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Old drugs, new medication

Viejas drogas, nuevos fármacos

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History has shown us in recent years how some compounds originally designed for medicinal purposes have ended up as part of the wide range of illicit drugs. Conversely, some synthetic drugs for recreational use have travelled in the opposite direction and are now part of the therapeutic vademecum.

The first case is the more common, with products for clinical use being used (and abused) for recreational purposes for their pleasant, stimulating, psychodysleptic or entactogenic properties. This has been happening with old acquaintances from the world of addiction since the time of morphine, originally an analgesic, which left more than 400,000 addicts at the end of the American Civil War and became a fashionable high-society drug in the late 19th and early 20th centuries. Subsequently, opioid analgesics followed the trail of morphine, also in terms of its power of abuse and addiction. This was boosted by a letter published in the New England Journal of Medicine in 1980 minimizing the addictive potential of opioid analgesics, which could have contributed to North America's epidemic of addiction to opioid analgesics (Guardia Serecigni, 2018). Something similar occurred with cocaine, also created as a product for anaesthesia and a common ingredient in elixirs and tonics early in the 20th century, which is now the second most widely used illicit drug in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2019); or benzodiazepines, considered nowadays to be a "silent epidemy," with a significant part of the Spanish general population using them as prescription medicines (Blasco-Fontecilla, 2018).

In the second scenario, where drugs of abuse are found to have clinical properties, we should highlight cannabis, the most widely used illegal drug in the world, and whose incorporation into the therapeutic arsenal of oncology in recent years has not been without controversy (Hill, Palastro & George, 2019).

Today, however, we need to turn our attention to a substance that would be in a third category, given the fact that it has made the round trip: ketamine.

From its origin as an anaesthetic, in the mid-1960s of the previous century, and having joined the world of drugs of abuse in the late 1980s for its hallucinogenic effects, ketamine (as well as its enantiomer, esketamina) is making a strong return to the world of therapy after its antidepressant properties and ability to reduce the risk of suicide were discovered.

Ketamine is a non-volatile anaesthetic agent synthesized in 1962 and subsequently marketed for human and veterinary use. It is presented as a translucent liquid and is a

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fat-soluble derivative of phencyclidine (PCP). Ketamine is used clinically as a general anaesthetic and, being considered a mild anaesthetic, is used is more widely in pediatrics and geriatrics. In our field of psychiatry, it is one of the commonly used anaesthetics in electroconvulsive therapy techniques (Mion, 2017).

Its psychodysleptic characteristics were discovered after a large number of patients reported what they felt on emerging from anaesthesia, and the first to use it as a drug of abuse were in fact veterans of the Vietnam War after experiencing its effects in field hospitals. Subsequently, cases of abuse began to appear among health professionals (as happened with morphine and derivatives). Those professionals who used it reported that a dose much lower than for anaesthetic use produced a psychedelic experience of great intensity. However, recreational use did not become widespread until the mid-1990s, coinciding with a drop in the purity of the cocaine distributed in Western countries, and was associated with the culture of electronic music and "rave parties." The perception of low risk, its short duration of action (compared to other hallucinogens) and low price contributed to its rapidly spreading use (Gómez-Arnau & Dolengevich, 2015).

On the illicit market, ketamine can come in many other forms: colourless liquid, white powder (crystals), tablets or capsules, so its use is possible through different routes of administration: intravenous, intramuscular (liquid), rectal (liquid), nasal (powder), pulmonary "smoked" (powder) and oral (liquid, tablet, or capsules). The pharmaceutical preparation of ketamine presented in liquid form can be converted to powder by the simple method of 'baking' or 'cooking' over low heat. This process can be carried out in a microwave, an oven at 90-95 Cº, or simply over a water bath until the liquid evaporates. The resulting crystals (like large grains of salt) are then crushed to produce a finer powder suitable for sniffing. This may be sold as is or may also be converted into tablets.

It was in the last ten years that the potential of ketamine as an antidepressant drug in subanaesthetic doses began to be considered. The first study to suggest this possibility dates back to the year 2000 and is a small-scale double-blind trial with a reduced sample of 7 patients, based on theories pondering the role of glutamate in the etiopathogenesis of depression (Berman, et al., 2000).

Findings in the following years point to an antidepressant as well as a potential anti-suicidal effect of ketamine and, interestingly, many of the data come from observing the clinical effects of the drug in the context of its use as an anaesthetic in ECT (Goforth & Holsinger, 2007; Okamoto, et al., 2010).

These preliminary data have led the scientific community to design clinical trials whose results have recently begun to see the light. The data yielded by these studies show ketamine as a fast-acting antidepressant (hours), whose clinical effects include the reduction of ideation and therefore of risk of suicide shortly after receiving the ketamine infusion. These effects, however, are not long-lasting, and disappear within a few days of the experimental treatment ending. Most trials use ketamine in the form of intravenous infusions in hospital settings, which presents a problem if the treatment is to be generalized as it would be consigned to limited use in serious situations requiring either partial or total hospitalization (Han, et al., 2016).

Fortunately, once the rapid antidepressant effect and anti-suicidal potential of ketamine had been verified, the pharmaceutical industry took a step further to facilitate wider use of this therapeutic alternative by synthesizing an intranasal formulation, more accessible to everyday clinical use than intravenous infusions of ketamine such as esketamine.

Esketamine, an enantiomer of ketamine, and therefore antagonist of the N-Methyl-D-Aspartate (NMDA) receptor that regulates glutamatergic transmission, has been developed as an intranasal formulation for the treatment of resistant depression, achieving a rapid reduction of major affective symptoms, including suicidal ideation in patients with imminent risk of suicide. The onset of action is so rapid that positive effects of the drug have been observed in as little as two hours, and relevant clinical effects within just 24 hours of intranasal administration of a single dose (Slomski, 2019).

The results of clinical trials in which esketamine is used in addition to the patient's usual treatment indicate that, compared with placebo, intranasal esketamine achieves rapid improvement of depressive symptoms, including suicidal ideation, in depressive patients with imminent risk of suicide (Canuso, et al., 2018). The efficacy demonstrated in trials has resulted in its approval by the United States Food and Drug Administration (FDA) as an adjunctive treatment for resistant depression in March 2019 (Cristea & Naudet, 2019) and by the European Medicine Agency (EMA) in December 2019.

The drug's potential is such that its clinical development by the pharmaceutical industry continues to advance, with more than 30 clinical trials of esketamine (ten in phase III) currently underway for short- and long-term treatment of both resistant depression and depression with suicidal ideation (Source: clinicaltrials.gov). Table 1 shows the published results of some of these trials.

Thus, a new direction is opened in the pharmacological treatment of depression and suicidal behaviour. It remains to be seen whether this anti-suicidal effect is limited to the context of the treatment and improvement of affective disorders, or whether it is an intrinsic effect of the drug which would allow its use in the plethora of mental pathologies which carry an increased risk of suicide. Clinical research will presumably provide data in this regard in the coming years.

Let us then welcome a substance which was beginning to be demonized by its potential for recreational use and abuse, and to which the avatars of advances in psychopharmacology have assigned a promising role in the treatment

Table 1. *Published results of clinical trials in depression with ketamine and esketamine*

Drug	Reference	Pathology	Study time	Result
Esketamine, nasal spray	NCT02133001	Major depression and suicidal ideation	4 weeks	Improvement in MADRS score compared to placebo at 4 and 24 h. Improvement in suicidal ideation at 4 h.
Esketamine, nasal spray	NCT01998958	Treatment resistant depression	10 weeks	Improvement in MADRS score compared to placebo, maintained over duration of study
Esketamine, nasal spray	NCT02493868	Treatment resistant depression	16 weeks	Esketamine + antidepressant reduced the risk of relapse by 51% compared to placebo + antidepressant
Esketamine, nasal spray	NCT02417064	Treatment resistant depression	4 weeks	Improvement in MADRS score compared to placebo. No differences in efficacy observed between doses of 56 mg and 84 mg
Ketamine, iv infusion	NCT02094898	Treatment resistant depression	4 weeks	Remission of clinical picture at one and four weeks in 41% of patients
Ketamine, iv infusion	NCT00088699	Major depression	1 weeks	Ketamine improved depressive symptoms compared to placebo at 110 minutes and one week after treatment
Ketamine, nasal spray	NCT01304147	Major depression	24 hours	Improvement in MADRS score compared with placebo at 24 h.
Ketamine, iv infusion	NCT01920555	Treatment resistant depression	3 days	Improvement in HAM-D and MADRS scores after an infusion of 0.5 or 1.0 mg/kg of iv ketamine

Note. clinicaltrials.gov

of affective disorders, a substance which can help keep in check the mortal enemy of professionals serving patients with mental disorders: suicidal behaviours.

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Conflicts of interest

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Influence of substance use and cognitive impairment on adherence to antiretroviral therapy in HIV+ patients

Influencia del consumo de sustancias y el deterioro cognitivo en la adherencia al tratamiento antirretroviral en pacientes VIH+

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Abstract

Strict adherence to antiretroviral treatment (ART) is needed to ensure the effectiveness of HIV treatment. The adverse effects of substance abuse and neurocognitive impairment on medication adherence have both been suggested by several studies. Therefore, the aim of this research is to study the relationship among adherence to ART, cognitive dysfunction, and abuse of certain substances (alcohol, heroin, cocaine, other stimulants, cannabis and benzodiazepines) and/or methadone treatment in our social environment. We performed an observational case-control study with a sample of 125 HIV+ patients, who were classified as patients with poor adherence (cases) and subjects with adequate compliance (controls). Adherence was defined by the Hospital Pharmacy and verified with the Simplified Medication Adherence Questionnaire (SMAQ) and the reference physician's clinical impression. Cognitive functioning was measured with the Zoo Map Test and Trail Making Test (TMT). Substance abuse was collected through a semi-structured clinical interview protocol. Statistical analysis was made using a binary logistic regression model. The results indicate that both alcohol abuse and neurocognitive impairment measured by Zoo Map Test were significantly associated with poorer adherence to ART. No significant association was found between adherence and other substance use, or between adherence and TMT score. Screening of cognitive impairment measured by the Zoo Map Test and alcohol abuse may lead to the development of strategies to improve de adherence to ART in HIV+ patients.

Keywords: HIV; Antiretroviral therapy; Medication adherence; Cognitive dysfunction; Substance use.

Resumen

La adherencia estricta al tratamiento antirretroviral (TAR) es imprescindible para que este sea eficaz en la disminución de la morbimortalidad asociada al VIH. Se ha sugerido que el consumo de sustancias y el deterioro cognitivo constituyen factores de riesgo para una mala adherencia. En este sentido, el objetivo de este estudio es evaluar cuál es la influencia sobre la adherencia al TAR de la disfunción cognitiva, así como del consumo de determinadas sustancias (alcohol, heroína, cocaína, otros estimulantes, cannabis y benzodizepinas) y/o el tratamiento con metadona, en el marco concreto de una población española de referencia. Se realizó un estudio observacional tipo casos y controles con una muestra de 125 pacientes VIH+, que se dividieron en sujetos malos adherentes (casos) y buenos adherentes al TAR (controles). La adherencia se evaluó mediante el reporte de Farmacia Hospitalaria, contrastada con la escala Simplified Medication Adherence Questionnaire (SMAQ) y la opinión del profesional médico de referencia. La función cognitiva fue evaluada con el Test del Mapa del Zoo y el Trail Making Test (TMT), y el consumo de sustancias, mediante un protocolo de historia clínica semi-estructurada. El análisis estadístico se realizó mediante regresión logística binaria. Los resultados mostraron que el abuso de alcohol y el deterioro en la función cognitiva ejecutiva, medida por el Test del Mapa del Zoo, constituyen factores de riesgo independientes para una mala adherencia. No se ha demostrado relación de la adherencia al TAR con el consumo de otras sustancias ni con la puntuación obtenida en el TMT. La detección de deterioro cognitivo mediante el Test del Mapa del Zoo, así como del consumo de alcohol, podrían ayudar a desarrollar estrategias de mejora del cumplimiento terapéutico en pacientes VIH+.

Palabras clave: VIH; Tratamiento antirretroviral; Adherencia terapéutica; Deterioro cognitivo; Consumo de sustancias.

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Introduction

Human Immunodeficiency Virus (HIV) belongs to the Retroviridae family and is the cause of the Acquired Immunodeficiency Syndrome (AIDS), which constitutes a worldwide public health problem of the greatest magnitude (Fauci & Lane, 2005). The establishment of treatment regimes consisting of the combination of antiretroviral drugs has allowed us to slow down the progression of HIV. Therefore, antiretroviral treatment (ART) has implied an important decrease in mortality and morbidity associated with HIV, and, in many cases, it turns an infection that used to be invariably lethal into a chronic disease (Lovejoy & Suhr, 2009; Tran, Nguyen, Nguyen, Hoang & Hwang, 2013). Nevertheless, to obtain a complete clinical and virological response, and prevent the onset of resistant viral strains, strict compliance to treatment is necessary, among other factors. The majority of authors defend that in order to ensure the efficacy of ART, compliance must be above 90-95%. However, maintaining such a high compliance can be difficult for many patients (Ingersoll, 2004; Lovejoy & Suhr, 2009).

In recent years, there has been an attempt to clarify the factors can have an impact on adherence to ART, in order to identify potentially modifiable risk factors and develop strategies to improve the therapeutic plans (Thaler, Sayegh, Kim, Castellon & Hinkin, 2015; Tran et al., 2013). It has been suggested that the following factors may be associated with poorer compliance: low socioeconomic level (Peltzer & Pengpid, 2013; Tsuyuki & Surratt, 2015), the presence of treatment side effects, patients' lack of perceived efficacy, emotional stress, the absence of social and family support, the complexity of the treatment regimen (Ammassari et al., 2002), youth, and cognitive impairment (Thaler et al., 2015). In addition, it has been proposed that poorer compliance is related to presence of psychopathology, mainly depressive (Ammassari et al., 2004), certain personality traits (Hutton & Treisman, 2008), and substance consumption (Azar et al., 2015). Nevertheless, there are few studies in this regard in our sociocultural context, so we believe that it is necessary to investigate the aforementioned associations in the Spanish population.

HIV is a neurotropic virus that invades the central nervous system (CNS) at an early stage, producing neurotoxicity, neuroinflammation, and neurodegeneration. The pernicious effect in the CNS can occur through the direct action of the virus, or indirectly by means of immunosuppression, which can affect the CNS in the form of opportunistic infections and malignancies: cryptococcosis, toxoplasmosis, progressive multifocal leukoencephalopathy, primary lymphoma of the brain, etc. (Bragança & Palha, 2011; Group of experts from the "Grupo de Estudio de Sida" (GeSIDA; in English AIDS Research Group) and the Secretariat of the "Plan Nacional sobre el Sida" (SPNS; National AIDS Plan, 2014). Prior to the introduction of ART, a great number of patients developed severe cognitive impairment in the last stage of the disease, called *HIV associated dementia* (HAD) by the American Neurology Association in 1991. This was differentiated from another entity that did not meet the criteria of dementia, but in which there were slight alterations that interfered with daily life: *Minor cognitive motor alteration* (MCMA). In recent years, HAD is increasingly rare; however, it has been found that a percentage of long-term patients presents cognitive impairment, some even with the infection systematically well controlled (Cysique & Brew, 2009; GeSIDA & SPNS, 2014; Solomon & Halkitis, 2008). With the progress of the disease, there is often a decline in the executive function, motor functioning, attention, memory, and processing speed, and some behavioral changes, such as apathy and lethargy, also appear (Anand, Springer, Copenhaver & Altice, 2010; Andrade et al., 2013, Vázquez-Justo, Vergara-Moragues, Piñón-Blanco, Guillén-Gestoso & Pérez-García, 2016). Antinori et al. (2007) conducted a nosological review of the cognitive alterations associated with HIV ("Frascati criteria"), included in the term *HIV associated neurocognitive disorders* (HAND). The new classification proposed divides this entity into three categories: *asymptomatic neurocognitive impairment* (ANI), *mild neurocognitive disorder* (MND), and *HIV associated dementia* (HAD). The first two are characterized by the development of a mild impairment in at least two neurocognitive domains, without meeting the criteria for dementia, and without interference or with mild interference, respectively, in the individual's habitual functioning. In HIV associated dementia, there is marked impairment and interference in daily life (Antinori et al., 2007; GeSIDA & SPNS, 2014).

In recent years, numerous studies have reported that this cognitive impairment is another factor related to poorer adherence to ART (Andrade et al., 2013; Hinkin et al., 2004; Lovejoy & Suhr, 2009). Diminished cognitive functioning may condition the presence of "forgetfulness", which is the most frequent reason for missed doses of medication in the treatment (Ammassari et al., 2004; Blackstone, Woods, Weber, Grant & Moore, 2013; Hinkin et al., 2002). Other authors have proposed that poor adherence to ART determines a worse cognitive evolution, as it accelerates the progression of the disease (Cysique & Brew, 2009; Waldrop-Valverde et al., 2006). Nevertheless, it is plausible to consider that this may actually be a bi-directional relationship (Andrade et al., 2013; Hinkin et al., 2004; Lovejoy & Suhr, 2009). It must be taken into account that ART usually involves a complex treatment regimen, which implies mechanisms related to planning and decision-making, and therefore requires a notable cognitive demand. In this case, the cognitive deficit has to be taken into account in the design of the treatment, in order to establish an adequate regime for each patient's characteristics (Blackstone et al., 2013; Hinkin et al., 2002; Solomon & Halkitis, 2008). There

is no uniformity in the literature regarding which cognitive areas have greater influence on adherence to ART. According to the available evidence, poorer adherence could be associated with deficits in the executive functions, the learning capacity, attention, the working memory, the prospective memory, and processing speed. Nevertheless, the results of the diverse studies are heterogeneous, and the mechanisms underlying this relation have not been clarified (Ammassari et al., 2004; Andrade et al., 2013; Lovejoy & Suhr, 2009). Knowing which cognitive areas are determinant to adherence would allow us to implement strategies to counterbalance failures due to cognitive dysfunction (Altice, Kamarulzaman, Soriano, Schechter & Friedland, 2010; Blackstone et al., 2013; Hinkin et al., 2002).

Substance use disorder has a very high prevalence in HIV+ patients, in whom it is especially problematic for several reasons: it is associated directly and indirectly with an increase in the transmission of the virus and with a worsening of the immune status, regardless of treatment-related factors, and with a increase in morbidity and mortality in general, as well as with poorer adherence to ART (Altice et al., 2010; Parsons, Starks, Millar, Boonrai & Marcotte, 2014). The substances that have proven to be risk factors for poor adherence are mainly, although not exclusively, alcohol, cannabis, cocaine, amphetamines, and heroin. However, the results regarding this association are not homogeneous in all the studies (Altice et al., 2010; Waldrop-Valverde et al., 2006). Whereas there is a fairly extensive consensus about the negative influence on adherence to ART of alcohol consumption (Azar, Springer, Meyer & Altice, 2010; Gonzalez, Barinas & O'Cleirigh, 2011), and cocaine consumption (Meade, Conn, Skalski & Safren, 2011; Rosen et al., 2013), the results are disparate for substances like cannabis (González-Álvarez, Madoz-Gúrpide, Parro-Torres, Hernández-Huerta & Ochoa Mangado, 2019; Lovejoy & Suhr, 2009). Concerning opioids, the consumption of heroin has been associated with poorer adherence (Azar et al., 2015). There are contradictory results about the influence on adherence found in a program of maintenance with methadone (PMM) in users of drugs by parenteral route (Azar et al., 2015; Cohn et al., 2011). In patients who consume multiple substances, it has been suggested that the combination of alcohol and cannabis could be more negative for adherence than the exclusive use of alcohol, and, in turn, the combination of alcohol and cocaine could be associated with the worst results in adherence (Parsons et al., 2014). The type of substance and the consumption patterns could be influential factors in this association. Different mechanisms have been proposed that could sustain this association: a chaotic lifestyle with unstable time schedules (Hinkin et al., 2007; Ingersoll, 2004), an increase in forgetting to take medication (Anand et al., 2010; Ingersoll, 2004), the failure to control impulses and disinhibition favored by consumption (Anand et al., 2010; Hinkin et al., 2007). In addition, some patients voluntarily omit their medication during periods of consumption, as they believe it is incompatible with treatment (Gonzalez et al., 2011; Kalichman et al., 2015).

However, the chronic consumption of substances can imply an increase in the risk of early cognitive impairment (Altice et al., 2010; Anand et al., 2010; Vázquez-Justo et al., 2016). Individuals taking opioids show deficits in attention, memory, and executive function both during their active use and in early abstinence. Moreover, it has been suggested that dependence on opioids worsens the neurocognitive disorders associated with HIV because they foment viral replication by means of a direct negative effect on the immune system. This effect is even more evident in combination with cocaine (Anand et al., 2010). There is a greater cognitive dysfunction and poorer therapeutic adherence in active consumers of cocaine compared to abstainers. It has been suggested that cognitive impairment partially moderates the association between cocaine consumption and adherence to ART (Gonzalez et al., 2011; Meade et al., 2011). With regard to alcohol, its dependence may cause persistent brain damage, subcortical atrophy, and hypometabolism in frontal lobes. Moreover, a synergistic pernicious effect of alcohol consumption and infection by HIV on the CNS has been described, as the cognitive impairment associated with chronic consumption of alcohol is greater in HIV+ individuals than in HIV- individuals (Anand et al., 2010). All this seems to suggest that there is an interrelationship between cognitive impairment, adherence to ART, and substance consumption (Anand et al., 2010; Hinkin et al., 2007).

The present work aims to analyze the relation between substance consumption and cognitive function in the adherence to ART in HIV+ patients. Although there is international literature in this respect, references of the impact of substance consumption and cognitive dysfunction in the adherence to ART are limited in the assistential environment of the Spanish population (González-Álvarez et al., 2019; Ortego, Huedo-Medina, Vejo & Llorca, 2011). The hypothesis of this study is that substance consumption and cognitive impairment can negatively influence adherence to ART in HIV+ patients.

Methodology

Area and population of study

A total of 125 patients were included in this study. Prior to the present article, preliminary data from a subset of these individuals were reported in another publication of our work group (González-Álvarez et al., 2019). In the aforementioned article, we studied the relation between adherence to ART and alcohol consumption, associated or not with the use of other substances; in this work, we also introduce the study of the cognitive component.

The inclusion criteria were: age between 18 and 65 years, diagnosis of HIV infection, being in regular follow-up in the Service of Infectious Diseases of the University Hospital Ramón y Cajal of Madrid, having initiated ART at least one year before the assessment, and that this treatment was dispensed only through the Hospital Pharmacy Service of this hospital. Regular follow-up was considered as having attended at least two scheduled visits in the past year (Tripathi, Youmans, Gibson & Duffus, 2011).

Exclusion criteria were: acute active infectious processes, active cancer processes, discrepancies in the classification of the patients as good or bad adherents between the different classification methods used, and the report of a rate of adherence between 90% and the 95%. Adherence to ART was assessed by means of the percentage of treatment withdrawn during the year prior to the assessment, according to the report of the Hospital Pharmacy. This data was verified by means of the questionnaire Simplified Medication Adherence Questionnaire (SMAQ), an instrument to assess adherence to treatment, validated for use in HIV+ patients (Knobel et al., 2002). Based on both parameters, we classified the patients as good or poor adherents, and we informed their respective reference physicians of the Department of Infectious Diseases of the group to which each patient had been assigned. If there was any inconsistency between adherence reported by the Hospital Pharmacy and the outcome of the SMAQ, or if the reference professional's clinical impression disagreed with the outcome of the classification of the two aforementioned methods, the patients were excluded. As there is no consensus about the minimum effective adherence (Viswanathan et al., 2015), we chose the most conservative minimum and maximum limits, in order to increase the power of classification of the method. For this reason, we excluded from the study those patients in whom adherence between 90% and 95% was reported.

All the patients included in the study were informed, accepted participation, and signed the informed consent. The study was approved by the Ethics Committee of Research Clinic of the University Hospital Ramón y Cajal.

Type and general Design of the study

This is of an observational, cross-sectional case-control study. Patients were assigned to each group as a function of adherence to ART. Patients with poor adherence to ART were considered "cases", defined according to the report of the Hospital Pharmacy as those patients who had picked up less than 90% of the ART doses during the past year. Patients of the same provenance, who, at the time of entering the study differed only in their good adherence to ART, were considered the "controls", defined as those who had withdrawn more than 95% of their ART doses during the past year (Paterson et al., 2000).

Procedure of the sample selection:

The selection of cases was carried out by consecutive sampling of a list of non-adhering patients generated ordinarily and with monthly frequency by the Hospital Pharmacy. The controls were selected by consecutive sampling of the list of patients who had an appointment in the monographic consultation of HIV of the Service of infectious Diseases. Sample selection took place between May 2013 and September 2015.

Data collection procedure:

Data collection was implemented according to a semi-structured clinical history protocol, specially designed for this research, which included the SMAQ scale. We also included in the protocol a battery of neuropsychological tests validated for Spanish population, among which were the Trail Making Test (TMT) and the Zoo Map Test.

- The Zoo Map Test is part of the neuropsychological exploration battery Behavioral Assessment of the Dysexecutive Syndrome (BADS). This tool is used especially to measure the skill of planning as part of the executive functions. Planning can be defined as the skill to organize behavior as a function of a specific goal that must be achieved by means of a series of intermediate steps. It has been suggested that it is a two-step process: formulation and execution. Formulation is the mental ability to develop a logical mental strategy guiding the course of action, while execution is the competence to carry out the plan developed in the formulation (Oosterman, Wijers, & Kessels, 2013).
- The Trail Making Test (TMT) is one of the most widely disseminated and used instruments in neuropsychological evaluations seeking to measure processing speed and executive function. Diverse studies agree that it has a complex structure that encompasses various cognitive mechanisms. Visual search, perceptual/motor speed, processing speed, working memory and general intelligence are some of the constructs most frequently cited that are thought to contribute to test performance. It consists of two parts: part A mainly examines visuo-perceptive skills, and part B mainly involves the working memory and secondarily, flexibility to switch tasks (Sánchez-Cubillo et al., 2009).

Definition of the variables of the study

Sociodemographic variables, such as age, sex, race, civil status, socioeconomic level, educational level, and work status were collected. In order to increase the statistical power of the analysis, some variables were recoded, preserving their clinical meaning. The categories of absence of profession, home-keeper, student, and unskilled worker were considered as unqualified profession; skilled workers with occupational qualification, employees, civil servants, and liberal professions were classified as qualified workers.

With regard to the sociodemographic level, the accumulation of debts, being unable to deal with payments, or the need for external aid to the family unit were considered as economic risk.

In addition, we included variables of HIV infection and its treatment: co-infection with Hepatitis C Virus (HCV), time in follow-up, time in treatment with ART, number of doses of medication a day, number of pills a day, and presence a supervisor of the treatment, among others. The history of substance consumption in the 12 months prior to assessment (alcohol, cocaine, heroin, cannabis, stimulants and benzodiazepine, as well as treatment with methadone) was described. We categorized alcohol consumption as harmful consumption or non-problematic consumption, as a function of the criteria of the tenth Review of the International Classification of Diseases (World Health Organization [WHO], 1992). For the remaining substances, we classified as positive any consumption pattern, although all individuals who admitted consumption presented at least weekly frequency. We also included the presence of risk behaviors associated with substance use by parenteral route: sharing and reusing syringes. Regarding the neuropsychological tests, in the Zoo Map Test, we collected the main variable Total Score and four secondary variables: Number of Hits, Number of Errors, Planning Time, and Total Test Performance Time. We defined the variables TMT-A score and TMT-B score: in both cases, the score was obtained directly as a function of the time spent to complete the task.

Statistical analysis

Firstly, we conducted a raw analysis of the results. By means of the Kolmogorov-Smirnov test and the viewing of the graphs, the quantitative variables were observed to follow a normal distribution. In the cases of discrepancy, we followed the graphic information. With regard to the descriptive analysis, in the variables that followed a normal distribution, the results are expressed as means and standard deviations. For the nonparametric variables, we used the median and the interquartile range (IQR) between 25% and 75%. For the qualitative variables, the descriptive statistic was the percentage. The comparison of cases and controls was carried out through Pearson's chi-square in the qualitative variables. For the quantitative variables that followed a normal distribution, we used Student's *t*-statistic for independent samples, and for those in which at least one of the groups followed a non-normal distribution, we used the Mann Whitney-*U* statistic

Lastly, stepwise multivariate binary logistic regression analysis was performed (odds ratio). Initially, we included variables that had been shown to be related to adherence to ART in the raw analysis, and that also met the criterion of biological plausibility, and were related to the object of our study. We also included variables that had been shown to be interesting in the prior literature. The following variables were included in the multivariate analysis: age, gender, socioeconomic level, educational level, number of pills prescribed per day, risk behaviors with regard to sharing syringes, supervision of mediation by third parties, co-infection with VHC, substance consumption (alcohol, cannabis, cocaine, heroin, and treatment with methadone), and psychometric test scores (Zoo Test and TMT-B).

Data with a p-value < 0.05 were considered significant.

Results

Results of the descriptive analysis and of the raw analysis

General description of the sample and comparative analysis of the sociodemographic and clinical variables. We analyzed a total sample 125 subjects, 79 controls and 46 cases. Of these, 68% were males, and 84% were Caucasian. The median of age of the sample was 48.4 years (IQR: 43.6 – 52.8).

No statistically significant differences were observed between cases and controls with regard to the variables sex, age, race and civil status. The absence of significant group differences in the variable age excludes age as a possible confounding factor in relation to cognitive impairment. A significant difference was found in academic level, as the frequency of higher studies was greater in the controls (p = .001). In addition, the cases had lower professional qualification (p = .027), and worse socioeconomic level (p < .001). Both academic and the socioeconomic level were included in the multivariate analysis in order to study the hypothesis of our study regardless of the possible influence of these heterogeneous variables between cases and controls. Occupational qualification was not included due to its lower statistical significance and to the need to limit the number of variables included in the multivariate analysis in proportion to our sample size. No differences were found between cases and controls for the variables time in treatment, time in follow-up, and number of doses of medication per day. There was a statistically significant difference in the number of pills that made up the daily treatment between the two groups, which was higher in the cases (p = .002). The greater need for supervision of ART by third parties was significant in the cases (p = .001) (Tables 1 and 2).

Co-infection with HCV was significantly greater in the group of the cases (70.5% compared to 34.6% of the controls, p < .001). In addition, the cases presented more risk behaviors of sharing syringes (58.7% versus 26.6%, respectively, p < .001).

