de riesgos (hazard ratio) fue 3,31 (IC del 95%: 2,08; 6,99) lo que indica una disminución del 74% del riesgo de recaída con TREVICTA en comparación con placebo. En la figura 1 se representa la gráfica de Kaplan-Meier del tiempo hasta la recaída para cada grupo de tratamiento. Se observó una diferencia significativa (p<0,0001) entre los dos grupos de tratamiento en el tiempo hasta la recaída a favor de TREVICTA. El tiempo hasta la recaída en el grupo de placebo (mediana a 395 días) fue significativamente más corto que en el grupo de TREVICTA (no fue posible calcular la mediana debido al bajo porcentaje de pacientes con recaída [8,8%]).

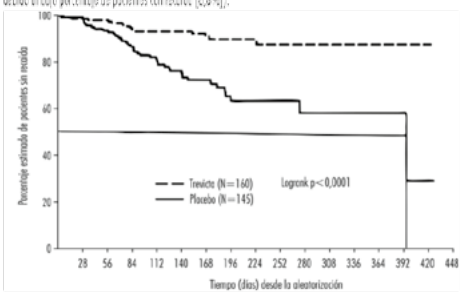


Figura 1. Gráfico de Kaplan-Meier del tiempo hasta la recaída – Análisis final

En el estudio de no inferioridad, 1.429 pacientes con enfermedad aguda (puntuación PANSS total media en el momento inicial: 85,7) que cumplían los criterios DSM-IV de esquizofrenia se incorporaron a la fase abierta y recibieron tratamiento con palmitato de paliperidona inyectable mensual durante 17 semanas. Se permitía ajustar la dosis (entre 50 mg, 75 mg, 100 mg o 150 mg) después de 5 semanas y 9 inyecciones y el lugar de inyección podía ser el deltoides o el glúteo. De los pacientes que cumplían los criterios de aleatorización en las semanas 14 y 17, 1.016 fueron aleatorizados en proporción 1:1 para seguir recibiendo una vez al mes la inyección de palmitato de paliperidona mensual o bien cambiar a TREVICTA, multiplicando por 3,5 la dosis de las semanas 9 y 13 de palmitato de paliperidona inyectable mensual, durante un periodo de 49 semanas. Los pacientes recibían TREVICTA una vez cada 3 meses y una medicación inyectable placebo durante los meses restantes para mantener el ciego. En este estudio, el criterio de valoración principal era el porcentaje de pacientes sin recaída al final de la fase doble ciego de 48 semanas, basado en la estimación de Kaplan-Meier de los 48 semanas (TREVICTA: 91,2%; palmitato de paliperidona inyectable mensual: 90,0%). No fue posible calcular la mediana de tiempo hasta la recaída en ninguno de los grupos, dado el escaso porcentaje de pacientes con recaídas. La diferencia (IC 95%) entre los grupos de tratamiento fue del 1,2% (-2,7%, 5,1%), lo que satisface el criterio de no inferioridad basado en un margen de -10%. Por tanto, el grupo de tratamiento con TREVICTA fue no inferior al grupo tratado con palmitato de paliperidona inyectable mensual. Las mayorías funcionales, determinadas según la Escala de Funcionamiento Personal y Social (PSP), que se observaron durante la fase de estabilización abierta se mantuvieron durante la fase de doble ciego en ambos de tratamiento.