Comparative analysis of variables related to substance consumption in the past year. Concerning substance consumption, 67.4% of the cases and 30.4% of the controls presented illegal substance consumption in the past year, and this difference was statistically significant (p < .001). Problematic consumption of alcohol was higher in the cases (p < .001). Likewise, consumption of cocaine (p = .001), other stimu-

Table 1. *Comparative analysis of sociodemographic variables.*

		Control subjects n (%)	Cases n (%)	χ^2 *p*
Sex	Male	52 (65.8%)	33 (71.7%)	0.494
	Female	27 (34.2%)	13 (28.3%)	
Race	Caucasian	70 (88.6%)	35 (76.1%)	0.066
	Other	9 (11.4%)	11 (23.9%)	
Marital status	Living with partner	28 (35.4%)	18 (39.1%)	0.680
	Other	51 (64.6%)	28 (60.9%)	
Academic level	Primary/Graduate	32 (40.5%)	33 (71.7%)	**0.001**
	High School/VT*/University	47 (59.5%)	13 (28.3%)	
Profession	Unqualified	31 (40.3%)	28 (60.9%)	**0.027**
	Qualified	46 (59.7%)	18 (39.1%)	
Socioeconomic level	No economic problems	69 (87.3%)	21 (45.7%)	**<0.001**
	Economic risk	10 (12.7%)	25 (54.3%)	
Supervision of treatment	Never	71 (89.9%)	30 (65.2%)	**0.001**
	Sometimes/always	8 (10.1%)	16 (34.8%)	

Note. *VT: Vocational training.

Table 2. *Comparative analysis of clinical variables.*

	Control subjects Median (IQR¥)	Cases Median (IQR¥)	Mann-Whitney U *p*
Age (years)	49.1 (45.3 – 53.4)	46.4 (6.3)*	0.079
Time in follow-up (years)	15.0 (8.0 – 21.0)	18.0 (9.0 – 22.0)	0.125
Time in treatment (years)	13.0 (5.0 – 19.0)	16.5 (8.0 – 20.0)	0.176
Number of pills/day	2.0 (1.0 – 3.0)	3.0 (2.7 – 4.0)	**0.002**
Number of doses/day	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.866

Note. ¥Interquartile range (IQR 25 – IQR 75); *Mean (Standard deviation).

Table 3. *Comparative analysis of variables related to substance consumption in the past year.*

	Control subjects n (%)	Cases n (%)	χ^2 *p*
Any illegal substance	24 (30.4%)	31 (67.4%)	**<0.001**
Alcohol (problematic)	12 (15.2%)	22 (47.8%)	**<0.001**
Cannabis	24 (30.4%)	19 (41.3%)	0.215
Cocaine	14 (17.7%)	21 (45.7%)	**0.001**
Other stimulants	0 (0%)	3 (6.5%)	**0.022**
Heroin	3 (3.8%)	7 (15.2%)	**0.023**
Treatment with methadone	5 (6.3%)	16 (34.8%)	**<0.001**
Benzodiazepines	2 (2.5%)	10 (21.7%)	**<0.001**

lants (p = .022), and heroin (p = .023) was also more frequent among the cases. The number of subjects who were in PMM for opiate addiction was significantly greater in the cases (p < .001). Also benzodiazepine abuse was statistically more frequent among the cases (p < .001). No significant differences were found with regard to the consumption of cannabis (Table 3).

Comparative analysis of variables related to the neuropsychological tests. In the Zoo Map Test, significant differences between cases and controls were found in four of the five variables included in our correction, with the controls always scoring higher: in Total Score (p = .002), Number of Hits (p = .045), Number of Errors (p = .014), and Total Test Performance Time (p = .038). With regard to the TMT, in both parts, the cases needed significantly more time to complete the tests than the controls (TMT-A: p = 0.003 and TMT-B: p = .001) (Table 4).

Adjusted analysis of variables related to adherence to ART. Logistic Regression

Of the 125 subjects of the total sample, 111 (88.8%) were included in the adjusted analysis . Of these, 74 were controls and 37 were cases. Due to missing some of the data that were introduced in the analysis —specifically, the score in TMT-B and/or the total score in the Zoo Map— 14 subjects were lost. The reason is that these patients dropped out of the interview prior to its completion, possibly due to fatigue and the prolonged duration of the interview. We estimated models of multiple imputation of the missing values, which did not show relevant changes or significant improvement of the final model; for this reason, we decided to assume the missing values.

The final model correctly classified 82.9% of the global sample, with more specificity than sensitivity (Hosmer & Lemeshow's test: 90.5% of the controls and 67.6% of the cases), and it explained 53.4% of the variable of adherence.

Table 5 presents the variables that showed a statistically significant relation with adherence to ART.

Sociodemographic and clinical data. According to the results obtained, the risk of poor adherence increases in the following cases: being younger, being male, low socioeconomic level, an ART guideline consisting of a higher number of pills per day, and HCV co-infection. In our model, the high-risk behavior of sharing syringes, the need for supervision of treatment, and the patient's educational level were not shown to be associated with poor adherence.

Substance consumption. Harmful consumption of alcohol increased the risk of being classified as a poor adherent by 3.398 (95% CI [1,040, 11,100]) versus the situation of abstinence or non-problematic consumption, after controlling for the variables identified in Table 5. However, the consumption of cannabis, cocaine, or heroin and the therapeutic use of methadone were not significantly associated with a worsening of therapeutic adherence.

Neuropsychological tests. The total score obtained on the Zoo Map, after controlling for the variables identified in Table 5, was significantly related to adherence to ART. Each additional point in the score of this test multiplies by 0.659 the probability of being considered a poor adherent. Inversely, each additional point multiplies by 1.517 (95% CI [1.149, 2.000]) the probability of being considered good adherent. However, no statistically significant relation between the score obtained in the TMT-B and adherence was found.

Table 4. *Comparative analysis of the variables related to neuropsychological tests.*

		Control subjects Median (IQR¥)	**Cases** Median (IQR¥)	**Mann-Whitney U** *p*
Trial Making Test	TMT-A (seconds)	41.0 (34.0 – 54.0)	53.5 (39.5 – 74.2)	**0.003**
	TMT-B (seconds)	85.0 (67.0 – 124.5)	143.0 (86.0 – 200.0)	**0.001**
Zoo Map Test	Nr. of hits	8.0 (7.0 – 8.0)	7.0 (7.0 – 8.0)	**0.045**
	Nr. of errors	1.0 (0.0 – 1.0)	1.0 (0.0 – 3.0)	**0.014**
	Total score	7.0 (6.0 – 8.0)	5.0 (3.5 – 5.0)	**0.002**
	Planning time (seconds)	75.0 (39.0 – 146.0)	70.0 (22.5 – 121.0)	0.205
	Total performance time (seconds)	145.0 (89.0 – 203.5)	187.5 (126.0 – 240.0)	**0.038**

Note. ¥Interquartile range (IQR 25 – IQR 75).

Discussion

The goal of the present study is to study whether substance consumption and cognitive impairment, evaluated by means of the Zoo Map Test and the TMT, negatively influence adherence to ART in HIV+ patients. The results obtained confirm partially our working hypothesis.

The differences between cases and controls in the performance of the neuropsychological tests were significant for almost all of the variables of interest. In the raw analysis of the Zoo Map Test, differences were observed in four of the five variables. No significant difference between cases and controls was found in the variable planning time, although the total performance time was significantly higher in poor adherents. This may be due to the fact that the cases usually began the task impulsively and overestimated their capacity to solve it, and then, they needed more time to complete the test and they committed more errors. Of the neuropsychological variables introduced in the multivariate analysis (TMT-B and total score on the Zoo Map), the latter was the only one that maintained the statistically significant association with adherence to ART in the final logistic regression model, after controlling for the rest of variables. The ART is a complex regimen whose adequate adherence requires skills of planning and performance; therefore, it is logical that a difficulty to plan, as measured by the Zoo Map Test, will lead to a poorer capacity to adhe-

Table 5. *Logistic regression, "Enter" method.*

	B	**Stand. error**	**Wald**	**Degrees of freedom**	***p***	**Exp(B)**	**95% CI for Exp(B)**
Age	-0.110	0.046	5.852	1	**0.016**	0.896	0.819 – 0.979
Sex	-1.338	0.655	4.173	1	**0.041**	0.262	0.073 – 0.947
Number of pills	0.514	0.211	5.938	1	**0.015**	1.672	1.106 – 2.528
Socioeconomic level	1.296	0.637	4.136	1	**0.042**	3.654	1.048 – 12.737
HCV co-infection	1.821	0.662	7.563	1	**0.006**	6.178	1.687 – 22.620
Alcohol	1.223	0.604	4.103	1	**0.043**	3.398	1.040 – 11.100
Total Zoo Map score	-0.417	0.142	8.662	1	**0.003**	0.659	0.500 – 0.870
Constant	-0.463	2.497	0.034	1	0.853	0.630	

re to this regimen. These results are congruent with those found in other studies, in which a significant association has been shown between a disturbance in executive functions and poorer adherence to ART (Andrade et al., 2013; Waldrop-Valverde et al., 2006).

It is also significant that the cases obtained worse scores than the controls in the performance of both versions of the TMT in the raw analysis. This supports the results obtained in previous studies that relate a deficit in working memory, analyzed by means of the TMT, with poorer adherence to ART (Wagner, 2002). Nevertheless, there is more support in the literature for the association between adherence to ART and the B version of the TMT (Solomon & Halkitis, 2008; Thaler et al., 2015). Due to the need introduce a proportionate number of variables to our sample size, we decided not to include the A version of the TMT in the multivariate analysis. Even so, the TMT-B showed no statistical significance in the final model, possibly because there is an overlap between the areas evaluated by the Zoo Map Test and the TMT-B.

The association between alcohol consumption and poorer adherence is maintained in our logistic regression model after controlling for other consumptions, such that alcohol is a risk factor for poor adherence, regardless of the use of other substances. According to the results of the raw analysis, the consumption of heroin, cocaine, and other stimulants is significantly higher in poor adherents but the association is not maintained in the multivariate model. This latter finding contrasts with the results obtained in other studies: Azar et al. (2015) found a significant relation between poorer adherence and the use of intravenous cocaine and heroin, independently; and Rosen et al. (2013) suggest a negative effect of the consumption of alcohol, heroin, cocaine, and other stimulants on adherence. The absence of such a relation in our study may be due to the scarce number of subjects who reported these consumptions, that patients with more severe consumptions are not represented in our sample, or that there is an overlap between alcohol consumption and these substances. No significant difference was found in the consumption of cannabis between cases and controls, which supports the results of previous studies (Rosen et al., 2013; Slawson et al., 2015). Regarding the PMM programs in users of drugs by parenteral route, they are statistically more frequent in poor adherents in the raw analysis, but this association was nonsignificant in the multivariate analysis. This finding differs from those suggested by other authors (Malta, Strathdee, Magnanini & Bastos, 2008), which might due to the fact that the profile of patients in PMM in our sample correlates with a worse socioeconomic level and clinical situation, which is congruent with the findings of other studies (Martínez-Luna et al., 2018; Pedrero-Pérez & Grupo MethaQoL, 2017).

The results show that HCV co-infection was significantly more frequent among the patients with poor adherence. This variable has not been shown to influence adherence to ART in other prior studies (Shuper et al., 2016). HCV co-infection may be associated with factors that hinder adherence: higher presence of hepatotoxicity, lower efficacy of ART, more prevalence of substance consumption, poorer cognitive performance, and greater social marginalization. Nevertheless, this possible relation is beyond the scope of our work, and other more specific studies are needed to determine it. The patients with the worst socioeconomic level are more likely to be poor adherents in the multivariate analysis, a finding that coincides with prior studies (Tsuyuki & Surratt, 2015). As already suggested by other authors (Nachega et al., 2014), in our study, ART regimes consisting of a greater number of pills are related to worse adherence. Nevertheless, this situation may be influenced by feedback, such that a worse immune status, related to poorer adherence and to resistances developed in that context, would require a more complex treatment regime, which, in turn, would hinder adherence even more. However, there is no difference between the number of daily doses, which probably reflects the professionals' effort to simplify the treatment regimes, in spite of the fact that cases require a greater number of pills a day.

From the data obtained in our work, it follows that harmful alcohol consumption and poorer cognitive executive functioning, as measured by the Zoo Map Test, are significantly related to poor adherence to ART. This finding corroborates a large part of the results published in the international literature within Spanish population (Andrade et al., 2013; Azar et al., 2010; Thaler et al., 2015). With regard to Spain, in the meta-analysis carried out by Ortego et al. (2011), a relation between poor adherence and consumption of alcohol and other substances was found, but only in the univariate model; cognitive impairment was not studied. In the prior study carried out by our group (González-Álvarez et al., 2019), it was found that harmful alcohol consumption is a risk factor for poor adherence to ART, independently of the consumption of other substances.

Part of the limitations of the study may be related to the provenance of the sample: an external consultation of the Infectious Diseases Service of a hospital that is a center of reference for the treatment of the HIV. Due to the assistential context, this may have been an aged population, with a high average follow-up and treatment time, which would have excluded more severe cases with a greater difficulty to maintain a regular follow-up in the consultation. However, although small, the loss of subjects in the multivariate analysis may have led to an exclusion bias of the more deteriorated profiles, which may present more difficulties to complete the tests.

The instruments employed in this work to study cognitive impairment specifically measure the executive functions.

In this sense, another possible limitation could be not having expanded the exploration to other cognitive domains.

With regard to substance consumption, we did not use any method to corroborate the criteria of abuse/dependence or substance consumption disorder; we only registered, through the interview with the patient, the presence or absence of consumption in the past year, and we did not perform screening tests of biological samples. However, the prevalence of consumption of heroin, cocaine, and other stimulants was scarce in the sample, which may have limited the capacity to assess the real effect of these variables on adherence. There may also be a bias concerning patients with more severe consumption patterns, who may have been excluded for not meeting the criterion of a regular outpatient follow-up. Hence, the results can only be extrapolated to a population with a similar profile. We recommend studying the impact of cognitive impairment and substance consumption on adherence to ART in populations characterized by more severe consumptions, greater psychosocial deterioration, and less access to health resources, to determine the nature of this association in patients with that profile.

Another possible limitation is that the method of quantifying adherence by the Hospital Pharmacy Service is based on the patients' withdrawal of the medication, not strictly on its consumption. Therefore, defects in the schedule of doses, duplicity of doses, or the loss of medication would be biased in the data collection. Nevertheless, a possible strength of the study is this count is confirmed by means of two complementary methods: the SMAQ instrument and the opinion of the professional in charge. This design could decrease the risk of overestimating adherence and increase the probability of a correct classification of the patients (Henegar et al., 2015).

The importance of adequate adherence to ART has been extensively described as a means to reduce the morbidity and mortality associated with HIV (Lovejoy & Suhr, 2009; Thaler et al., 2015). Patients with cognitive dysfunction, as well as those who problematically consume illegal substances and/or alcohol are at greater risk of being poor adherents. As already suggested in the prior literature, these variables act as independent risk factors, whose combined effects are summed for poor adherence (Moore et al., 2012; Thaler et al., 2015). Nevertheless, the present study does not allow us to elucidate the mechanisms underlying this association. Cognitive impairment may be a partial mediator between substance consumption and adherence to ART, as has been suggested in previous studies (Gonzalez et al., 2011; Meade et al., 2011). It would be necessary to carry out studies with larger samples and a different design to propose more specific hypotheses in this regard.

On the one hand, it is essential to inquire about the existence and pattern of substance consumption in order to establish measures to decrease its influence and to facilitate access to therapeutic resources (Gonzalez et al., 2011; Parsons et al., 2014). However, it is necessary to detect cognitive impairment in the habitual clinical practice, but there is currently no specific neuropsychological battery for HIV+ patients (GeSIDA & SPNS, 2014; Muñoz-Moreno et al., 2014). In this sense, the TMT-B and the Zoo Map Test can be useful screening tools that are easy to apply (GeSIDA & SPNS, 2014; Oosterman et al., 2013; Sánchez-Cubillo et al., 2009). Prior studies have shown that more complex treatment regimes are related to poorer adherence, particularly in individuals with cognitive deficits (Hinkin et al., 2002). In patients who score positive in the screening of impairment of cognitive functions, simplification of the treatment regime might promote better adherence. In addition, cognitive stimulation strategies, motivational work, and the use of devices of environmental support (alarms, lists, involvement of relatives or third persons…), among others, have been suggested as potentially beneficial strategies in these patients (Bragança & Palha, 2011; Parsons et al., 2014; Tran et al., 2013).

To conclude, the study shows the importance of cognitive dysfunction and alcohol consumption, after controlling for the rest of the variables, as independent risk factors of poor adherence to ART. However, sociodemographic and clinical variables, such as the male sex, youth, low socioeconomic level, co-infection with HCV, or a large number of pills per day are also associated with worse adherence. The relevance of these results in the clinical practice lies in the importance of expanding our knowledge of the factors that modulate adherence to ART, in order to implement primary and secondary prevention strategies.

Intervention on the modifiable risk factors is necessary in order to minimize therapeutic noncompliance in HIV patients. The screening and the detection of substance consumption could help to implement measures to promote access to specific treatment facilities. In addition, the systematic detection of deficits in cognitive functioning would allow us to establish strategies to improve treatment adherence. The improvement of therapeutic adherence, in turn, constitutes a preventive measure for the development of cognitive impairment and helps to decrease the morbidity and mortality associated with HIV.

Conflict of interest

The authors declare that no there is conflict of interest for the present work. Carlos Parro Torres declares that, in recent years, he has received funding as speaker and has collaborated in projects of *Lundbeck, Servier and Janssen.* Daniel Hernández Huerta declares that, in recent years, he has received funding as speaker and has collaborated in projects of *Otsuka and Janssen.* Enriqueta Ochoa Mangado declares that, in recent years, she has received funding as speaker and has collaborated in projects of *Lundbeck, Servier, Reckitt Benckiser/Indivior* and *Ferrer-Brainfarma.*

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Cognitive profile of long-term abstinent alcoholics in comparison with non-alcoholics

Perfil cognitivo de los alcohólicos abstinentes durante un periodo de tiempo prolongado en comparación con un grupo de hombres que no consumen alcohol

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Abstract

Scarce studies have focused on the cognitive profile of chronic alcoholic men after long-term abstinence. Thus, we examined neuropsychological differences between long-term abstinent alcoholics for an average of 3.2 years (n = 40, LTAA; age = 45.55 ± 8.99) and matched for socio-demographic variables with non-alcoholic controls (n = 39; age = 42.05 ± 11.33). To this aim, we employed a neuropsychological assessment battery covered relevant cognitive domains: IQ, memory, attention, executive functions and empathy. LTAA presented deficits in abstract reasoning, speed processing, sustained attention, working and long-term memory (verbal and visuospatial), cognitive flexibility, inhibition and planning. Although our results must be interpreted with caution because of the cross-sectional nature of our study, it may offer a broader knowledge and understanding of alcohol-related socio-cognitive deficits after long-term abstinence. These deficits might entail risk factors for relapse in alcohol consumption, as they may interfere with recording therapeutic advice and internalizing the verbal material presented in rehabilitation programs. In turn, these impair the global efficacy of alcohol-relapse prevention programs. Hence, this knowledge could be applicable in guiding the development of early coadjutant treatments.

Keywords: Abstinence; Alcohol related-cognitive deficits; Alcoholism; Empathy; Neuropsychology.

Resumen

Solo pocos estudios han analizado el perfil cognitivo de los hombres con un trastorno por consumo de alcohol tras un periodo de abstinencia prolongado. Por tanto, este estudio tiene como principal objetivo analizar las diferencias neuropsicológicas entre un grupo de hombres con trastorno por consumo de alcohol pero abstinentes de forma ininterrumpida durante 3,2 años (n = 40, edad = 45,55 ± 8,99) en comparación con un grupo de hombres sin trastorno por consumo de alcohol pero con unas características socio-demográficas similares a las del grupo experimental (n = 39; edad = 42,05 ± 11,33) para establecer diferentes perfiles neuropsicológicos. Empleamos una batería neuropsicológica exhaustiva que evaluó los siguientes dominios cognitivos: CI, memoria, atención, funciones ejecutivas y empatía. El grupo de hombres alcohólicos abstinentes presentaron déficits en razonamiento abstracto, velocidad de procesamiento, atención sostenida, memoria de trabajo y a largo plazo (para información verbal y visuoespacial), flexibilidad cognitiva, y en las capacidades de inhibición y planificación. A pesar de que nuestros resultados deben interpretarse con cautela dado el carácter transversal de nuestro estudio, ofrece información relevante sobre el estado cognitivo de los hombres con un trastorno por consumo de alcohol tras una abstinencia prolongada. Estos déficits podrían estar implicados en las frecuentes recaídas en esta población. Del mismo modo, interferirían en la asimilación de contenidos teóricos de intervenciones psicoterapéuticas, lo que, a su vez, disminuiría la eficacia de las mismas. Por ello, estos resultados deberían ser empleados para el desarrollo de programas de rehabilitación cognitivos coadyuvantes a la psicoterapia.

Palabras clave: Abstinencia; Alcoholismo; Déficits cognitivos; Empatía; Neuropsicología.

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Several studies have demonstrated that long-term chronic alcoholism is associated with potentially long-term deleterious effects on neuropsychological functioning (Le Berre, Fama & Sullivan, 2017; Stavro, Pelletier & Potvin, 2013; Valmas, Mosher-Ruiz, Gansler, Sawyer & Oscar-Berman, 2014), but these deficits depends on variables such as drinking patterns (the amount, type, frequency...), the age of initiation of alcohol; the duration of the hazardous and harmful alcohol consumption and the alcohol abstinence (Bernardin, Maheut-Bosser & Paille, 2014; Sullivan, Rosenbloom, Lim & Pfefferbaum, 2000a; Sullivan, Rosenbloom & Pfefferbaum, 2000b; Rosenbloom, O'Reilly, Sassoon, Sullivan & Pfefferbaum, 2005). Given that alcoholic cognitive deficits are not evently distributed among individuals, it has been suggested that long-term alcohol abusers vary along of a continuum (Bates, Voelbel, Buckman, Labouvie & Barry, 2005; Oscar-Berman, Valmas, Sawyer, Ruiz, Luhar & Gravitz, 2014).

Unfortunately there are several limitations in the study of cognitive function in abstinence. In fact, it remains unclear the time of abstinence needed for normalization of cognitive function and which cognitive domains improve during this period of abstinence (Pelletier, Nalpas, Alarcon, Rigole & Perney, 2016). Although several studies have shown certain improvements in specific cognitive domains such as visuospatial capacity, memory, and executive function after the first months to one year of abstinence (Alhassoon et al., 2012; Bernardin et al., 2014; Erickson & White, 2009; Oscar-Berman et al., 2014; Pfefferbaum, Adalsteinsson & Sullivan, 2006; Sullivan et al., 2000a; Sullivan et al., 2000b), a recent meta-analysis suggested persistent dysfunctions in multiple cognitive processes after months of alcohol abstinence (Stavro et al., 2013). Impairments and/or improvements in each cognitive ability may differ depending on the recovery rate of each brain system, which underlie to these cognitive processes (Kish, Hagen, Woody & Harvey, 1980; Pelletier et al., 2016; Pfefferbaum, Sullivan, Mathalon, Shear, Rosenbloom & Lim, 1995; Stavro et al., 2013; Yohman, Parsons & Leber, 1985).

Alcohol-related cognitive deficits may explain why therapeutic programs are not adequately processed (e.g., low participation in therapeutic workshops, absence of recording of therapeutic advice…), which in turn affect the effectiveness of rehabilitation programs due to the complexity in therapy programs (Berking, Margraf, Ebert, Wupperman, Hofmann & Junghanns, 2011). Hence, a wider knowledge of cognitive and affective deficits could be employed to guide the development of early coadjuvant treatments, which allows to improve the affected cognitive domains and in turn reduce the rate of alcohol recidivism.

The current study was designed to address this gap in our understanding by investigating differences between long-term abstinent alcoholics (LTAA) and non-alcoholic individuals (control group), to establish differential neuropsychological profiles. In the light of previous findings regarding persistent cognitive impairments in patients with alcohol use disorders (AUD) after long-term periods of abstinence (Alhassoon et al., 2012; Fein, Torres, Price & Di Sclafani, 2006; Munro, Saxton & Butters, 2000; Nowakowska-Domagała, Jabłkowska-Górecka, Mokros, Koprowicz & Pietras, 2017; Pfefferbaum et al., 2006; Stavro et al., 2013; Yohman et al., 1985), we hypothesized that LTAA would manifest neuropsychological dysfunctions relative to controls. The analysis of these cognitive profiles in LTAA are crucial for the patient's participation in relapse prevention programs.

Method

Participants

The final sample was composed of 79 men who participated voluntarily in the study: 40 LTAA and 39 individuals with no history of alcohol or drug consumption, as the control group. LTAA participants were recruited from Asociación Valenciana de Ex-Alcohólicos (*AVEX)*, which offer a psychoeducational treatment program conducted by two psychotherapists. Moreover, participants were also recruited from the community by postings at Alcoholics Anonymous (AA) meetings, mailings and subject referrals. Inclusion criteria in the current study were diagnosis of Alcohol Use Disorder (AUD) assessed by the DSM 5; participants who have been abstinent for a minimum of twelve months (Fein et al., 2006); age above 18 and less than 60 years old; and ability to understand and speak Spanish. Exclusion criteria were suffer from any neurologic or psychiatric disease such as Alzheimer's or any type of dementia, past history of stroke or brain injurys, encephalopathy, and refusal to participate. All the individuals who were candidate participants were interviewed by trained researchers (with extensive experience treating AUD) to assess their mental health. Cohen's kappa, used to assess inter-rater agreement between qualitative interviewers in the nine psychopathological dimensions evaluated (the same dimensions as the Symptom Checklist 90-R, SCL-90-R), ranged from .67 to .84. Regardless of the SCL-90-R scores, the interviewees were considered not to have any psychopathological signs and symptoms if they scored less than the mean for their age for each dimension. They were then considered eligible to participate if the qualitative interviews and SCL-90-R scores confirmed they were free of mental illness. Four LTAA participants and five controls were excluded because their results suggested psychological disorders and additional current drug abuse.

Controls were recruited via internet advertisements and posting flyers around our city from January, 2016 to August, 2016. They were matched on socio-demographic characteristics. Furthermore, it would be necessary that they present alcohol consumption lower than 30 g/day,

and less than two DSM-5 symptoms of AUD. High alcohol consumption was operationally defined as alcohol intake higher than 30 g/day (Cao, Willett, Rimm, Stampfer & Giovannucci, 2015; Cho, Lee, Rimm, Fuchs & Giovannucci, 2012; Scoccianti et al., 2016).

All participants were right-handed and healthy, were properly informed about the research protocol and gave written informed consent. The research was conducted taking into account current ethical and legal guidelines on the protection of personal data and research with human beings in accordance with the Declaration of Helsinki and was approved by the University of Valencia Ethics Committee (H1348835571691).

Procedure

All participants attended three sessions at the Faculty of Psychology. In the first session, participants were interviewed to exclude those with organic diseases and socio-demographic data were collected through a semi-structured interview. Then, participants were asked about their consumption of alcohol and cigarettes, in terms of both the amount consumed and how long they had been abstinent. Moreover, it was employed a breathalyzer to assess whether participants present a 0,0% alcohol concentration. Subsequently, they completed an inventory based on DSM-5 to check for the presence of AUD, and the Fragerström test of nicotine dependence to assess addiction level. Lastly, they were asked if they had a history of traumatic brain injury, noting whether they had lost consciousness during the trauma; for example, had they been involved in fights, and if so, how often had this resulted in head injuries and had they had blackouts after these injuries. In fact, there were excluded those participants who suffered a severe TBI. Finally, other psychological tests were studied in order to complete participant's profile.

The second and third sessions spread over two consecutive days, a range of neuropsychological variables were assessed using traditional tests and also the computer-based Cambridge Neuropsychological Test Automated Battery (CANTAB) ordered as presented in table 2. This neuropsychological testing was build based on Ruiz-Sánchez de León, Pedrero-Pérez, Rojo-Mota, Llanero-Luque & Puerta-García (2011) recommendations. If any of participants was a smoker, he was asked to smoke previously to the neuropsychological assessment to avoid any bias related to the abstinence of nicotine

The end of the assessment was marked by displaying a sign saying "Thank you very much", participants were paid €20 for their participation and told that they could leave.

Frontal Behaviour

Spanish version of *Frontal Systems Behaviour Scale (FrSBe)* is composed of 46 items that measure frontally-based behavioural syndromes such as disinhibition (15 items), apathy (14 items) and executive dysfunction (17 items) (Pedrero-Pérez, Ruiz-Sánchez de León, Llanero-Luque, Rojo-Mota, Olivar-Arroyo & Puerta-García, 2009), all being rated on a 5-point Likert-type scale (1 = 'not at all' to 5 = 'very much so').

We used the translated into Spanish version of the Montreal cognitive assessment (MoCA) (http://www.MoCA-test.org/). The MoCA measures eight cognitive domains such as naming, attention, language, abstraction, delayed memory, orientation, visuospatial and executive abilities. The initially proposed normal MoCA score is ≥ 26, but a point must be added to the total score in participants with low educational level (less than 12 years of education).

IQ (abstract reasoning and processing speed) (table 1)

Abstract reasoning and processing speed were measured by the subtests matrix reasoning, digit symbol-coding, symbol search and similarities of the WAIS-III (Wechler, 1999).

Attention (table 1)

We employed the translated version into Spanish of the d2 test, which measures the ability to focus on relevant stimulus while ignoring irrelevant (Seisdedos, 2004). It consists in 14 lines with 47 characters each one, which contains letters such as «d» and «p». Participants should check during 20 seconds for each line from left to right, the contents of each line marking only «d» showing two little dashes (both above, below or one above and one below). Dependent scores for this study were: TR, overall answer; TA, number of correct guesses; O, omitted elements; C, commissions; TOT, total test effectiveness; and CON concentration index.

Attention Switching Task (ATS) measures the ability to switch attention between the direction of an arrow and its location on the screen and avoiding distracting events. It is a highly cognitive demanding test as participants should switch their attention between congruent (e.g., arrow on the right side of the screen pointing to the right) and incongruent stimuli (e.g., arrow on the right side of the screen pointing to the left) presentation. Dependent variables for this study were switch cost, percentage of correct responses and congruency cost (Cambridge Cognition Ltd, 2012).

Rapid Visual Information Processing (RVP) measures sustained attention. This test consists in a white box appears in the centre of the computer screen, inside which digits, from 2 to 9 are presented randomized. Subjects should detect specific target sequences of three consecutive digits (e.g., 2,4,6; 3,5,7 and 4,6,8). Dependent variable for this study was target sensitivity.

Choice Reaction Time (CRT) is a 2-choice reaction time test that assesses attentional ability and reaction times, which includes a practice stage of 24 trials and two assessment stages of 50 trials each. Dependent variables for this study were percentage of correct answers and mean correct latency (ms) (Cambridge Cognition Ltd, 2012).

Table 1. *Neuropsychological test battery.*

Neuropsychological test	
IQ	
Matrix reasoning WAIS-III	Abstract reasoning
Digit symbol-coding and symbol search	Processing speed
Similarities of the WAIS-III	Verbal reasoning
Attention	
d2 test	Sustained attention
Rapid Visual Information Processing (RVP)	Sustained attention
Attention Switching Task (AST)	Switch-attention
Choice Reaction Time (CRT)	Reaction times
Memory	
Word List WAIS-III	Immediate recall, delayed recall and recognition.
Rey–Osterrieth Complex Figure Test	Visuospatial constructional ability and visual memory
Logical Memory WMS-III	Short and long-term memory and recognition
Digit Span WAIS-III	Short-term memory, attention, and concentration
Letter-Number Sequencing WAIS-III	Simultaneously recall and organize stimuli (working memory)
Spatial Span WMS-III	Working memory capacity (visuospatial)
Spatial Span Test (CANTAB)	Working memory capacity (visuospatial)
Executive functions	
Semantic categorial evocation of animals and FAS verbal phonemic fluency	Verbal fluency
Stroop	Divided attention and resistance to interference
Hayling test	Verbal inhibition
Five-Point test	Design fluency
Wisconsin Card Sorting Test (WCST)	Abstract reasoning and the ability to change cognitive strategies in response to environmental changes (cognitive flexibility)
Zoo test and Key test	Ability to plan a strategy to solve a problema (planning)
One Touch Stockings of Cambridge (OTS)	Spatial planning and working memory
Cambridge Gambling Task (CGT)	Decision-making and risk-taking behaviour
Empathy	
Reading the mind in the eyes	Emotion decoding abilities

Memory (table 1)

Word List is a subscale of the WMS-III (Wechler, 1997). Participants must recall a list of words presented five times, and each time, the participant has to repeat the maximum number of words that he/she can recall. Moreover, there is an interference list. This test consists of three test conditions: immediate recall, delayed recall and recognition.

Rey–Osterrieth Complex Figure Test assessed visuospatial constructional ability and visual memory. This test consists of three test conditions: copy, immediate recall and delayed recall. Initially, participants must copy a stimulus card. Afterwards, the card is taken away and they are instructed to draw what they remember of the figure. Finally, participants must draw the same figure once again after 30 minutes.

WMS-III *Logical Memory* evaluates short and long-term memory and recognition of two stories. Participants should remember as many ideas as possible from two stories (Wechler, 1997).

Digit Span is a subscale of the WAIS-III, which measures short-term memory, attention, and concentration. Participants are asked to repeat digits in direct and inverse order (Wechsler, 1999).

Letter-Number Sequencing is a subscale of the WAIS-III, which measures the ability to simultaneously recall and organize stimuli (working memory). Subject should repeat several series by repeating the numbers in ascending order, and then the letters in alphabetical order (e.g., 9-L-2-A; correct response is 2-9-A-L) (Wechsler, 1999).

Spatial Span is a subscale of the WMS-III, in which participants must copy a series of moves made by the evaluator with increasing difficulty. There are also two parts (direct and inverse order).

Spatial Span Test from the CANTAB measures working memory capacity. It has been presented white squares, some of which briefly change colour in a variable sequence. This test is stopped when the subject fails three consecutive trials at any specific level. The maximum number of boxes correctly defines the final score obtained (Cambridge Cognition Ltd, 2012).

Executive function tests (table 1)

Verbal fluency

Semantic categorial evocation of animals consists of asking the patient to say as many animal names as he can in about 60 seconds. It has been assigned 1 point for each correct animal name evoked in that time interval, without a maximum score (Del Ser Quijano, Sanchez Sánchez, Garcia de Yebenes, Otero Puime, Zunzunegui & Muñoz, 2004). Moreover, in the F-A-S verbal phonemic fluency participants must produce as many words as possible with each of the three test letters previously presented during 60 seconds each one.

Inhibition

The Stroop color and word test measures the ability of divided attention and resistance to interference (Spreen & Strauss, 1991).

For the assessment of verbal inhibition we employed the Hayling test (Burgess & Shallice, 1997).

Cognitive flexibility

For *Design fluency* was employed the Five-Point test, which involves the uses of a structured background that consists of a sheet of paper with 40- dot matrices (five columns x eight rows). Participants should draw as many different figures as possible by connecting any numbers of dots from the 5 dots within each cell to create novel designs within 60 seconds (Lezak, 2004).

Wisconsin Card Sorting Test (WCST) measures abstract reasoning and the ability to change cognitive strategies in response to environmental changes. It consists of 4 stimulus cards and 128 response cards containing various colours (red, blue, yellow or green), shapes (circle, cross, star or triangle) and numbers (one, two, three or four) of figures (Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

Planning

Zoo test and *Key test* are part of the Behavioural Assessment of Dysexecutive Syndrome (Wilson, Alderman, Burgess, Emslie & Evans, 1996).

One Touch Stockings of Cambridge assesses spatial planning and working memory based upon the Tower of Hanoi test. The participant is shown two displays containing three coloured balls. Dependent variables are problems solved on first choice, mean choices to correct, mean latency to first choice and mean latency to correct (Cambridge Cognition Ltd, 2012).

Decision making

Cambridge Gambling Task measures decision-making and risk-taking behaviour. It has been presented a row of ten boxes across the top of the screen, some red and some blue. Rectangles containing the words 'red' and 'blue' can be seen at the bottom of the screen. Participants then have to decide whether the yellow taken is hidden in a red box or in a blue box. A set of points to gamble with is shown on the screen, which are displayed in rising or falling order. Participants are allow to place whatever bet they want with the number of points provided in order to gamble on their confidence in this judgement. The participants are aske to earns as many points as possible (Cambridge Cognition Ltd, 2012).

Empathy (table 1)

Eyes Test measures emotion decoding abilities by identifying the emotion that best represents the expression of the eyes in 36 photographs that show the eye region of the face of different men and women. In fact, subjects must choose one of a set of four adjectives. Total score, which ranged from 0 to 36 points, is obtained by summing the number of correct answers (Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001), being interpreted a higher score as indicative stronger emotional decoding abilities.

The Spanish version *Interpersonal Reactivity Index* measures empathic response (Mestre, Frías & Samper, 2004), which includes four subscales such as perspective taking and fantasy (cognitive empathy) and emotional empathic concern and personal distress (emotional empathy). Responses are given on a 5-point Likert scale. The total score ranged from 7 to 35 points in each subscale, and a higher score indicate higher empathic skills.

Alexithymia was assessed using the Spanish version of the Toronto Scale of 20 Elements (TAS-20) by Bagby, Parker & Taylor (1994). It is a scale of 20 Likert type reagents with 6 variation points per element (from 0 to 5).

Data analysis

The Shapiro-Wilk test was used for exploring whether the data were normally distributed. Due to the fact that the majority of variables did not meet the assumption of normality ($p < .05$), therefore, it was decided to carry out nonparametric tests for statistical analysis of the results. U Mann–Whitney test was used to check for significant differences between the groups in socio-demographic, questionnaire scores and neuropsychological test. In addition, chi square analyses were performed for categorical variables such as socio-demographic characteristics (nationality, marital status, level of education, employment status, etc.).

Data analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, USA). P values < 0.05 were considered statistically significant. Average values are reported in tables as mean±SD.

Results

Sample characteristics

Descriptive characteristics for LTAA and controls are presented in Table 2. Regarding AVEX (85% sample) and AA patients (15% sample) there were not differences between clinical and socio-demographic characteristics. Groups did not differ in anthropometric or socio-demographic variables, personal history of traumatic brain injury, or temporary loss of consciousness. Nevertheless, they differed in self-reported executive dysfunction, (Mann–Whitney $U = -2.64$, $p = 0.008$), and apathy, (Mann–Whitney $U = -2.80$, $p = 0.005$), with LTAA obtaining higher scores than controls. Moreover, a significant effect for group was found in IQ matrix Reasoning, (Mann–Whitney $U = -3.42$, $p = 0.001$), IQ similarities, (Mann–Whitney $U = -3.42$, $p = 0.001$), and IQ copy (Mann–Whitney $U = -3.03$, $p = 0.002$), having LTAA higher scores in all these scales than controls.

Table 2. *Mean ± SD of descriptive characteristics for all groups (*p ‹ .05).*

	Alcohol group (n = 40)	Controls (n = 39)
Age (years)	45.55 ±8.99	42.05 ±11.33
BMI (Kg/m²)	27.74 ±3.42	26.90 ±4.96
Nationality		
Spanish	34 (85%)	32 (82%)
Latin Americans	6 (15%)	7 (18%)
Marital status		
Single	15 (38%)	17 (44%)
Married	9 (23%)	9 (23%)
Separate/Divorced/Widowed	16 (40%)	10 (26%)
Number of children	.94 ±1.03	1.20 ±0.95
Level of education		
Primary/lower secondary	18 (45%)	18 (46%)
Upper secondary/vocational training	17 (43%)	17 (44%)
University	5 (12%)	4 (10%)
Employment status		
Employed	18 (45%)	18 (46%)
Unemployed	22 (55%)	21 (54%)
Income level		
1800€ – 12000€	25 (63%)	25 (64%)
12000€ – 30000€	12 (30%)	12 (31%)
› 30000€ – 90000€	3 (7%)	2 (5%)
Personal history of traumatic brain injury	13 (48.14%)	14 (40%)
Yes	14 (51.85%)	21 (60%)
No		
Temporary loss of consciousness		
Yes	8 (29.36%)	14 (40%)
No	19 (70.37%)	21 (60%)
Alcohol Use Variables		
Age started drinking	17.74 ±8.82	-
Age at first heavy use	22.75 ±7.92	-
Average lifetime drinking dose (gr/day)	202.84 ±148.69	
Duration of active drinking (years)	22.80 ±8.82	-
Time of alcohol abstinence (months)	40.72 ±77.40	-
Family members with AUD		
Yes	37%	-
No	63%	-
Cigarettes/day*	16.61 ±10.13	9.75 ±7.21
Fagerstrom test	4.84 ±3.91	3.17 ±1.11
Frontal Behavior test		
Executive dysfunction**	19.77 ±9.54	13.14 ±7.14
Apathy**	10.33 ±5.77	6.25 ±4.94
Desinhibition	9.33 ±4.47	7.05 ±3.51

Neuropsychological assessment
Attention and memory (table 3)

Attention

We checked group differences and observed a number of differences that approached significance in the D2 Test, especially the total number of characters processed (Mann–Whitney U = -3.42, p = 0.001), total correctly processed (Mann–Whitney U = -2.97, p = 0.003), total number of errors (Mann–Whitney U = -2.83, p = 0.005), total performance (Mann–Whitney U = -3.42, p = 0.001) and concentration performance (Mann–Whitney U = -3.37, p = 0.001), while LTAA had a lower number total number of characters processed and total correctly processed, worse D2 and concentration performance and made more errors than controls. Regarding RVP, a significant group effect was found (Mann–Whitney U = -2.32, p = 0.021), LTAA performing less well in detecting the target sequences than controls.

Memory

Regarding the Wechsler Memory Scale-III Word List subscale, the difference between groups for the total number of words remembered (Mann–Whitney U = -4.19, p > 0.001), the number of words remembered in the first trial (Mann–Whitney U = –3.19, p = 0.001), short-term memory (Mann–Whitney U = -2.32, p = 0.020), the interference list (Mann–Whitney U = -4.19, p > 0.001) and recognition (Mann–Whitney U = -2.74, p = 0.006) were significant. LTAA remembered and recognized fewer words than controls.

For the ROCF test, "group" proved to be significant for copy time (Mann–Whitney U = -3.12, p = 0.002), short-term memory score (Mann–Whitney U = -3.17, p = 0.001), and long-term memory score (Mann–Whitney U = -3.48, p = 0.001), with LTAA needing more time to copy the figure and remembering the figure less well (both short-term and long-term) than controls.

Regarding the Logical Memory subscale, a significant effect of group was found in the first time that text A was read (Mann–Whitney U = -2.85, p = 0.004), text A units (Mann–Whitney U = -2.93, p = 0.003), and text B units 1, (Mann–Whitney U = -2.57, p = 0.010), and topics 1 (Mann–Whitney U = -2.12, p = 0.034) and text B units 2, (Mann–Whitney U = -2.05, p = 0.040), and topics 2 (Mann–Whitney U = -2.07, p = 0.039), LTAA remembered fewer units and topics than controls. Therefore, there were also group effects for delayed recalled of text A units (Mann–Whitney U = -2.06, p = 0.039) and topics, (Mann–Whitney U = -2.87, p = 0.004) and text B units (Mann–Whitney U = -1.97, p = 0.004), LTAA obtaining worse scores, meaning that they remembered both texts less well, than controls. There were also group effects for the recognition task (Mann–Whitney U = -3.72, p < 0.001), the LTAA group having lower scores than controls.

In the Digits Span subscale, though no significant differences were found between groups in direct scores, "group" was found to be significant in inverse order (Mann–Whitney U = -3.83, p < 0.001),, LTAA remembering fewer digits, especially in inverse order, than controls. Similarly, regarding the Letter-Number Sequencing subscale, there was a "group" effect (Mann–Whitney U = -3.83, p < 0.001), with LTAA remembering fewer letters and numbers than controls.

Tabla 3. *Mean ±SD of Memory tests of all grups (*p ‹ .05)*

	Alcohol group (n = 40)	Controls (N = 39)
IQ		
Speed processing		
Symbol search	30.05 ±8.89	33.98 ±9.35
Abstract reasoning		
Digit Symbol - Coding		
Coding**	60.72 ±14.31	70.58 ±14.08
Incidental Learning Pairing*	10.21 ±5.39	12.50 ±4.96
Incidental Learning Free Recall	6.41 ±2.55	7.40 ±1.46
Copy**	103.51 ±23.16	117.40 ±18.76
Matrix Reasoning***	11.74 ±4.51	16.55 ±6.49
Similarities*	16.33 ±4.52	18.73 ±4.33
Attention		
D2		
TR***	387.18 ±95.94	485.70 ±79.37
O	23.92 ±22.64	30.55 ±31.00
C**	17.87 ±31.53	8.93 ±18.80
TA**	136.97 ±39.72	165.78 ±41.07
TOT= TR - (0 ± C)***	345.38 ±88.85	419.23 ±88.37
CON= TA –C***	119.10 ±42.93	156.85 ±51.49
E%= (100(O ±C))/TR	10.78 ±7.68	8.80 ±9.99
AST		
Switch cost	-146.33 ±136.41	-142.44 ±116.85
Percentage of correct responses (%)	89.31 ±11.24	93.03 ±6.73
Congruency cost	115.25 ±119.01	92.17 ±81.56
RVP Sensitivity (from .0 to 1.00)*	0.89 ±0.05	0.91 ±0.08
CRT		
Percentage of correct answers (%)	99.15 ±1.05	99.32 ±0.91
Mean correct latency (ms)	424.15 ±81.47	411.20 ±93.76
Memory		
Word Lists test		
Total words recalled***	28.91 ±5.38	34.64 ±4.99
Short-term memory*	7.51 ±2.00	8.36 ±1.94
Long-term memory*	6.76 ±2.14	7.72 ±2.16
First trial***	4.92 ±1.49	6.00 ±1.37
Learning curve	3.75 ±1.92	4.54 ±1.57
Interference list***	3.73 ±1.61	5.28 ±1.67
Omission	1.78 ±1.64	2.31 ±1.49
Recognition**	22.43 ±1.21	22.97 ±1.55
Rey Figure		
Copy score	34.86 ±1.39	35.31 ±1.23
Copy time**	152.24 ±59.70	118.93 ±44.86
Short-term memory score***	19.92 ±7.25	25.10 ±6.01
Short-term memory time	119.54 ±43.19	110.08 ±45.23
Long-term memory score***	19.19 ±6.21	24.46 ±6.38
Long-term memory time	95.77 ±33.82	93.46 ±32.57
Logical Memory test		
Delayed recall:		
Total score on the first try**	22.65 ±7.85	27.23 ±6.85
Text A		
Units**	11.93 ±3.45	14.15 ±3.84
Topics	4.60 ±1.99	5.41 ±1.27
Text B		
Units 1*	10.45 ±4.53	13.08 ±3.72
Topics 1*	4.45 ±2.36	5.72 ±1.10
Units 2*	10.45 ±4.53	10.45 ±4.53
Topics 2*	4.45 ±2.36	4.45 ±2.36
Delayed recall:		
Text A		
Units*	9.00 ±4.37	10.87 ±3.85
Topics**	4.10 ±2.01	5.38 ±1.37
Text B		
Units*	14.45 ±4.85	16.41 ±4.93
Topics	5.13 ±1.91	5.92 ±1.27
Recognition***	23.70 ±3.24	25.82 ±4.93
Digits		
Direct order	8.47 ±1.61	9.00 ±2.71
Inverse order***	5.06 ±1.53	6.90 ±2.19
Total score**	13.55 ±2.56	15.90 ±4.47
Letters and numbers		
Total score***	8.44 ±2.10	10.85 ±2.77
Spatial location		
Direct order	8.64 ±1.76	9.23 ±1.77
Inverse order**	7.14 ±1.59	8.38 ±2.18
Total score*	15.79 ±2.80	17.62 ±3.38

Table 4. *Mean ±SD of executive functions and empathy tests scores for all groups (*p ‹ .05).*

	HA (n = 40)	LA (n = 39)
Verbal fluency		
Semantic (animals)	21.64 ±5.62	23.85 ±4.68
Phonemic (F, A and S)	37.33 ±12.11	40.38 ±13.82
Design fluency		
Part A***	15.26 ±5.15	19.38 ±5.53
Part B*	16.97 ±5.10	10.30 ±5.16
Inhibition		
Stroop 1*	100.23 ±14.34	108.38 ±14.52
Stroop 2	70.23 ±11.07	72.00 ±11.95
Stroop interference*	39.33 ±8.47	44.03 ±11.24
Hayling part A		
Time (sec)*	1.87 ±1.06	1.43 ±0.84
Score**	14.00 ±0.93	14.37 ±0.95
Hayling part B		
Time (sec)	4.65 ±3.82	3.83 ±3.09
Score	13.97 ±8.05	11.90 ±8.15
Cognitive flexibility		
Total trials***	113.32 ±19.41	93.40 ±21.17
Correct trials*	74.11 ±12.61	67.45 ±9.68
Total errors*	39.21 ±22.14	26.35 ±21.64
Perseverative mistakes*	21.71 ±13.07	13.90 ±13.57
Non perseverative mistakes*	17.39 ±11.79	11.87 ±10.22
Random not perseverative errors*	24.18 ±19.46	15.97 ±16.58
Completed categories*	4.34 ±1.79	5.33 ±1.56
Attempts to complete the first category	21.32 ±22.70	16.02 ±19.02
Failure to maintain the set**	1.37 ±1.65	0.40 ±0.95
Planning		
Zoo version 1		
Planning time (sec)	72.32 ±45.88	61.27 ±26.50
Execution time (sec)*	71.56 ±33.59	56.40 ±33.84
Errors	1.41 ±1.74	1.13 ±1.20
Total score version 1	3.15 ±3.45	3.97 ±2.81
Zoo version 2		
Planning time (sec)	32.51 ±19.03	23.19 ±12.72
Execution time (sec)*	45.23 ±20.14	35.37 ±18.66
Errors	0.59 ±0.97	0.36 ±0.67
Total score version 2	6.26 ±2.11	7.03 ±1.97
TOTAL SCORE	9.49 ±4.80	11.00 ±3.80
Key Test		
Planning time (sec)	20.76 ±29.39	14.94 ±14.53
Execution time (sec)*	36.51 ±36.23	32.64 ±26.18
Total score***	6.79 ±3.51	11.21 ±3.58
OTS problems solved on first choice* **	15.03 ±3.02	16.00 ±4.45
OTS mean choices to correct* **	1.71 ±0.53	1.63 ±0.46
Problems with:		
1 moves	1.17 ±0.53	1.12 ±0.22
2 moves	1.25 ±0.39	1.17 ±0.42
3 moves**	1.42 ±0.49	1.37 ±0.46
4 moves***	1.67 ±0.58	1.60 ±0.59
5 moves*	1.97 ±0.84	1.79 ±0.73
6 move***	2.79 ±1.15	2.72 ±1.08
OTS mean latency to first choice	14673.62 ±7265.36	18906.10 ±11429.33
Problems with:		
1 moves***	8747.65 ±3302.95	12087.74 ±9363.30
2 moves*	7082.91 ±22705.63	7825.22 ±23041.18
3 moves	8965.16 ±4337.98	10427.44 ±4870.10
4 moves	14439.84 ±11311.03	16357.72 ±9071.56
5 moves	24721.74 ±16877.17	26256.96 ±18742.32
6 move	24084.41 ±17827.82	40481.52 ±48533.45
OTS mean latency to correct		
Problems with:		
1 moves***	9313.49 ±3694.57	14111.03 ±11395.22
2 moves*	8902.96 ±3818.69	10136.43 ±7401.45
3 moves*	11758.40 ±8527.88	13884.02 ±8386.89
4 moves*	22097.44 ±24259.04	22477.01 ±13627.41
5 moves	35255.63 ±25785.04	35885.43 ±23406.45
6 moves	39906.75 ±28624.96	57317.70 ±51771.00
CGT		
Delay aversion	.19 ±.28	.13 ±.19
Deliberation time	2722.61 ±893.26	2587.29 ±801.52
Proportion bet	.50 ±.13	.51 ±.18
Quality of decision making	.88 ±.11	.85 ±.16
Risk adjustment	.95 ±.88	.78 ±.90
Risk taking	.54 ±.13	.55 ±.17
Empathy		
IRI		
Perspective taking	22.86 ±5.87	22.79 ±4.81
Fantasy	18.59 ±5.05	19.21 ±6.67
Empathic concern	25.47 ±4.17	25.95 ±3.54
Personal distress***	16.21 ±4.26	12.00 ±3.00
Eyes Test		
Total score	23.03 ±4.50	22.43 ±4.261
TAS**	63.92 ±12.93	54.89 ±11.60

With regards to the Spatial Span subscale, "group" proved to be significant in inverse order (Mann–Whitney U = -2.65, p = 0.008), and total score (Mann–Whitney U = -2.13, p = 0.033), with LTAA being less able to repeat the series of movements made by the evaluator than controls. However, there were no significant differences between groups in direct order Spatial Span score.

Executive functions and empathic skills (table 4)

Cognitive flexibility

A significant "group" effect was found for the following WCST scales: total trials, (Mann–Whitney U = -3.83, p < 0.001); correct trials, (Mann–Whitney U = -2.89, p = 0.004); total errors, (Mann–Whitney U = -2.82, p = 0.005); perseverative errors, (Mann–Whitney U = -3.29, p = 0.001); rate of perseverative errors, (Mann–Whitney U = -2.61, p = 0.009); non-perseverative errors, (Mann–Whitney U = -2.34, p = 0.019); completed categories, (Mann–Whitney U = -3.02, p = 0.003), and failures to maintain the set, (Mann–Whitney U = -3.54, p < 0.001). LTAA needed more trials, made more errors, completed fewer categories, and more often failed to maintain the set than controls (Table 4).

Planning

Regarding the Zoo test, group proved to be significant in execution time (Mann–Whitney U = -2.27, p = 0.023), and execution time of version 2 (Mann–Whitney U = –2.92, p = 0.008), with LTAA spending more time planning than controls, which means that they had more problems developing logical strategies than controls.

There was a significant group effect for the total score on the Key test (Mann–Whitney U = -4.65, p < 0.001), LTAA being less able to plan a strategy to solve a problem than controls. Nevertheless, no significant differences were found between groups in planning and execution time.

A significant "group" effect was found in the OTS problems solved on the first choice (Mann–Whitney U = -3.84, p < 0.001), and in mean choices to correct total (Mann–Whitney U = -3.70, p < 0.001), third (Mann–Whitney U = -3.11, p = 0.002), fourth (Mann–Whitney U = -3.44, p = 0.001), fifth (Mann–Whitney U = -2.30, p = 0.022) and sixth (Mann–Whitney U = -3.77, p < 0.001) movements to correct, LTAA requiring more movements to finish the exercises and achieving less good performance than controls. Nonetheless, there were no significant differences in trials which only required one or two movements. Finally, a group effect was also found for latency to first choice (1 move) (Mann–Whitney U = -3.61, p < 0.001), (2 moves) (Mann–Whitney U = -2.52, p = 0.012) and latency to finish exercises correctly in exercises that need one movement (Mann–Whitney U = -3.84, p < 0.001), 2 moves (Mann–Whitney U = -2.35, p = 0.019), and 4 moves (Mann–Whitney U = -2.08, p = 0.038). Specifically, LTAA took more time to do the movements than controls.

Decision making

Regarding the CGT, no significant differences were found between groups in the proportion bets (Mann–Whitney U = -.13, p = 0.895), delay aversion (Mann–Whitney U = -1.26, p = 0.208), deliberation time (Mann–Whitney U = -.71, p = 0.474), quality of decision making (Mann–Whitney U = -.11, p = 0.914), risk adjustment (Mann–Whitney U = -.95, p = 0. 344) and risk taking (Mann–Whitney U = -.05, p = 0.953).

Empathy

A significant group effect was found in the IRI Personal distress (Mann–Whitney U = -4.29, p < 0.001), with LTAA presenting higher scores than controls. Nonetheless, groups did not differ in fantasy, empathic concern or perspective taking. With regards to the TAS, group proved to be significant (Mann–Whitney U = -2.94, p = 0.003), LTAA obtaining higher scores than controls. Finally, there were not found differences between groups in eye test.

The calculated type II error ranged from 1% to 12% in all the analysis.

Discussion

In the present study, we compared the neuropsychological performance on a computerized battery with pencil-and-paper tests of LTAA with non-alcoholic matched for demographic variables controls. We initially hypothesized that LTAA would manifest more neuropsychological dysfunctions, particularly memory and executive dysfunction, than controls. As expected, the LTAA group presented deficits in the abstract reasoning, speed processing, sustained attention, working and long-term memory (verbal, logical and visuospatial), cognitive flexibility, inhibition and time of planning. In addition, the LTAA had significantly more personal distress and alexithymic symptoms than the controls, though they did not differ from the controls in perspective taking, fantasy, empathic concern and emotional decoding skills.

Our study reinforces that certain cognitive skills such as abstract reasoning, speed processing, sustained attention, working and long-term memory (verbal, logical and visuospatial), cognitive flexibility, inhibition and time of planning might be persistently impaired after long term abstinence (Fein et al., 2006; Stavro et al., 2013). Additionally, LTAA also showed higher self-reported executive dysfunction, apathy, disinhibition and impulsivity in comparison with controls. In fact, it has been suggested that a result of chronic hazardous alcohol use could increase the risk of disinhibition and impulsivity, which entails a lack of concern for the consequences of inappropriate behaviours (Kravitz et al., 2015; Staples & Mandyam, 2016). These alcohol-related disinhibitory behaviors can be traced by neurobiological abnormalities such as prefrontal cortex, which is part of

the substrate for executive control (Abernathy, Chandler & Woodward, 2010).

Based on WCST and OTS performance, LTAA presented less cognitive flexibility and weaker planning skills than controls. This means that they have problems to use negative feedback, suggesting they are less able to learn from aversive experience and modify behaviours in light of this learning. They also had problems developing logical strategies, with their abstract reasoning and they also need more time to planning their decisions and inhibit inappropriate responses than controls. It seems logical to conclude that these deficits could be explained by LTAA sustained attention and working memory impairments', which constrain the ability to learn, remember and adaptively utilize associations, reasoning, and problem solving.

Whether good decision making is a result of an accurate judgment of anticipated outcomes (Clark et al., 2011), attention and memory complaints may lead to ignorance of possibly advantageous choice alternatives or avoid unnecesary risks in decision-making situations. In fact, speed processing, attention and memory are important for these abilities, allowing focus on relevant stimuli and in inhibiting automatic thinking. Nonetheless, as LTAA did not differ from controls in CGT decision-making, we can't assume that LTAA make risky and/or impulsive decisions. Conversely, a previos research concluded that LTAA exhibited poor decision-making on the Iowa Gambling Task, which was attributed to their tendency to immediate reward than by delayed punishment (Fein et al., 2006). These differences between studies could be attributed to methodological reasons such as the neuropsychological tests employed in each study and/or by heterogeneity of AUD samples (time of abstinence, number of years of alcohol consumption, *polydrug* abuse, etc). However, it is important to note that in our study other cognitive processes requiring switch-attention, reaction times, verbal fluency, verbal inhibition, cognitive empathy and emotional decoding abilities seem well preserved. As the somatic marker model proposes that decision-making depends on cognitive and emotional processes (Gutnik, Hakimzada, Yoskowitz & Patel, 2006), the relatively well preserved cognitive and emotional abilities may help LTAA avoid unnecessary risks, but our data demonstrated that LTAA need more time to plan o make a choice than non-alcoholic controls. Therefore, our results underscoring the view that cognitive flexibility, inhibition or planning impairments are the main and determinant cause of decision-making deficits.

Several studies have been reported persistent deficits for processes related to social cognitive information, decoding of affective states, empathic ability, and in theory-of-mind in individuals with prolonged alcohol abstinence (Grynberg, Maurage & Nandrino, 2017; Maurage, Pesenti, Philippot, Joassin & Campanella, 2009; Stasiewicz et al., 2012). Additionally, sober alcohol patients tend to present difficulties to identify, differentiate, and express feelings (alexithymic symptoms) (Stasiewicz et al., 2012). Our results partially reinforced previous research in this field. Indeed, LTAA exhibited higher self-reported personal distress and alexithymic symptoms in comparison with controls. Conversely, they did not showed differences in cognitive empathy and emotional decoding abilities in comparison with controls. Based on or data, we could conclude that specific empathic measures did not present deficits after long-term abstinence, with the notable exception of personal distress and alexhitimia, on which alcoholism-related deficits remained. As regulate distressing emotional experiences and interpersonal difficulties to identify, differentiate, and express feelings has been associated with relapse after detoxification (Zywiak, Westerberg Connors & Maisto 2003), this suggest the importance to consider emotional and interpersonal difficulties in clinical treatment for alcoholics.