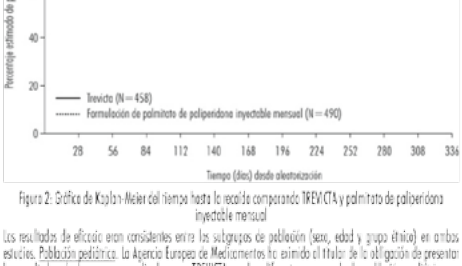


Figura 2: Gráfico de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido el titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** *Absorción y distribución.* Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA con lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{max}. La relación media pico-valle en el estado estacionario para una dosis de TREVICTA es de 1,6 después de la administración en el glúteo y de 1,7 después de la administración en el músculo deltoides. La paliperidona reclínica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (-) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (−) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza intensivamente en el hígado. Se recuperó aproximadamente el 80% de la radioactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 10% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se sugirieron que los enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos *in vivo* de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observa ninguna diferencia conocable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentes de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2B6/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP2C8. Estudios *in vitro* han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos *in vivo* y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. *Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona.* TREVICTA está diseñado para liberar paliperidona durante un periodo de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces mas altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. *Insuficiencia hepática.* Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (ClCr=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (ClCr=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (ClCr=10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{∞}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con personas sanas. Población de edad avanzada. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con la edad. Índice de masa corporal (IMC)/peso corporal. En los pacientes obesos y con sobrepeso se observaron valores de C_{ss} más bajos. En el estado estacionario aparente de TREVICTA, las concentraciones valle eran similares en los pacientes normales, con sobrepeso y obesos. *Raza.* El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el origen racial. *Sexo.* El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el sexo. *Tabaquismo.* Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no tiene un efecto en la farmacocinética de paliperidona. El efecto del consumo de tabaco sobre la farmacocinética de paliperidona no se ha estudiado en el caso de TREVICTA. Un análisis de farmacocinética poblacional basado en los datos obtenidos con comprimidos de liberación prolongada de paliperidona demostró una exposición a paliperidona ligeramente más baja en los fumadores que en los no fumadores. No es probable que este diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) en inyección intramuscular y de paliperidona en administración oral a ratas y perros mostraron efectos fundamentalmente farmacológicos, como sedación y efectos mediados por la prolactina en glándulas mamarias y genitales. En animales tratados con palmitato de paliperidona se observó una reacción inflamatoria en el lugar de inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas con risperidona oral, que se convierte en gran medida en paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y en la supervivencia de las crías. No se han observado embriotoxicidad ni malformaciones después de la administración intramuscular de palmitato de paliperidona a ratas gestantes a dosis máximas (160 mg/kg/día), equivalentes a 2,2 veces el nivel de exposición de los humanos a la dosis máxima recomendada de 525 mg. Otras antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la methidiol y del aprendizaje en las crías cuando se administraron a animales gestantes. Ni el palmitato de paliperidona ni la paliperidona han demostrado ser genotóxicos. En estudios sobre el potencial carcinogénico de la risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (rata), de los adenomas del páncreas endocrino (rata) y de los adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico del palmitato de paliperidona administrado en inyección intramuscular a ratas. Se observó un incremento estadísticamente significativo de adenocarcinomas de las glándulas mamarias en ratas hembra a las que se administraron dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho experimentaron un incremento estadísticamente significativo de adenomas y carcinomas de las glándulas mamarias cuando se expusieron a dosis de 30 y 60 mg/kg/mes, que representan 0,6 y 1,2 veces el nivel de exposición humana a la dosis máxima recomendada de 525 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la relevancia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACEÚTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajustar el pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina cíclica) con émbolo, tapa-husera y capuchón protector (goma bromobutílica), equipada con una aguja de seguridad de pared fina de 22 G 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 pulgadas (0,72 mm x 25,4 mm). Formato del envase: Envases con 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 515,00 €; PVP: 570,91 €; PVP (IVA): 593,75 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 673,00 €; PVP: 725,91 €; PVP (IVA): 754,95 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 924,00 €; PVP: 879,91 €; PVP (IVA): 915,11 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.236,00 €; PVP: 1.291,91 €; PVP (IVA): 1.343,59 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas de uso y manejo de TREVICTA (*Ver Información reservada para médicos o profesionales sanitarios*). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007 EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 5 de diciembre de 2014. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 09/2016. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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