The main limitation of the study is that the sample sizes were modest. For this reason, the findings should be considered preliminary, and further research is needed to explore these patterns in larger samples. Another limitation of the current study is the use of cross-sectional data rather than longitudinal data, and hence definitive conclusions cannot be drawn regarding the long-term effects of alcohol in these cognitive skills. Moreover, it would be possible that alcoholics present pre-existent cognitive deficits to alcohol consumption, which increase their proneness to alcohol abuse. Hence, we can not demonstrate cognitive recovery or impairments over time. Longitudinal studies are necessary to understand how duration of alcohol abstinence could contribute to scope and limitations of recovery of emotional and social abilities. Additionally, it would be necessary to specify the role of these cognitive deficits in alcohol-relapse. Another limitation, the neuropsychological tests employed to assess these deficits tend to measure broad categories of abilities without a homogeneous consensus on which specific attributes define these functions.

Finally, it seems logical that these deficits may interfere in workshops, and psychotherapy in alcoholic patients during the detoxification period. Indeed, the large amounts of verbal and complex material presented in therapy programs is not being adequately processed due to conceptual thinking and abstract reasoning impairments in alcoholics. Nevertheless, it should be mentioned that the absence of recording therapeutic advice or low participation in workshops might also reflects participants' non-engagement with the program and not necessarily cognitive deficits. It may be necessary to develop early coadjuvant neuropsychological rehabilitation program to existent psychotherapy programs after detoxification (Frías-Torres, Moreno-España, Ortega, Barrio, Gual & Teixidor López, 2018). Hence, this knowledge could be employed to guide the development of early coadjuvant treatments, which allows to im-

prove the affected cognitive domains and in turn reduce the rate of alcohol recidivism.

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Onset and progression of drug use in the general population of Catalonia, Spain

Inicio y progresión en el uso de sustancias en la población general de Cataluña, España

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Abstract

The aim of the present study was to retrospectively study the onset and progression sequence of the most frequent pathways of drug use initiation in a sample of the Spanish general population. Data come from the 2011 household survey on drug use in Catalonia, Spain, on non-institutionalized individuals aged 15-64 in the general population. The final sample was of 2,069 individuals and had the same age distribution as the general population. Progressions of drug initiation were pictured by quantifying transitions from a previous state in terms of the number of individuals and weighted percentages. Survival analyses were employed to assess the most prevalent pathways found in the descriptive analysis using additive regression models. Median ages of onset were decreasing in every cohort from 1965 to 1985-1996: from 17 to 15 in tobacco, 20 to 16 in cannabis and 21 to 18 in cocaine. In people who consumed the three drugs studied, the most frequent pathway was "tobacco-daily tobacco-cannabis-cocaine". These results demand health policies and prevention strategies in order to increase perception of the risks of legal and illegal substances. This, together with well-designed peer interventions could reduce the risk of exposure to illegal drugs such as cannabis and cocaine, thus reducing the likelihood of future problem drug use.

Keywords: Tobacco; Cannabis; Cocaine; Age of onset; Population surveillance.

Resumen

Este estudio tuvo como finalidad realizar un análisis retrospectivo de la secuencia de inicio y progresión de las vías más comunes del inicio del uso de sustancias en una muestra de la población general española. Recopilamos datos de la encuesta nacional de las viviendas del año 2011 sobre el uso de sustancias en Cataluña, España, respecto de personas no-institucionalizadas de la población general con edades entre los 15-64 años. La muestra final estaba compuesta de 2.069 personas con la misma distribución de edad que la población general. Mostramos la progresión en el inicio de uso de sustancias mediante la cuantificación de los cambios de un estado anterior, en términos de número de personas y porcentajes ponderados. Aplicamos análisis de supervivencia para valorar las vías más prevalentes halladas en el análisis descriptivo usando modelos de regresión aditivos. La edad media de inicio de uso fue decreciendo en todas las cohortes desde 1965 hasta 1985-1996: de 17 a 15 para tabaco, de 20 a 16 para cannabis y de 21 a 18 para cocaína. En las personas que usaban las tres sustancias estudiadas, la vía más frecuente fue "tabaco-uso diario de tabaco-cannabis-cocaína". Dichos resultados requieren políticas de salud y estrategias de prevención para aumentar la percepción de los riesgos de las sustancias legales e ilegales. Esto, unido a intervenciones de compañeros bien diseñadas, podría reducir el riesgo de exposición de sustancias ilegales, como cannabis y cocaína, y, por tanto, reducir la probabilidad de un problema de uso de sustancias en un futuro.

Palabras clave: Tabaco; Cannabis; Cocaína; Edad de inicio; Vigilancia poblacional

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Early onset of drug use is associated with a variety of long term negative outcomes (Poudel & Gautam, 2017), being one of the factors most strongly associated to a higher prevalence of drug use, as well as to engaging in other risky health behaviors (DuRant, Smith, Kreiter & Krowchuk, 1999). An early initiation of tobacco and/or cannabis could increase the risk of initiating other illicit drugs and later dependence problems (Anthony, 2012; Baggio et al., 2014; Choo, Roh & Robinson, 2008; Fergusson & Boden, 2014; Swift et al., 2012; van Leeuwen et al., 2011), as well as family, social, and legal problems (Hser, Grella, Collins & Teruya, 2003).

The most frequent sequence of drug use involves initiation with legal substances, like tobacco, and followed by use of illicit substances like cannabis and then of cocaine and other stimulants (Mayet, Legleye, Chau & Falissard, 2010; Mayet, Legleye, Chau & Falissard, 2011; Mayet, Legleye, Falissard & Chau, 2012; Secades-Villa, Garcia-Rodríguez, Jin, Wang & Blanco, 2015). In spite of this progression having been found to be stable over time in different countries and samples, two important aspects must be taken into account. First, heavy drug-users are less likely to follow the typical sequence of use (Mackesy-Amiti, Fendrich & Goldstein, 1997), this population being particularly relevant when it comes to establishing preventive measures: those youths who are most at risk of becoming serious drug users may be the ones who are least likely to follow the typical sequence of drug use initiation (Mackesy-Amiti, Fendrich & Goldstein, 1997). Second, initiation sequences, despite having a more or less defined pattern, have been shown to vary with the age when the initiation occurs (Patrick et al., 2011), especially true for the earlier ages (Moss, Chen & Yi, 2014).

The drugs scene in Spain has changed in the last two decades. Incidence rates for heroin use have decreased and have remained very low in recent years (Sánchez-Niubò et al., 2009; Sánchez-Niubò et al., 2013). However, life-time prevalence of cannabis and cocaine use are among the highest in the European Union –EU- (European Monitoring Centre for Drugs and Drug Addiction, 2016). Moreover, last year use of cannabis increased from 14.5% in 1995 to 32.1% in 2009, and that for cocaine from 3.4 to 10.2% over the same period (Observatorio Español de la Droga y las Toxicomanías, 2014). Nevertheless, incidences of cocaine and cannabis although very high, seemed stable since the year 2000 (standardized rates: around 9 per 1,000) (Sánchez-Niubò, Sordo, Fortiana, Brugal & Domingo-Salvany, 2013). More specifically, the highest incidences were for those aged 15-19 both in males and females (Sánchez-Niubò, Sordo, Fortiana, Brugal & Domingo-Salvany, 2013), and the differences between sexes have been narrowing in recent birth cohorts (Colell, Sánchez-Niubò & Domingo-Salvany, 2013). Tobacco incidence rates are not available, nevertheless the slight decrease of prevalence between 2003 and 2009 may indicate a possible decrease of incidence (Observatorio Español de la Droga y las Toxicomanías, 2014). Of interest, women have experienced a growing and earlier incorporation to tobacco use in recent cohorts achieving the rates in men (Colell, Sánchez-Niubò & Domingo-Salvany, 2013).

These changes, also observed in neighboring countries (European Monitoring Centre for Drugs and Drug Addiction, 2016), have not been followed by any research on age of onset and progression patterns. Identifying onset of drug use would be helpful to indicate prevention efforts as well as its relation with future drug use.

Therefore, the main aim of the present work was to retrospectively study the onset and progression sequence of the most frequent pathways of drug use initiation in a sample of the Spanish general population and observe their evolution in different birth cohorts.

Material and Methods

All data were drawn from the Household Survey on Alcohol and Drugs (EDADES) 2011 (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2011). EDADES is a biennial nationwide representative household survey carried out since 1995 to monitor use, perceptions and opinions of non- institutionalized 15–64-year-old residents in Spain with respect to alcohol and drug consumption. This study used the information obtained in Catalonia, the second largest region of Spain. Sampling followed a three-stage clustering design (census tract, household and random individual) without substitution in urban and rural populations. Participation rates were over 50%, samples being previously oversized to achieve desired effective numbers. The survey was self-administered and collected through a household survey. The final sample was of 2,069 individuals and had the same age distribution as the general population.

For the purposes of this study, we considered the age of onset of four behaviors: tobacco use (range: 6-48), daily tobacco use (range: 10-49), cannabis use (range: 11-45) and cocaine use (range: 12-40). All analyses were adjusted by sex and the following year birth cohorts: <1965, 1965-1974, 1975-1984 and 1985-1996. These birth cohorts correspond to the following ages at the time of the survey: >46, 37-46, 27-36 and 15-26. For inference to the whole population, individuals were weighted according to sampling design.

Age at first alcohol use was not included due to the high prevalence of ever alcohol use in Spain (91% in 2011), and because the association with initiation of other substances could be rather vague and uninformative (Golpe, Isorna, Barreiro, Braña & Rial, 2017; Teixidó-Compañó et al., 2019). On the other hand, as information about onset age of daily tobacco use was available, tobacco use ever, despite being prevalent (72% in 2011), was considered for comparisons.

Descriptive analyses were performed with medians of ages of drug initiation by sex and birth cohorts. Progressions of drug initiation were pictured by quantifying the transitions from a previous state in terms of the number of individuals and weighted percentages. As ages of onset are discrete integer values, coincidences were found between the ages of onset of different substances. To solve this problem, we considered the following ordered pattern: tobacco, daily tobacco, cannabis and cocaine; i.e., if onset age of tobacco use coincided with cannabis, we considered tobacco use earlier than cannabis. These assumptions were based on National data (Observatorio Español de la Droga y las Toxicomanías, 2014). Nevertheless, ties following other ordering patterns were checked.

Survival analyses were employed to assess the most prevalent pathways found in the descriptive analysis, while taking into account censures for individuals who have not yet had a chance to start using a drug. Specifically, we used additive hazard regression which can provide a better picture of how effects of covariates develop over time than Cox regression models (Aalen, Borgan & Gjessing, 2008). Parameters of these models are arbitrary cumulative regression functions that represent the cumulative excess risk at each unit of time and are useful to assess changes over time graphically (Xie et al., 2013). Events in each survival analysis were the ages at first use of cannabis and of cocaine. People not reporting the event in the period of observation were considered censures at the age of the survey. In the analyses for both substances, cumulative excess risk estimates were obtained for the categories: having never smoked tobacco (reference category), having ever smoked but not daily, and having ever smoked daily, always previous to the event. Also for cocaine, cumulative excess risk estimates were obtained from those having never used cannabis (reference category) to having ever used cannabis, previous to the event. Note that onset ages for tobacco and cannabis were treated as time-varying covariates.

All analyses were done with R (R Foundation for Statistical Computing, 2015) and survival analyses with the R package "survival"(Therneau & Grambsch, 2000).

Results

1,498 (72.4%) individuals reported at least one behavior: 1,473 tobacco use, 947 of them being daily tobacco users, 631 cannabis use and 183 cocaine use. Weighted medians and confidence interval of age of onset by behaviour and stratified by sex and birth cohorts are shown in table 1. We observe that onset age medians were ordered by tobacco, daily tobacco, cannabis and cocaine and have decreased over the years since 1965. Furthermore, age ranges differ between birth cohorts, median age in more recent cohort tending to be lower than those in older cohorts. Median ages for tobacco use ever and daily, were equal for males and females, whereas for cannabis and cocaine, those for males were lower, although in general not significantly.

Figure 1 shows all possible pathway combinations of the progression of drug use initiation found in the sample. Among the 143 individuals who had initiated all four considered behaviors, the most frequent pathway was tobacco- daily tobacco- cannabis- cocaine (92 individuals). The

Table 1. *Age of first use of selected behaviors by birth cohort and sex.*

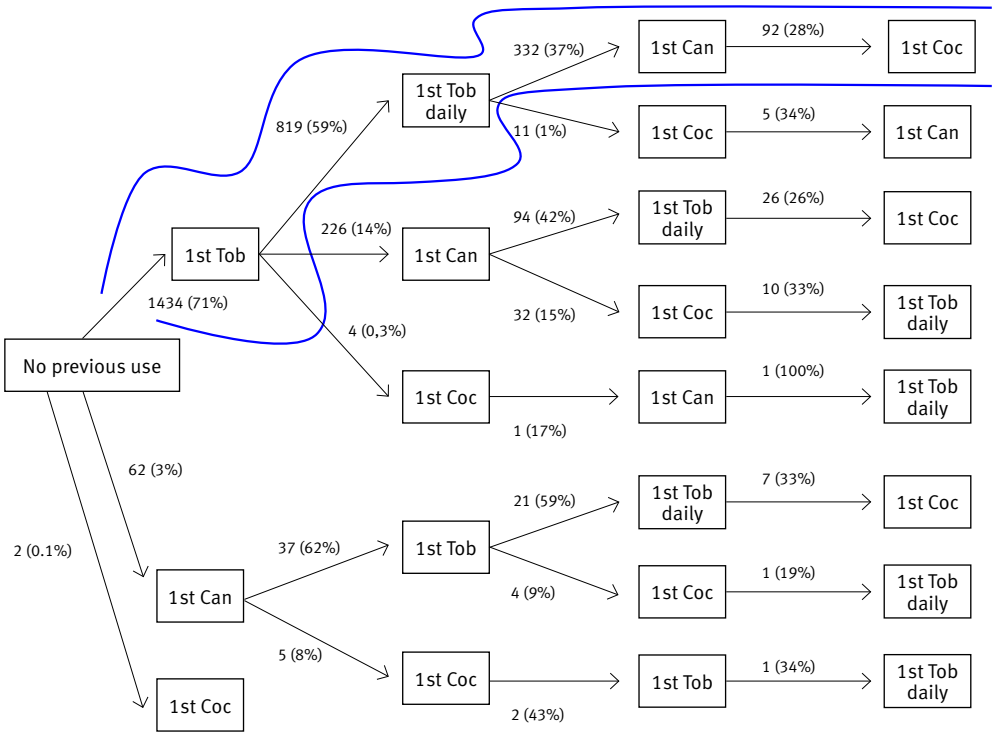
Weighted Median Age (CI 95%)	Females								Males								
	Birth cohorts																
	› 1965			1965 - 1974			1975 - 1984		1985 - 1996			› 1965			1965 - 1974			1975 - 1984		1985 - 1996			
	n	med.	CI95%	n	med.	CI95%	n	med.	CI95%	n	med.	CI95%	n	med.	CI95%	n	med.	CI95%	n	med.	CI95%	TOTAL
Age of survey	250	55	(54, 56)	239	41	(40, 42)	285	32	(31, 32)	247	22	(21, 23)	241	55	(54, 57)	247	41	(40, 41)	299	32	(31, 32)	261	22	(20, 23)	2069
1st tobacco use	155	17	(16, 18)	165	16	(16, 16)	186	16	(16, 16)	141	15	(15, 16)	209	16	(15, 16)	210	16	(16, 17)	231	16	(16, 16)	176	15	(15, 16)	1473
1st tobacco use non daily users ever	68	16	(16, 18)	57	17	(15, 18)	84	16	(16, 17)	54	15	(15, 16)	46	17	(15, 18)	63	17	(16, 18)	71	16	(15, 17)	83	16	(15, 16)	526
1st tobacco use daily users ever	87	18	(18, 20)	108	18	(17, 18)	102	17	(16, 18)	87	16	(15, 17)	163	18	(17, 18)	147	18	(17, 18)	160	17	(17, 18)	93	16	(16, 17)	947
1st cannabis use	27	20	(18, 24)	42	20	(18, 22)	64	18	(17, 18)	83	17	(16, 17)	52	19	(18, 21)	108	18	(18, 18)	139	17	(17, 18)	116	16	(16, 17)	631
1st cannabis use non-tobacco users	4	23	(17, 29)	7	17	(16, 20)	16	17	(16, 18)	20	16	(15, 18)	10	18	(17, 18)	26	17	(15, 18)	48	16	(16, 17)	36	15	(15, 17)	167
1st cannabis use tobacco users non daily ever	4	24	(18, 54)	7	18	(16, 25)	19	18	(16, 19)	20	16	(15, 17)	8	20	(15, 23)	15	18	(17, 20)	20	17	(16, 19)	34	16	(16, 17)	127
1st cannabis use tobacco users daily ever	19	19	(18, 20)	28	20	(18, 24)	29	18	(16, 19)	43	17	(16, 17)	34	20	(18, 21)	67	18	(18, 20)	71	18	(17, 18)	46	17	(16, 17)	337
1st cocaine use	9	20	(18, 24)	10	25	(20, 30)	18	20	(20. 21)	16	18	(17, 20)	13	21	(18, 26)	41	20	(20, 22)	58	19	(18, 20)	18	18	(17, 19)	183
1st cocaine use non-tobacco users	1	32	n/a	0		n/a	1	22	n/a	2	16	(16, 18)	2	18	(18, 40)	3	17	(14, 25)	8	18	(15, 20)	2	17	(17, 19)	19
1st cocaine use tobacco users non daily ever	2	21	(20, 24)	1	25		6	20	(18, 24)	1	20	n/a	2	26	(26, 28)	4	21	(20, 25)	7	20	(15, 25)	5	18	(18, 18)	28
1st cocaine use tobacco users daily ever	6	20	(18, 23)	9	25	(19, 31)	11	20	(19, 20)	13	18	(17, 20)	9	20	(18, 24)	34	20	(20, 22)	43	19	(18, 20)	11	17	(16, 19)	136
1st cocaine use non-cannabis users	4	21	(18, 24)	2	25	(22, 35)	2	19	(18, 23)	1	15	n/a	1	40	n/a	4	23	(14, 23)	3	21	(20, 24)	0		n/a	17
1st cocaine use cannabis users	5	20	(18, 30)	8	25	(20, 25)	16	20	(20, 20)	15	18	(17, 20)	12	20	(18, 25)	37	20	(20, 22)	55	18	(18, 20)	18	18	(17, 19)	166

second most frequent pathway was tobacco- cannabis- daily tobacco- cocaine (26 individuals).

Coincidences in the age of onset of some behaviors were relatively frequent, such as tobacco and cannabis use (n = 117, 19% of people with both behaviors), daily tobacco and cannabis use (n=111, 24% of cannabis users) and ever tobacco, daily tobacco and cannabis use (n=56, 12% of people with the three behaviors). Ties with cocaine were with cannabis (n=24, 14% of cocaine users), tobacco (n=6, 3%) and daily tobacco (n=8, 5%). As a sensitivity study, when the age of onset in both behaviors was coincident the assumption that cannabis had been used before tobacco was considered. In that case, the number of individuals in the pathway tobacco- daily tobacco- cannabis- cocaine would have decreased from 92 to 57 individuals, still remaining as the most frequent pathway. Also, the second most frequent pathway would have increased from 26 to 35 individuals, and the third most frequent pathway would have been cannabis- tobacco- daily tobacco- cocaine increasing from 7 to 33 individuals.

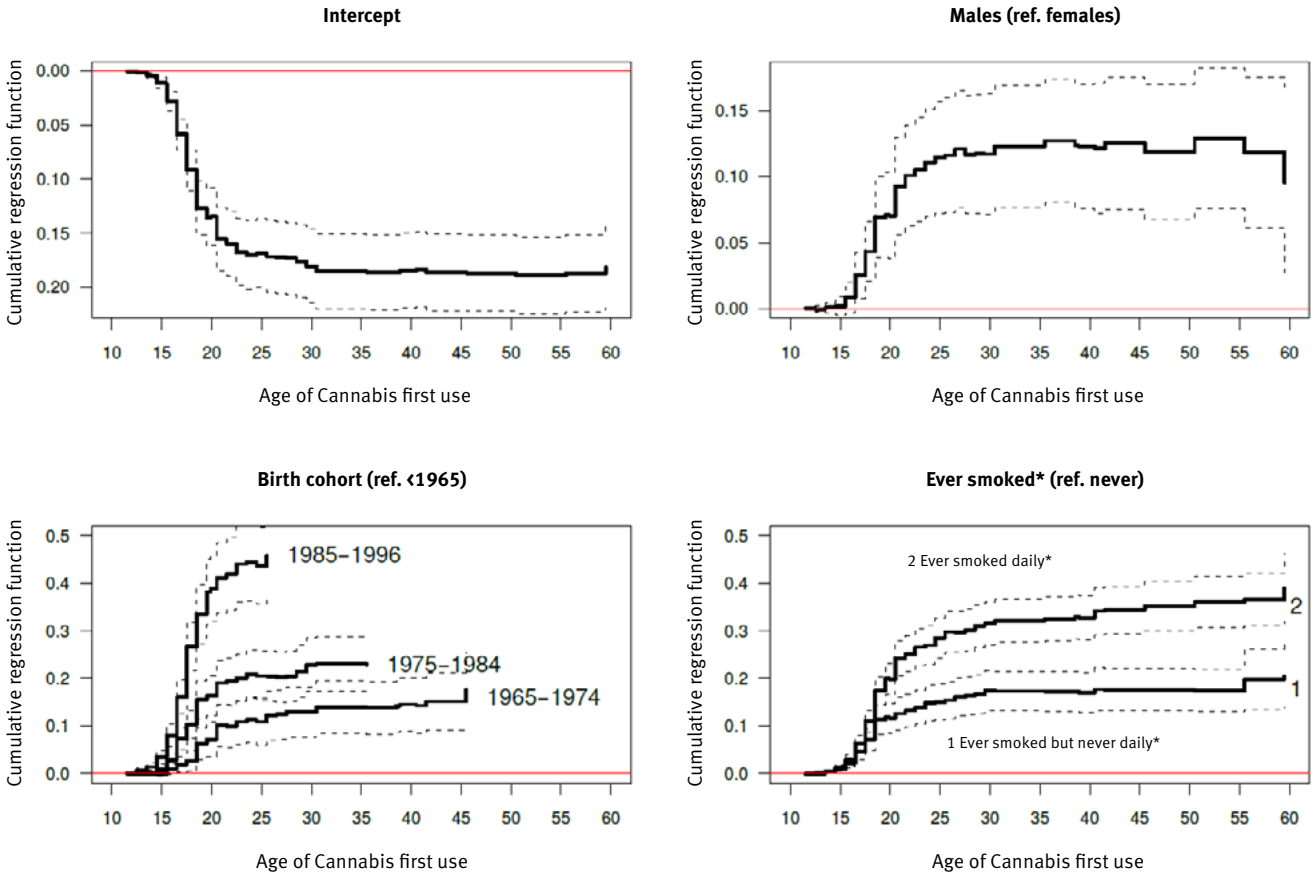
The additive hazard regression model with the age at first cannabis use as outcome was used to obtain the cumulative excess risk estimates and 95% confidence intervals over time in terms of age for the variables sex, birth cohort and previous tobacco use. The most relevant results were the following: males had a steep significant slope between 16 and 25 years old maintained afterwards as a cumulative excess risk of around 0.12 over females. Compared to never smoked tobacco, ever smoked tobacco (but never daily) had a significant slope from age 15 to 18 reaching a cumulative excess risk of around 0.12 maintained afterwards; and, ever daily tobacco use surpassed the previous category in the age of 19 to a cumulative excess risk of around 0.2, following a smooth slope afterwards. Each younger cohort had a significant higher slope reaching cumulative excess risks of around 0.15, 0.2 and 0.45, respectively, over the oldest cohort (see figure 2).

Regarding the results of the additive regression model with age of first cocaine use as outcome, and variables sex, birth cohort, and previous tobacco and cannabis use, the most relevant results were the following: males had a significant but very low cumulative excess risk between 18 and 21 years old, and later, between 27 and 35 years old had a cumulative excess risk of around 0.03. Ever smoked tobacco (but never daily) had a similar effect to never smoked; in contrast, ever daily tobacco and ever cannabis use had higher and significant slopes, between 17 and 24 years old for daily tobacco (a cumulative excess risk of around 0.03), and 26 years old for cannabis (around 0.17). Regarding birth cohorts, the one for 1965-1974 had a non-significantly different cumulative excess risk compared to the oldest cohort (see figure 3); the 1975-1984 birth cohort had a significant steep slope between 18 and 25 years old reaching a cumulative excess risk of around 0.06; the more recent cohort had a significant



Note. *Most frequent pathway in blue.

Figure 1. Progression of drug use initiation of 2,069 individuals: pathway combinations and their sample sizes and weighted percentages.



Note. *Previous first cannabis use.

Figure 2. Cumulative excess of risk for cannabis first use by sex, birth cohort and previous tobacco first use.

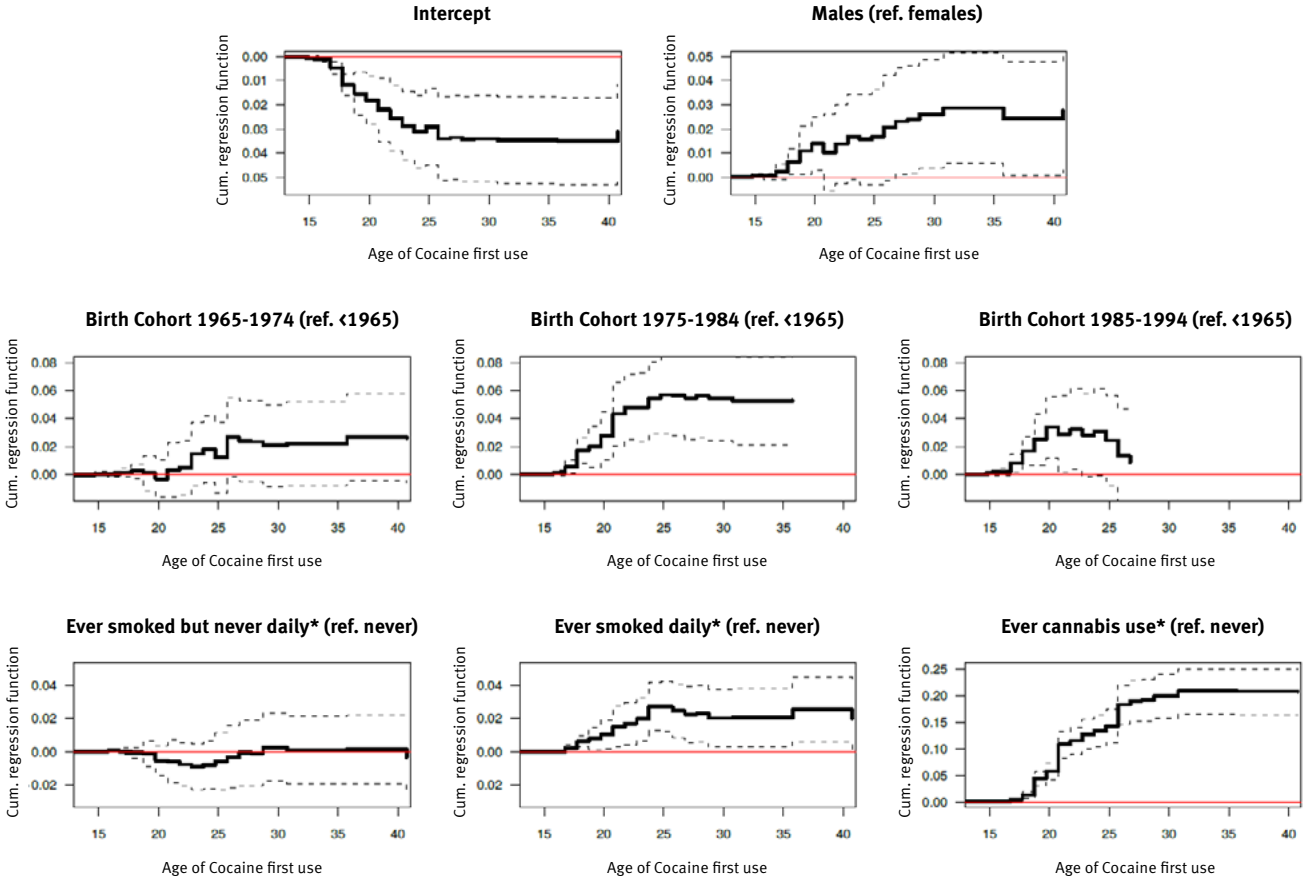
but lower slope than the previous cohort between 17 and 21 years old with a cumulative excess risk of around 0.03, but was not significant afterwards (see figure 3).

Discussion

Study findings show the expected usual progression in the age of starting use of different drugs: the most frequent progression in our sample is from first tobacco use to daily tobacco use, then to cannabis use and in a small proportion to cocaine use. Onset of consumption has changed over the years studied, being especially relevant the drop in age of onset, and the progressive acquisition by women of patterns considered masculine in previous generations.

Regarding progression of consumption, their interpretation under the Gateway theory (tobacco and alcohol could be considered as gateway substances to the use of certain other illicit drugs) should be done with caution. This theory has been heavily criticized and alternative theories have tried to address the development of involvement with psychoactive substances in the young: from the fact that what we call gateway substances are merely those substances which are most prevalent and hence accessible, to the fact that individual characteristics or environmental factors could explain the sequence better than the legal/illegal explanation (Mayet, Legleye, Beck, Falissard & Chau, 2016; Otten, Mun & Dishion, 2017; Vanyukov et al., 2012). Nevertheless, what nobody denies is the potential relevance of these repeatedly observed sequences in drug use initiation and the need for a better analysis of this phenomena. Some substances are consumed before others and a deeper study of their relationship would allow us to understand better drug use patterns and to provide adequate prevention and early intervention services for young people, especially youth at high-risk.

One of the most interesting findings of this study is the correlation between smoking and consumption of other drugs. Tobacco is not only the drug most used initially, but also its consumption is related with the subsequent increase in the consumption of other drugs. In this sense, this study shows an excess of risk in the relationship between tobacco and cannabis that had been pointed out before (Degenhardt et al., 2010; Mayet et al., 2012). In the specific case of Spain, the fact that the usual way to consume cannabis is smoking mixed with tobacco, could facilitate such an experience. Moreover, recent reports of the National Plan on Drugs for Spain have pointed out that incidence of cannabis is overtaking tobacco (Observatorio Español de la Dro-



Note. * Previous first cocaine use.