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

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

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). Dosis omitidas. ***Medidas para evitar la omisión de dosis.*** Se recomienda que la segunda dosis de inicición de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y las siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8 ± 4 días), el momento se reinicia recomendada dependerá del tiempo que haya transcurrido desde la primera inyección del paciente. ***Omisión de la segunda dosis de iniciación (<4 semanas desde la primera inyección).*** Si han transcurrido menos de 4 semanas desde la primera inyección, se le debe administrar al paciente la segunda inyección de 100 mg en el músculo deltoides tan pronto como sea posible. Se debe administrar una tercera inyección de Xeplion en 25 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo. ***Omisión de la segunda dosis de iniciación (entre 4 y 7 semanas desde la primera inyección).*** Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xeplion, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo. Se 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. ***Omisión de la segunda dosis de iniciación (>7 semanas desde la primera inyección).*** Si han transcurrido más de 7 semanas desde la primera inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. ***Omisión de la dosis de mantenimiento mensual (1 mes a 6 semanas).*** Tras la iniciación, el ciclo de inyección recomendado de Xeplion es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. ***Omisión de la dosis de mantenimiento mensual (>6 semanas a 6 meses).*** Si han transcurrido más de 6 semanas desde la última inyección de Xeplion, la recomendación es la siguiente: ***Para los pacientes estabilizados con dosis de 25 a 100 mg.*** 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. ***Para los pacientes estabilizados con 150 mg.*** 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. ***Omisión de la dosis de mantenimiento mensual (>6 meses).*** Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. ***Población de edad avanzada.*** No se ha establecido la eficacia y la seguridad en la población de edad avanzada >65 años. En general, la dosis recomendada de Xeplion en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (*ver **Insuficiencia renal*** más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). ***Insuficiencia renal.*** No se ha estudiado Xeplion sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se recomienda iniciar Xeplion con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambas administradas en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina < 50 ml/min) (ver sección 4.4). ***Insuficiencia hepática.*** Basándose en la experiencia con paliperidona oral, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve a moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes (ver sección 5.2). ***Población pediátrica.*** No se ha establecido la seguridad y la eficacia de Xeplion en niños y adolescentes <18 años de edad. No hay datos disponibles. Forma de administración. Xeplion se utiliza únicamente para uso intramuscular. No se debe administrar por ninguna otra vía. Se debe inyectar lentamente, profundamente en el músculo deltoides o en el glúteo. Cada inyección debe ser administrada por un profesional sanitario. La administración debe realizarse en una sola inyección. La dosis no se debe administrar en inyecciones divididas. Las dosis de iniciación del día 1 y del día 8 se deben administrar ambas en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. Se debe cambiar del glúteo al deltoides (y viceversa) en caso de dolor en el lugar de inyección si no se tolera bien el malestar en el lugar de inyección (ver sección 4.8). También se recomienda alternar entre los lados izquierdo y derecho (ver más adelante). Para consultar las instrucciones de uso y manipulación de Xeplion, ver prospecto (información destinada únicamente a médicos o profesionales del sector sanitario). ***Administración en el músculo deltoides.*** El tamaño de la aguja recomendado para la administración inicial y de mantenimiento de Xeplion en el músculo deltoides viene determinado por el peso del paciente. En los pacientes ≥90 kg, se recomienda la aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). En los pacientes <90 kg, se recomienda la aguja de calibre 23 de 1 pulgada (25,4 mm x 0,64 mm). Las inyecciones en el deltoides se deben alternar entre los dos músculos deltoides. ***Administración en el músculo glúteo.*** El tamaño de la aguja recomendado para la administración de mantenimiento de Xeplion en el músculo glúteo es el de una aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). La administración se debe realizar en el cuadrante superior externo de la zona glútea. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en pacientes que se encuentran en un estado sumamente agitado o psicótico grave. Xeplion no se debe utilizar para el tratamiento de estados agitados agudos o psicóticos graves cuando esté justificado el control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al recetar paliperidona a pacientes con enfermedad cardiovascular conocida o antecedentes familiares de prolongación del intervalo QT, y en caso de uso concomitante con otros medicamentos que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos del Síndrome Neuroléptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la consciencia y elevación de los niveles séricos de creatina fosfocinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiolisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de paliperidona. Discinesia tardía. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (< 1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB en ausencia de otras factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados para la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento basal de neutrófilos <1x10⁹/L) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia post-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si aparecen reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre existente que induce coma diabético y cetoacidosis, durante el tratamiento con paliperidona. Se recomienda una monitorización clínica coherente de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con Xeplion se les deben monitorizar los síntomas de la hiperglucemia (tales como polidipsia, poliuria, polifagia y debilidad) y los pacientes con diabetes mellitus se les debe monitorizar regularmente el empeoramiento del control de glucosa. Aumento de peso. Se ha notificado un aumento de peso significativo con el uso de Xeplion. El peso debe controlarse regularmente. Uso en pacientes con tumores dependientes de prolactina. Los estudios de cultivo de tejidos sugieren que la prolactina puede estimular el crecimiento de células en los tumores de mama humanos. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona se debe utilizar con precaución en pacientes con un tumor preexistente que pueda ser dependiente de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes sobre la base de su actividad alfa-1 bloqueante. Según los datos agrupados de las tres ensayos controlados con placebo, de dosis fijas y 6 semanas de duración con comprimidos orales de paliperidona de liberación prolongada (3, 6, 9 y 12 mg), el 2,5% de los pacientes tratados con paliperidona oral comunicaron hipotensión ortostática, en comparación con el 0,8% de los sujetos tratados con placebo. Xeplion debe utilizarse con precaución en pacientes con enfermedad cardiovascular conocida (p. ej., insuficiencia cardíaca, infarto de miocardio o isquemia, trastornos de la conducción), enfermedad cerebrovascular o afecciones que predispongan al paciente a la hipotensión (p. ej. deshidratación e hipovolemia). Convulsiones. Xeplion debe utilizarse con precaución en pacientes con antecedentes de convulsiones u otros trastornos que potencialmente puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona aumentan en pacientes con insuficiencia renal y por tanto, se recomienda un ajuste de la dosis en pacientes con insuficiencia renal leve. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina < 50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos en pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en dichos pacientes. Pacientes de edad avanzada con demencia. No se ha estudiado Xeplion en pacientes de edad avanzada con demencia. Xeplion se debe utilizar con precaución en pacientes de edad avanzada con demencia y con factores de riesgo de padecer ictus. La experiencia con risperidona oral más adelante se considera válida también para paliperidona. ***Mortalidad global.*** En un metanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, tales como risperidona, aripiprazol, olanzapino y quetiapina, tenían un mayor riesgo de mortalidad en comparación con placebo. Entre los pacientes tratados con risperidona, la mortalidad fue del 4% frente al 3,1% con placebo. ***Reacciones adversas cerebrovasculares.*** Se ha observado un aumento de aproximadamente 3 veces del riesgo de reacciones adversas cerebrovasculares en los ensayos clínicos aleatorizados controlados con placebo en la población con demencia al utilizar algunos antipsicóticos atípicos, tales como risperidona, aripiprazol y olanzapina. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y los beneficios de prescribir Xeplion a los pacientes con enfermedad de Parkinson o Demencia con Cuerpos de Lewy (DCL), ya que ambos grupos pueden tener mayor riesgo de padecer Síndrome Neuroléptico Maligno, así como tener una mayor sensibilidad a los antipsicóticos. Los manifestaciones de este aumento de la sensibilidad pueden incluir confusión, obnubilación, inestabilidad postural con caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (incluida risperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Durante la vigilancia post-comercialización, también se han notificado casos de priapismo con paliperidona oral, que es el metabolito activo de risperidona. Se ha de informar a los pacientes de la necesidad de acudir al médico urgentemente en caso de que el priapismo no haya sido resuelto en la transcurso de 4 horas. Regulación de la temperatura del organismo. Se ha atribuido a los medicamentos antipsicóticos la interrupción de la capacidad del organismo para reducir la temperatura corporal central. Se aconseja proceder con especial cautela cuando se prescriba Xeplion a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej. ejercicio físico intenso, exposición a calor extremo, que reciben medicamentos concomitantes con actividad anticolinérgica o que estén sujetos a deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con medicamentos antipsicóticos. Dado que los pacientes tratados con antipsicóticos suelen presentar factores de riesgo adquiridos de TEV, se han de identificar todos los posibles factores de riesgo de TEV antes y durante el tratamiento con Xeplion y adoptar medidas preventivas. Efecto antiemético. Se observó un efecto antiemético en los estudios preclínicos con paliperidona. Esta efecto, si se produce en humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de enfermedades como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de Xeplion en un vaso sanguíneo. Síndrome de Iris Flácido Intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1-adrenérgico, como Xeplion (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir Xeplion con medicamentos que prolonguen el intervalo QT, p. ej. antiarrítmicos de clase IA (p. ej., quinidina, disopiramida) y antiarrítmicos de clase III (p. ej. amiodarona, sotalol), algunos antihistamínicos, algunos otros antipsicóticos y algunos antipalúdicos (p. ej. mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que Xeplion afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos que sean metabolizados por las isoenzimas del citocromo P-450. Dado que los efectos principales de paliperidona se ejercen sobre el sistema nervioso central (SNC) (ver sección 4.8), Xeplion debe utilizarse con precaución en combinación con otros medicamentos de acción central, p. ej., ansiolíticos, la mayoría de los antipsicóticos, hipnóticos, opiáceos, etc. o con el alcohol. Paliperidona puede antagonizar el efecto de levodopa y otros agonistas de dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se debe recetar la dosis mínima eficaz de cada tratamiento. Debido a la posibilidad de que induzca hipotensión ortostática (ver sección 4.4), se puede observar un efecto aditivo si se combina con fármacos que también tengan esta posibilidad, p. ej., otros antipsicóticos, triciclicos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenotiazinas o butirofenonas, triciclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de comprimidos orales de paliperidona de liberación prolongada en estado estacionario (12 mg una vez al día) con comprimidos de divalproex sódico de liberación prolongada (de 500 mg a 2000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xeplion y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a Xeplion. Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vitro ni in vivo* de que esas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{ss} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad de principio activo inalterada excretada en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP o en la biodisponibilidad de paliperidona. Con dosis más altas de carbamazepina, podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al inicio del tratamiento con carbamazepina, se debe reevaluar y aumentar la dosis de Xeplion, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xeplion, si es necesario. La administración concomitante de una sola dosis de un comprimido de paliperidona oral de liberación prolongada de 12 mg con comprimidos de divalproex sódico de liberación prolongada (dos comprimidos de 500 mg una vez al día) tuvo como resultado un aumento de aproximadamente el 50% en la C_{max} y el AUC de paliperidona, probablemente como resultado de un aumento de la absorción oral. Dado que no se observó ningún efecto sobre el aclaramiento sistémico, no se espera que se produzca una interacción clínicamente significativa entre los comprimidos de divalproex sódico de liberación prolongada y la inyección intramuscular de Xeplion. Esta interacción no se ha estudiado con Xeplion. Uso concomitante de Xeplion y risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando Xeplion sea administrado de forma conjunta con risperidona o con paliperidona oral durante periodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrado por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a paliperidona durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xeplion no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas o medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblor, dolor abdominal, vómitos, diarrea, fatiga y distonía. De estos, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con palmitato de paliperidona. Se aplican los siguientes términos y frecuencias: ***muy frecuentes*** (≥1/10); ***frecuentes*** (≥1/100 a <1/10); ***poco frecuentes*** (≥1/1.000 a <1/100); ***raras*** (≥1/10.000 a <1/1.000); ***muy raras*** (<1/10.000); y ***frecuencia no conocida*** (no puede estimarse a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento				
	Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raros	No conocidas*
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, otitis, infección de oídos, amigdalitis, candidiasis, celulitis	infección de ojos, dermatomicosis, absceso subcutáneo	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, trombocitopenia, anemia	neutropenia, recuento de eosinófilos aumentado	agranulocitosis
Trastornos del sistema inmunológico			hipersensibilidad		reacción anafiláctica
Trastornos endocrinos		hiperprolactinemia†		secreción inapropiada de la hormona antidiurética, presencia de glucosa en orina	
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, disminución de peso, apetito disminuido	diabetes mellitus‡, hiperinsulinemia, aumento del apetito, anorexia, aumento de los triglicéridos en sangre, aumento del colesterol en sangre	cetoacidosis diabética, hipoglucemia, polidipsia	intoxicación por agua
Trastornos psiquiátricos	insomnio†	agitación, depresión, ansiedad	trastorno del sueño, manía, disminución de la libido, nerviosismo, pesadillas	estado confusional, embotamiento afectivo, orgasmo	
Trastornos del sistema nervioso		parkinsonismo†, acatisia†, sedación/somnolencia, distonía†, mareos, discinesia†, temblor, cefalea	discinesia tardía, síncope, hiperactividad psicomotora, marcha postural, alteración de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, sin respuesta a estímulos, pérdida de la consciencia, disminución del nivel de consciencia, convulsión†, trastorno del equilibrio, coordinación anormal	coma diabético, temblor cefálico en reposo
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma, trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	síndrome del iris flácido (intraoperatorio)
Trastornos del oído y del laberinto			vértigo, acufenos, dolor de oído		
Trastornos cardíacos		taquicardia	bloqueo auriculoventricular, trastorno de conducción, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, bradicardia, anomalías del electrocardiograma, palpitaciones	fibrilación auricular, arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipertensión ortostática	hemtosis venosa, rubor	embolismo pulmonar, isquemia
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión del tracto respiratorio, sibilancias, dolor faringolaríngeo, epistaxis	síndrome de apnea del sueño, congestión pulmonar, estertores	hiperventilación, neumonía por aspiración, disfonía
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, disfagia, sequedad de boca, flatulencia	pancreatitis, hinchazón de la lengua, incontinencia fecal, fecaloma, queilitis	obstrucción del intestino, íleo
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas		ictericia

Trastornos de la piel y del tejido subcutáneo			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	rabdomiolisis, inflamación de las articulaciones	anomalía postural
Trastornos renales y urinarios			incontinencia urinaria, poliaquiuria, 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*, 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, asenia, fatiga, reacción en el lugar de la inyección	edema facial, edema†, 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, abceso 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, ulceración en el lugar de la inyección
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

*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 posmercantilización y la frecuencia no se puede determinar, a proceden de datos de ensayos clínicos con risperidona (cualquier formulación) o con paliperidona oral. †Referida a "hiperprolactinemia" a continuación. ‡Referido a "Síntomas extrapiramidales" a continuación. §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 estas compuestas (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. Descripción de algunas reacciones adversas. ***Reacción anafiláctica.*** Durante la experiencia post comercializacion, en raros ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de Xeplion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). ***Reacciones en el lugar de la inyección.*** La reacción adverse 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. Los 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, marcha de andar parkinsoniano y reflejo de la glabella anormal, temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hiperactividad y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreoatetosis, atetosis y miodistonía), distonía (incluye distonía, hipertonía, tortícolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistotonos, 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 recaídas 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 (4,77) kg. ***Hiperprolactinemia.*** En ensayos clínicos, se observaron medianas de cumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un cumento 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, crítimias 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 crítimias. La hipotensión y el trastorno circulatorio deben tratarse con los medidos terapéuticos adecuados, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales intensos, se administrará medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros antipsicóticos. Código ATC: N05AX13. Xeplion contiene una mezcla racémica de paliperidona (+) y (-). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une fuertemente 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 el 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 (una de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recaída 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 coloandos durante el tratamiento agudo de la esquizofrenia con Xeplion. El criterio principal de eficacia del estudio se definió como una reducción de los 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 todo 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 crojeron resultados estadísticamente significativos a favor de Xeplion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