Figure 3. Cumulative excess of risk for cocaine first use by sex, birth cohort, previous tobacco and cannabis first use.

ga y las Toxicomanías, 2014). All this suggests, in line with findings of recent surveys conducted in Spain (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2011), that people's perceptions of the risks of tobacco and cannabis use are similar.

This study shows that the age of initiation of cannabis use has been decreasing in recent birth cohorts in both genders and among daily smokers. This trend has been reported previously in the European context in those countries that have produced a recent survey estimate (since 2013) (European Monitoring Centre for Drugs and Drug Addiction, 2016). This fact is important by itself (younger, more vulnerable, people starting earlier) as well as for its implications for the future: there is a relationship between early age of onset of a substance with more persistence of its use and more severe behavioural problems related to it (Poudel & Gautam, 2017).

For first ever cocaine use, the two more recent birth cohorts had a substantial excess of risk over the previous birth cohorts, also a significant increase for cannabis smokers, and a small but significant increase in risk from never to daily tobacco smokers. Once initiated in the illicit use of cannabis, the risk of initiating cocaine seems to be substantial. Initiating cannabis use may not be a direct cause of onset of cocaine use but rather a mediator that increases the risk of cocaine use. This could be explained by factors such as substance availability and also selection of drug-using friends contributing to the progression to potentially more rewarding and damaging illicit drugs as well as a reduction in risk perception (Otten et al., 2017).

In short, this study indicates (especially in older cohorts) that the ages of onset of consumption vary depending on whether other substances have been consumed previously (Patrick et al., 2011). Tobacco over cannabis and both over cocaine, appear to have the capacity to modify the onset and progression of drug use. For this reason, it is necessary to emphasize the need to make an effort to prevent (or delay) initiation of drugs, especially that of cannabis.

Our findings also highlighted the fact that the gender-gap in lifetime occurrence of substance use is narrowing (cannabis and cocaine) and even reversing (tobacco) in the more recent cohorts. This has been pointed out by a previous study in a wider context (Colell et al., 2013). Also outside of Spain or even Europe, similar results have been observed (Degenhardt, Lynskey & Hall, 2000; Degenhardt, Chiu, Sampson, Kessler & Anthony, 2007; Johnson & Gerstein, 1998; Johnson & Gerstein, 2000; Kerr, Greenfield, Bond, Ye & Rehm, 2004). This trend is parallel to the

change of roles of women in society, with evidence about possible specific preventive interventions being very limited (Stockings et al., 2016). More research along these lines is needed.

The findings of this study should be interpreted in the light of its limitations. As we are dealing with data from a cross-sectional study to build a retrospective cohort, selection bias should be taken into account. We handled data from birth cohorts that have been followed up to 2011. Moreover, the survey was home-based, so institutionalized and homeless people were not included. So, deaths previous to 2011 and institutionalized or homeless people were not considered even as censures in the survival analysis; this can lead to a selection bias if these people are not represented in the observed sample. Furthermore, we shouldn't forget the difficulty to include subjects with more extreme patterns of substance use as they are likely not to be considered in the Census and probably exhibit atypical initiation sequences (Mackesy-Amiti et al., 1997).

Regarding coincidences between age of onset for the different substances, we found that even assuming cannabis use prior to tobacco use in all cases, the most frequent pattern remained the same. Adding the fact that we are dealing with the general population, our results support previous studies that showed a similar sequence in drug use initiation. But some considerations should be taken into account: in most of the cases their first use was just mixing tobacco and cannabis, and this could lead to later daily tobacco use and subsequently use of cocaine. So, it is of concern that using the same route of administration may lead to a higher risk of subsequent dependence on tobacco and to trying other illicit drugs. Besides our analysis could not take into account how many were experimental users, and how many became regular cannabis or cocaine users, since the only data available for these substances was whether they had ever been used. Finally, it is important to point out that the sample of 2,069 individuals may be considered representative of the autonomous region of Catalonia, but its extrapolation to other communities is questionable due to different regional plans of addiction disorders.

The present study describes and reinforces the commonly accepted sequence pattern of drug use initiation for Catalonia, which has not changed recently, although we do observe a drop in age of onset, and certain changes in patterns of relationship between different substances. There is a need to promote studies analysing the underlying mechanisms of the progression and its real causes through the incorporation of appropriate questions in surveys, for example, about social habits, risk perceptions and mental disorders. Health policies and prevention strategies should try to act in three different areas: 1) Raising risk perception of legal substances; 2) Delaying age of onset of consumption of all drugs (legal and illegal) using effective measures; and 3) Separating cocaine from cannabis, given the difference in magnitude of harm related with each substance: separation of the information provided about them, as well as their markets.

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Competing interests

All authors have no relationships or activities that could appear to have influenced the submitted work.

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Psychotic-like experiences and cannabis use in adolescents from the general population

Experiencias psicóticas atenuadas y consumo de cannabis en adolescentes de la población general

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Abstract

The purpose of this study was to analyze the relationship between psychotic-like experiences and cannabis use in a representative sample of adolescents from the general population. A total of 1,588 students (*M*=16.13 years, *SD* = 1.36), 739 men (46.5%), selected by stratified random sampling by conglomerates from 98 classes in 34 schools participated in the survey. The instruments used were the Prodromal Questionnaire-Brief, the Strengths and Difficulties Questionnaire, the Modified Substance Use Questionnaire, the Penn Matrix Reasoning Test, the Family Affluence Scale-II, and the Oviedo Infrequency Scale. Results showed that a percentage of adolescents reported psychotic-like experiences and/or cannabis use. Prior to controlling for multiple confounders (gender, age, socio-economic level, smoking, alcohol use, emotional and behavioral problems, and IQ), cannabis use was associated with psychotic-like experiences. After adjustment for confounders, psychotic-like experiences were not seen to be associated with cannabis use. Mediational analyses showed that emotional and behavioral problems mediate the relationship between cannabis use and risk of psychosis. It seems that once the effect of multiple confounding variables is controlled for, the use of cannabis increases the risk of comorbid psychopathology and this, in turn, increases the risk of psychosis. These results suggest that the relationships established between psychotic-like experiences and cannabis are complex and mediated by relevant variables. Further studies should examine this relationship in follow-up studies and gene-environmental designs.

Keywords: Risk of psychosis; Adolescence; Cannabis; Drugs use; Psychotic-like experiences.

Resumen

El propósito de este estudio fue analizar la relación entre las experiencias psicóticas atenuadas y el consumo de cannabis en una muestra representativa de adolescentes de la población general. Un total de 1,588 estudiantes (*M*=16,13 años; *DT* = 1,36), 739 eran hombres (46,5%), pertenecientes a 34 escuelas y 98 aulas, seleccionados mediante muestreo aleatorio estratificado por conglomerados, fueron encuestados. Los instrumentos administrados fueron el Cuestionario de Pródromos de Psicosis-Breve, el Cuestionario de Capacidades y Dificultades, el Cuestionario de Consumo de Sustancias Modificado, el *Penn Matrix Reasoning Test* (PMRT), la *Family Affluence Scale*-II y la Escala Oviedo de Infrecuencia de Respuesta. Los resultados mostraron que un porcentaje de adolescentes informaron de experiencias psicóticas atenuadas y/o consumo de cannabis. Antes de controlar el efecto de múltiples covariables (género, edad, nivel socio-económico, consumo de tabaco y alcohol, problemas emocionales y CI), los jóvenes consumidores de cannabis informaron de un mayor riesgo teórico de psicosis. Cuando se controló el efecto de las covariables, las experiencias psicóticas no se asociaron con el consumo de cannabis. El análisis mediacional indicó que los problemas en el ajuste emocional y comportamental mediaban en la relación entre consumo de cannabis y experiencias psicotiformes. Parece ser que, una vez controlado el efecto de las múltiples variables de confundido, el uso de cannabis aumenta el riesgo de psicopatología comórbida y esta a su vez el riesgo de psicosis (mayor frecuencia de experiencias psicóticas). Estos resultados sugieren que la relación que se establece entre las experiencias psicóticas y el cannabis es compleja y se encuentra mediada por variables relevantes. Futuros estudios deberán examinar las interacciones Gen x Ambiente en estudios longitudinales.

Palabras clave: Riesgo de psicosis; Adolescencia; Cannabis; Consumo de drogas; Experiencias psicóticas atenuadas.

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Psychotic-like experiences during adolescence can be considered a risk marker for suffering from psychotic spectrum disorders (Debbané et al., 2015; Kaymaz et al., 2012; Zammit et al., 2013) or mental health (e.g. depression) in later adult life (Fisher et al., 2013). Previous studies have also shown that such experiences are associated with the same genetic, sociodemographic, and environmental risk factors found in patients with psychosis, such as affective symptoms, trauma experiences, cannabis and alcohol use, or family history of mental disorder (Dolphin, Dooley & Fitzgerald, 2015; Fonseca-Pedrero et al., 2018; Fonseca-Pedrero & Debbané, 2017; Linscott & van Os, 2013; Strauss, Raugh, Mittal, Gibb & Coles, 2018).

Having such subclinical experiences during adolescence is a predictor with low specificity and prognostic capacity of developing mental related problems in later stages (Wallace & Linscott, 2018). Therefore, they cannot be considered a necessary or sufficient condition for the subsequent development of a psychotic disorder (or other mental disorder). Nevertheless, previous studies indicate that their persistence, associated with substance consumption, affective symptomatology or trauma, increases the subsequent risk of psychosis (Bak et al., 2005; Fonseca-Pedrero, 2018; Fusar-Poli et al., 2017; Kelleher et al., 2013; Linscott & van Os, 2013). It is therefore necessary to analyze their relationship and interaction with other factors and variables from multiple levels of analysis (e.g., genetic, brain, cognitive, behavioral) in order to improve prevention strategies and/or understand the possible etiological mechanisms underlying psychotic spectrum disorders.

One of the most widely analyzed risk factors in the field of psychosis is cannabis use. Prior studies appear to show that early cannabis use increases the risk of developing later psychosis spectrum disorders, with a dose-response relationship between level of use and the risk of psychosis (Giordano, Ohlsson, Sundquist, Sundquist & Kendler, 2015; Henquet et al., 2005; Large, Sharma, Compton, Slade & Nielssen, 2011; Marconi, Di Forti, Lewis, Murray & Vassos, 2016; Moore et al., 2007; Verdoux, Sorbara, Gindre, Swendsen & van Os, 2002). Cannabis use has been specifically associated with different expressions of the psychosis phenotype (Linscott & van Os, 2013), such as schizotypal traits (Esterberg, Goulding, McClure-Tone & Compton, 2009; Szoke et al., 2014), psychotic-like experiences (Dolphin et al., 2015; Fonseca-Pedrero, Ortuño-Sierra, Paino & Muñiz, 2016; Hides et al., 2009; MacKie, Castellanos-Ryan & Conrod, 2011), high-risk mental states (Carney, Yung, et al., 2017; Carney, Cotter, Firth, Bradshaw & Yung, 2017; Kraan et al., 2016; Valmaggia et al., 2014), schizotypal personality disorder (Davis, Compton, Wang, Levin & Blanco, 2013), and clinical psychosis (Davis et al., 2013; Stanley Zammit & Lewis, 2004).

Within the dimensional models, it is hypothesized that the relationship between cannabis use and psychosis will become apparent at both clinical and subclinical levels. More specifically, cannabis use is linked to earlier onset of the first psychotic experiences (Large et al., 2011), predicts later psychotic experiences (Jones et al., 2018), and is associated with their greater persistence (Mackie et al., 2013). In adittion, cannabis use moderately increases the risk of psychotic symptoms but has a much stronger effect in those with evidence of predisposition for psychosis or those reporting a family history of psychosis (Henquet et al., 2005; Stowkowy & Addington, 2013). Furthermore, the possible effect of substance use in individuals at risk of psychosis (e.g., those reporting psychotic experiences or subclinical symptoms) is modulated by different factors such as the age of onset, the pattern and frequency of substance use (particularly tobacco), preexisting vulnerability, gender, educational level or emotional symptomatology (Mackie et al., 2013; Mackie et al., 2011). The cannabis-psychosis links across the psychosis phenotype are, thus, complex and bidirectional, so that many people with substance abuse develop psychotic symptoms, or people with psychotic symptoms develop substance use and abuse (Degenhardt et al., 2018). Similarly, gene-environment interactions and those between different environmental risk factors (e.g., cannabis-trauma) should not be overlooked (Henquet, Di Forti, Morrison, Kuepper & Murray, 2008; Morgan et al., 2014; Nesvåg et al., 2016; Shakoor et al., 2015; Van Winkel, 2015).

The relationship between psychotic-like experiences, the risk of psychosis and the use and abuse of cannabis seems to be clear enough; nevertheless, causality between the two has not yet been definitively established and some studies still present certain methodological limitations. Indeed, previous studies have not examined the joint influence of multiple relevant variables such as age, gender, educational level, socioeconomic status, smoking or comorbid psychopathology (e.g., emotional and behavioral problems) on the relationship between cannabis use and risk of psychosis. There is ongoing debate about the possible factors that may be modifying the complex interactions taking place between the risk of psychosis and cannabis use. Applying more complex models and adequate methodology is necessary to investigate the multiple interactions that occur between variables more realistically and to draw appropriate conclusions (Fonseca-Pedrero, 2017). In Spain, such relationships have scarcely been analyzed in representative samples of young people from the general population.

Given that polydrug use is a public health problem at both national and international levels (Bousoño et al., 2017; Hernández Serrano, Font-Mayolas & Gras Pérez, 2015), and that cannabis is the most widely used illicit drug in Spain (Díaz Geada, Busto Miramontes & Caamaño Isorna, 2018; Ministerio de Sanidad Servicios Sociales e Igual-

dad, 2016) (e.g., in 2014, 29.1% of the participants had used cannabis *at some time in their lives*), while also being associated with a low perception of risk and yet seemingly linked to an increased risk of suffering a serious mental disorder such as psychosis, it appears logical that a more detailed analysis between the extended psychosis phenotype and the use of cannabis is justified.

Within this research framework, the main objective of our study was to explore the relationship between psychotic-like experiences and cannabis use in a representative sample of Spanish adolescents. To this end, the effect of gender, age, socioeconomic level, smoking, alcohol use, and IQ was controlled for. Similarly, the possible mediating factor of comorbid psychopathology in the relationship between cannabis use and risk of psychosis was examined. In accordance with the literature, we expect to find a relationship between psychotic-like experiences and cannabis use.

Method

Participants

We applied stratified random sampling by conglomerates at the school classroom level in a population of approximately 15,000 students selected from the Autonomous Community of La Rioja and attending different schools (public and state-funded private) and vocational training centers (basic, middle and higher levels). The strata were created according to school (public/private) and the school level (lower and higher secondary school, and vocational training), where the probability that a particular class at a given school was selected was based on the number of students.

Of the initial sample of 1,881 students, those with a high score on the Oviedo Response Frequency Scale (more than 3 points) (n = 104) were eliminated, as were those aged over 19 (n = 170) and those who did not complete the test (n = 76). This left a total of 1,588 students, with 739 men (46.5%) and 849 (53.5%) women, from 98 classes in 34 schools participating in the study. Average age was 16.13 years (SD = 1.36), ranging from 14 to 19 years (14 years: n = 213, 15: n = 337, 16: n = 400, 17: n = 382, 18: n = 180, 19: n = 76).

Nationalities were distributed as follows: 89.9% Spanish, 3.7% Latin American (from Bolivia, Argentina, Colombia and Ecuador), 0.7% Portuguese, 2.4% Romanian, 1% Moroccan, 0.7% Pakistani, and 2% other nationalities.

Instruments

Prodromal Questionnaire-Brief Version (PQ-B) (Loewy, Pearson, Vinogradov, Bearden & Cannon, 2011). The PQ-B is a self-report questionnaire with 21 items assessing prodromal symptoms of positive dimension of psychosis. The item format is true/false dichotomous response. An affirmative response to an item requires the participant to indicate the degree of concern or discomfort that it causes on a five-option Likert scale (1 = totally disagree, 5 = totally agree). In the general population, this instrument can also be used as a screening tool for the risk of psychosis (Savill, D'Ambrosio, Cannon & Loewy, 2017) or as a measure in the assessment of psychotic-like experiences. The PQ-B has demonstrated its usefulness in the assessment of attenuated psychotic symptoms in young people (Kline & Schiffman, 2014).

The PQ-B possesses adequate psychometric properties in terms of reliability (Internal consistency = 0.93), as well as an essentially one-dimensional structure in samples of Spanish adolescents (Fonseca-Pedrero, Gooding, Ortuño-Sierra & Paino, 2016).

Modified Substance Use Questionnaire. The substance use questionnaire employed in our study is an abbreviated modification of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST v3.0) (WHO ASSIST Working Group, 2002). ASSIST is an interview used as a screening tool in the detection of drug users developed by the WHO. It consists of different items for the assessment of, among other aspects, the frequency of use of different substances (alcohol, tobacco, cannabis, cocaine, etc.) in the three months prior to the completion of the questionnaire. ASSIST has been translated into Spanish and validated (Soto-Brandt et al., 2014).

Our study used two of the ASSIST questions applied in self-report format. Item 1 asked: "In your life, which of the following substances have you ever used?" Participants respond in a dichotomous format, Yes/No, for the following substances: a) Tobacco (cigarettes, cigars, chewing tobacco, pipe, etc.); b) Alcoholic beverages (beer, wine, liqueurs, spirits, etc.); c) Cannabis (marijuana, pot, grass, hashish, etc.); and d) Other (e.g., cocaine, amphetamines, inhalants, hallucinogens, opiates, etc.). An affirmative answer to any substances in item 1 then led to item 2, which asked about the frequency of use in the previous three months.

Strengths and Difficulties Questionnaire, self-report version, (SDQ) (Goodman, 1997). This measurement instrument is used for the detection of behavioral and emotional difficulties and has also been used as a tool for screening and epidemiological analysis of mental health status in children and adolescents (Ortuño-Sierra, Fonseca-Pedrero, Paino, Sastre i Riba & Muñiz, 2015; Ortuño-Sierra, Fonseca-Pedrero, Inchausti & Sastre i Riba, 2016). The SDQ comprises 25 items in a Likert-type response format with three options (0 = No, never, 1 = Sometimes, 2 = Yes, always). Items are grouped into five dimensions (with five items each): emotional symptoms, behavior problems, hyperactivity, peer problems, and prosocial behavior. The first four subscales make up a Total Difficulties score. The higher the score, the greater the level of emotional and behavioral difficulty, except for the subscale of Prosocial Behavior, where a lower score means worse adjustment.

The psychometric properties of the SDQ have been analyzed in previous studies at international and national level (Ortuño-Sierra, Fonseca-Pedrero, Aritio-Solana, et al., 2015; Ortuño-Sierra, Fonseca-Pedrero, Paino, Sastre i Riba & Muñiz, 2015).

Penn Matrix Reasoning Test (PMRT) (Gur et al., 2012; Moore, Reise, Gur, Hakonarson & Gur, 2015). This is a task from the Penn-Computerized Neurocognitive Battery, developed to measure nonverbal reasoning (using matrix reasoning problems as in the Raven Progressive Matrices Test), within the domain of complex cognition. This 20-item task can be seen as an estimate of IQ. The battery includes different neurobehavioral indicators, with different tasks adapted to guarantee psychometric properties and their connection with brain systems among children.

The Family Affluence Scale-II (FAS-II) (Boyce, Torsheim, Currie & Zambon, 2006). Socioeconomic status was calculated using a measure of family wealth involving four items appropriate to children with score ranging from 0 to 9. Previous international studies have shown adequate psychometric properties (Boyce et al., 2006).

Oviedo Infrequency Scale (INF-OV) (Fonseca-Pedrero, Paino-Piñeiro, Lemos-Giráldez, Villazón-García & Muñiz, 2009). The INF-OV was developed to detect random, pseudo-random or untruthful responses to the measurement instruments administered. The INF-OV is a 12-item Likert-type self-report instrument with five responses reflecting degrees of agreement (1 = Strongly disagree, 2 = Disagree, 3 = Neither disagree nor agree; = Agree, and 5 = Strongly agree). After dichotomizing the items, students scoring more than two items of the INF-OV incorrectly are eliminated from the study.

Procedure

The research was approved by the General Directorate of Education of the Government of La Rioja and the Clinical Research Ethics Committee of La Rioja (CEICLAR). Schools were contacted by phone, email or by mail. Initial contact with schools was via the director, the Head of Studies, or the orientation department.

To standardize the administration process, all researchers were provided with a protocol and guidelines to be adhered to before, during and after administration of measurement instruments. The questionnaires were administered by computer and collectively in groups of between 10 and 30 participants.

Participants were informed at all times regarding the confidentiality of their responses and the voluntary nature of their participation. Participation was not remunerated. Whenever necessary, authorization was sought to allow minors to participate. This study forms part of a broader project on the early detection of mental health problems.

Data analysis

First, the percentage of participants with psychotic-like experiences and substance use was analyzed.

Second, to examine the relationship between psychotic-like experiences and cannabis use, several analyses were carried out as follows:

A) Multivariate analysis of variance (MANOVA) was use to examine the relationship between total PQ-B scores for frequency of cannabis use and discomfort without the role of possible covariates.

B) In order to examine the relationship between theoretical risk or non-risk of psychosis and cannabis, two groups of participants were created according to the PQ-B total frequency score (values higher than 8 points). To analyze if there were statistically significant differences, a χ^2 test was performed.

C) Given that gender, age, socioeconomic level, smoking, alcohol use, IQ, and emotional-behavioral problems may affect the expression of the relationship between psychotic-like experiences and cannabis use, these were considered covariables and multivariate analysis of covariance (MANCOVA) was performed. Partial eta squared (partial η^2) was used to calculate effect size.

Third, in order to examine the possible mediating role of difficulties in emotional and behavioral adjustment in the relationship between cannabis use and risk of psychosis, a mediation analysis was performed using the PROCESS macro (Hayes, 2013). Gender, age, socioeconomic level, smoking, alcohol use, and IQ were included in the analysis as covariates. To estimate the significance of the indirect effect, a bootstrapping (1000 re-samples) with a confidence interval of 95% was applied. The effect is significant if the associated confidence interval does not contain zero. The Sobel test was also carried out to verify the significance of the possible indirect effect.

The analyses were carried out using the statistical package SPSS v22 (IBM Corp Released, 2013) and the PROCESS macro (Hayes, 2013).

Results

Descriptive statistics: prevalence

The lifetime prevalence of substance use was 40.4% (n = 641) for tobacco and 23.7% (n = 377) for cannabis. Using cannabis once or twice in their life was reported by 15.1% (n = 239) of the sample, monthly cannabis use by 2.9% (n = 46), weekly use by 1.8% (n = 29), and daily use by 1.8% (n = 29), while 65.9% (n = 1047) indicated that they had never used cannabis. The question regarding cannabis use in the previous 3 months was left unanswered by 12.5% (n = 198) of the sample.

The results showed that 27.3% (n = 434) of the adolescents obtained scores of 8 or higher on the PQ-B were con-

sidered as a risk group. While 8.6% (n = 136) of the sample did not report any psychotic-like experiences (score 0 in the PQ-B), this type of experience did not cause any kind of discomfort for 13.9% (n = 220).

Relationship between psychotic-like experiences and cannabis use

Regarding, exclusively, the relationship between PQ-B score dimensions (frequency and distress) and cannabis use, the MANOVA revealed the existence of statistically significant differences ($\lambda = 0.994$; $F_{(2,1585)} = 5.049$, $p = 0.007$). Compared to non-users, the frequency and distress associated with psychotic-like experiences among adolescent cannabis users increased. The results are shown in Table 1.

Similar results were found when comparing psychosis risk groups (risk vs. no risk) with cannabis use ($\chi^2_{(1)} = 8.450$, $p = 0.004$). The results are shown in Table 2.

A MANCOVA was then carried out with PQ-B scores as dependent variables, cannabis consumption as fixed factor (lifetime prevalence) and controlling for covariates gender, age, smoking, alcohol use, IQ, socioeconomic level and emotional and behavioral problems. In this case, results yielded an absence of statistically significant differences between groups ($\lambda = 0.999$, $F_{(1.1580)} = 0.523$, $p = 0.593$). More specifically, the largest effect size was observed for the total score of SDQ ($\lambda = 0.695$, $F_{(2.1580)} = 347.71$, $p < 0.001$, partial $\eta^2 = 0.306$). Given these results, and bearing in mind previous studies, the possible mediating role of emotional and behavioral problems between cannabis and psychotic-like experiences was investigated.

Psychotic-like experiences and cannabis: the mediating role of emotional and behavioral difficulties

Mediation analysis revealed that the total effect of cannabis use on psychotic-like experiences was positive and statistically significant ($B = 0.687$, $p < 0.05$, 95% CI: 0.06 – 1.32). However, the direct effect was not statistically significant ($B = 0.084$, $p = 0.76$, 95% CI: -0.45 – 0.62). The indirect effect was also positive and significant ($B = 0.603$, 95% CI: 0.25-0.94), indicating that the SDQ scores fully mediated the relationship between cannabis use and the risk of psychosis. Similarly, the Sobel test also revealed the significance of the indirect effect ($z = 3.56$, $p < 0.001$). These results show that difficulties in emotional and behavioral adjustment fully mediate the relationship between cannabis use and risk of psychosis. In the mediation analysis, the variables gender, age, socioeconomic level, smoking, alcohol use and IQ were controlled for.

Discussion

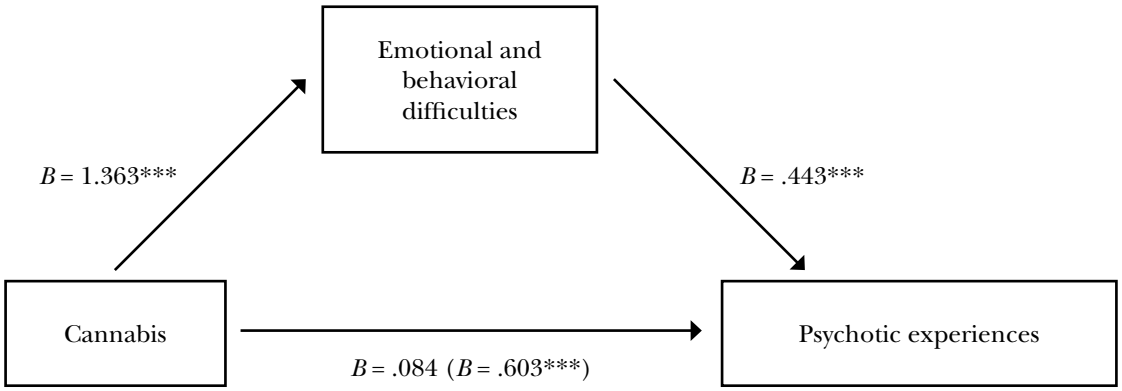
Our main goal was to analyze the relationship between psychotic-like experiences and cannabis use in a representative sample of Spanish adolescents. The results derived from this study show that: a) young cannabis users reported higher levels of psychotic-like experiences, both in terms of frequency and associated distress compared to non-users; b) the link between cannabis use and psychotic experiences disappeared when the effect of multiple covariates was taken into account; and c) mediational analysis

Table 1. *Means' comparisons between users and non-users of cannabis and psychotic-like experiences (frequency and distress)*

	Non-users		Users				
	M	SD	M	ST	F	p	partial n²
PQ-B distress	10.64	11.12	12.59	12.45	8.341	0.004	0.005
PQ-B frequency	5.83	4.37	6.64	4.41	9.883	0.002	0.006

Table 2. *Relationship between risk of psychosis and cannabis prevalence*

			Risk of psychosis		
			No	Yes	Total
Cannabis prevalence	No	n	902	309	1211
		% cannabis prevalence	74.50%	25.50%	100.00%
		% risk of psychosis	78.20%	71.20%	76.30%
	Yes	n	252	125	377
		% cannabis prevalence	66.80%	33.20%	100.00%
		% risk of psychosis	21.80%	28.80%	23.70%
Total		N	1154	434	1588
		% cannabis prevalence	72.70%	27.30%	100.00%
		% risk of psychosis	100.00%	100.00%	100.00%



Note. *** $p < .001$

Figure 1. Direct and indirect effects of cannabis use and emotional and behavioral difficulties on psychotic experiences. The indirect effect of cannabis use on the risk of psychosis through emotional and behavioral difficulties is in parentheses. Non-standardized coefficients.

indicated that emotional and behavioral problems mediated the relationship between cannabis use and the risk of psychosis, after controlling for the effect of multiple confounding variables.

Previous studies appear to show, on the one hand, that cannabis use increases the risk of developing psychosis spectrum disorders, with a dose-response relationship (Davis, Compton, Wang, Levin & Blanco, 2013; Degenhardt et al., 2018; Henquet et al., 2008; Kuepper et al., 2011), and on the other hand, that the association between cannabis and psychosis is found throughout the continuum of the psychosis phenotype (attenuated psychotic experiences, schizotypal traits, subclinical psychotic symptoms, psychotic symptoms) (Dolphin et al., 2015; Esterberg et al., 2009; Fonseca-Pedrero et al., 2016; Hides et al., 2009; Linscott & van Os, 2013; Mackie et al., 2011); nevertheless, there is ongoing debate as to possible moderating, mediating or confounding factors, as well as cause-effect relationships that may be modifying the complex interactions between genetic and environmental influences and between the psychosis phenotype and substance use, specifically cannabis.

In this study, it was found that after controlling for the effect of the multiple relevant covariables, the use of cannabis was not related to the frequency and distress associated with psychotic experiences reported by adolescents. Previous studies with adolescents and young adults have met with similar results when analyzing the psychotic phenotype at subclinical or population level (Dolphin et al., 2015; Fusar-Poli et al., 2017; Mackie et al., 2011); others, however, did find such a link (Hides et al., 2009; Jones et al., 2018). For example, in a representative sample of adolescents, Dolphin et al. (2015) revealed that all relationships were significant in the univariate analysis between substance abuse and psychotic experiences, although the only significant relationship in the multivariate analysis was between auditory hallucinations and cannabis use in the past 30 days, which points to a confounding with other predictor variables. A recent meta-analysis conducted by Fusar-Poli et al. (2017) found no relationship between cannabis use and the ultra-high risk of psychosis.

The mediational analysis indicated that reported comorbid psychopathology mediated the relationship between cannabis use and the frequency of psychotic experiences, after adjustment for multiple confounding variables. More specifically, the use of cannabis increased the risk of comorbid psychopathology and this, in turn, the frequency of psychotic experiences. Previous studies of young people in the general population reach similar conclusions (Bourque, Afzali, O'Leary-Barrett & Conrod, 2017). For example, a longitudinal study with adolescents by Bourque et al. (2017) found that symptoms of depression partially mediated the longitudinal link between cannabis use and psychotic experiences. Analogous results are found in adults, where the mediating role of anxiety between cannabis use and psychotic experiences is observed (Reeves et al., 2014). More complex studies involving gene-environment interaction have found that the link between symptoms of substance use disorder and psychotic-like experiences is explained by shared genetic and environmental factors and by the direct effects between substance use and the risk of psychotic experiences (Nesvåg et al., 2016). Nevertheless, it seems that cannabis use accounts for 2-5% of the variance in psychotic-like experiences of a positive, cognitive, and negative type (Shakoor et al., 2015). Overall, these results highlight the importance of the study of environmental and psychological variables such as comorbid psychopathology, attachment, smoking or trauma, and victimization experiences in developmental stages at special risk of suffering mental disorders and before the transition to a clinical phase and the need for treatment.

As risk markers for psychosis spectrum disorders, psychotic-like experiences should be used in combination with other risk markers (proximal or distal) and variables such as substance use or abuse, trauma experiences, family

history of obstetric disorders or complications (Linscott & van Os, 2013; Van Os & Linscott, 2012). Possible underlying etiological mechanisms can, thus, be analyzed, and strategies and programs for early detection and prevention can be improved. At the same time, the most current etiological hypotheses in this field, such as the propensity-persistence-disability model (Cougnard et al., 2007; Linscott & van Os, 2013) or neurodevelopmental models (Fonseca-Pedrero, 2018; Fusar-Poli et al., 2017; Millan et al., 2016), believe that certain environmental impacts (environmental or adverse risk) occur during the course of development, both in the pre/perinatal (first wave) and in adolescent (second wave) stages, which, in combination with genetic and/or personal factors, can lead to such psychotic experiences (as a phenotypic expression of existing vulnerability) becoming abnormally persistent, triggering a first psychotic episode, disability, and a need for treatment.

This study allows us to tentatively draw some relevant clinical and prevention implications. As regards prevention, the mediating role of emotional and behavioral problems in young people with psychotic-like experiences and cannabis use highlights the need for early intervention programs in psychosis to be aimed not only at preventing the use of cannabis, but also, and in particular, at preventing and intervening in emotional and behavioral difficulties. It, therefore, seems sensible to design emotional well-being programs to promote social-emotional competence in school contexts. For example by providing young people with tools to better manage their emotions and build an appropriate image of themselves with positive personal motivations and values, and encouraging the implementation of adaptive strategies to cope with their problems. Furthering the positive development of adolescents and the strengthening of school students (Oliva, 2015) is crucial. Prevention will always be the most thorough response when it comes to reducing mental health problems and risk factors and while also promoting protective factors and the development of socio-emotional strategies.

The present study is not without limitations, some of which are discussed below. First, mental health indicators were assessed using self-report instruments, with the corresponding limitations of these types of tools. Second, the sample is from a Spanish autonomous community, which, despite stratified random sampling by conglomerates, partially limits the generalization of the results to the whole country. Third, a cross-sectional study, such as this, does not permit causal relationships to be established. Fourth, it would have been interesting to collect data on other levels of analysis (e.g., genetic, cerebral, physiological, etc.), which are aspects that could modulate the results. Finally, this paper only analyzed the role of psychotic experiences of the positive dimension (e.g., delusional ideation or hallucinatory experiences), so future studies should investigate the relationship between the negative (e.g., flattened affect or anhedonia) or disorganized dimensions of the psychotic phenotype (Fonseca-Pedrero et al., 2018).

Despite its limitations, the present study yields new results in the study of the relationship between cannabis use and psychotic experiences at the population level. Future studies should continue to analyze the complex interactions that are established between the use of substances such as cannabis, and the risk of psychosis in longitudinal studies, taking into account the complexity of gene-environment interactions and people's real-life settings (ecological validity). This, will provide knowledge of the underlying and etiological mechanisms that can inform the design of mental health promotion programs as well as the setting of new therapeutic targets.

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The age of onset for alcohol consumption among adolescents: Implications and related variables

La edad de inicio en el consumo de alcohol en adolescentes: implicaciones y variables asociadas

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Abstract

Adolescence is a critical period in the development of addictive behaviors. In particular, the age at which adolescents start drinking is not a trivial matter, given the important consequences that it has. However, relatively little is known about what it is that causes them to start drinking at an ever earlier age. The aim of this paper is to collect new empirical data about the implications of an early age of onset and, at the same time, to identify possible associated variables. Furthermore, the mean age of onset of the different substances is updated by expanding the sample frame of the ESTUDES (14-18 years) to incorporate adolescents aged 12 and 13. The results obtained with a sample of 3,419 adolescents from the Autonomous Community of Galicia (M = 14.57 and SD = 1.76) reveal that at 13.4 years of age, the age at which adolescents tend to start drinking is lower than suggested by ESTUDES 2016-2017. In addition, those who start drinking earlier are more likely to use other substances, their rates of high-risk consumption are 3 times higher and they are more involved in potentially dangerous practices. Finally, variables such as risk perception and expectations of use yield very limited explanatory capacity, especially if they are compared with those related to drinking within the family or peer group. These results reinforce the need to delay the age of alcohol onset as one of the strategic objectives of prevention policies.

Keywords: Adolescents; Alcohol; Drugs; Age of onset; Related variables.

Resumen

La adolescencia constituye un período crítico en el desarrollo de conductas adictivas. En particular, la edad a la que los jóvenes se inician en el consumo de alcohol no es una cuestión banal, habida cuenta de las importantes repercusiones que posee a diferentes niveles. Sin embargo se sabe poco de por qué cada vez se empieza a consumir de manera más precoz. El objetivo del presente trabajo ha sido recabar nuevos datos empíricos sobre las implicaciones de una edad de inicio temprana e identificar, al mismo tiempo, posibles variables asociadas. Se han actualizado además las edades medias de inicio de consumo de distintas sustancias, ampliando el marco muestral habitual del ESTUDES (14-18 años), incorporando a los adolescentes de 12 y 13 años. Los resultados obtenidos con una muestra de 3419 adolescentes de la comunidad gallega (*M* = 14,57 y *DT* = 1,76) permiten constatar que la edad a la que los adolescentes suelen iniciarse en el consumo de alcohol es menor de lo que sugiere el ESTUDES 2016-2017, situándose en 13,4 años. Además quienes se inician antes en su consumo presentan una mayor probabilidad de consumir otras sustancias, tasas de consumo de riesgo 3 veces superiores y se implican más en prácticas potencialmente peligrosas. Por último, variables como la percepción del riesgo o las expectativas presentan una capacidad explicativa escasa, sobre todo si se compara con otras relacionadas con el consumo del entorno familiar o entre iguales. Los resultados refuerzan la necesidad de retrasar la edad de inicio del consumo de alcohol como uno de los objetivos estratégicos de las políticas de prevención.

Palabras clave: Adolescentes; Alcohol; Drogas; Edad de inicio; Variables asociadas.

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Adolescence is a complex developmental stage in which changes occur at physical, psychological, biological, intellectual and social levels, marking the transition from childhood to adulthood. It is essentially a critical period during which new capacities are acquired and objective and subjective needs specific to this developmental present themselves. All this makes adolescents as a group particularly vulnerable to developing certain high-risk behaviors, among them drug use (Rosabal, Romero, Gaquín & Hernández, 2015). Recent research carried out in Spain has attempted to provide evidence to emphasize the importance of drinking and use of other substances in adolescence, both at a socio-sanitary level in general and for mental health in particular (Bousoño et al., 2017; Carbia, López-Caneda, Corral & Cadaveira, 2008; Díaz Geada, Busto Miramontes & Caamaño-Isorna, 2018; Fonseca, Ortuño, Paino & Muñiz, 2016; López-Caneda et al., 2014), as well as the link between them and the appearance of new behavioral addictions, mainly related to the use of Internet and social networks (Golpe, Gómez, Braña, Varela & Rial, 2017). The research shows beyond doubt that these issue are enormously complex both from an explanatory and an applied point of view (Teixidó-Compañó et al., 2019; Vargas-Martinez, Trapero-Bertran, Gil-Garcia & Lima-Serrano, 2018).

The age at which adolescents start drinking alcohol is not a trivial matter. Numerous studies have pointed out that adolescents who begin drinking earlier have a higher risk of brain damage and neurocognitive consequences (Cadaveira, 2009; Carbia, Cadaveira, Caamaño-Isorna, Rodríguez & Corral, 2017; Zeigler et al., 2005). Moreover, the probability of involvement in numerous risky practices, such as fighting or acts of violence (Gruber, DiClemente, Anderson & Lodico, 1996; Hingson, Edwards, Heeren & Rosenbloom, 2009), worse educational performance (Rothman, Dejong, Palfai & Saitz, 2008), high-risk sexual practices (Donovan, 2004; Stueve & O´Donnell, 2005) or traffic accidents (Hingson, Heeren, Levenson, Jamanka & Voas, 2002) is also higher among those who start drinking early. Another aspect for which the age of alcohol onset raises great concern is that, for many researchers and professionals, alcohol serves as a "gateway" to the use of other substances (Kirby & Barry, 2012; Yu & Williford, 1992). The literature linking the early use of alcohol to a greater likelihood of consuming other substances is extensive (Barry et al., 2016; Ellickson, Tucker & Klein, 2003; Gruber et al., 1996). The greater risk of developing abusive drinking or even a possible disorder after earlier onset has also been documented (Caamaño-Isorna, Corral, Parada & Cadaveira, 2008; Moss, Chen & Yi, 2014).

However, despite the enormous importance that has been attached to the subject, relatively little is still known about what it is that makes adolescents begin drinking alcohol at an increasingly earlier age. While there is ample literature on the possible variables at the root of alcohol use (Steketee, Jonkman, Berten & Vettenburg, 2013), binge drinking (Golpe, Isorna, Barreiro, Braña & Rial, 2017; Motos, Cortés, Giménez & Cadaveira, 2015) or even the practice of street drinking (Golpe, Barreiro, Isorna, Varela & Rial, 2017; González, 2015), not many studies have specifically focused on attempting to explain the age of onset. Some of them have tried to analyze the differences based on gender. Thus, not only have studies been done showing that boys have a greater propensity for displaying externalizing behaviors (Kessler et al., 2012; Ortuño, Aritio & Fonseca, 2017; Ortuño, Fonseca, Paíno & Aritio, 2014), but that they also tend to begin drinking sooner (Sartor, Lynskey, Heath, Jacob & True, 2007; Trim, Schuckit & Smith, 2010). Others have linked early consumption to personal variables such as favorable expectations towards alcohol (Adolfsen et al., 2014; Fisher, Miles, Austin, Camargo & Colditz, 2007) or a low perception of risk (Moral, Rodríguez & Sirvent, 2006), while yet others have emphasized the influence of the human environment in terms of both family (Donovan & Molina, 2011; Sher, Walitzer, Wood & Brent, 1991; Trim et al., 2010) and peers (Fisher et al., 2007; Hawkins et al., 1997; Mundt, 2011).

According to the data collected by the latest national survey on drug use in secondary education (ESTUDES 2016-2017) (Plan Nacional sobre Drogas, 2018a), the age of onset of alcohol consumption is just 14, slightly below that of smoking (14.1). With respect to other substances, it should be noted that cannabis is usually tried for the first time on average at 14.8 years and cocaine and amphetamines at 15.1. However, it is conceivable that given the technical-methodological limitations connected with the sample design of ESTUDES itself, these data may not faithfully represent what is actually happening in reality. It is logical to think that if alcohol onset age is assumed to be getting younger and younger, it would be recommendable to expand the sampling frame by incorporating adolescents aged 12 and 13. Although the ESTUDES 2016-17 (Plan Nacional sobre Drogas, 2018a) data on alcohol use invite us to draw positive conclusions regarding the effort made over recent years in terms of prevention, one of the issues that continues to worry professionals and researchers has to do with the early age at which adolescents begin to drink alcohol (Marshall, 2014). So much so that delaying the age of onset was already set as one of the objectives of the *Action Plan on Drugs (Plan de Acción sobre Drogas) 2013-2016* (Plan Nacional sobre Drogas, 2013) (general objective 4) and one of the general objectives of the current *National Strategy against Addiction (Estrategia Nacional sobre Adicciones) 2017-2014* (Plan Nacional sobre Drogas, 2018b). The same can be said of different regional plans, as is the case with the *Galician Plan on Addictive Disorders (Plan de Trastornos Adictivos de Galicia) 2011-2016* (Xunta de Galicia, 2010) (specific objective 1.3).

The present study pursues two fundamental objectives: on the one hand, to provide new evidence regarding the implications of starting alcohol use early, both in terms of habits of use, intensive use and high-risk use of alcohol and drugs in general (assessed through specific tools such as AUDIT or CRAFFT), as well as participation in different high-risk practices; on the other hand, to identify some of the possible variables associated with early onset by trying to compare the explanatory capacity of some personal variables with others that have to do with how alcohol is used in the environment.

Regarding the first objective, the working hypothesis in the existing literature is that the younger the adolescents are when they begin drinking alcohol, the greater the likelihood of them using both alcohol and other substances (Barry et al., 2016) and of having higher rates of intensive and high-risk consumption (Moss et al., 2014), and the more likely they are to be involved in high-risk practices (Donovan, 2004, Gruber et al., 1996). As regards the second objective, the working hypothesis is that the age of alcohol onset is linked to both individual and environmental variables (Fisher et al., 2007), although there is controversy as to which of them is more influential (Blackson & Tarter, 1994; Donovan, 2004).

Finally, although it is not the main objective of the work, it is also a good opportunity to update the onset ages for use of the different substances, incorporating the 12-13 year age range into the sampling frame and, on the other hand, to compare if there are significant variations in this respect in terms of gender.

Method

Participants

To put the proposed objectives into practice, a survey was carried out among the student population in compulsory secondary education (ESO), higher secondary education (Baccalaureate) and vocational training programs of the Autonomous Community of Galicia. For sample selection purposes, a two-stage sampling process was used: by cluster for the selection of first level units (schools) and by quota, according to gender and course year, for the selection of second level units (individuals). A total of 37 schools, both public and private/charter, from the four provinces in Galicia participated in the study, with equal quotas at the population level.

Initially, 3,714 questionnaires were collected. After scrutiny of the database, 295 cases were eliminated, either because the questionnaire was incomplete (15), because they had inconsistent response patterns (22) with serious contradictions in the information collected across different sections, or because they were outside the age range (258). The final sample consisted of a total of 3,419 adolescents (50.6% boys and 49.4% girls) aged between 12 and 18 (M = 14.57, SD = 1.76). Of these, 2,236 attended public and 1,183 attended private/charter schools, with 73.3% studying ESO (38.2% in the first phase 35.1% in the second phase), 20.4% higher secondary (Bachillerato) and 6.2% basic vocational training (PCPI) or an intermediate level vocational program (Ciclo Formativo de Grado medio).

Instrument

Data collection was by means of an ad hoc questionnaire prepared expressly for the present study which included a total of 116 items grouped into 3 blocks: (1) the first block was extracted from the 2010 national survey on drug use in secondary education (ESTUDES 2010) (National Plan on Drugs, 2011) and contained questions regarding substance use habits (alcohol and other) during one's lifetime, in the last year and in the last month, as well as questions about the age of onset for the different substances; (2) the aim of the second block was to assess the possible implications of alcohol consumption. To this end, a block extracted from the European School Survey on Alcohol and Other Drugs [ESPAD 2011] (Hibell et al., 2012) was included. It covers participation in different high-risk practices (fights, accidents, unprotected sex, going to ER, etc.) and two screening tools for high-risk use: the Alcohol Use Disorder Identification Test (AUDIT) in its self-administered version (Rial, Golpe, Araujo, Braña & Varela, 2017), with satisfactory internal consistency (α = .77), and the CRAFFT Substance Abuse Screening Test validated empirically in the work of Rial et al. (2019) with a Cronbach's α of .74; (3) a third block included questions similar to those in the 2010 ESTUDES and the 2011 ESPAD to assess possible variables linked to the age of alcohol onset that could in some way be interpreted as prognostic factors. The perception of risk was assessed with three items which, although not constituting a scale in themselves, presented acceptable reliability through their internal consistency (α = .64) (Pardo & Ruiz, 2001; Prieto & Delgado, 2010). Expectations regarding alcohol use were assessed with a set of 10 items. Exploratory factor analysis (EFA) provided two factors (positive expectations and negative expectations) which jointly explained 64.43% of the variance of the data, the former 37.04% and the latter 27.39%. Each factor comprised five items and both had a high Cronbach's α coefficient ($\alpha_{\text{positive expectations}}$ = .86 and $\alpha_{\text{negative expectations}}$ = .84). Finally, five items were included to assess alcohol use both in the family environment and by peers, as well as various sociodemographic questions. This questionnaire was also used in the piloting of the study by Rial et al. (2019).

Procedure

The data was gathered in the school classrooms, in small groups, through a questionnaire completed individually by each student, with psychologists experienced in performing this type of task responsible for collecting the infor-

mation. Each subject was informed of the purpose of the study and that the data would be treated in a completely confidential and anonymous manner. Consent and collaboration was obtained from both the school management and the respective parental associations. Participation was completely voluntary and the time necessary for completion of the questionnaire was approximately 25 minutes. The study was approved by the Bioethics Committee of the University of Santiago de Compostela.

Data analysis

After an initial descriptive analysis, a correlation analysis was carried out by calculating the Pearson correlation between metric variables. In the case of quantitative variables, the differences between the three questionnaire groups according to the age of onset were analyzed by applying a one-way ANOVA (with a *post-hoc* Tukey test for the comparison of groups and the partial eta squared coefficient (η2p) to estimate effect size. In the case of qualitative or categorical variables, chi-square tests were used along with the calculation of contingency coefficients (CC). Finally, a logistic regression analysis was carried out to estimate the associated odds ratios for different variables. The analyses were performed with the statistical package IBM SPSS Statistics 20.

Results

Table 1 shows the prevalences of use for the different substances among adolescents aged between 12 and 18 during their lifetime, in the last year and in the last month. As can be seen, alcohol is the most widely used substance by adolescents (58.7% in the last year and 37.9% in the last month), followed by tobacco (30.4% and 19.9%, respectively) and cannabis (18.9% and 10.7%).

Regarding the average age of onset of the different substances, this is earliest for alcohol and tobacco (13.4 and 13.6 respectively). The first episode of drunkenness takes place at 14.5 years, immediately before the start of cannabis use (14.6). Cocaine and other substances (ecstasy, amphetamines and hallucinogens) are those with the latest onset (14.9 and 15.3 respectively). A look at the prevalence of use in under 14-year-olds, an age range not included in ESTUDES, shows that 4 out of 10 adolescents who have tried alcohol or tobacco at some time in their lives (44.8% and 44.1% respectively) did so before age 14, with 22.4% in the case of cannabis. Furthermore, as expected, the incorporation of the 12-13 age range into the sample has caused the age of onset to decrease for all substances.

With regard to gender (Table 2), results show the existence of statistically significant differences in the age of alcohol onset (M_{boys} = 13.1 vs M_{girls} = 13.8) (t = - 7.27; $p < .001$), first drunkenness (M_{boys} = 14.2 vs M_{girls} = 14.8) (t = -5.25; $p < .001$), and smoking (M_{boys} = 13.4 vs M_{girls} = 13.8) (t = -3.09; $p < .01$) – particularly in the first two cases – with the boys being those who started earlier.

Implications or associated risks

The correlations shown in Table 3 indicate that the earlier adolescents start drinking alcohol, the sooner they begin to use other substances, such as tobacco. (r_{xy} = .55; $p < .001$), cannabis (r_{xy} = .55; $p < .001$) and cocaine (r_{xy} = .44; $p = .001$). Moreover, a negative and statistically significant correlation between the age of onset and high-risk use, both of alcohol ($r_{xy\ AUDIT}$ = -.36; $p < .001$) and drugs in general ($r_{xy\ CRAFFT}$ = -.34; $p < .001$) was also found.

In an attempt to illustrate the importance of the age of alcohol onset on drinking patterns, intensive and high-risk drinking, and different high-risk practices, participants aged between 16 and 18 who had drunk alcohol in the last year were selected and assigned to three groups: those that had first tried alcohol (a) aged between 12-13; (b) between 14-15 and (c) between 16 and 18.

In relation to drinking habits (Table 4), the percentage of those drinking alcohol during the last month is significantly higher among those who had started earlier. Specifically, 84.8% of those who had started drinking alcohol aged 12-13 drank in the last month (compared to 64.1% of those who had started aged 16-18 years). The data also show that an earlier onset age is significantly associated with a more

Table 1. *Prevalence of consumption and descriptive statistics for age of onset.*

	Consumption			Age of onset				
				12-18 years		14-18 years		% Users under 14
	Lifetime (%)	Last year (%)	Last month (%)	Mean	SD	Mean	SD	
Alcohol	58.7	58.7	37.9	13.41	2.16	13.62	2.02	44.8
Tobacco	34.7	30.4	19.9	13.59	1.86	13.70	2.06	44.1
Getting drunk	36.1	34.4	16.5	14.46	1.86	14.52	1.84	22.8
Cannabis	21	18.9	10.7	14.62	1.81	14.67	1.80	22.4
Cocaine	2.2	1.7	1.2	14.89	1.41	14.97	1.43	10
Ecstasy/amph./hallucin.	2.6	2.4	1.1	15.28	1.37	15.36	1.38	6.1

Table 2. *Comparative age of onset by gender.*

	Boys (Media)	Girls (Media)	t	*p*
Alcohol	13.1	13.8	-7.27	‹.001
Tobacco	13.4	13.8	-3.09	‹.01
EGetting drunk	14.2	14.8	-5.25	‹.001
Cannabis	14.6	14.73	-1.17	.22
Cocaine	14.8	15.15	-1.03	.30
Ecstasy/amph./ hallucin.	15.3	15.25	0.18ns	.85

Table 3. *Correlation between the age of alcohol onset and other substance use.*

	Age of alcohol onset	
	r_{xy}	*p*
Tobacco	.55	‹.001
Cannabis	.55	‹.001
Cocaine	.44	‹.001
Ecstasy/amphetamines and hallucenogens	.40	‹.001

intensive drinking pattern, also known as binge drinking. In fact, 44.5% of those who had started drinking alcohol at 12-13 years of age reported having had six or more alcoholic beverages in the same sitting during the last month, compared to 19.1% of those who had started drinking aged between 16-18. Along the same lines, 53.3% said they had got drunk (compared to 26.7%). The same can be said for tobacco, cannabis, ecstasy/amphetamines or hallucinogens. Regarding cocaine, although slightly higher percentages of use were found in the group of adolescents with early onset, the differences did not reach statistical significance.

With regard to high-risk drinking, the data reveal that the age of alcohol onset increases the likelihood of developing hazardous use. Rates of alcohol and drug abuse in general are shown to be almost three times higher among those who started drinking at 12-13 compared to those who started aged 16-18 years ($\chi^2_{AUDIT} = 94.54$; $p < .001$) ($\chi^2_{CRAFFT} = 77.41$; $p < .001$).

As shown in Table 4, the most prevalent high-risk behavior across the three comparison groups is being driven by someone under the influence of alcohol, but among those who started drinking at 12-13 the percentage is 60.3%, compared to 36.3% among those who started at 14-15 and 28.4% for those starting at 16-18. Statistically significant differences have been found in all risky behaviors explored (except for being the victim of assault or robbery). The percentage in all of them is significantly higher among early starters, although the greatest effect size is found in "being driven by someone under the influence of alcohol" (CC = .23), "getting involved in fights" (CC = .22), "suffering accidents and injury" (CC = .20) and "getting into trouble with the police" (CC = .20).

Table 4. *Consumption habits in the last month and high-risk practices by age of onset.*

Hábitos de consumo	**Edad de inicio alcohol**					
	12-13 (%)	**14-15 (%)**	**16-18 (%)**	χ^2	***p***	**CC**
Alcohol	84.8	72.3	64.1	24.29	‹.001	.16
Getting drunk	53.3	33	26.7	37.91	‹.001	.20
6 o more alcoholic drinks	44.5	22.4	19.1	46.62	‹.001	.22
Tobacco	55.3	38.6	18.9	58.93	‹.001	.24
Cannabis	35.9	19.3	6.2	58.19	‹.001	.24
Cocaine	2.2	1.2	0.5	2.45	.29	-
Ecstasy/amphetamines /hallucenogens	3.9	0.6	1	12.35	.002	.11
High-risk practices	**12-13 (%)**	**14-15 (%)**	**16-18 (%)**	χ^2	***p***	**CC**
Being driven by someone under the effect of alcohol	60.3	36.3	28.4	53.58	‹.001	.23
Fights	35.8	20.,2	9.1	45.94	‹.001	.22
Accidents or injury	26	14	4.1	40.75	‹.001	.20
Parental problems	15.1	9	1.5	24.13	‹.001	.16
Poor academic performance	12.5	6	3.6	14.79	.001	.12
Victim of assault/robbery	3.5	4.3	2.5	1.26	.53	-
Trouble with the police	13.8	3.3	2.6	37.07	‹.001	.20
ER or hospitalization	7.8	3.5	2	10.20	.006	.10
Unprotected sex	18.5	11.7	4.6	19.77	‹.001	.14
Regretful sex	16.4	11.4	2	23.67	‹.001	.16

Associated variables

Perception of risk and expectations of use

As shown in Table 5, adolescents who begin drinking alcohol earlier have a significantly lower perception of risk than those who start later; this holds true in all three indicators used. In terms of the expectations that adolescents have about the effects of alcohol, statistically significant differences have also been found, fundamentally with regard to positive expectations or expected benefits of consumption. Those who started drinking between 12-13 years have significantly higher average scores in all cases: "feeling relaxed" (2.16 vs. 1.93 vs. 1.77), "feeling happy" (2.76 vs. 2.49 vs. 2.26), "forgetting about problems" (2.67 vs. 2.33 vs. 2.03), "feeling more sociable and extroverted" (2.85 vs. 2.71 vs. 2.52) or "having a lot of fun" (3.07 vs. 2.75 vs. 2.48).

The user's environment

With regard to the family environment, Table 6 shows that the highest percentage of adolescents who indicate that both their parents and siblings drink alcohol regularly are found in the early onset (12-13) group, although the differences were only statistically significant for siblings ($\chi^2 = 15.33$; $p < .001$; CC = .14). On the other hand, in terms of peer group, the percentage of adolescents reporting that most or all of their friends drink alcohol is significantly higher among those who started drinking between 12-13 (88.4%) in comparison with those who started later (82.3% for those who started between 14-15 and 70.1% between 16-18). The same is true when we look at the frequency with which friends get drunk (60.6%, 43.6% and 34.7%, respectively).

Finally, given that the greatest explanatory capacity of the variables explored (perception of risk, expectations and environment) was found in those connected with peer drinking and, in particular, by siblings and friends, it was decided to perform a logistic regression in order to analyze the extent to which the risk of early alcohol onset increases when peers are also users (Table 7). In order to maximize the differences, the two groups of with extreme starting ages were compared: those who started drinking at 12-13 with those who did so aged 16-18. The results obtained show that the rate of early onset is 2.30 times higher when siblings drink alcohol regularly and 2.77 times higher when most or all friends get drunk.

Discussion

The results obtained in the present study show, firstly, that expanding the sampling frame to 12-18 years of age leads to a downward adjustment in the age of onset estimation for the different substances and to significantly earlier ages than those found in ESTUDES 2016-2017 except in the case of smoking, which hardly changes. It can be seen, for example, that four out of ten adolescents who had tried alcohol did so before the age of 14, as is also the case with tobacco; this is something that has important implications at the level of prevention, requiring intensive work in the early stages of compulsory secondary education or even during the final years of primary education. Research by, for example, Cadaveira (2009), Jacobus & Tapert (2014) or Yuan, Cross, Loughlin & Leslie (2015) has highlighted the

Table 5. *Perception of risk and expectations of use.*

	Age of alcohol onset					
Perception of risk	**12-13 (M)**	**14-15 (M)**	**16-18 (M)**	**F**	***p***	**η^2_p**
1 or 2 alcoholic drinks almost every day	1.50	1.60	1.76	4.27	.01	.01
5 or 6 alcoholic drinks almost every day	2.53	2.59	2.73	5.75	.003	.01
6 or more alcoholic drinks every weekend	2.18	2.37	2.59	14.62	<.001	.03
Expectations	**12-13 (M)**	**14-15 (M)**	**16-18 (M)**	**F**	***p***	**η^2_p**
Feel relaxed	2.16	1.93	1.77	5.78	.003	.01
Feel happy	2.76	2.49	2.26	10.06	<.001	.02
Forget my problems	2.67	2.33	2.03	13.10	<.001	.02
Feel more sociable/extrovert	2.85	2.71	2.52	4.36	.01	.01
Have a great time	3.07	2.75	2.48	16.04	<.001	.03
Average POSITIVE EXPECTATIONS	2.70	2.44	2.19	16.92	<.001	.03
Trouble with the police	1.32	1.26	1.24	.27	.76	-
Jeopardize my health	2.69	2.53	2.58	1.31	.27	-
Can't stop drinking	1.45	1.08	1.36	8.95	<.001	.02
Do something I will regret	2.32	2.15	2.12	1.75	.17	-
Feel bad	2.17	2.20	2.44	3.25	.04	.01
Average NEGATIVE EXPECTATIONS	2.01	1.84	1.94	2.50	.08	-

Table 6. *Alcohol use among family and peer group.*

		Age of alcohol onset					
		12-13 (%)	14-15 (%)	16-18 (%)	χ^2	*p*	CC
Mother	Never/almost never	65.4	72.1	70.4	3.42	.18	.06
	Habitually	34.6	27.9	29.6			
Father	Never/almost never	37.4	44.4	49.5	6.12	.05	.08
	Habitually	62.6	55.6	50.5			
Siblings	Never/almost never	46.2	53.5	66.7	15.33	<.001	.14
	Habitually	53.8	46.5	33.3			
Friends who drink alcohol	None/ a few	11.6	17.7	29.9	24.43	<.001	.16
	The majority/all	88.4	82.3	70.1			
Friends who get drunk	None/ a few	39.4	56.4	65.3	31.14	<.001	.18
	The majority/all	60.6	43.6	34.7			

Table 7. *Calculation of Odds Ratios for peer group consumption.*

	ONSET AGE	
Variable	**Univariate ORP (95% IC)**	**Multivariate[1] ORP (95% IC)**
SIBLINGS WHO DRINK		
Never/almost never	1	1
Habitually	2.34 (1.52-3.61)	2.30 (1.46-3.63)
FRIENDS WHO DRINK		
None/a few	1	1
The majority/all	3.29 (1.98-5.46)	1.86 (0.98-3.51)
FRIENDS WHO GET DRUNK		
None/a few	1	1
The majority/all	2.91 (1.96-4.32)	2.77 (1.68-4.56)

Note. ORP = odds ratio prevalence; CI= confidence interval;
[1] Adjusted for the other independent variables listed in the column.

serious implications that the use of these substances can have in brain development.