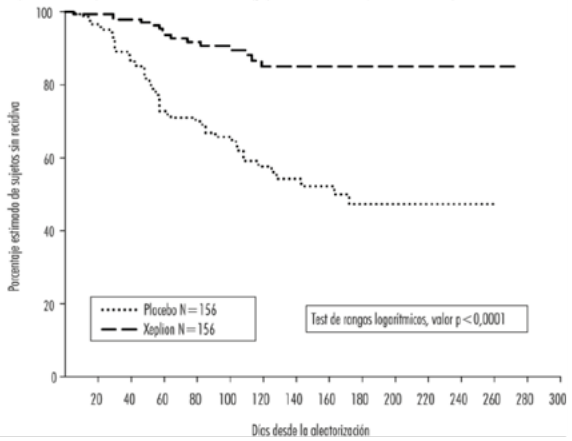
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración 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 (12,35)	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 periodo de extensión abierta 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 periodo de transición de 9 semanas de duración, seguido de un periodo de mantenimiento de 24 semanas, en el que los sujetos debían tener una puntuación PANSS ≤75. Los ajustes de la dosis sólo se permitieron en las primeras 12 semanas del periodo 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 experimentaron una recidiva de los síntomas de la esquizofrenia en la fase doble ciego de duración variable. El ensayo se suspendió antes de lo previsto 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 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 pico 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 observa 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 rato 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 observa un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona in vitro 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 inalterada 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 sabe 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 aparente 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 periodo mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1/día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (días 8 y 36). Debido a la diferencia en la medida 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 principalmente 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 la hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve [ClCl = 50 a < 80 ml/min], un 64% en sujetos con insuficiencia renal moderada [ClCl = 30 a < 50 ml/min] y un 71% en sujetos con insuficiencia renal grave [ClCl = 10 a < 30 ml/min], lo que corresponde con un aumento promedio de la exposición (AUC_∞) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. 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 depresión 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 rasivamente 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 4,7 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 genotóxicas. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (rata), de los adenomas del páncreas endocrino (rata) y los de adenomas de las glándulas mamarias (ratón y, en menor medida, rata). Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. Fosfato ácido disódico anhidro. Fosfato dibásico de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cídico-olefina-copolímero) con un tapón de látex 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: 171,61 €; PVP: 217,52 €; PVP (IVA): 226,22 €. Xeplion 75 mg suspensión inyectable de liberación prolongada PVL: 223,08 €; PVP: 273,99 €; PVP (IVA): 284,55 €. Xeplion 100 mg suspensión inyectable de liberación prolongada PVL: 274,59 €; PVP: 325,50 €; PVP (IVA): 338,52 €. Xeplion 150 mg suspensión inyectable de liberación prolongada PVL: 410,88 €; PVP: 462,79 €; PVP (IVA): 481,30 €. **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.** 11/2016. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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[¥] N= 506. Estudio aleatorizado, doble ciego, controlado con placebo que evaluó la eficacia y seguridad del retraso del tiempo hasta la recaída de Trevicta® *vs.* placebo. 93% de los pacientes sin recaídas.

[§] N= 1.429. Estudio aleatorizado, doble ciego, de grupos paralelos, multicéntrico, de no inferioridad de Trevicta® *vs.* Xeplion®, de 48 semanas de duración. La tasa de recaídas fue similar en ambos grupos. Los perfiles de seguridad y tolerabilidad de Trevicta® y Xeplion® fueron comparables a lo largo de la fase doble-ciego de 48 semanas y consistentes con lo observado en otros ensayos con palmitato de paliperidona.

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

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