Furthermore, the results obtained may reinforce the existence of a "cycle of use" in which three major stages or moments can be identified. The first of these occurs when adolescents begin to drink alcohol, this being the first substance that they experience at 13.4 years on average, immediately followed by tobacco at 13.6. Approximately one year later, the first drunkenness (14.5 years) takes place, closely linked to experimentation with cannabis (14.6 years). A little later (at around 15) they start using other illicit substances, such as cocaine, ecstasy, hallucinogens or amphetamines. There is, therefore, a critical period between 13.5 and 15.5 years of age which sees the onset of different psychoactive substances, with alcohol usually being the first with which adolescents come into contact. According to the results obtained, the age at which this occurs (and it is also important to point out that it is the age which has a greater standard deviation) has an enormous effect on the use of other substances and in drinking patterns themselves. The correlation analysis shows that the earlier adolescents start drinking alcohol, the sooner they begin to consume other substances. This coincides with the approaches of authors such as Kirby & Barry (2012) or Yu & Williford (1992), who point to alcohol as the "gateway" to the use of other substances.

Regarding the implications of onset age, it has been observed that the percentage of adolescents who smoke and use other substances is much higher among those who started drinking earlier. This finding is in line with many other studies, such as Ellickson et al. (2003), Gruber et al. (1996), and Hérnandez et al. (2009). Similarly, it has also been proven that the percentage of adolescents involved in numerous risky practices (fights, being driven by someone under the influence of alcohol, having regretful sex, accidents or injuries) is significantly greater among those who started drinking earlier, as pointed out by Hingson et al. (2002), and Stueve and O'Donnell (2005). Regarding the greater probability of developing abusive or high-risk drinking patterns, in line with the findings of Caamaño-Isorna et al. (2008), and Moss et al. (2014), the results obtained through the use of AUDIT reveal a 3 times higher rate of alcohol problems among early onset adolescents, to such an extent that 7 out of 10 early onset adolescents tested positive in AUDIT.

Finally, an attempt was made to explore the role that some of the variables highlighted in the literature may play as possible explanatory factors regarding early alcohol onset. Although the results obtained with respect to personal variables, such as risk perception or expectations of use, concur with the literature reviewed, their explanatory capacity is rather limited. Beyond such variables of an individual nature, the results obtained show the importance of the user's environment, especially the peer group. The prevailing patterns of use in the adolescent's reference group exert an important influence on the age of onset of alcohol use, as Gascón et al. (1997) pointed out two decades ago. The rate of early onset is 2.31 times higher

among adolescents when siblings drink alcohol and 2.77 times higher when their friends get drunk. Nevertheless, it is important to point out that the explanatory capacity of these variables remains small without the possibility of establishing cause-effect relationships. It is not possible to determine whether adolescents who start drinking earlier do so because their peers also drink or, conversely, whether they have more friends who drink because they started earlier. This is precisely one of the limitations of this work.

It should also be noted that, by using a sample of adolescents exclusively from the Galician autonomous community, the external validity of the results obtained is limited, as is, in other words, the capacity of generalization to other autonomous communities, especially in terms of the specific estimation of the onset ages for each substance. A further limitation is that all the variables have been self-reported, making it impossible to know with certainty to what extent adolescents may have under- or overestimated their levels of use. However, as various experts in the field of addictive behavior have previously noted, self-report measures have proven to be reliable and even better than other methods when evaluating levels of alcohol and other drug use (Babor, Kranzler & Lauerman, 1989; Winters, Stinchfield, Henly & Schwartz, 1990).

With regard to the possible analysis of correlations between the age of onset of the different substances (not only of alcohol with the rest), despite the fact that these may be of interest, this deviated from the key goal of this study, which was none other than to analyze specifically how the age of alcohol onset is related to the age of onset in the use of other substances, as well as possible implications of this and associated variables. This was the core of the research project and its ultimate purpose. Future studies will enable an analysis of the relationship between the onset ages of other substances with a broader perspective.

Finally, it is important to remember that this research is of a correlational nature, which does not allow causal relationships to be established. Although it may be possible conceptually to "anticipate" which variables could be acting as "predictors" or as "consequences" of the age of onset, only a longitudinal design could confirm this type of cause-effect relationships. There is no doubt that there is still a long way to go in terms of the development and validation of explanatory models regarding the early start of alcohol use. It would be of great interest if future work in this field could incorporate new variables and focus their efforts on the development of parsimonious explanatory models capable of improving current prevention.

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Conflict of interests

The authors of this article declare no conflict of interests.

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Influence of the type of childhood violence on cannabis abuse and dependence among adolescents: a systematic review and meta-analysis

Tipos de violencia en la infancia que inciden en el abuso y dependencia de cannabis entre adolescentes: una revisión sistemática y metaanálisis

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Abstract

The use of cannabis for recreational purposes has increased worldwide, and the proportion of cannabis users in the adolescent population is high. Susceptibility to cannabis use involves various factors, including childhood adversity; however, the effects of different types of violence on cannabis use have not been evaluated. The aim of this review was to analyze the effects of different types of violence on cannabis use in adolescence. We searched electronic databases (PubMed, Science Direct, Web of Science, Ovid and CONRICyT) using the following algorithm: ((“Cannabis” OR “Marijuana Smoking” OR “Marijuana Abuse”) AND (“Child Abuse” OR “Domestic Violence” AND “Adolescent”)), considering all articles published up to November 3th, 2017. Odds ratios (ORs) were calculated for the effects of experiencing different types of violence during childhood on cannabis use. Six studies, representing 10 843 adolescents of both sexes, were ultimately included in the systematic review and meta-analysis. Three types of early-life adversity were associated with cannabis abuse/dependence: physical abuse (OR: 1.58, 95% CI [1.01-2.46]), sexual abuse (OR: 2.35, 95% CI [1.64-3.35]), and witnessing violence (OR: 3.22, 95% CI [0.63-16.54]). The results indicated that two specific types of child maltreatment, sexual and physical abuse, were critical factors affecting vulnerability to cannabis use in adolescence. The number of studies examining other types of violence was limited. The results highlighted the importance of enhancing efforts to prevent violence, particularly sexual abuse, as part of integral programs designed to prevent cannabis abuse and dependence.

Keywords: Cannabis abuse; Child abuse; Childhood; Adolescents; Violence.

Resumen

El uso recreativo de cannabis ha incrementado en todo el mundo, principalmente en la población adolescente. Se ha propuesto que la adversidad en la infancia contribuye al consumo de esta droga. El objetivo de esta revisión sistemática y metaanálisis fue analizar el efecto de diferentes tipos de violencia en la infancia sobre el consumo de cannabis en la adolescencia. Se realizó una búsqueda en diferentes bases de datos (PubMed, Science Direct, Web of Science, Ovid y CONRICyT) usando los términos de búsqueda: ((“Cannabis” OR “Marijuana Smoking” OR “Marijuana Abuse”) AND (“Child Abuse” OR “Domestic Violence” AND “Adolescent”)), considerando todos los artículos publicados hasta el 3 de noviembre de 2017. Se calcularon los Odds Ratio (OR) del consumo de cannabis en adolescentes, para los diferentes tipos de abuso infantil, así como sus intervalos de confianza del 95% (IC 95%). Se identificaron seis estudios, que incluyeron 10 843 adolescentes de ambos sexos. Las siguientes adversidades fueron asociadas con abuso/dependencia de cannabis en la adolescencia: abuso físico (OR: 1,58, IC 95% [1,01-2,46]), abuso sexual (OR: 2,35, IC 95% [1,64-3,35]), y ser testigo de violencia (OR: 3,22, IC 95% [0,63-16,54]). Los resultados sugieren que el abuso sexual o físico durante etapas tempranas de la vida aumenta el riesgo de consumo de cannabis en la adolescencia. Los estudios que evaluaron otras formas de violencia fueron escasos. Los resultados destacan la importancia de diseñar programas integrales para reducir el uso y la dependencia de cannabis mediante estrategias enfocadas a la prevención de la violencia en la infancia.

Palabras clave: Uso de cannabis; Abuso infantil; Infancia; Adolescencia; Violencia.

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The use of cannabis for recreational purposes has increased worldwide (United Nations Office on Drugs and Crime, 2015). Eleven million cases of dependence were reported globally in 1990, and this figure had increased to 13 million in 2010 (Degenhardt et al., 2013). For example, prevalence rates of 15.2% and 13.7% have been reported for cannabis use in the general populations of the Czech Republic and United States, respectively (Villatoro-Velázquez et al., 2012; United Nations Office on Drugs and Crime, 2015). Remarkably, the proportion of cannabis users in the adolescent population is high. In the United States, the Youth Risk Behavior Survey showed an increase, from 19.7% in 2007 to 23.4% in 2013, in prevalence rate for cannabis use in high school students aged between 14 and 18 years (Substance Abuse and Mental Health Services Administration, 2015).

Enhancement of social behavior, risk taking, and novelty seeking is observed during adolescence. This period of life is also a critical period for brain development, during which the efficiency and velocity of neuronal communication are enhanced via synaptic pruning and increased myelination (Spear, 2000; Spear, 2013). Cannabis use during this stage of increased neurodevelopment could lead to aberrant connections and failure in cerebral cortex remodeling, with consequent alterations in behavior (de la Fuente et al., 2015). Users who initiate cannabis use during adolescence are likely to exhibit deficits in memory, verbal fluency, decision making, and cognitive flexibility (de la Fuente et al., 2015), and chronic consumption could lead to the deterioration of general intelligence, short-term memory, executive function, judgment, and major motor impulsivity (Meier et al., 2012; Ramaekers et al., 2006). In addition, the social consequences of cannabis abuse during late adolescence have been associated with poor academic performance and a lack of opportunity to secure stable employment and build a family (Substance Abuse and Mental Health Services Administration, 2015).

It should be noted that the risk of initiating cannabis use and developing dependence differs between individuals. The etiology of these differences involves a combination of biological, genetic, and environmental factors, which enhances vulnerability (Buisman-Pijlman et al., 2014). The development of risk behaviors, such as cannabis use and the development of dependence, has been associated with events that occur during the early stages of development (i.e., childhood and early adolescence; Benjet, Borges & Medina-Mora, 2010). This is the main reason why interventions designed to prevent drug use should focus on children.

Childhood adversity, including physical abuse, sexual abuse, neglect, poverty, and parental loss or separation, is highly prevalent worldwide (38.4% to 39.1%; World Health Organization, 2016) and has been associated with increased risk of psychiatric disorders (Kessler et al., 2010). Analysis of data clustering by adversities show that family dysfunction and abuse adversities (i.e., physical abuse) are the strongest and most consistent predictors of psychopathologies such as substance abuse and externalizing behaviors, influencing the onset of these disorders throughout of childhood, adolescence or even adulthood (Benjet et al., 2010). Enduring effects of chronic stress on brain structures (Benjet et al., 2010), dysfunctional coping mechanisms (Folkman & Lazarus, 1988; Folkman, Lazarus, Gruen & DeLongis, 1986) or poor emotional regulation (Zimmermann et al., 2017) seem explain the impact of adversity throughout of life course.

Children's exposure to violence covers a broad range of community, family and media violence (Osofsky, 1999). This exposure can be direct in form of victimization or indirect in the form of witnessing (Foster & Brooks-Gunn, 2009). Being expose to violence in childhood leads to higher rates of posttraumatic stress disorder, depression and behavioral problems (Jester, Steinberg, Heitzeg & Zucker, 2015). Furthermore, exposure to violence during early stages of life has been identified as risk factor for development of substance abuse (Benjet et al., 2010; Jester et al., 2015; Kuhar, 2012). For instance, children witnessing of violence are more vulnerable to develop substance abuse in adulthood (OR 2.84, 95% CI [1.53–5.26]) (Kuhar, 2012; Benjet et al., 2010). Furthermore, severe sexual abuse in childhood has been related to increased risk to alcohol abuse/dependence (OR 3.3, 95% CI [1.7-6.6]) or other drugs abuse/dependence (OR 5.1, 95% CI [2.5-10.2]) at 18 years old (Fergusson, Horwood & Lynskey, 1996). Additionally, childhood maltreatment history (including sexual abuse, physical abuse, emotional abuse and neglect) has been described as important predictor of cannabis problems among young adults (Vilhena-Churchill & Goldstein, 2014). However, the relationships between the type of violence during childhood and cannabis use in adolescence have not been evaluated systematically in the literature. Altogether, the main aims of this systematic review and meta-analysis were to examine the relationships between exposure to various types of violence during childhood and cannabis abuse or dependence in adolescence and determine the main risk factors for the development of cannabis abuse and dependence.

Methods

Study types

We included all studies involving case-control, cross-sectional, or longitudinal study designs and data regarding the relationship between childhood exposure to violence and use of cannabis prior to adulthood. Childhood abuse (or childhood violence) was defined as violence perpetrated by parents, primary caregivers or community members

in any environment. Physical abuse was assessed with questions about being hit, kicked, throttled, or attacked with a gun, knife, or some other weapon, by any person, or about being spanked by parents until to induce marks. Sexual abuse is defined as different extents of sexual approaches between adult and children. Sexual abuse was assessed with questions about noncontact episodes including indecent exposure, public masturbation, sexual propositions, and incidents involving sexual contact attempted or completed intercourse. Witnessing was defined as exposure to violence directed against another family member or any person, in any environment (home, community). Witnessed violence was assessed with questions about witnessing interparental slap, hit, kick, grap or threaten any person with a knife, gun or other weapon. Adolescence was defined the period between the ages of 12 and 17 years. Use (or abuse) of cannabis included all forms of consumption including use on a single occasion, infrequent or intermittent use, and chronic use. We excluded studies in which cannabis use was reported during adulthood or via prenatal exposure.

Participants

Participants included persons who were incorporated in the samples of national studies that included adolescents or young adults and used various types of data analysis. All participants gave informed consent prior to being interviewed, and approval of Institutional Review Boards is mentioned in each study.

Types of exposure

Studies examining exposure to all types of violence perpetrated by adults during childhood were included.

Outcome measures

The outcome measures included the use or abuse of cannabis during adolescence, and sex differences were analyzed where possible.

Search methods for study identification

Studies suitable for inclusion were identified via a search of the following electronic databases: PubMed (MEDLINE), Science Direct, Web of Science, Ovid (MEDLINE), and CONRICyT (database of the National Council for Science and Technology). Studies conducted prior to November 3th 2017 were included. We performed a broad search using the following Medical Subject Headings and Boolean terms: ((“Cannabis” OR “Marijuana Smoking” OR “Marijuana Abuse”) AND (“Child Abuse” OR “Domestic Violence” AND “Adolescent”)). Entry terms for Cannabis included: Marihuana; Marijuana; Hashish; Cannabis sativa. Terms for Marijuana Abuse included: Cannabis-related Disorder; Cannabis Abuse; Marijuana Dependence; Marihuana Abuse; Hashish Abuse. Terms for Marijuana Smoking included: Marihuana Smoking; Hashish Smoking; Cannabis Smoking. Entry terms for child abuse include: Abuse, Child; Child Mistreatment; Mistreatment, Child; Child Maltreatment; Maltreatment, Child; Child Neglect; Neglect, Child. Domestic violence includes terms: Violence, Domestic; Family Violence; Violence, Family. There were no restrictions with respect to language or publication status.

Searching other resources

The reference lists of all included studies were analyzed to identify further studies of interest that were not retrieved via the database search.

Data collection

Two authors performed independent reviews of all of the titles, abstracts, and potentially relevant full-text reports according to the established inclusion and exclusion criteria. Disagreements were resolved via discussion or consultation with a third judge (Figure 1).

A predesigned data abstraction form was used to extract relevant information. Data extracted from each study included the name of the first author, year of publication, study type, participant details, sample size, type of childhood abuse examined, cannabis use during adolescence, study findings, and odds ratios (ORs). The studies’ key findings were summarized descriptively in the first instance, and the feasibility for quantitative meta-analysis was considered.

Statistical methods

Measurement of effects and assessment of heterogeneity ORs with 95% confidence intervals (CIs) were calculated for dichotomous outcomes (e.g., cannabis use) in case-control and cross-sectional studies, and relative risk was calculated for longitudinal studies (e.g., cohort studies). The results of the analyses were presented as forest plots.

The statistical heterogeneity of each meta-analysis was assessed using I^2 and χ^2 (with P values). We regarded heterogeneity as substantial if I^2 values were higher than 50%. Data were analyzed using random- or fixed-effects models as appropriate.

Data synthesis

Data were analyzed using Review Manager Software 5.3.

Results

The literature search yielded 190 articles. Of these, 135 were excluded based on their abstracts, and 36 were excluded following full-text analysis, as they did not fulfill the inclusion criteria. Ultimately, only six studies acomplished all of the inclusion criteria (Figure 1).

Description of the studies

All types of violence were included in the database research; however, frequencies of cases for childhood violence and cannabis abuse were reported only in six articles. These publications reported frequencies for sexual, physical and witnessing violence in childhood and cannabis abuse in adolescence. Five studies were referred to as cohort studies involving cross-sectional evaluation within specific periods during the lifespan (Dubowitz et al., 2016; Duncan et al., 2008; Fergusson & Horwood, 1998; Fergusson & Lynskey, 1997; Sartor et al., 2015) and one study included a National Household Survey probability sample (Kilpatrick et al., 2000). Although two studies, which were conducted by Fergusson & Horwood (1998) and Fergusson & Lynskey (1997), involved the same sample, they were both included in the systematic review, as they analyzed different types of violence (Table 1).

The studies conducted by Fergusson & Horwood (1998) and Fergusson & Lynskey (1997) were conducted in New Zealand (Fergusson, Horwood, Shannon & Lawton, 1989), while those conducted by Kilpatrick et al. (2000), Duncan et al. (2008), Sartor et al. (2015) and Dubowitz et al. (2016) were conducted in the United States.

Three studies evaluated violence using structured, personal interviews and questionnaires to collect data regarding the characteristics of abuse experienced during childhood (Dubowitz et al., 2016; Fergusson & Horwood, 1998; Fergusson & Lynskey, 1997). In addition, in Dubowitz et al. (2016) study the data was collected from multiple informants: reports from the Child Protective Services (CPS), and later from parents and children interviewed. One study obtained data via ad-hoc, structured, telephone-based interview designed by the authors (Kilpatrick et al., 2000), while two studies evaluated the characteristics of abuse with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) via telephone (Duncan et al., 2008; Sartor et al., 2015) (Table 2). Therefore, the evaluation of exposure to types of abuse examined (i.e., sexual abuse, physical abuse, and witnessing violence) included heterogeneous interviews.

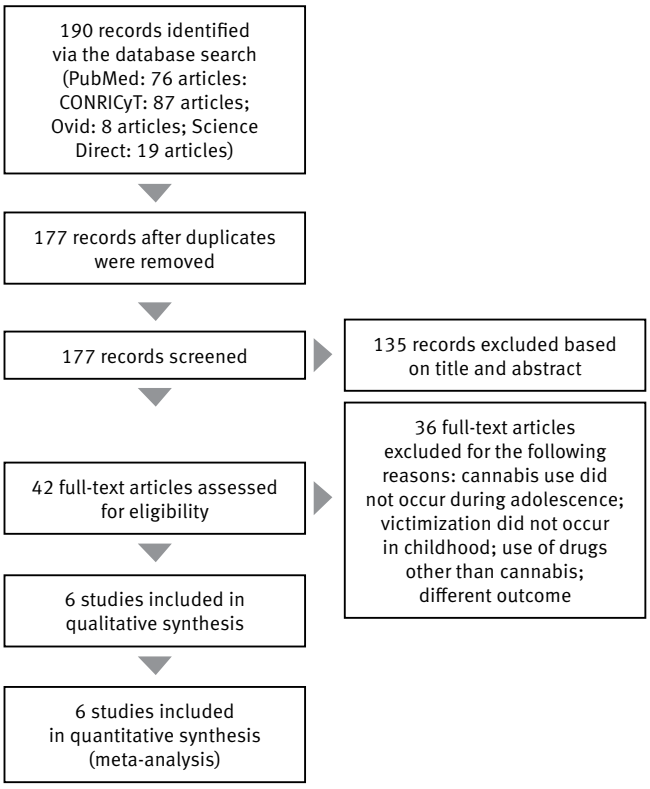


Figure 1. Flow chart of the identification and selection of studies for systematic review.

Physical abuse was identified four studies (Dubowitz et al., 2016; Duncan et al., 2008; Fergusson & Lynskey, 1997; Kilpatrick et al., 2000). Additionally, Dubowitz and co-workers reported information of other forms of abuse, as neglect and emotional abuse, in the studied population. All articles, with exception of Fergusson & Lynskey (1997), reported data of sexual abuse in children, while two reports showed data of witnessing violence in childhood (Fergusson & Horwood, 1998; Kilpatrick et al., 2000). Duncan et al. (2008) and Kilpatrick et al. (2000) included three and six interview questions pertaining to sexual abuse, respectively. Questions for physical abuse fluctuated from three to ten. Finally, for witness of violence Kilpatrick et al. (2000) asked one general question and Fergusson and Horwood (1998) consisted of eight questions (i.e., type of incident and frequency of occurrence). Dubowitz et al. (2016) followed the LONGSCAN protocol (English, Bangdiwala & Runyan, 2005; Runyan et al., 1998) consisting in collection of data from reports from the CPS, and interviews from parents and children, in order to categorize five forms of maltreatment (Table 1).

The main outcome of the analysis (Table 2), use or abuse of cannabis during the preceding year or before 18 years old, was determined via personal interviews (three studies), two of them by the administration of the World Health Organization Composite International Diagnostic Interview (Cottler & Compton, 1993), or by telephone-based interviews (three studies). Instruments of five studies were based on the criteria for the diagnosis of substance abuse disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association, 1994). One study identified use of cannabis by a dichotomous question at any of the age 12, 14, 16 and 18 interviews. If participants answered positively they were further questioned about the heavy or occasional consume (Dubowitz et al., 2016).

The analysis of biases showed that only the cohort study (Kilpatrick et al., 2000) selected a randomly representative community sample of adolescents, while the other five studies did not randomize the selection of their popula-

Table 1. *Characteristics of epidemiological studies of childhood exposure to violence on use, consume or dependence of cannabis.*

Authors, Year	Country	Study	TE	Exposure definition	Instrument/ Evaluation	Outcome/ Diagnosis	Sample size/ Demographics	Age exposure	Age evaluation	Estimated/Note
Fergusson & Lynskey, 1997	NZ	CHDS	T	PA	F-to-FA, I, Q	Cannabis abuse or dependence DSM-IV	N = 1265	‹16 y. o.	‹18 y. o.	Rates of substance abuse by extent of intraparental violence
Fergusson & Horwood, 1998	NZ	CHDS	T	IA SA	F-to-FA, I, Q	Cannabis abuse or dependence DSM-IV	N = 1265 Male and female	‹16 y. o.	‹18 y. o.	Rates of substance abuse by extent of intraparental violence
Kilpatrick et al., 2000	USA	NSA	T	PAS SAS WV	Structured T I	Cannabis abuse or dependence DSM-IV	N = 3907 Male and female	Past year	12-17 y. o.	PA: OR 4.84 SA: OR 3.80 WV: OR 8.42 95% CI were no reported
Duncan et al., 2008	USA	VETR	T	SA PA	T I-SSAGA	Cannabis abuse or dependence DSM-IV	N = 819 Male and female	‹16 y. o.	Adolescent or Young adult	HR 2,16 (95% CI 1.48-3.16)
Sartor et al., 2015	USA	MOAFTS MOFAM	T	SA	TI-SSAGA	Cannabis abuse or dependence DSM-IV	N = 4150 Female twings and siblings	‹16 y. o.	18-29 y. o.	Eur American HR 1.57 (95% CI 1.37-1.79) African American HR 2.52 (95% CI 1.52-4.18)
Dubowitz et al., 2016	USA	LONG-SCAN	T	SA PA N EM	MMCS	Dichotomous response: Never use cannabis or use of cannabis	N = 702; 332 males and 370 women	From birth to 18 y. o.	18 y. o.	EM OR 1.32 (95% CI 0.98-1.78) N OR 0.78 (95% CI 0.49-1.25)

Note. NZ: New Zeland; USA: United States of America. Studies: CHDS Christchurch Health & Development Study; NSA: National Survey of Adolescents; VETR: The Vietnam Era Twin Registry (registers from offsprings); MOAFTS: Missouri Adolescent Female Twin Study; MOFAM: Missouri Family Study; LONGSCAN: Longitudinal Studies of Child Abuse and Neglect project; F-to-F A: Face to face assessment for parents and children; obtained from Fergusson et al., 1989; T: Transversal evaluation; I: Interview; Q: Questionnaire; PA: Physical abuse; IA: Intraparental abuse; SA: Sexual abuse; PAS: Physical assault; SAS: Sexual assault; WV: Witnessed violence; N: Neglect; EM: Emotional maltreatment; SSAGA: Semi-Structured Assessment for the Genetics of Alcoholism, for telephone interview (TI); MMCS: Maltreatment Coding Scheme Modified version of Barnett et al., 1993.

tions. As the studies included cohorts, no allocation concealment or blinding procedures were used in any of the studies. On the contrary, the collection of data regarding demographic characteristics and the establishment of one or more clinical diagnoses occurred on separate occasions. All six studies, including those involving structured telephonic interviews, reported acceptable compliance. The baseline age of exposure to abuse was almost uniform, as four studies reported that participants were younger than 16 years of age when the abuse occurred, one study reported occurrence during the year preceding evaluation, and one study reported information of abuse from birth to 18 years old. The timing of evaluations varied between studies, with the exception of those conducted by Fergusson & Horwood (1998) and Fergusson & Lynskey (1997), as they included the same population. All studies reported participant withdrawal and evaluated the main outcomes via personal or telephone-based interviews, five of them based on the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994). The validity of the telephone-based evaluations performed by Kilpatrick et al. (2000), Duncan et al. (2008), and Sartor et al. (2015) was of concern, as if adolescents discussed their childhood and substance abuse freely. In addition, there was an increased risk of bias in these studies, because of high levels of variation in sampling procedures and the evaluation of comorbidity during adolescence and early adulthood.

Populations studied

Overall, the number of participants included in the reviewed studies was 10,843 (3,395 men and 7,448 women). Half of the studies collected data via telephone-based and the other by means of personal interviews. The types of childhood violence included in the studies were sexual abuse, physical abuse, and witnessing violence, for instance the evaluation of exposure to violence was heterogeneous, as the number of interview questions used in the studies ranged from one to ten. In the Dubowitz´s study violence identified by reports from the CPS was categorized by the Maltreatment Coding Scheme (MMCS, Barnett, Manly & Cicchetti, 1993) in a modified version for LONGSCAN (Table 2).

Table 2. *Items used for defining childhood abuse or dependence of cannabis.*

Authors/year	Exposure violence	Items for establishing abuse exposure	Outcome/diagnosis criterion for abuse/dependence of cannabis
Fergusson & Lynskey 1997	PA	Subjects were questioned about: — Being frequently smacking — Being hit around head of body with fists — Being frequently hit on the button with a cane, strap or similar object — Being hit around head or body with a cane, strap or similar objects — Receiving severe beating — Being kicked, choked or throttled, — Being locked in a cupboard or shed — Being burnt or being injured as results of physical abuse.	Instrument Composite International Diagnostic Interview DSM-IV
Fergusson & Horwood 1998	IPA (being a witness of violence)	Report of rating of: — Threaten to hit or throw something at partner — Push, grab or shove partner — Slap, hit or punch partner — Throw, hit or smash something — Kick partner choke or strangle partner — Threaten partner with knife, gun or other weapon — Call partner names, criticize partner — At least one of the above	Instrument Composite International Diagnostic Interview DSM-IV
	PA	Items referred in Fergusson & Lynskey, 1997	
	SA	Items referred in Fergusson et al., 1996 Face-to-face interview which participants were questioned about occurrence of SA before 16 y.o. Questions established 15 sexual activities comprising: 1) noncontact episodes including indecent exposure, public masturbation by others, and unwanted sexual propositions or lewd suggestions; 2) incidents involving sexual contact including sexual fondling, genital contact, and attempts to undress the respondent; and 3) incidents involving attempted or completed oral, anal, or vaginal intercourse.	
Kilpatrick et al., 2000	SA	Questionnaire — Has a man or boy ever put a sexual part of his body inside your private sexual part, inside your rear end, or inside your mouth when you didn't want them to? — Has anyone, male or female, ever put fingers or objects inside your private sexual parts or inside your rear end when you didn't want them to? — Has anyone, male or female, ever put their mouth on your private sexual parts when you didn't want them to? — Has anyone, male or female, ever touched your private sexual parts when you didn't want them to? — Has anyone ever made you touch their private sexual parts when you didn't want them to? — [For boys] Has a woman or girl ever put your private sexual part in her mouth or inside her body when you didn´t want her to?	Structured interview based on DSM-IV
	PA	Questionnaire — Has anyone—including family members or friends—ever attacked you with a gun, knife or some other weapon, regardless of when it happened or whether you ever reported it or not? — Has anyone—including family members and friends—ever attacked you without a weapon, but you thought they were trying to kill or seriously injure you? — Has anyone—including family members and friends—ever threatened you with a gun or knife but didn't actually shoot or cut you? — Has anyone—including family members and friends—ever beat you up, attacked you, or hit you with something like a stick, club, or bottle so hard that you were hurt pretty bad? — Has anyone—including family members and friends—ever beat you up with their fists so hard that you were hurt pretty bad? — Families have different ways of punishing young people if they think they have done something wrong. — Some families spank young people as a form of punishment. Has a parent or some adult in charge of you ever spanked you so hard that you had to see a doctor because you were hurt so bad? — Has a parent or someone in charge of you ever spanked you so hard that you got bad marks, bruises, cuts, or welts? — Has a parent or someone in charge of you ever punished you by burning you, cutting you, or tying you up? — Adolescents who responded affirmatively to any of these questions were classified as having experienced a PAs.	

Duncan et al., 2008	PA SA	An individual was considered to have experienced PA in childhood (6-12 y.o.) if he or she: a) reported having been physically abused before the age of 16 in the traumatic events section of the interview or b) answered "yes" to "When you were 6 to 12, did any adult ever physically injure or hurt you on purpose? or c) reported "often" being "punched or hit with a belt or stick or something like that by your mother or father CSA was considered to have occurred if an individual reported having been: a) raped or b) sexually molested before age 16 or c) forced to have sex before age 16	Structured interview based on DSM-IV Abuse diagnosis, if he or she endorsed any of the four DSM-IV cannabis abuse Dependence, if he or she endorsed three or more of seven cannabis dependence symptoms, including withdrawal
Sartor et al., 2015	SA	First questionnaire: Raped, sexually molested at 15 years or younger Second questionnaire: Has anyone ever forced you to have sexual intercourse at 15 years or younger Third questionnaire: Before you turned 16, was there any forced sexual contact between you and any family member? And, Before you turned 16, was there any forced sexual contact between you and anyone who was 5 or more years older than you (other than a family member)?	Semi-structured interview based on DSM-IV Individuals who endorsed to one or more symptoms of abuse or dependence of cannabis
Dubowitz et al., 2016	SA PA	Subjects were questioned: Exposure, exploitation, molest and penetration. Once they received blows in: Head, torso, buttocks, limbs, violent handling, choking Burns, shaking, nondescript.	Dichotomous response: never use cannabis or use of cannabis

Note. PA: Physical abuse; SA: sexual abuse; IPA: intraparental abuse.

Effect of exposure to violence

The statistical analysis of associations showed that the three types of childhood violence contributed to the likelihood that cannabis abuse or dependence would occur during adolescence (physical abuse: OR: 1.58, 95% CI [1.01–2.46], Figure 2, panel A; sexual abuse: OR: 2.35, 95% CI [1.64–3.35], Figure 2, panel B; witnessing violence: OR: 3.22, 95% CI [0.63–16.54], Figure 2, panel C), to varying degrees. It was not possible to perform an analysis of physical abuse or witnessing violence according to sex. However, data from two articles were used to obtain an association between sexual abuse in childhood and cannabis use in adolescent girls, OR 2.22 (95% CI [1.86–2.66], Figure 2, panel D).

Discussion

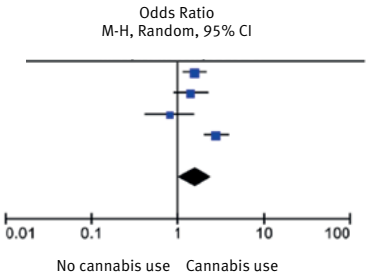
The main finding of the systematic review and meta-analysis was that adolescents who had been physically or sexually victimized or witnessed violence during childhood were at increased risk of cannabis abuse or dependence. Although a great number of studies in the literature have the focus in the addictive capacity of the substance itself there is lack of evidence on the causality of the use of drugs in youth. Present results support the notion that sexual abuse appeared to be a stronger predictor of cannabis abuse or dependence during adolescence, relative to the other two types of adversities.

The results also showed that violence in childhood played a variable role in the development of cannabis abuse or dependence. Participants who had experienced sexual abuse were at higher risk of cannabis use, relative to those who had experienced physical abuse or witnessed violence. In contrast, physical abuse exerted a marginally significant effect on the development of cannabis abuse or dependence, and witnessing violence exerted a weak effect, inducing only a tendency toward this outcome. The increases in the risk of cannabis use following these types of violence observed in the current review were smaller relative to those reported by Kilpatrick et al. (2000) (physical abuse: OR: 4.84, sexual abuse: OR: 3.80, witnessing violence: OR: 8.42; Table 1). However, outcomes were assessed during the year preceding the evaluation, and 95% CIs were not provided for the ORs in Kilpatrick et al.'s study (2000); therefore, it was difficult to compare the results directly. In addition, the heterogeneity of the definitions of violence in the studies included in the review could have limited the appropriate risk values for these items.

A study conducted by Caravaca, Navarro, Luna Ruiz-Cabello, Falcon & Luna (2017) in college students in Spain showed similar results to our present work. This study including men and women with an average of 22.6 years old showed high rates of physical abuse OR 2.00 (95% CI [1.12-3.58]) and sexual abuse OR 2.72 (95% CI [1.06-6.95]) among users of cannabis. However, this study is a transversal design then causality and direction of this relationship (i.e., sexual victimization increases the risk of cannabis use) cannot be established. Findings showed by Caravaca et al. (2017) further support the notion that abuse has an impact on the vulnerability for use of drugs in young population, and highlight the importance of investigate this association in other population worldwide.

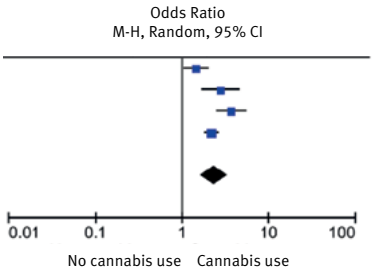
A

	Physical abuse		No physical abuse			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Dubowitz et al., 2016	226	389	147	313	28.6%	1.57 [1.16-2.11]
Duncan et al., 2008	30	105	158	714	24.4%	1.41 [0.89-2.23]
Fergusson & Lynskey, 1997	11	111	110	914	19.3%	0.80 [0.42-1.55]
Kilpatrick et al., 2000	83	940	64	1912	27.7%	2.80 [2.00-3.91]
Total (95% CI)		1545		3853	100.0%	1.58 [1.01-2.46]
Total events	350		479			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 14.32$, df = 3 (P = 0.002); $I^2 = 79\%$						
Test for overall effect: Z = 1.99 (P = 0.05)						



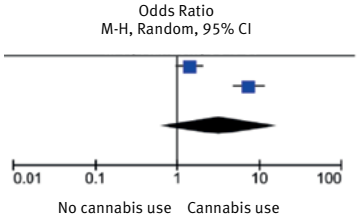
B

	Sexual abuse		No sexual abuse			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Dubowitz et al., 2016	118	196	258	506	25.8%	1.45 [1.04-2.03]
Duncan et al., 2008	30	70	158	749	20.0%	2.81 [1.69-4.65]
Kilpatrick et al., 2000	35	327	112	3580	23.6%	3.71 [2.49-5.53]
Sartor et al., 2015	406	589	1790	3561	30.6%	2.20 [1.82-2.64]
Total (95% CI)		1182		8396	100.0%	2.35 [1.64-3.35]
Total events	589		2318			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 13.51$, df = 3 (P = 0.004); $I^2 = 78\%$						
Test for overall effect: Z = 4.70 (P = 0.00001)						



C

	Witnessed violence		No witnessed violence			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Fergusson & Lynskey, 1997	57	121	353	914	50.2%	1.42 [0.97-2.07]
Kilpatrick et al., 2000	123	147	1540	3760	49.8%	7.39 [4.75-11.50]
Total (95% CI)		268		4674	100.0%	3.22 [0.63-16.54]
Total events	180		1893			
Heterogeneity: $Tau^2 = 1.35$; $Chi^2 = 31.44$, df = 1 (P = 0.00001); $I^2 = 97\%$						
Test for overall effect: Z = 1.40 (P = 0.16)						



D

	Sexual abuse		No sexual abuse			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Duncan et al., 2008	18	70	37	324	5.8%	2.69 [1.42-5.07]
Sartor et al., 2015	406	589	1790	3561	94.2%	2.20 [1.82-2.64]
Total (95% CI)		659		3885	100.0%	2.22 [1.86-2.66]
Total events	424		1827			
Heterogeneity: $Chi^2 = 0.36$; df = 1 (P = 0.55); $I^2 = 0\%$						
Test for overall effect: Z = 8.73 (P = 0.00001)						

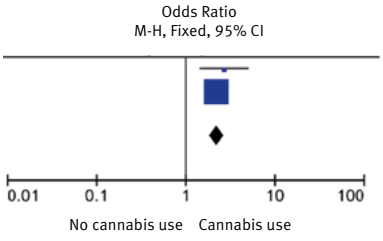


Figure 2. Odds ratios and 95% CI for cannabis use in female and male population who experienced physical abuse (panel A), sexual abuse (panel B) or witnessed violence (panel C) during childhood. Odds ratios and 95% CI for cannabis use in females who experienced sexual abuse (panel D) in childhood.

Note. Odds ratios were calculated using the number of events involving cannabis use recorded in the adolescence. Data were analyzed using random- or fixed-effects models, depending on the heterogeneity of the studies. CI = confidence interval. Overall effect for each forest plot was estimated with the Z test.

The results of the four studies that evaluated the effects of sexual abuse on cannabis abuse or dependence were consistent, in that the 95% CI values were similar and exceeded the unity value, which suggested an association between exposure and the outcome and indicated that the results were reliable. The analysis of these four studies showed that sexual abuse in childhood doubled the risk of cannabis abuse or dependence in adolescence for both sexes. Interestingly, sexual abuse in girls was an important factor in the development of cannabis use, even though the numbers of studies (two) and subjects (3 885 girls) included in the analysis were relatively low. This was also indicated in the results regarding the homogeneity of reports, narrow CIs, and statistical significance of the association. With respect to physical abuse, four studies reported a relationship between physical abuse and cannabis abuse or dependence, and the 95% CI values exceeded the unity value in the forest plot; however, the CIs were sufficiently high to indicate that the difference was barely significant. The relationship between witnessing violence and cannabis use was difficult to interpret because only two studies examined this association. Furthermore, one of the two studies included a small sample, and the OR for the other was high, leading to a wide 95% CI. This finding was supported by the results of the heterogeneity test, which were statistically significant for the comparison of physical abuse and witnessing violence.

The mild effect of physical abuse and the marginal effect of witnessing violence and their relationships with cannabis use could be explained by higher rates of dependence on other substances such as alcohol (physical abuse: OR: 3.93; witnessing violence: OR: 4.87) and hard drugs (physical abuse: OR: 12.35; witnessing violence: OR: 13.22) (Kilpatrick et al., 2000). Furthermore, levels of consumption of other drugs have been found to be higher in users who initiated cannabis use at an early age or used the drug frequently, relative to those observed in other users (de la Fuente et al., 2015).

Ecological studies examining contextual factors involved in substance use have identified multiple social and economic disadvantages as factors affecting substance use in individuals exposed to violence. In addition, marital discord, poor parent-child attachment, and parental substance use have been identified as risk factors for children, and living in impoverished, disorganized neighborhoods in which drugs are obtained easily increased their vulnerability to drug abuse (Duncan et al., 2008; Fergusson & Lynskey, 1997; Rogosch, Oshri & Cicchetti, 2010). All of these factors contributed to substance use in individuals who had experienced multiple types of child abuse (Rogosch et al., 2010). In this context, coping theory suggests that individuals initiate substance abuse in an attempt to regulate the negative effects of violence (Foster & Brooks-Gunn, 2009; Harrison, Hoffmann & Edwall, 1989; Kilpatrick et al., 2000; Wright, Fagan & Pinchevsky, 2013). For instance, behaviors observed in girls who had experienced childhood sexual abuse included helplessness, somatic complaints, emotional withdrawal, and posttraumatic stress disorder. Endocannabinoids signaling has been found to be involved in stress regulation and acute effects of cannabinoids such tetra-hydrocannabinol include anxiolytic effects (Zimmermann et al., 2017). Cannabis use may thus down-regulate negative effect. Therefore substance use can become an emotion regulation tactic and cannabis use might represent a self-medication with lower emotion regulation efficacy (Khantzian, 1997; Zimmermann et al., 2017).

From another perspective, violence exposure could lead to the development of adjustment difficulties resulting in externalizing behaviors during adolescence; in consequence, behavioral and mental health problems, juvenile delinquency, and substance abuse disorders are commonly observed in maltreated children (Fergusson & Horwood, 1998; Fergusson & Lynskey, 1997; Oshri, Rogosch, Burnette & Cicchetti, 2011). Evaluation of the different types of substance abuse demonstrated two scenarios involving adolescents: those who used alcohol because it was accessible and legal, and those in whom cannabis use resulted from deviant behavior, as it is illegal (Oshri et al., 2011; Sartor et al., 2013). Furthermore, increases in substance use could lead to additional victimization or revictimization, which increased the risk of future substance use, perpetuating the cycle (Kilpatrick et al., 2000).

It should be noted that the early onset of cannabis use (i.e., during a critical period of brain development), could have serious, long-lasting consequences (Sartor et al., 2013). Despite empirical evidence for and against the concept, the literature suggests that long-term cannabis use could lead to addiction (Volkow, Compton & Weiss, 2014). Furthermore, cannabis use appears to be a robust risk factor for subsequent consumption of other illicit drugs (Fergusson, Boden & Horwood, 2008).

Empirical evidence shows that long-term cannabis use affects neurocognitive functioning, particularly in those who initiate cannabis use during early adolescence, which results in significant reductions in intelligence quotient and impaired performance in a variety of attention, memory, and executive function tasks. All of these factors contribute to psychosocial difficulties such as academic underachievement and/or school dropout (Ganzer, Broning, Kraft, Sack & Thomasius, 2016; Grant, Gonzalez, Carey, Natarajan & Wolfson, 2003; Volkow et al., 2014). In addition, alterations in motor function (e.g., coordination) have negative consequences, which could lead to motor vehicle accidents (Volkow et al., 2014). Empirical evidence has also shown an increase in the risk of psychosis, including that associated with schizophrenia, mainly in subjects with genetic predisposition (Fergusson, Lynskey & Horwood, 1996; Marconi, Di, Lewis, Murray & Vassos, 2016; Volkow et

al., 2014). Moreover, a longitudinal study showed that cannabis use predicted the development of anxiety disorders, depression, certain personality disorders, and interpersonal violence (Copeland, Rooke & Swift, 2013). Interestingly, results of a recent study indicated that both occasional and chronic cannabis use increased the risk of suicidality in adolescents and young adults. Suicidality is characterized by suicidal ideation and intent (Borges, Bagge & Orozco, 2016) and is considered the most severe symptom of several psychiatric disorders (American Psychiatric Association, 2013). In contrast to the claim that cannabis use involves lower levels of risk of severe mental illness, relative to those observed with tobacco use, the findings described above suggest that cannabis exerts important effects on health, which affects quality of life.

The results of the current review demonstrated the importance of enhancing efforts to prevent childhood violence. In addition, they highlighted the need for early intervention to prevent cannabis abuse or dependence, particularly in children who experience sexual abuse. Cannabis use could exert cumulative effects on health, family life, and social problems. This study highlights the importance of assessing for a history of violence when considering individuals for prevention or intervention strategies pertaining to cannabis use. Individuals with a history of violence in childhood who are seeking treatment to address cannabis problems would benefit from a modality that focuses on establishing strategies for emotion regulation, including exploring more adaptative methods of coping with negative affect (Vilhena-Churchill & Goldstein, 2014). Interventions should include a broad perspective that considers the general social and family contexts in which violence occurs, rather than focusing exclusively on the issue of cannabis abuse/dependence (Fergusson & Horwood, 1998). As policy shifts toward the legalization of cannabis in various countries, the development of such programs is urgent.

Risk of bias and study limitations

One of the main limitations of the analysis of the impact of childhood abuse on cannabis use in adolescence involved evidence quality from researches, as the results showed an important selection bias, because sampling was not randomized. The other main limitation involved performance bias, as the evaluation of violence in the included studies was heterogeneous, and participants underwent multiple evaluations with different aims (e.g., genetic outcomes) in the examination of cannabis use. Exposure to violence during childhood requires immediate attention; however, ethical considerations should be taking account in the design of prospective studies that would increase the children's vulnerability. For instance, the Dubowitz et al. study's (2016) describes that child in risk of abuse or, those with sustained abuse, were included in protocols for the protection of human subjects, including referrals for subjects in need of services (Runyan et al., 1998). Additionally, most studies included in this systematic review were retrospective, and analysis of the effects of abuse was performed during the final stages of investigation.

Another limitation involved the availability of data from the studies that were evaluated in the review, as we were unable to explore the chronicity or severity of childhood violence. A previous study showed that younger age during sexual abuse enhanced the risk of cannabis use (Sartor et al., 2013); however, it was impossible to perform this type of evaluation in the current review. In addition, we were unable to consider the frequency of consumption, amounts consumed, age at initiation of consumption, or the time lag between interventions and outcomes, with exception of the Dubowitz et al. study's (2016) that included level of cannabis use (never, some or heavy). In addition, it was impossible to perform an analysis of sex differences according to the subtypes of violence, which could have provided important results, as previous research has shown that boys were at greater risk of cannabis use, relative to girls (United Nations Office on Drugs and Crime, 2015).

In conclusion, the results of this review identified specific types of childhood violence, such as sexual and physical abuse, as factors affecting vulnerability to cannabis use. However, the number of studies examining other types of violence is limited. Much of the research in this area focuses on physical or sexual abuse. In spite that, neglect is the most common form of maltreatment and emotional maltreatment has been identified as significant in terms of later development of psychopathologies (Dubowitz et al., 2016; Vilhena-Churchill & Goldstein, 2014). The current results demonstrated the importance of enhancing efforts to prevent violence, particularly sexual abuse, as part of integral programs designed to reduce cannabis abuse and dependence.

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Authors' contributions

NPM and LMM developed the review protocol, extracted the data, and wrote the first draft of the manuscript. OTHH and GJR performed independent reviews of all of the titles according to the established inclusion and exclusion criteria, and prepared the final figures and tables. All authors read and approved the final version.

Conflict of interest

The authors have no conflicts of interest to declare.

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- Nombre de los autores completo (no sólo iniciales), y uno o dos apellidos del/los autor/es (p. ej.: Miguel García o Miguel García Rodríguez o bien Miguel García-Rodríguez, teniendo en cuenta que la forma que hayan utilizado los autores es la que se enviará a las bases de datos) en minúsculas, excepto la letra inicial. Los distintos autores vendrán separados por punto y coma. Detrás del apellido de cada autor, sin espacio intermedio y en superíndice, deberá ir un asterisco de llamada (1 asterisco para el primero, 2 para el segundo, etc.). Estos asteriscos son necesarios para indicar en el siguiente punto la institución donde se ha realizado el trabajo.
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Al final de la primera página (no como 'nota al pie') se colocará este texto: "Enviar correspondencia a: ...", indicando el nombre, la dirección postal, correo electrónico u otra información mediante la cual el autor elegido podrá ser contactado. Este será

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

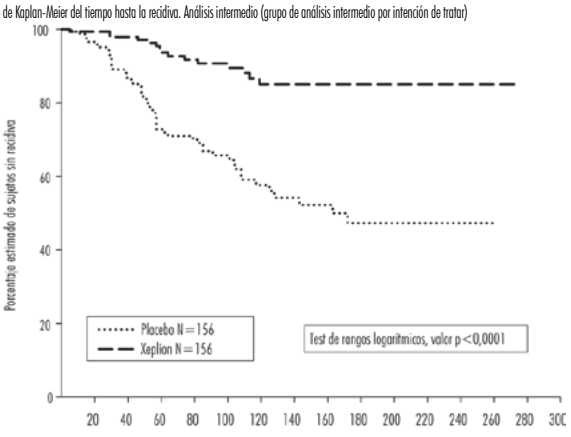
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración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

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

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

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

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



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

1. NOMBRE DEL MEDICAMENTO. TREVICTA 175 mg suspensión inyectable de liberación prolongada. TREVICTA 263 mg suspensión inyectable de liberación prolongada. TREVICTA 350 mg suspensión inyectable de liberación prolongada. TREVICTA 525 mg suspensión inyectable de liberación prolongada. **2. 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 CLINICOS. 4.1. Indicaciones terapéuticas. TREVICTA, inyección trimestral, está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos clínicamente estables con la formulación inyectable mensual de palmitato de paliperidona (ver sección 5.1). **4.2. Posología y forma de administración.** Posología. Los pacientes que están adecuadamente tratados con palmitato de paliperidona inyectable mensual (preferiblemente durante cuatro meses o más) y no requieren ajuste de dosis pueden ser cambiados a la inyección trimestral de palmitato de paliperidona. TREVICTA debe ser iniciado en sustitución de la siguiente dosis programada de palmitato de paliperidona inyectable mensual (±7 días). La dosis de TREVICTA se debe basar en la dosis previa de palmitato de paliperidona inyectable mensual, utilizando una dosis 3,5 veces más alta como se indica en la tabla siguiente:

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

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

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

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

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

Cambio desde TREVICTA a los comprimidos diarios de liberación prolongada de paliperidona oral. Para cambiar desde TREVICTA a los comprimidos de palmitato de paliperidona de liberación prolongada, se debe iniciar la administración diaria de los comprimidos 3 meses después de la última dosis de TREVICTA y continuar el tratamiento con los comprimidos de paliperidona de liberación prolongada según se describe en la tabla siguiente. La tabla siguiente indica las pautas recomendadas de conversión de las dosis para que los pacientes previamente 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 18, incluida	de la semana 19 a la 24, incluida	desde la semana 25 y en adelante
Última dosis de TREVICTA (semana 0)	Dosis diaria de los comprimidos de paliperidona de liberación prolongada		
175 mg	3 mg	3 mg	3 mg
263 mg	3 mg	3 mg	6 mg
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

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

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

Dosis omitidas

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

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

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

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

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

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

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

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

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

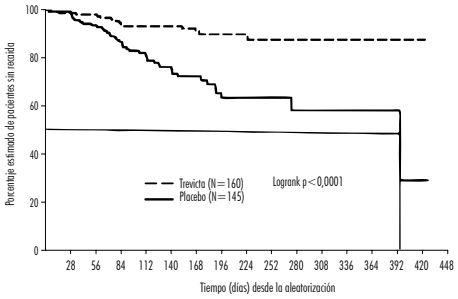


Figura 1: Gráfica de Kaplan-Meier del tiempo hasta la recaída - Análisis final

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

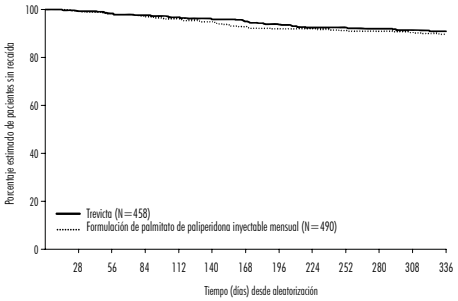


Figura 2: Gráfica de Kaplan-Meier del tiempo hasta la recaída comparando TREVICTA y palmitato de paliperidona inyectable mensual

Los resultados de eficacia eran consistentes entre los subgrupos de población (sexo, edad y grupo étnico) en ambos estudios. Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con TREVICTA en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Debido a su hidrosolubilidad extremadamente baja, la formulación trimestral de palmitato de paliperidona se disuelve lentamente después de la inyección intramuscular antes de hidrolizarse a paliperidona y absorberse a la circulación sistémica. La liberación del principio activo comienza ya a partir del día 1 y dura hasta 18 meses. Los datos presentados en este apartado se basan en un análisis de farmacocinética poblacional. Después de una sola dosis intramuscular de TREVICTA, las concentraciones plasmáticas de paliperidona aumentan gradualmente hasta alcanzar concentraciones plasmáticas máximas en una mediana de T_{max} de 30-33 días. Tras la inyección intramuscular de TREVICTA en dosis de 175-525 mg en el músculo deltoides se observó, en promedio, una C_{max} del 11-12% más elevada que la que se obtiene tras la inyección en el músculo glúteo. El perfil de liberación y la pauta de administración de TREVICTA dan lugar a concentraciones terapéuticas sostenidas. La exposición total a paliperidona después de la administración de TREVICTA es proporcional a la dosis en un intervalo de dosificación de 175-525 mg y aproximadamente proporcional a la dosis en cuanto a valores de C_{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 racémica se une en un 74% a las proteínas plasmáticas. Tras la administración de TREVICTA, los enantiómeros (+) y (–) de la paliperidona se interconvierten, alcanzando un cociente entre el AUC (+) y (–) de aproximadamente 1,7-1,8. Biotransformación y eliminación. En un estudio realizado con ^{14}C-paliperidona oral de liberación inmediata, una semana después de la administración de una dosis oral única de 1 mg de ^{14}C-paliperidona de liberación inmediata, el 59% de la dosis fue excretada inalterada con la orina, indicando que la paliperidona no se metaboliza masivamente en el hígado. Se recuperó aproximadamente el 80% de la 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 señalaron que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de la paliperidona, no hay datos in vivo de que estas isoenzimas desempeñen un papel significativo en el metabolismo de la paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios in vitro realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. Estudios in vitro han demostrado que la paliperidona es sustrato de la P-gp y un inhibidor débil de la P-gp a concentraciones elevadas. No existen datos in vivo y no se conoce su importancia clínica. Según el análisis de farmacocinética poblacional, la vida media aparente de paliperidona después de la administración de TREVICTA en el intervalo de dosis de 175-525 mg está comprendida entre 84-95 días cuando se inyecta en el deltoides y 118-139 días cuando se inyecta en el glúteo. Comparación de palmitato de paliperidona inyectable trimestral de larga acción con otras formulaciones de paliperidona. TREVICTA está diseñado para liberar paliperidona durante un período de 3 meses, mientras que la inyección mensual de palmitato de paliperidona se administra una vez al mes. TREVICTA, cuando se administra a dosis 3,5 veces más altas que la dosis correspondiente de palmitato de paliperidona inyectable mensual (ver sección 4.2), produce exposiciones a la paliperidona similares a las que se obtienen con la dosis correspondiente de palmitato de paliperidona inyectable mensual y con la dosis diaria equivalente de los comprimidos de paliperidona de liberación prolongada. El intervalo de exposición obtenido con TREVICTA está dentro del intervalo de exposición obtenido con las dosis aprobadas de los comprimidos de paliperidona de liberación prolongada. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque no se ha investigado el uso de TREVICTA en pacientes con insuficiencia hepática, no es necesario un ajuste de dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio en el que participaron pacientes con insuficiencia hepática moderada (clase B de Child-Pugh) las concentraciones plasmáticas de paliperidona libre fueron similares a las observadas en personas sanas. No se ha investigado el uso de paliperidona en pacientes con insuficiencia hepática grave. Insuficiencia renal. TREVICTA no se ha estudiado de manera sistemática en pacientes con insuficiencia renal. Se ha estudiado la eliminación de una dosis oral única de un comprimido de 3 mg de paliperidona de liberación prolongada en pacientes con diversos grados de función renal. La eliminación de la paliperidona disminuye al disminuir el aclaramiento de creatinina estimado. El aclaramiento total de paliperidona disminuyó un 32% en pacientes con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en pacientes con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en pacientes con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde a un aumento medio de la exposición (AUC_{τ}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con personas sanas. Población de edad avanzada. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con la edad. Índice de masa corporal (IMC/peso corporal. En los pacientes obesos y con sobrepeso se observaron valores de C_{max} más bajos. En el estado estacionario aparente de TREVICTA, las concentraciones valle eran similares en los pacientes normales, con sobrepeso y obesos. Raza. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el origen racial. Sexo. El análisis de farmacocinética poblacional no ha revelado indicios de diferencias farmacocinéticas relacionadas con el sexo. Tabaquismo. Según estudios in vitro realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no tiene un efecto en la farmacocinética de paliperidona. El efecto del consumo de tabaco sobre la farmacocinética de paliperidona no se ha estudiado en el caso de TREVICTA. Un análisis de farmacocinética poblacional basado en los datos obtenidos con comprimidos de liberación prolongada de paliperidona demostró una exposición a paliperidona ligeramente más baja en los fumadores que en los no fumadores. No es probable que esta diferencia tenga relevancia clínica. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona (formulación mensual) en inyección intramuscular y de paliperidona en administración oral a ratas y perros mostraron efectos fundamentalmente farmacológicos, como sedación y efectos mediados por la prolactina en glándulas mamarias y genitales. En animales tratados con palmitato de paliperidona se observó una reacción inflamatoria en el lugar de inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas con risperidona oral, que se convierte en gran medida en paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y en la supervivencia de las crías. No se han observado embriotoxicidad ni malformaciones después de la administración intramuscular de palmitato de paliperidona a ratas gestantes a dosis máximas (160 mg/kg/día), equivalentes a 2,2 veces el nivel de exposición de los humanos a la dosis máxima recomendada de 525 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo de la motricidad y del aprendizaje en las crías cuando se administraron a animales gestantes. Ni el palmitato de paliperidona ni la paliperidona han demostrado ser genotóxicos. En estudios sobre el potencial carcinogénico de la risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y de los adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico del palmitato de paliperidona administrado en inyección intramuscular a ratas. Se observó un incremento estadísticamente significativo de adenocarcinomas de las glándulas mamarias en ratas hembra a las que se administraron dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho experimentaron un incremento estadísticamente significativo de adenomas y carcinomas de las glándulas mamarias cuando se expusieron a dosis de 30 y 60 mg/kg/mes, que representan 0,6 y 1,2 veces el nivel de exposición humana a la dosis máxima recomendada de 525 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la relevancia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidratado. Dihidrogenofosfato sódico monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no se debe mezclar con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (copolímero de olefina cíclica) con émbolo, tope trasero y capuchón protector (goma bromobutílica), equipada con una aguja de seguridad de pared fina de 22 G 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad de pared fina de 22 G 1 pulgadas (0,72 mm x 25,4 mm). Tamaño del envase: Envases con 1 jeringa precargada y 2 agujas. Presentaciones y precios. Trevicta 175 mg suspensión inyectable de liberación prolongada: PVL: 489,25 €; PVP: 540,16 €; PVP (IVA): 561,77 €. Trevicta 263 mg suspensión inyectable de liberación prolongada: PVL: 636,50 €; PVP: 692,41 €; PVP (IVA): 720,11 €. Trevicta 350 mg suspensión inyectable de liberación prolongada: PVL: 782,80 €; PVP: 838,71 €; PVP (IVA): 872,26 €. Trevicta 525 mg suspensión inyectable de liberación prolongada: PVL: 1.174,20 €; PVP: 1.230,11 €; PVP (IVA): 1.279,31 €. Condiciones de prescripción y dispensación. Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se debe realizar de acuerdo con la normativa local. En el prospecto del envase se incluyen instrucciones completas del uso y manejo de TREVICTA (Ver Información reservada para médicos o profesionales sanitarios). **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** EU/1/14/971/007. EU/1/14/971/008. EU/1/14/971/009. EU/1/14/971/010. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/ RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 5 de diciembre de 2014. Fecha de la última renovación: 14 noviembre 2019. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 11/2019. 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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